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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

This special issue of the journal is dedicated to the Rare Diseases
Guest Editor – Professor Karaman Pagava

Номер журнала посвящается проблематике редких болезней
Приглашенный редактор – профессор Караман Пагава

ნომერი ეძღვნება იშვიათი დაავადებების პრობლემატიკას
მოწვეული რედაქტორი – პროფესორი ყარამან ფაღავა

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.
GMN is indexed in MEDLINE, SCOPUS, VINITI Russian Academy of Sciences, is available on-line at www.geomednews.ge

In 2009, GMN's SJR - 0.038; SNIP- 0.030

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, рецензии, научные сообщения, новости медицины и здравоохранения.
Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS и ВИНИТИ РАН, доступен в режиме on-line на www.geomednews.ge

В 2009 году рейтинг журнала (SJR) - 0.038; импакт фактор (SNIP)- 0.030.

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4. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

5. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

6. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

7. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით.

8. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

9. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

10. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: შესავალი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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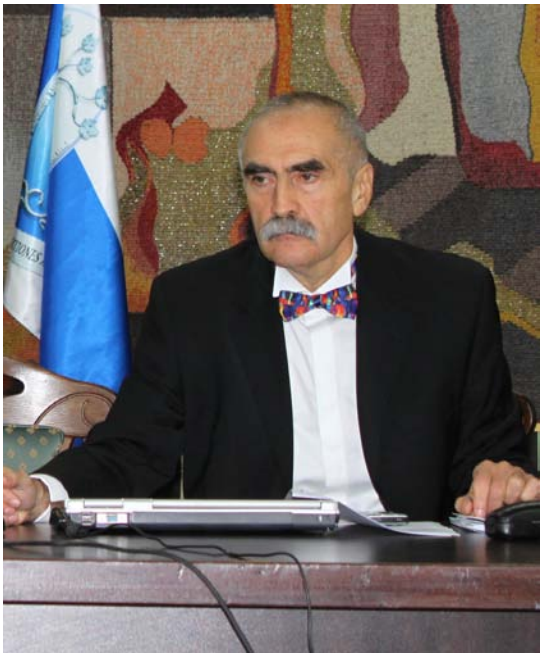
Guest Editorial

Rare diseases management served always as a yardstick of the health care level. Successful diagnosis and treatment of complex sophisticated cases was and stays the pride of clinicians.

In the last years one can mention a dramatic increase of the interest towards rare diseases, especially in the developed countries. There are several reasons for this: bioethical issues – every patient has a right to be provided with the optimal clinical management - diagnostics and treatment; objective difficulties – general practitioners lack knowledge and skills to deal with these diseases, which occur very seldom but their total number is huge (about 8.000-9.000), assumption of the paradoxical data, indicating that despite of the exceptional rarity of certain rare diseases, their aggregated frequency is reasonably high (approximately 5% of population suffer from these diseases). Thus, the problem of rare diseases has become an important challenge of public health.

In Georgia we can observe the similar situation. Establishment of an umbrella organization - Georgian Alliance of Rare Diseases had a considerable impact on the activation of efforts towards appropriate response to this challenge. The Alliance is acting in frames of the charitable foundation SOCO, founded and headed by the First Lady of country – Mrs. Sandra Elisabeth Roelofs.

Since 2009 at the Tbilisi State Medical University (Child & Adolescent Medicine department) the special project "Management optimization of rare diseases in children and adolescents" (Grant #GNSF/ST08/6-460), supported by [Georgian] Shota Rustaveli National Science Foundation has started. The presented special issue of the journal "Georgian Medical News", dedicated to the problem of rare diseases is a paper collection, reflecting at least partially results of our work. The invited papers of our counterparts (actual or presumable collaborators) both from Georgia and beyond are included as well.



The issue contains scientific-organizational and epidemiological works, review papers, results of clinical research and case reports. Information on the International Conference on Rare Diseases, held in Tbilisi, Georgia, 2010 and book review of the "Rare Diseases Epidemiology", 2011 (edited by M. Posada de La Paz & Stephen C. Groft) are also attached.

We dare to express our hope that publishing of such special issues will be carried out on the regular basis and thus will contribute to further research in this direction.

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MANAGEMENT OPTIONS FOR RARE DISEASES IN CHILDREN AND ADOLESCENTS IN GEORGIA (EXPERIENCE OF THE COUNTRY WITH TRANSITIONAL ECONOMY)

[1]Pagava K., [1]Abesadze G., [1]Uberi N., [1]Korinteli I., [1]Paghava I., [1]Kvezereli-Kopadze M., [1]Parulava T., [1]Korinteli M., [2]Kiseliova T.

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The nosologic entities with prevalence not exceeding 0.05% of general population are defined as rare diseases (disorders). There exist several thousands rare diseases in total. Their overall clinical and financial burden is quite significant as up to 5-6% of population have some rare disease [1-3]. The prevalence as well as relative density of the rare diseases is increasing all over the world in children and adolescents in terms of the morbidity structure. This rise is particularly evident in the developed countries.

As to the countries with transitional economics, including Georgia, the precise statistical information on their prevalence and incidence is hardly available. However, this issue seems to be gaining an importance in Georgia as well. The rate of the relatively ordinary infectious diseases was reduced successfully (the latter, along with the vaccination plan disruption, undernutrition of many strata of the society and extremely limited funding has constituted a major challenge to the national healthcare system in the 1990s following the collapse of the Soviet Union and the ensuing economic crisis, civil war, annexation of the substantial part of the national territory by the Russian Federation invoking mass ethnic cleansing and generating several hundreds thousands of internal displaced persons). The economical upheaval along with substantial increase in funding following the Revolution of Roses of 2003 led to the changes in the national morbidity structure, making it more expedient in terms of the national healthcare system to put more emphasis on the management of the conditions like rare diseases. One should mention that the Alliance for Rare Diseases (SOCO-ARD, Georgia) was set up as an affiliated branch of SOCO Foundation – charitable humanitarian organization, founded and headed by Mrs. Sandra Elisabeth Roelofs, the First Lady of Georgia. The Alliance became an umbrella body for a number of organizations, including different NGOs, like Georgian Foundation for Genetic and Rare Diseases, the Associations for Autism, Phenylketouria, Cystic Fibrosis, Blood Dseases, Musculoskeletal Disorders, Mental Retardation. The Georgian Law on Patients' Rights was accepted in 2000, featuring the rare diseases and declaring the government's obligations to support the patients suffering from the rare diseases (clause 13, items 1&2). There is a number of regulations of the Ministry of Labor, Health and Social Affairs of Georgia facilitating import and vending of the so called orphan drugs used for the management of the rare diseases. Neonatal screening is available for only two diseases in Georgia: phenylketonuria and congenital hypothyroidism. There are also some state programs with the view of medical support for the patients with some rare diseases and their families.

However, it seemed that the practitioners, at least in Georgia, were not well-acquainted with the whole issue of the rare diseases, and it predetermined the prescription of a multitude of unnecessary and potentially hazardous invasive diagnostic interventions; because of the rarity of this group of medical disorders and insufficient implementation of the evidence based medicine principles as well as the absence of special algorithms, the correct diagnosis was usually belated; quite frequently it was not established at all. It was noteworthy, that according to the preliminary research, there was virtually no pediatric software in the world, which could be applied to an object-orientated diagnostics of clusters of various rare diseases (the diagnostic software for the rare diseases manifested by various dysmorphic signs constituted the sole exclusion); similarly, fuzzy logic approaches were not employed; the treatment and, generally, management of these diseases could not be considered to be adequate and efficient - the fact particularly jeopardizing the children and adolescents' health. It was also noteworthy that due to the rareness of the individual rare diseases, it was not financially rational for private companies to invest into this area; correspondingly, the relevant research and overall efforts in this direction were quite limited. Moreover, because of the limited number of cases it was quite difficult to establish the efficiency of some specific therapeutic interventions by employing the classical methods. This fact in its turn indicated the advisability of elaborating new methods and means of management for the rare diseases, including the multi-center cooperation.

The foregoing analysis of the current situation in the field inspired our team to undertake to development and implementation of the project targeted at the management optimization of the rare diseases, with particular emphasis on the children and adolescents, as up to 80% of the rare disorders constitute the hereditary conditions and first manifest in the childhood/adolescence.

We elaborated a comprehensive plan of actions [8]. Our work according to the plan yielded some remarkable results; namely, we:

- Compiled a list of the rare diseases actual for Georgia; the following sub-tasks were fulfilled thereto:
  - A list of all rare diseases was compiled;

- A fuzzy logic based model for selecting the most significant rare diseases was elaborated; it was implied that the latter would constitute a top-priority in terms of training the clinicians;
- An expert system was developed for solving this task based on the aforementioned model;
- A respective list of the rare diseases was compiled.

- Assessed the awareness level for the rare diseases of the general practioners in Georgia by means of
  - Surveying 300 doctors in various regions of Georgia, the questionnairies being filled in anonymously;
  - An unsatisfactory level of awareness was detected.
- Translated into Georgian and adapted 80 textual materials regarding the management of various rare disorders, with a view to publish them online (post to the special section of the Tbilisi State Medical University official website);
- Established working relations with the Rare Diseases' Group of the European Academy of Pediatrics in order to obtain the up-to-date materials with regard to the rare diseases;
- Organized 11 conferences and seminars, including an international one, in various regions of Georgia for the purpose of acquainting the clinicians with the selected issues of the rare diseases;
- Elaborated a model of the expert system based on the fuzzy logic principles for unmasking the cases suspicious for the rare disease;
- Elaborated algorythms and expert systems supporting the diagnosis making process for various clusters of the rare diseases (haematologic, endocrinological, gastroenterologic);
- Laid the foundation of the national register for some rare diseases in children and adolescents;
- Elaborated an addition to the extant methodology for producing and adapting medical guidelines. Our additions constituted the selections of respective data and the extant guidelines in order to produce the regional as well as national guidelines;
- Elaborated additions to the current methodology or performing clinical trials in the area of the rare diseases. The additions were based on the fuzzy logic;
- Developed training curriculum for the continuous education of physicians in the field of the rare diseases;
- Organized the center for the rare diseases;
- Conducted a regular analysis of the materials required for producing the evidence based recommendations aimed at elaborating the national policy with regard to the optimal management of the rare diseases in Georgia.

Some of our results and achievements were reflected in publications [4,7,10].

We consider that the obtained results would facilitate the optimization of the rare diseases management in children and adolescents, particularly in terms of diagnostics and treatment. The employing of the expert systems and new approaches (fuzzy logic) in clinical medicine and particularly in pediatrics would constitute an efficient tool for further perfection of the children and adolescent healthcare system. Up to 5-6 % of children and adolescents' population as well as their family members and care-givers suffer from some rare disorder and would benefit substantially from our efforts. The management algorithms that we composed being guided by the novel approaches and evidence in the area of the rare diseases, would also reduce the financial burden induced by this group of disorders.

Last but not least, we suppose that that obtained expertise would be useful for other countries with transitionaly economy as well, in terms of producing the national priorities and plans of actions with subsequent implementation of the specific activities targeted at the management optimization for the rare diseases.

Acknowledgement. The paper was prepared within the framework of the project funded by the Georgian National Science Foundation (Grant #GNSF/ST08/6-460). Any ideas expressed by means of this publication belong to the authors and may not represent the opinion of the Georgian National Science Foundation.

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SUMMARY

MANAGEMENT OPTIONS FOR RARE DI-SEASES IN CHILDREN AND ADOLESCENTS IN GEORGIA (EXPERIENCE OF THE COUNTRY WITH TRANSITIONAL ECONOMY)

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We present the results of our research and organizational work aimed at the management optimization for the rare diseases in Georgia (the Country with Transitional Economy). We compiled a list of the rare diseases actual for Georgia; elaborated algorythms and expert systems supporting the diagnosis making process for various clusters of the rare diseases; translated into Georgian and adapted textual materials regarding the management of various rare disorders; assessed the awareness level for the rare diseases of the pediatricians and general practioners in Georgia and attempted to raise it by organizing seminars and conferences, including international ones, in various regions of Georgia; elaborated a model of the expert system (based on the fuzzy logic principles) for unmasking the cases suspicious for the rare disease; laid the foundation for the national register of the rare diseases in children and adolescents; elaborated the module for post-graduate education regarding rare diseases; organized the center for the rare diseases.

Key words: rare diseases, management.

РЕЗЮМЕ

ВОЗМОЖНОСТИ МЕНЕДЖМЕНТА РЕДКИХ БОЛЕЗНЕЙ У ДЕТЕЙ И ПОДРОСТКОВ (ОПЫТ СТРАНЫ С ПЕРЕХОДНОЙ ЭКОНОМИКОЙ)

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В статье представлены результаты научной и организационной работы по оптимизации менеджмента редких болезней в Грузии (стране с переходной экономикой). Составлен список редких болезней, актуальных для Грузии; созданы алгоритмы и экспертные системы для дифференциальной диагностики различных кластеров редких болезней; переведены на грузинский язык и адаптированы тексты по менеджменту различных редких болезней; оценен уровень информированности педиатров и врачей общей практики в Грузии о редких болезнях и предпринята попытка его повышения путем организации семинаров и конференций (в том числе – международных) в различных регионах страны; выработана модель экспертной системы, основанной на принципах нечеткой логики, для выявления клинических случаев с подозрением на редкую болезнь; заложена основа национального регистра редких болезней у детей и подростков; выработан модуль для последипломного образования в области редких болезней; представлена структура и положение о работе Центра редких болезней.

რეზიუმე

ბავშვებსა და მოზარდებში იშვიათი დაავადებების ოპტიმიზაცია საქართველოში (გარდამავალი ეკონომიკის მქონე ქვეყნის გამოცდილება)

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განხილულია საქართველოში (გარდამავალი ეკონომიკის მქონე ქვეყანაში) იშვიათი დაავადებების მართვის ოპტიმიზაციისკენ მიმართული ჩვენი კვლევითი და საორგანიზაციო მუშაობის შედეგები. შედგენილია საქართველოსთვის აქტუა-

ლური იშვიათი დაავადებების სია; გამომუშავებულია ალგორითმები და საექსპერტო სისტემები იშვიათი დაავადებების სხვადასხვა კლასტერის დიაგნოსტიკის გასაადვილებლად; ქართულად ნათარგმნია სხვადასხვა ტექსტური მასალა იშვიათი დაავადების მართვის თემაზე და განხორციელებულია მათი ადაპტაცია; შესწავლილი და შეფასებულია იშვიათი დაავადებების დარგში ქართველი ექიმების გათვითცნობიერებულობის დონე. საქართველოს სხვადასხვა რეგიონში სემინარებისა და კონფერენციების (მათ შორის, საერთაშორისო კონფერენციების) ჩატარების გეგმა და თემატიკა, აგრეთვე არამკაფიო ლოგიკის პრინციპებზე დაფუძნებული ექსპერტული სისტემის მოდელი იშვიათ დაავადებაზე საჭვო კლინიკური შემთხვევების გამოსავლენად; ჩავუყარეთ საფუძველი ბავშვებსა და მოზარდებში იშვიათი დაავადებების ეროვნულ რეგისტრს; წარმოდგენილია იშვიათი დაავადებების დარგში დიპლომისშემდგომი განათლების მოდული; შემუშავებულია იშვიათი დაავადებების ცენტრის სტრუქტურა და დებულება.

PUBLIC HEALTH RESEARCH ON RARE DISEASES

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Rare diseases (RD) are conditions whose prevalence is below 5 cases per 10,000 inhabitants in Europe [8]. Most cases are diagnosed during paediatric age and affect the patient throughout his life, but they can also be diagnosed during adult age. Nevertheless, a higher prevalence is seen during adulthood as most of the diseases are very severe and patients die during childhood. At the same time, higher survival rates are related to some chronic RD in adults.

Beyond the diversity of the diseases, RD patients and their families are confronted with the same wide range of difficulties arising directly from the rarity of these pathologies (Table).

Table. Problems related to the low frequency of rare diseases (RD) [16]

RD PROBLEMS	DESCRIPTION
Lack of access to correct diagnosis	long period between the emergence of the first symptoms and the appropriate diagnosis (highly risky delays), as well as wrong diagnosis leading to inaccurate treatments
Lack of information	about both the disease itself and about where to obtain help, including lack of referral to qualified and expert professionals
Lack of scientific knowledge	difficulties in developing therapeutic tools, in defining the therapeutic strategy and in shortage of therapeutic products
Social consequences	living with a rare disease has implications in all areas of life, and it may lead to stigmatisation, isolation, exclusion from social community, discrimination for insurance subscription, and often reduced professional opportunities
Lack of appropriate quality healthcare	different specialists are needed for RD patients; patients can live for several years in precarious situations without competent medical attention
High cost of the few existing drugs and care	additional expense of coping with the disease, combined with the lack of social benefits and reimbursement, cause an overall pauperisation of the family, and dramatically increases the inequity of access to care for rare disease patients
Inequities in availability of treatment and care	delays in price determination and/or reimbursement decision, lack of experience of the treating physicians and the absence of treatment consensus recommendations

In general, it is difficult to diagnose these serious chronic diseases that lead to high disability. In Spain, the average delay in diagnosis has been estimated at almost 5 years, although it can be 10 years or over for one out of five patients [12]. Moreover, about 10% of RD patients reported that obtaining a diagnosis was only possible with a 'high' or 'very high' personal financial contribution [17].

RD have a direct impact on both the family and society, which must develop specific social, health and educational programs to support these patients. The number of medical and social services required depends heavily on the complexity of the disease they are affected, and on the accumulation of consultations, examinations, tests and inefficient treatments are a major source of financial burden for both families and society[17]. As an example of social dependence – when people need some help from a third person for developing their daily activities - 44% of RD patients require help in their daily life and 68% need an adapted housing. [12].

RD are receiving increasing attention within both scientific community and society in general. They are becoming a new group of diseases with different aetiologies, prognoses and clinical features, yet with similar social and medical problems affecting patients, their families and society alike. It is also a general agreement that for improving diagnosis and monitoring, it is necessary to develop reference units at national level that will improve our knowledge of these diseases.

Epidemiology does have an important role to play in the field of RD, since it provides appropriate methods and tools for assessing exposures and health outcomes. However, there are few reliable epidemiological data on RD in the national and global populations [19]. Moreover, most epidemiological studies about prevalence/incidence, mortality or burden of disease (among other) are focused on single RD [1,18,28,29]. In this scenario, epidemiology must be the benchmark for drawing up heath policies affecting RD because it has a crucial role in the design and development of aetiological research and health planning into such diseases.

Rare diseases epidemiology

RD epidemiology is still largely unexplored and represents a novel work area. National RD health plans have been developed in some European countries, and efforts are focused on the promotion and coordination of international research projects on RD, regulation of orphan drugs, and some other important aspects such as social, education and patients' empowerment [8,9,11,15,20].

One of the main problems of facing RD health care planning is that the burden of most of these diseases remains invisible to health system, due to misclassification and lack of appropriate coding [7]. The 9th and 10th revision of the International Classification of Diseases (ICD) are being simultaneously used by several countries and by different health information systems in a given country. Moreover, fewer than 300 specific RD can be identified with a single ICD-10 code [26]. RD recognition by national healthcare and surveillance systems would be facilitated by an appropriate classification and coding system that covered all RD and afforded adequate codes and valid traceable mechanisms. Such a system is thus urgently needed to promote well-conducted epidemiological studies [7].

Registries

Patient registries are essentials tools for public health surveillance and research inquiry, and are a particularly important resource for understanding RD [27]. They involve a systematic data collection program for the storage, retrieval and dissemination of a clearly defined set of data collected on identifiable individuals for specific purpose (e.g. scientific or epidemiological research).

The lack of information systems harmonization, the various purposes and stakeholders, complicate any attempts to inventory, standardize, or prescribe good design features for patient registries in general. The need for global cooperation for RD research creates a difficult situation for designing clinical guidelines and best practices for patient registry projects.

In addition, RD are specially vulnerable to possible identification because some of them have very visible phenotypes, bad prognoses and small number of affected individuals. The creation and use of special algorithms, techniques, and qualified oversight are especially critical for RD to prevent unwanted identification of cases by association with other data sets [27].

Biobanking

Biobanks can be thought of as registries of patient characteristics (usually genetic) with a biological data collection component. Biobanking is a useful tool to provide access to human biomaterial for fundamental and translational research [22].

Many features of RD biobanks are similar to larger common-disease or population biobanks. Other considerations are of particular importance to RD biobanking, because there are small donor numbers and a limited number of biological samples available for most of rare disorders.

The EuroBioBank network is the first operating network of RD biobanks in Europe providing human DNA, cell and tissue samples as a service to the scientific community conducting research [14]. Its main goals are: identify and localise biological material of interest to researchers; build a critical mass of RD sample collections; distribute high quality material and associated data to users; promote best-practice guidelines for biobanking activities; disseminate knowledge and know-how to

the scientific community through training courses; and enhance collaboration with the medical and scientific community in the field of RD.

As RD patients often play a very important and proactive role, in addition to be donors of biological material, the concept of "benefit sharing" has been developed in this medical area. This may include regular information to patients and patient organizations on the activities of the biobank, and on the results of the research based on the biomaterial provided [22].

Population-Based surveillance
Collection of population-based surveillance data is a first step in the discovery of aetiologies for rare disorders of unknown cause, in examining outcomes, and evaluating treatments and interventions for patients with all types of congenital, inherited or acquired diseases. RD can have a lifelong impact on health, causing long-term disability and costing billions of dollars in care, and the infrequency of these disorders does not reduce their collective impact or burden on individuals and their families [4].

Population-based surveillance systems are designed to detect all severities of multiple disorders and thus have the potential to provide more accurate prevalence estimates. For example, global birth defect surveillance is composed of hundred of well-established programs and can potentially be used as conduit for studies of rare congenital diseases, but many challenges are associated with its development, such as difficulty in ascertaining appropriate diagnoses and frequent unavailability of necessary resources [21].

Quality of life and cost of illness
Some RD do not necessarily affect life expectancy, but most of them lead to physical, emotional and/or psychosocial limitations with a wide rage of disabilities. Quality of life is very important as a clinical outcome, since its assessment can help to identify healthcare needs, to evaluate the impact of disease and treatments and to assess the evolution in health status through the natural history of disease. Recently, the interest on health-related quality of life has increased, although efforts for improving its interpretation and clinical application of the appropriate instruments of measure are still required. Given the impact of RD on the quality of life of both patients and carers, improving their quality of life should and will be one of the most important goals of any health care intervention or multidisciplinary approach [25].

On the other hand, cost of illness is essential for appraising the magnitude of a particular health problem. A distinction must be drawn among different types of costs: 1) direct medical costs (value of the resources used in the diagnosis, treatment, costs of inpatient and outpatient care and drugs); 2) direct non-medical costs (support activities provided to persons with limited autonomy, being formal -publicly or privately funded- or informal -provided by people who usually belong to the emotional environment of the patient-); 3) indirect costs (loss of productivity due to temporal or permanent disability); and 4) "intangible costs" (health-related quality of life, loss of quality-adjusted life years). RD may well represent a significant societal burden that should rightly receive appropriate prioritisation of health care resources. For instance, in a study carried out in 2001 in Spain, scleroderma generated 1732 disability-adjusted life-years (DALY), comprising 562 (32%) years of life lost and 1170 (68%) years lived with disability [29].

It is not enough for new health care technologies to be safe and highly specific: the main questions to be addressed are whether they result in better health outcomes and for which patients they are useful. Economic studies in heath care should be aimed at encouraging the adoption of decisions and actions based on cost and effectiveness, thereby reducing arbitrary prioritisation in the financing of health care programmes [23]. In this regard, the main aim of BURQOL-RD (a 3 year project under the 2nd Programme of Community Action in the Field of Public Health, promoted by the DG Sanco) is to generate a model to quantify the socio-economic costs and Health Related Quality of Life (HRQOL), of both patients and caregivers, for up to 10 RD in different European countries [3].

European Policy
RD are singled out as a unique domain of very high European added-value due to their limited number of patients and the scarcity of relevant knowledge and expertise. There is probably no other area in health where collaboration between 27 different approaches can be as efficient and effective. Coordination at EU level is probably the best way of pooling the very limited resources available [24].

After the decision of adopting a Community action programme on RD for the period 1999-2003 [8], the programme of Community action in public health (2003-08) was the first integrated Community programme in this field, and it has already delivered a number of important developments and improvements [10]. Most recently, in the following second Community Action Programme in public health 2008-13 [9], two important European decisions highlight the recognition of RD as a public health priority [5,6].

European action can be more effective than Member States acting on their own and it includes several steps, among others: making RD more visible, encouraging Member States to develop national RD plans in their health policies and providing European support and cooperation, ensuring coordination in several areas (classification and codification, European Reference Networks, orphan drugs, etc) [24]. In addition, the European Union Committee of Experts on Rare Diseases (EUCERD) is in charge with aiding the European Commission with the preparation and implementation of Community activities in the field of RD for the next years [13].

Ethical features

Regarding ethical features on RD, it is important to take into account some general aspects such as the socio-psychological problems that confront the RD patients and their families that finally could lead to marginalization and exclusion from the health programs, even in wealthy countries. Critical situations could be related to diagnosis and to some ethical aspects of newborn screening, prenatal, pre-implantation diagnosis. The research related to RD in children is other especially vulnerable condition, joint to the general need of informed consent, confidentiality of the information, samples included in biobanks, pharmacogenetics and other aspects that are evaluated by ethics review board [2].

In summary, despite low prevalence of RD, both families and society have to bear an important burden of disease. Specific social, health and educational intervention programs to support RD patients have to be developed in order to deal with suffering and difficulties of patients and their families. The utility of registries, biobanks and population-based surveillance systems in this field have been important issues recommended by European Commission. European Council and Parliament have encouraged Member States to implement national RD plans among their health policies in close cooperation with European authorities. RD require the combined efforts of health and social care professionals, politicians, managers and researchers to increase the availability of effective disease management tools to improve care and to extend both life expectancy and Health Related Quality of Life.

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SUMMARY

PUBLIC HEALTH RESEARCH ON RARE DISEASES

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Despite the low prevalence of Rare Diseases (RD), over 30 million EU citizens suffer from these conditions. This paper summarizes some aspects of these life-threatening chronic and debilitating diseases that usually require long term specialist care and costly formal and informal surveillance. Epidemiology does have an important role to play in the field of RD, since it provides appropriate methods and tools for assessing exposures and health outcomes. In this regard, the utility of registries, biobanks and population-based surveillance systems are discussed. The lack of effective diagnoses and treatments in RD patients often underlies their shortened life expectancy and quality of life. Due to the limited number of patients and the scarcity of relevant knowledge and expertise, coordination at European level is probably the best way of pooling the very limited resources available and provides a very high added-value. RD require the combined efforts of health and social care professionals, politicians, managers and researchers to increase the availability of effective disease management tools to improve care and to extend both life expectancy and Health Related Quality of Life.

Key words: rare diseases, epidemiology, population-based registry, quality of life, social difficulties.

РЕЗЮМЕ

ИССЛЕДОВАНИЯ В ОБЛАСТИ ОБЩЕСТВЕННОГО ЗДРАВООХРАНЕНИЯ ПО РЕДКИМ БОЛЕЗНЯМ

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Несмотря на невысокий показатель распространенности редких болезней (РБ), более чем 30 миллионов граждан Евросоюза страдают от подобных состояний. В статье рассматриваются некоторые аспекты этих хронических, опасных для жизни и ослабляющих заболеваний, которые обычно требуют долгосрочного профессионального ухода и дорогостоящего формального и неформального наблюдения.

Эпидемиология занимает значимую роль в изучении РБ, так как она обеспечивает соответствующие методы и инструменты для оценки воздействия различных факторов на здоровье. Обсуждается полезность в этом отношении регистров, биобанков и систем наблюдения за населением. Недостаточно эффективные диагностика и лечение являются причиной сокращенной продолжительности и низкого уровня качества жизни больных РБ.

Ввиду ограниченного числа пациентов и дефицита соответствующего знания и экспертизы, координация на европейском уровне, по всей вероятности, является наилучшим способом объединения весьма ограниченных ресурсов для обеспечения улучшения медицинской помощи. РБ требуют комбинированных усилий со стороны врачей, социальных работников, политических деятелей, менеджеров и исследователей

с целью увеличения доступности эффективных средств менеджмента и повышения уровня медицинской помощи, продления продолжительности и улучшения качества жизни больных РБ.

რეზიუმე

საზოგადოებრივი ჯანდაცვის კვლევა იშვიათი დაავადებებზე

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იშვიათი დაავადებები (იდ), დაბალი სიხშირის მიუხედავად, აღნიშნება ევროკავშირის 30 მილიონზე მეტ მოქალაქეს. სტატიაში განხილულია ამ დაავადებების სიცოცხლისათვის სახიფათო და დამასუსტებელი ზოგიერთი ასპექტი, რომელიც თხოულობს ხანგრძლივ სპეციალიზირებულ მოვლას და ძვირადღირებულ ფორმალურ და არაფორმალურ მეთვალყურეობას.

იდ სფეროში ეპიდემიოლოგია მნიშვნელოვან როლს ასრულებს, ვინაიდან იგი ფლობს სხვადასხვა ფაქტორის ჯანმრთელობაზე ზემოქმედების შესატყვის მეთოდებსა და საშუალებებს. ამ თვალსაზრისიდან გამომდინარე, განიხილება რეგისტრების,ბიობანკებისა და პოპულაციაზე ზედამხედველობის სისტემები. იდ-ის დროს არაეფექტური დიაგნოსტიკა და მკურნალობა ხშირად განაპირობებს სიცოცხლის ხან-გრძლივობის შემცირებასა და ცხოვრების ხარისხის გაუარესებას. პაციენტების რაოდენობის, შესაბამისი ცოდნისა და ექსპერტიზის სიმცირის გამო, ძალზე მცირე რესურსების აკუმულაციისა და მაღალი ხარისხის დახმარების აღმოსაჩენად ევროპულ დონეზე კოორდინაცია საუკეთესო გზას წარმოადგენს. იდ თხოულობს ჯანდაცვის, სოციალური დარგის მუშაკების, პოლიტიკოსების, მენეჯერებისა და მკვლევარების ერთობლივ ძალისხმევას, მისი მენეჯმენტის საშუალებების გამოყენების ეფექტურობის ასამაღლებლად, რაც ხელს შეუწყობს სიცოცხლის ხარისხის გაუმჯობესებასა და გახანგრძლივებას.

GENERAL KNOWLEDGE AND AWARENESS ON RARE DISEASES AMONG GENERAL PRACTITIONERS IN BULGARIA

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In recent years, EU social and public health policy initiatives focus on the health inequalities and discrimination of minority groups – immigrants, refugees, marginal social groups, people with rare diseases etc. The Council of the European Union in its Recommendation of 8 June 2009 identifies rare diseases as a serious public health problem and “a threat to the health of EU citizens, insofar as they are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity” [2]. It also underlines the need for adequate education and training for all health professionals to make them aware of the existence of these diseases and of the resources available for their care. Emphasis is put on helping the development of medical training in fields relevant to the diagnosis and management of rare diseases such as genetics, immunology, neurology, oncology or pediatrics.

Important role in the area of rare diseases have the medical specialists who diagnose and monitor the course of the disease of each patient [1]. Before patients consult with a medical specialist, they have the first contact with the health system is at the level of primary care [3-5]. General practitioners (GPs) are the ones that are closer to the population and usually are the first to identify “unusual” patients that might have a rare disease [7]. The GPs awareness and knowledge about rare diseases is a strong factor for the timely and accurate forwarding of patients to specialized hospitals and expert centers for accurate diagnosis and adequate treatment of rare diseases conditions [6]. The aim of this paper is to study the level of knowledge and general awareness on rare diseases among Bulgarian general practitioners.

Material and methods. A telephone interview was conducted among the general practitioners in Bulgaria between January and March 2008. From the National Health Insurance Fund's public database for the GPs in Bulgaria, that have a contract for primary medical care in 2008 (n=5106 GPs), was extracted a 40% (n=2042 GPs) random sample by a specially designed computer software. The doctors were contacted by a team of interviewers, previously trained for the purpose of the study. A set of 17 questions with pre-defined answers was constructed in order to determine the level of knowledge and awareness of rare diseases of the GPs. The questionnaire included five groups of questions. The first group consisted of items related to age, gender, length of service and specialty. The second group contained questions that concerned the definition and frequency of rare diseases. The third group gathered items aimed to determine the level of knowledge of specific rare diseases (multiple sclerosis, mucoviscidosis, Fabry disease, MPS, lysosomal storage diseases, Gaucher's disease). This group also had questions for self-esteem of GPs concerning their knowledge and competence in the field of rare diseases. Very important were the items of the fourth group related to GPs' daily practice within the last calendar year - whether they had patients with rare diseases and where they refer them for a specialized consultation. The last group of questions defined the interest of the GPs to raise the level of knowledge through postgraduate studies or through providing specialized information and visits to conferences related to rare diseases. Data were statistically processed using specialized software SPSS version 9.0 (SPSS, Inc., Chicago IL) by descriptive statistics, correlation analysis and nonparametric tests for comparison of quantitative and qualitative categories.

Results and their discussion. From the random sample of 2042 GPs almost half of them (n=1002 GPs) agreed to be interviewed (49.0% response rate). Study participants (n=404 (40.30%) men and n=598 (59.70%) women) were from all regions of the country. The larger number of women could be explained with a stronger affinity for their prominent participation in such studies. The mean age of the participants was 45.91±8.23 years, ranging between 29 and 76 years. The average length of service among was 18.54±8.51 years for men, and 19.63±7.81 years for women ($p<0.05$).

GPs who have no medical specialty at all are 19.36% (n=194) from all surveyed. The relative part of doctors with only one specialty is 67.47% (n=676) and those with two or more specialties - 13.17% (n=132). Among doctors with one medical specialty, the most common specialty is that of general medicine (n=280, 41.50%), followed by internal medicine (n=143, 21.10%) and pediatrics (n=89, 13.10%). The rarest is the specialty of obstetrics and gynecology (n=10, 1.40%.) Among the 132 GPs with a second specialty, the most common are that of pediatrics (n=39, 29.80%) and internal medicine (n=38, 29.00%). The occurrence of the other reported medical specialties (obstetrics and gynecology, infectious disease, cardiology, endocrinology, pulmonology, social medicine and health management, occupational health, physiotherapy, radiography, gastroenterology, ears-nose-throat, psychiatry, dermatology, neurology, sports medicine, hematology and surgery) is almost evenly distributed with frequencies between 0.8-6%.

The participants were asked two questions concerning the definition of a rare disease in the European Union and the frequency with which rare diseases are widespread in a population. Only one fifth of GPs (n=198, 19.82%) know the exact definition of a rare disease in Europe (a disease that affects less than 5 persons per 10 000). The majority of physicians (n=549, 54.78%) considered a rare disease is a disease that has a frequency of 1:100 000. The remaining part of the GPs (n=255, 25.40%) could not answer the question and preferred to skip it. Regarding the perception of GPs about the estimated number of people with rare diseases in a population (which is 6-8%), only 6.90% (n=69) of respondents answered correctly. Similarly to the first question, more than half (n=606, 60.50%) significantly underestimated the social and public health importance of this problem and the rest (n=327, 32.60%) had no answer. When combining the correct answers from both questions, only 23 GPs (2.30%) appeared to know the definition of a rare disease and their distribution. This low percentage of correct answers could be explained with lack of time and resources for access to specialized information or lack of interest in the rare disease topic.

Respondents were asked to determine the rare/common status of a set of four diseases, according to their best knowledge - multiple sclerosis (with a border prevalence of 4.45/10000 in Bulgaria), cystic fibrosis (prevalence around 0.50-1/10000), Fabry disease (prevalence around 0.10-0 .90/10000) and MPS (prevalence about 0.01-0.09/10000). Results show that physicians have a relatively good idea of the "rareness" of the surveyed diseases. Reducing the prevalence of the disease increases their confidence in the rareness of the disease (Fig. 1).

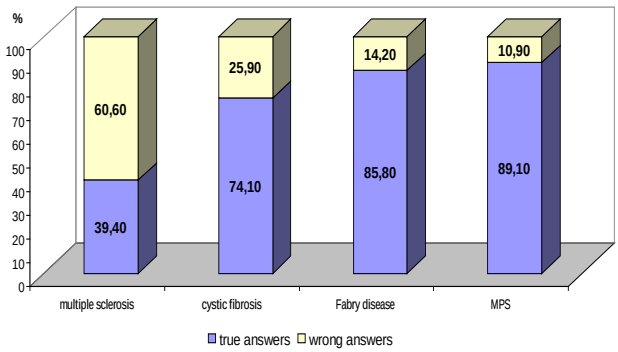

Fig. 1. Correct and wrong answers of the GPs about the rareness of multiple sclerosis, cystic fibrosis, Fabry disease and MPS in Bulgaria

GPs were asked to evaluate the level of their professional knowledge of Lysosomal storage diseases (LSD) on a scale from 1 (I have not heard about it) to 5 (I am very well aware). Only 7.90% (n=79) of all GPs responded that know this group of diseases well or very well. The rest (n=923, 92.10%) either have not heard about them or have declared very low level of knowledge. The self-assessment of GPs about their level of awareness of Gaucher's disease did not differ significantly from the previous questions (Fig. 2).

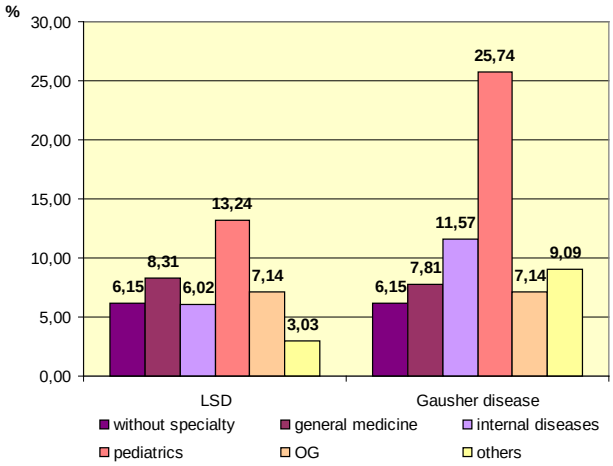

Fig. 2. Very good and good level of knowledge of main symptoms of LSD and Gaucher disease by GPs' primary specialty (self-assessment)

On the open question to name some LSD, that come in mind right away, only 84 GPs (0.80% of all respondents) gave correct answers - Gaucher's disease (75.00%), mucopolysaccharidosis (11.90%), Fabry disease (7.10%) glycogenoses (3.60%) and gangliosidosis (2.40%). Only 4.20 percent of doctors (n=42) declared, that have had a patient with a rare disease during the last year. More than half of all GPs have directed their "difficult patients" to the university hospitals (n=556, 55.50%) in the county or other big hospitals for active treatment (n=98, 9.80%). Around one third of GPs refer their patients with rare diseases to specialists in nonhospital care (n=285, 28.40%), and only 6.30 percent (n=63) seek a consultation with a medical geneticist. The impact of gender, age and work experience of GPs have been analyzed but showed no influence upon their awareness and knowledge about rare diseases ($p>0.05$).

This study is the first to explore the level of awareness and knowledge of GPs in Bulgaria about rare diseases. Its design and very high response rate could guarantee a high level of representativeness for the results. The responses of surveyed doctor indicate a low level of general knowledge and awareness. This means, that GPs from the primary health care system could not provide sufficient in quality and timeliness specific information to their patients with rare diseases. Particularly worrying is the underestimation of the prevalence of rare diseases by GPs. Doctors in primary care neglect the importance and do not fully exploit the possibilities of medico-genetic consultations services in the country for patients with rare diseases. Changing this attitude would lead to more timely diagnosis and faster referral of patients to available rare disease experts.

A campaign for increasing the awareness of GPs about rare diseases (prevention, diagnosis, treatment and rehabilitation) is needed. Besides awareness, facultative courses for undergraduate students in medicine and post-graduate courses for GPs could boost their knowledge about the frequency of rare diseases, adequate approach to "difficult" patients and available information sources and treatment options in the country.

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SUMMARY

GENERAL KNOWLEDGE AND AWARENESS ON RARE DISEASES AMONG GENERAL PRACTITIONERS IN BULGARIA

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Rare diseases are a serious public health problem and are a threat to the health of EU citizens. Important role in the area of rare diseases have the medical specialists who diagnose and monitor the course of the disease of each patient. General practitioners (GPs) are usually the first to identify "unusual" patients that might have a rare disease. The GPs awareness and knowledge about rare diseases is a strong factor for the timely and accurate diagnosis and adequate treatment of rare diseases conditions.

A telephone interview was conducted among the GPs in Bulgaria between January and March 2008. A set of 10 questions with pre-defined answers was constructed and offered to the GPs in order to determine their level of knowledge and awareness of rare diseases. Data were statistically processed using specialized software SPSS version 9.0 (SPSS, Inc., Chicago IL).

The responses of surveyed doctor indicate a low level of general knowledge and awareness. This means, that GPs from the primary health care system in Bulgaria could not provide sufficient in quality and timeliness specific information to their patients with rare diseases. A campaign for increasing the awareness of GPs about rare diseases is needed.

Key words: rare disease, general practitioners, knowledge, awareness.

РЕЗЮМЕ

УРОВЕНЬ ЗНАНИЙ И ИНФОРМИРОВАННОСТЬ ВРАЧЕЙ ОБЩЕЙ ПРАКТИКИ В ОТНОШЕНИИ РЕДКИХ БОЛЕЗНЕЙ В БОЛГАРИИ

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Редкие болезни - значительная проблема общественного здравоохранения, представляет собой угрозу для здоровья граждан. В этом отношении значительная роль в постановке диагноза, проведении адекватного лечения и установлении его эффективности принадлежит врачам первого звена, которые ставят диагноз и осуществляют мониторинг заболевания. Идентифицировать «необычных» пациентов, у которых могут наличествовать те или иные редкие болезни, в основном, прерогатива врачей общего профиля. Уровень знаний и информированность этих врачей по вопросам редких болезней являются факторами, определяющими своевременную, полноценную диагностику и эффективность лечения этих болезней.

В январе-марте 2008 года в Болгарии был проведен телефонный опрос врачей общей практики. Вопросник состоял из десяти вопросов с заранее определенными ответами. Цель исследования заключалась в определении уровня знаний и информированности врачей общей практики в области редких болезней. Полученные результаты были обработаны с использованием статистической программы SPSS version 9.0 (SPSS, Inc., Chicago IL).

Исследование выявило низкий уровень знаний и информированности опрошенных врачей. Это указывает на то, что врачи общей практики в Болгарии не в состоянии предоставить пациентам с редкими болезнями качественно достаточную и своевременную помощь. Исходя из вышеизложенного, считаем целесообразным проведение специальной компании с целью повышения осведомленности врачей общей практики по вопросам редких болезней.

რეზიუმე

ზოგადი პრაქტიკის ექიმების ცოდნის დონე და ინფორმირებულობა იშვიათი დაავადებების შესახებ ბულგარეთში

ც. მიტევა, რ. იორდანოვა, გ. ისკროვი, რ. სტეფანოვი

იშვიათი დაავადებების ცენტრი, პლოვდივი, ბულგარეთი

იშვიათი დაავადებები საზოგადოებრივი ჯანდაცვის სერიოზულ პრობლემას, ხოლო მოქალაქეებისთვის კი ჯანმრთელობის საფრთხეს წარმოადგენენ. ამ მიმართულებით მნიშვნელოვანი როლი ენიჭება მედიცინის დარგის იმ სპეციალისტებს, რომლებიც სვამენ დიაგნოზს და განახორციელებენ დაავადების მონიტორინგს. ზოგადი პროფილის ექიმები ჩვეულებრივ იმ პირველ რგოლს წარმოადგენენ, რომლებმაც იდენტიფიკაცია უნდა მოახდინონ "არაჩვეულებრივი" პაციენტებისა, რომელთაც ესა თუ ის იშვიათი დაავადება შეიძლება ჰქონდეთ. აქედან გამომდინარე, ზოგადი პრაქტიკის სპეციალისტების ცოდნა და ინფორმირებულობა იშვიათი დაავადებების შესახებ მნიშვნელოვანი ფაქტორებია მათი დროული და სრულყოფილი დიაგნოსტიკისა და ადექვატური მკურნალობის ჩასატარებლად.

ბულგარეთში 2008 წლის იანვარ-მარტში ჩატარდა ზოგადი პროფილის ექიმების სატელეფონო გამოკითხვა. კითხვარი მოიცავდა 10 საკითხს წინასწარ განსაზღვრული პასუხებით. ჩატარებული კვლევის მიზანს წარმოადგენდა ექიმების ცოდნის დონისა და ინფორმირებულობის დადგენა იშვიათ დაავადებებთან მიმართებაში. მიღებული შედეგები დამუშავებული იქნა სტატისტიკური პროგრამით SPSS version 9.0 (SPSS, Inc., Chicago IL).

კვლევის შედეგად დადგინდა გამოკითხულ ექიმთა ზოგადი ცოდნისა და გათვითცნობიერობულობის დაბალი დონე, რაც იმაზე მეტყველებს, რომ ზოგადი პრაქტიკის ექიმებს ბულგარეთში არ შეუძლიათ მიაწოდონ იშვიათი დაავადებების მქონე პაციენტებს ხარისხობრივად მაღალი საკმარისი და დროული ინფორმაცია. სპეციალური ძალისხმევაა საჭირო ზოგადი პრაქტიკის ექიმების ცოდნის ასამაღლებლად იშვიათი დაავადებების საკითხებში.

УНИВЕРСИТЕТСКИЙ ЦЕНТР ПО РЕДКИМ БОЛЕЗНЯМ КАК ПРИМЕР УСПЕШНОЙ ИНТЕГРАЦИИ КЛИНИЧЕСКОГО СЕКТОРА В СИСТЕМУ МЕДИЦИНСКОГО ОБРАЗОВАНИЯ

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Оптимизация медицинского образования является залогом повышения уровня медицинской помощи населению, одним из основных факторов, способствующих оздоровлению нации. Медицинское образование, в основном, прерогатива университетов/высших медицинских школ. Решающее значение в подготовке врача принадлежит клиническому сектору – комплексу медицинских баз, клиник университета. Университетская клиника – это медицинское учреждение высшего уровня, в котором проводятся медицинская помощь пациентам на III-IV уровнях, обучение студентов, резидентов и врачей (в рамках постдипломного непрерывного обучения), научные исследования. Руководство университетской клиникой, как правило, осуществляется профессорским составом, непосредственно лечебная работа – с широким участием резидентов, врачей на рабочих местах.

В последние годы все большее внимание привлекают т.н. редкие болезни. Существуют различные дефиниции этого понятия. Наиболее общепринятым является следующее – редкая болезнь – это нозологическая единица, частота которой не превышает 1:2000 [1-4]. Несмотря на то, что отдельно взятые редкие болезни действительно весьма редки, суммарно они составляют растущую проблему общественного здравоохранения, так как примерно 5% населения имеют ту или иную редкую болезнь. Наиболее актуальна проблема редких заболеваний в развитых странах, хотя и в других странах интерес к ним неуклонно повышается, что обусловлено изменением структуры заболеваемости и смертности и увеличением удельного веса этой патологии. Во всем мире отмечаются трудности в их диагностике; врачи первого звена, как правило, плохо знают эти заболевания, чем и объясняется запаздывание соответствующих диагностических процедур и проведения адекватных лечебных мероприятий. Лечение также имеет свои особенности. Фармацевтические фирмы не особенно заинтересованы в разработке соответствующих медикаментов, в связи с чем эти болезни называют также – болезнями-сиротами.

В странах с переходной экономикой, включая Грузию, эти заболевания также привлекают возрастающее внимание [5]. Следует отметить, что по инициативе Первой леди Грузии госпожи Сандры Рулофс создан Альянс по редким болезням как филиал благотворительной организации SOCO, основанной и руководимой ею же. Альянс осуществляет общую координацию работ, проводимых в данном направлении.

Одним из подходов преодоления вызовов, связанных с этой проблемой, следует признать создание специальных центров по редким болезням. В настоящее время их число весьма ограничено, хотя в последние годы отмечается выраженная тенденция к их учащению. К настоящему времени наличие подобных центров, за исключением Болгарии, нами не выявлено.

Главнейшими задачами подобных центров, наряду с клинической активностью, являются создание информационных ресурсов, проведение учебных курсов, соответствующих исследований, повышение уровня знаний в области редких болезней не только профессионалов, но и населения в целом. Полагаем, что наиболее целесообразным является образование этих центров при медицинских университетах на базе университетских клиник. В пользу данного суждения свидетельствуют наличие высококвалифицированных кадров, работающих в этих учреждениях, а также естественная кумуляция сложных больных, в том числе страдающих редкими болезнями.

На основании литературных данных и с учетом мнения экспертов, нами разработана модель функционирования Центра редких болезней при Тбилисском государственном медицинском университете, разработано положение, согласно которому основными задачами центра являются:
- оптимизация обучения по редким болезням (с акцентом на заболевания, приоритетные для страны);
- оптимизация ведения редких болезней;
- осуществление научно-исследовательской деятельности;
- создание регистров и банков данных;
- экспертиза вопросов, связанных с редкими болезнями;
- содействие информированности общества о редких болезнях.

С целью реализации указанных задач Центр создает и адаптирует стандарты, протоколы и гайдлайны ведения редких болезней, разрабатывает соответствующие учебные программы, модули для студентовов, резидентов, врачей (в рамках непрерывного обучения), проводит учебно-методическую работу, научные исследования, участвует в международных проектах, разрабатывает соответствующие магистрантские и докторские программы, участвует в различных конкурсах и тендерах, посредством печатных и электронных средств способствует повышению информированности населения, служит клиническим реферральным-информационным центром.

В рамках поставленных целей центр сотрудничает с правительственными и неправительственными структурами, законодательными органами, межправительственными и другими международными организациями. Центр свою деятельность осуществляет под эгидой Альянса по редким болезням – филиала благотворительного гуманитарного фонда SOCO.

Как уже отмечалось выше, одним из основных направлений деятельности центра является повышение уровня знаний врачей различных специальностей в области редких болезней. Создан и, соответственно, утвержден на министерском уровне специальный модуль по редким болезням. Модуль рассчитан на 30 учебных часов и содержит следующие вопросы:

- Общая информация о редких болезнях.
- Редкие болезни, актуальные для Грузии и медицинские сервисы.
- Применение диагностических алгоритмов редких болезней в повседневной клинической практике.
- Лечение, реабилитация и превенция редких болезней.
- Методика проведения поиска информации по редким болезням в интернете с помощью соответствующих поисковых машин.
- Наследственные редкие болезни.
- Приобретенные редкие болезни.
- Медикаментозное обеспечение редких болезней.
- Возможности фармацевтического рынка в Грузии с точки зрения лечения редких болезней.
- Законодательство и редкие болезни.
- Ведение различных редких болезней (по специальностям).
- Инвалидность, ограничение возможностей и редкие болезни.
-

Планируется внесение вопросов, касающихся редких болезней в программы обучения студентов и резидентов.

Таким образом, можно считать вполне обоснованным образование Университетского центра по редким болезням. Полагаем, что такой центр является примером успешной интеграции клинического сектора в систему высшего медицинского образования. Разработана модель функционирования центра, создано специальное положение. Подготовлен специальный учебный модуль по редким болезням для врачей различных специальностей. Считаем, что подобная деятельность будет способствовать существенному улучшению уровня медицинской помощи больным редкими болезнями, а также профессиональной подготовке студентов медиков, резидентов и врачей.

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SUMMARY

UNIVERSITY CENTER ON RARE DISEASES, AS A SUCCESSFUL EXAMPLE OF THE INTEGRATION OF THE CLINICAL SECTOR INTO THE SYSTEM OF MEDICAL EDUCATION

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There is substantiated appropriateness of the establishment of the University Center on Rare Diseases. It is indicated that the center could illustrate a successful integration of the clinical sector into the system of medical education. The model of the functioning of center and its regulations are presented. The main topics of the special teaching module on rare diseases for physicians are submitted as well.

Key words: University Center on Rare Diseases, regulations, teaching module.

РЕЗЮМЕ

УНИВЕРСИТЕТСКИЙ ЦЕНТР ПО РЕДКИМ БОЛЕЗНЯМ КАК ПРИМЕР УСПЕШНОЙ ИНТЕГРАЦИИ КЛИНИЧЕСКОГО СЕКТОРА В СИСТЕМУ МЕДИЦИНСКОГО ОБРАЗОВАНИЯ

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В работе обосновывается целесообразность образования Университетского центра по редким болезням.

Указывается, что подобный центр является примером успешной интеграции клинического сектора в систему высшего медицинского образования. Представлены модель функционирования центра и специальное положение, а также основные элементы учебного модуля по редким болезням для врачей различных специальностей.

რეზიუმე

იშვიათი დაავადებების საუნივერსიტეტო ცენტრი, როგორც კლინიკური სექტორის წარმატებითი ინტეგრაციის მაგალითი სამედიცინო განათლების სისტემაში

ზ. ვადაჭკორია, გ. აბესაძე, ყ. ფაღავა, ი. კორინთელი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ნაშრომში დასაბუთებულია იშვიათი დაავადებების საუნივერსიტეტო ცენტრის ჩამოყალიბების მიზანშეწონილობა. ნაჩვენებია, რომ იგი შეიძლება განხილული იქნას,როგორც კლინიკური სექტორის წარმატებითი ინტეგრაციის მაგალითი სამედიცინო განათლების სისტემაში. წარმოდგენილია ცენტრის ფუნქციონირების მოდელი და სპეციალური დებულება, აგრეთვე სხვადასხვა სპეციალობის ექიმებისთვის გამიზნული იშვიათი დაავადებების სასწავლო მოდულის ძირითადი ელემენტები.

ЦЕЛЕСООБРАЗНОСТЬ ПРИМЕНЕНИЯ ПОДХОДОВ, ОСНОВАННЫХ НА ПРИНЦИПАХ НЕЧЕТКОЙ ЛОГИКИ, ДЛЯ ПРОВЕДЕНИЯ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ ПРИ РЕДКИХ БОЛЕЗНЯХ

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Редкие болезни стали новым вызовом современной медицины. Несмотря на крайне низкую частоту отдельно взятой нозологической единицы, отвечающей общепринятым определениям (в большинстве источников указано, что заболевание может считаться редким, если его частота не превышает 0,05%), их суммарная частота достаточно высока. По некоторым оценкам, каждый двадцатый житель Европы имеет то или иное редкое заболевание.

Исходя из требований доказательной медицины применение различных диагностических исследований и лечебных вмешательств должно основываться на результатах соответствующих клинических испытаний. Стандартные методические подходы хорошо зарекомендовали себя и, поэтому, когда это возможно, необходимо им следовать. Подобная тактика позволяет получить необходимое формальное заключение, к чему и стремятся исследователи. Однако существуют обстоятельства, при которых число наблюдений, безусловно, немногочисленно. В первую очередь это касается редких заболеваний. Именно их редкость и, следовательно, трудность рекрутирования достаточного числа больных, определяют сложность и, зачастую, невозможность проведения клинических исследований по классическому дизайну.

Вышеизложенное обусловило цель исследования – провести сравнительную оценку предлагаемых подходов ведения клинических исследований у больных редкими заболеваниями с акцентом на метод нечеткой логики.

Ниже мы вкратце рассмотрим основные методики ведения клинических испытаний, в основном, для оценки различных лечебных воздействий при редких заболеваниях. Подобные исследования называются малыми клиническими испытаниями [3]. Эти методики можно распределить в следующие две группы – 1) модифицированные подходы, основанные на классическом анализе, включая статистические, и 2) альтернативные подходы. Такая группировка предлагается с целью выявления их положительных и отрицательных сторон, определения соответствующего места для предложенных нами подходов, основанных на нечеткой логике.

К группе модифицированных подходов, используемых для малых клинических исследований относятся:
- Адаптативная рандомизация. Согласно этому подходу, распределение пациентов в различные группы, подвергающиеся исследованиям, заранее не определено. Это распределение зависит от промежуточных наблюдений в разных исследуемых группах и имеет вероятностную природу. Преимущество подобного подхода состоит в

том, что возрастает число пациентов, участвующих в исследованиях, которым назначается лечение, требующее оценки.
- Групповой последовательный адаптивный подход. В этом случае общее число пациентов, принимающих участие в исследованиях, заранее не определяется. Это число меняется на каждой стадии набора. Это выборочное множество пациентов оценивается на основе эффективности лечения, которое, в свою очередь, оценивается заранее, до сбора данных. Такие предопределенные оценки могут привести к некорректным статистическим оценкам на заключительной стадии исследования.
- Повторяющиеся измерения. Согласно этому подходу, результаты исследования оцениваются не по одному критерию для каждого пациента, а по его (пациента) нескольким характеристикам, что позволит не только провести сравнение пациентов между собой, но и оценить каждого пациента по нескольким параметрам.
- Мета-анализ. Понятие мета-анализа относится к набору статистических процедур, которые используются для объединения результатов независимых испытаний в общую оценку [2,5].

Альтернативными подходами являются следующие:
- Рапределение пациентов в разные группы риска. Пациентов распределяют в группы малого риска и большого риска. Лечение может быть назначено стандартного типа или с включением исследуемого вмешательства (усиленное лечение). Пациентов из группы малого риска случайным образом распределяют в подгруппы, получающих стандартное и усиленное лечение, соответственно. Пациенты из группы повышенного риска получают усиленное лечение. Эффективность лечения оценивается согласно модели прогнозирования, которая строится на основе экстраполяции результатов пациентов из групп с низким риском на пациентов из групп с высоким риском.
- Статистические предсказания. Этот подход включает в себя оценку распределения контрольных измерений исследуемого условия. Контрольное распределение позволяет устанавливать ожидаемый интервал для будущих измерений.
- Ранжирование и выбор. В клинических испытаниях участвуют группы с определенными средними оценками. Без ограничения общности можно считать, что более высокие оценки пред-почтительнее низких. На этой основе оцениваются разные подходы к лечению, например: лучшее лечение, среднее и т.д.
- Байесовский метод. Этот известный подход решает следующие проблемы в медицинских исследованиях: какова вероятность определенного активного лечения по сравнению с плацебо, в какой степени гипотеза удачного эффекта от активного лечения превалирует над противоположной неэффективной гипотезой и т.д. Оцениваются априорные и постериорные частоты исследуемых изменений.

Таким образом, существует несколько методических подходов для сравнения эффектов лечения различных заболеваний, включая редкие. Каждый из этих подходов представляет собой либо расширение существующих стандартных методов, либо является альтернативным. Необходимо отметить, что не существует золотого стандарта в выборе соответствующего подхода. Каждый из них имеет свои преимущества и недостатки [2]. Мы полагаем, что к перечню методов, используемых при клинических испытаниях, включая т.н. малые клинические наблюдения, следует отнести подход, основанный на нечеткой логике [1,4,6,7,8]. Было бы целесообразно сравнить «нечеткий» подход с описанными выше методами клинических испытаний. Однако в этой статье мы ограничимся сравнением лишь с Байесовским подходом. Этот выбор для сравнения основан на неутихающей полемике между учеными, которые поддерживают теорию нечетких множеств (опираясь на ее состоятельность) и теми, кто рассматривает ее как бесполезное расширение теории альтернативной Байесовскому подходу. Одна из особенностей Байесовского подхода заключается в том, что он позволяет естественным образом включать априорные знания в статистический анализ. Но Байесовский подход основывается на допущении, что точность результата зависит от достаточности первоначальной информации. В противном случае, последующая вероятность может быть некорректной. Мы здесь не рассматриваем альтернативный (так называемый, частотный) статистический подход, так как для редких болезней он неприменим. Классическое клиническое испытание при редких болезнях, как правило, весьма затруднительно.

Что касается Байесовского подхода, необходимо отметить один из его недостатков. Он заключается в том, что в статистический анализ, в определенной степени, входит субъективность. Другими словами, если несколько экспертов анализируют одни и те же данные, субъективность ведет к тому, что другие исследователи, воспроизведя соответствующий анализ, могут прийти к другим результатам.

«Нечеткий» подход естественным образом формализует субъективность на основе строгой формальной теории. Таким образом, в «нечетком» подходе субъективность – это преимущество. Адаптируя пример из [2], который описывает ситуацию, когда клинические исследования в педиатрии основываются на оценках эффективности соответствующих лекарств у взрослых, «нечеткий» подход формализовал бы подобную ситуацию более гибко, т.к. этот подход не ограничен свойством аддитивности вероятностей. «Нечеткие» подходы позволяют формализовать такую ситуацию, используя мягкий переход от детского возраста в подростковый и взрослый. Кроме того, «нечеткий» подход позволяет представить экспертные оценки, которые не всегда могут быть даны в виде статистической информации в виде правил «если - то» («if – then»), весьма

удобных для врачебного восприятия. «Нечеткий» подход позволяет сформировать кластеры, где граница между «обычной» и редкой болезнью не определяется точно, что, в свою очередь, позволяет довольно гибко прогнозировать эффект лечения.

Вышеизложенное позволяет нам заключить, что в ряду методов, используемых для проведения клинических испытаний, свое место должен найти и подход, основанный на принципах нечеткой логики.

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SUMMARY

PURPOSEFULNESS OF USING FUZZY LOGIC APPROACHES IN THE RARE DISEASE CLINICAL TRIALS

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Different methods being used in the rare diseases clinical trials are examined. There is shown the purposefulness of using fuzzy approaches for such studies. Some advantages of Fuzzy logic methods in comparison with Baysian approach are substantiated.

Key words: rare diseases, fuzzy logic methods.

РЕЗЮМЕ

ЦЕЛЕСООБРАЗНОСТЬ ПРИМЕНЕНИЯ ПОДХОДОВ, ОСНОВАННЫХ НА ПРИНЦИПАХ НЕЧЕТКОЙ ЛОГИКИ, ДЛЯ ПРОВЕДЕНИЯ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ ПРИ РЕДКИХ БОЛЕЗНЯХ

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Рассматриваются различные методы, применяемые для проведения клинических исследований при редких болезнях. Показана целесообразность применения с этой целью подходов, основанных на принципах нечеткой логики. Обосновывается их определенное преимущество по сравнению с методом Байеса.

რეზიუმე

არამკაფიო ლოგიკის პრინციპებზე დაფუძნებული მეთოდების გამოყენება კლინიკური კვლევების ჩატარებისას იშვიათი და-ავადებების დროს

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განხილულია იშვიათი დაავადებების დროს გამოყენებული კლინიკური კვლევების სხვადასხვა მეთოდი. ნაჩვენებია ამ მიზნით არამკაფიო ლოგიკის მეთოდების გამოყენების მიზანშეწონილობა დასაბუთებულია მათი უპირატესობა ბაიესის მეთოდთან შედარებით.

UNILATERAL ASYMPTOMATIC TESTIS ENLARGEMENT IN CHILDREN AND ADOLESCENTS

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In the last 40 years, scientific literature has been enriched with studies which demonstrate the importance of evaluating testis volume to recognize certain genetic and clinical diseases [2,3,5,8,10,11,15].

Before getting to the heart of the matter one might ask whether it is possible to provide the reader with a definition of unilateral asymptomatic testis enlargement. In literature a well codified definition does not exist. Therefore in these cases the pediatrician or adolescentologist will have to make a clinical and diagnostic evaluation in order to exclude: a) an enlarged testis secondary to tumors, surgery, or endocrinological diseases; b) a small testis due to a previous (ex. cryptorchidism) or current disease (e.g. varicocele).

Physiology of testis development and evaluation of volume
At birth testes measure about 1 ml, during the following 2-3 months volume increases to 2 ml, and then decreases again around 6 months of life. These changes are due to increase and following decrease of androgens during early infancy. Few changes occur until age 11-12, when the first signs of puberty develop with an increase in testes volume (3-4 ml). the instrument used to evaluate is Prader's orchidometer [7,18,19].

During puberty, testes enlargement is mainly due to the increase in volume and tortuosity of seminiferous tubules. Histologically, cells which line the tubules increase in number and dimension, so that the mean tubular diameter reaches 85 μm. Later, with great individual variability, the diameters progressively increase and reach complete development (200-300 μm) only after years of spermatogenic activity [18].

Physical examination of scrotum and testes
The scrotum may seem swollen for testicular or extratesticular causes. The examiner must perform a complete evaluation of the scrotum and the testicular volume. In particular one must consider: a) the presence of edema and swelling of the scrotum; b) scrotal transilluminability; c) the presence of varicocele. In this case the vascular disease can cause reduced development of a testis and volume asymmetry. The easiest way to identify this condition is with the patient in the erect position during the Valsalva maneuver; d) volume, consistency, and surface of testis and epididymis.

Unilateral asymptomatic testis enlargement can be caused by surgical, neoplastic, or endocrinological diseases [1,3,14,15,17].

Surgical causes
Neonatal spermatic cord torsion
Cases of unilateral painless testis enlargement in a newborns, secondary to extra-vaginal cord torsion, have been reported in literature[1,3]. This condition is favoured by laxity of the connections between the vaginal tunica and the scrotal wall. Clinical signs are swollen scrotum and increased consistency of the testis. A reactive hydrocele can be present. If derotation of the testis is performed within 6 hours prognosis is favourable in 92% of cases, while the percentage decreases to 62% after 6-12 hours. However, we must underline that in the newborn torsion occurs in utero therefore at birth the testis is often already necrotic.

Neoplastic causes
Primitive tumours of the testis are rare in paediatric age and represent 1-2% of all childhood tumours. In 70% of cases these originate from germ cells, 25% from stromal cells (Sertoli, Leydig) and the remaining 5% from supporting structures or are secondary to systemic tumours (leukaemia, lymphoma)[15,17]. In these cases the testis appears swollen, of increased consistency or frankly hard, with an irregular or nodular surface. In some cases, there may be reactive hydrocele. Dosage of α-fetoprotein, β-HCG and testis ultrasound are fundamental diagnostic instruments, which must be immediately performed when a testicular tumour is suspected.

The α-fetoprotein is increased in serum of patients with yolk sac tumours. β-HCG are specific for gonadal stromal tumours.

Normally at ultrasound examination the testis appears as an oval body with a homogeneous echostructure surrounded by an echogenic line which represents the albugineal tunica and the visceral layer of the tunica vaginalis propria which adhere to the testis . The echographic characteristics of a tumour vary according to its histological nature and for the possible presence of inflammation. Indicatively, according to dishomogeneity of the testicular echostructure one can hypothesize that:
a) if dishomogeneous and hyperechogenic: seminoma or necrotic embrionary carcinoma can be suspected;

b) if dishomogeneous and tubularifrom: corioncarcinoma or necrotic embrionary carcinoma;
c) if hypoechogenic with well-defined, hyperechogenic border: epidermoid cyst, Leydig cell tumour, epithelial cyst, mesothelioma;
d) if hyperechogenic and well-delimitated: lymphoma, seminoma. Leydig cell tumour;
e) if anechogenic with posterior reinforcement: a spermatocele or a cyst.
Considering the rarity and clinical peculiarity, we will describe two of these conditions: the intratesticular cyst and the Leydig cell tumour [1,17].

Intratesticual cysts
This condition has been described both in adults and newborns [1]. The testis can be homogeneously enlarged or of normal volume. In this case the diagnosis is accidental during an ultrasound performed for other reasons. At ultrasound the cyst appears as a round structure with well defined margins without intermediate echoes. Differential diagnosis is with a cyst of the albugineal tunica or an epidermoid cyst. When ultrasound characteristics are those of a benign mass, treatment can be conservative, otherwise, surgical exploration and removal of the cyst are recommended.

Leydig cell tumour
It derives from stromal cells. Clinical characteristics are variable: the testis can be normal, enlarged, nodular with a homogeneous or irregular surface [1,17]. Often the tumour may not be noticed during the physical examination, if very small. The tumour produces androgens, which can cause signs of puberal development or acceleration of linear growth in the prepuberal child.

Gonadotropine levels are low both at baseline and after stimulus with GnRH, while testosterone is elevated. Bone age is accelerated. In some cases Δ4 androstenedione and 17-OH progesterone are increased and can be confused with an adrenogenital syndrome with aberrant adrenal tissue. This increase is not surprising considering that Δ4 androstenedione and 17-OH progesterone are physiological testosterone precursors. A test with desametasone may be useful when in doubt.

Ultrasound allows early diagnosis. It is important to accurately explore both testes, because in 10% of cases the Leydig cell tumour is bilateral. Unlike what has been described previously, the lesion can be both hyper- or hypoechogenic. Differential diagnosis is with surrenal hyperplasia with ectopic adrenal tissue or with HCG-producing teratoma. Surgical treatment is indicated.

Endocrinological causes
Adrenogenital syndrome
This disease has been described in untreated patients with classic 21-hydroxylase deficit and in a 36 year old adult with late-onset enzymatic deficit [5]. Nodular or diffuse, uni- or bilateral testis enlargement is due to the presence of aberrant hyperplastic cortical tissue. This tissue can be found in about 10% of all children and increases in response to excess production of ACTH secondary to 21-hydroxylase deficit. An endocrinological evaluation shows high levels of adrenal androgens, in particular 17OH progesterone. Medical treatment is indicated. In 75% of patients treatment with corticosteroids determines reduction of testis volume or of the nodular lesion. In non-responders one must suspect transformation of the aberrant hyperplastic cortical tissue into an adenomatous lesion.

Compensatory testicular hypertrophy
This condition was first described by Laron in 1969 [11]. It can be defined as a progressive testis enlargement, which exceeds the normal volume for age, in patients with absent, cryptorchid, or hypoplastic contralateral testis. During puberal development, the hypertrophic testis continues to grow until advanced puberty (Table 1). The incidence of compensatory testicular hypertrophy varies from 6.5% to 12% [12,13,16]. The left testis is affected in 75% of cases. In 40% of patients hypertrophy appears before puberty [12].

Table 1. Progression of testicular volume during puberty in patients with compensatory testicular hypertrophy

Pubic hair (PH)	CTH (volume range in ml)	Normal values of testis volume (according to Laron)
1	3-6	2
2	3-12	2.5-4
3	6-15	4.5-8
4	8-25	8.5-10
5	10-30	12

Modified from Laron et al, [12]

The consistency of the testis is normal and the surface is smooth.

At baseline conditions, the endocrinological evaluation shows an increase of FSH and variable levels of LH. After GnRH stimulus the response of gonadotropines can be variable. However, mean values are usually higher than those of normal individuals. These data lead to suspecting a role of the increase of FSH secondary to the altered production of inhibin from the Sertoli cells. Testosterone levels at baseline

and after stimulus with GnRH are low in affected patients compared to controls. Unilateral testicular hypertrophy does not seem to guarantee normal spermatogenesis. In fact, Laron and coll. [12] described oligoastenospermia and azoospermia in 8 patients with compensatory testicular hypertrophy between 17 years and 18 years and 8 months of life, and low inhibin B and high FSH levels were reported by Gaudino et al [9].

Unilateral testicular hypertrophy of puberty

Unilateral testicular hypertrophy was represented by Eracle in 300 a.C. in a statue exhibited in the museum of Siracusa (Italy) and later by Lee and coll. [13] in puberal patients without clinical history of cryptorchidism, orchidopexy, or diseases of the contralateral testis. The hypertrophic testis has normal consistency and surface, and appears enlarged compared to the contralateral testis. During follow-up, which varied between 4 months and 3 years, the unilateral testicular hypertrophy remained stable, reaching a volume of 60 ml in one case.

Two years later the same clinical condition was described by El Kholy and coll. [8] in two patients aged 10 years and 6 months and 15 years and 6 months. The endocrinological evaluation, the testicular ultrasound, and dosage of tumour markers for testicular neoplasia were normal. Therefore, the authors concluded that testis enlargement could be due to a different receptorial response to gonadotropines and androgens.

In our Endocrinology and Adolescentology Service we observed 14 patients with unilateral testis enlargement. At the first examination, mean age was 12.3±1.2 years and the volume of the enlarged testis varied between 4 ml and 20 ml (mean volume 10±4 ml) versus 1.5 ml and 10 ml (mean volume 5±2 ml) of the contralateral testis. In 75% of cases the right testis was affected (Fig.). During the ten year follow-up, the volume of the enlarged testis never exceeded 25 ml and progressive reduction of the difference between the two testes was demonstrated. Therefore, we propose another clinical condition defined as transitory unilateral testis enlargement of puberty.

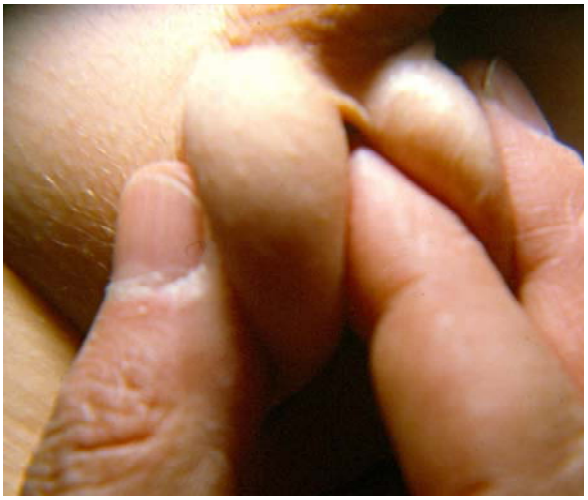

Fig. Idiopathic testicular enlargement in a 11-year-old boy (De Sanctis V, personal observation)

Differential diagnosis of this variant of normal puberal development is mainly with tumours, endocrinological diseases, previously described, and epididymal cysts. In table 2 we report the clinical and echographic characteristics of these diseases.

Table 2 Epididymal cysts

Incidence	Uncommon in childhood and adolescence
Pain	Absent/mild
Presentation	Gradual
Localization	Upper pole of the testis in the groove between the testis and the epididymis
Clinical and echographic characteristics	• Round lesion, tense • Often multiple, may be bilateral • Liquid content (water-like or white-opalescent) • Transilluminable • Not associated with symptoms or signs of infection (fever, urethritis, pyuria, bacteriuria)

McCune Albright syndrome (MAS)

Atypical MAS associated to unilateral testis enlargement and no sexual precocity has been reported in children aged 3.8-9 years. The oldest patient also presented bilateral testicular microlithiasis on sonography. These findings are consistent with the occurrence of an activating mutation of the G(s)alpha gene mainly expressed in Sertoli cells and weakly expressed or absent in Leydig cells.

Abnormal prepubertal testicular enlargement extends the clinical spectrum of MAS, suggesting that determination of serum inhibin B and anti-Mullerian hormone should be considered in boys with this syndrome [2,4,6].

It is common experience that at all ages a unilateral enlargement of a testis can be the clinical sign of a disease. The presence of a mild difference in testis volumes during puberty is not at all rare. This situation may be due to the technique used for evaluation of testis volume or secondary to a varicocele.

The identification of variants of testis enlargement is important, because, while on one hand there are conditions without clinical relevance, on the other hand, there are diseases that require early diagnosis and immediate treatment.

Therefore, unilateral testicular enlargement is not necessarily an indication for exploration if there are no clinical or echographic grounds for suspicion of neoplasia. However, a close follow-up is essential to confirm the diagnosis

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SUMMARY

UNILATERAL ASYMPTOMATIC TESTIS ENLARGEMENT IN CHILDREN AND ADOLESCENTS

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In literature a well codified definition of unilateral asymptomatic testis enlargement does not exist. Therefore in these cases the pediatrician or adolescentologist will have to make a clinical and diagnostic evaluation in order to exclude: a) an enlarged testis secondary to tumors, surgery, or endocrinological diseases; b) a small testis due to a previous (ex. cryptorchidism) or current disease (e.g. varicocele).The presence of a mild difference in testis volumes during puberty is not at all rare. This situation may be due to the technique used for evaluation of testis volume or secondary to a varicocele. The identification of variants of testis enlargement is important, because, while on one hand there are conditions without clinical relevance, on the other hand, there are diseases that require early diagnosis and immediate treatment. The Authors report a brief review of the literature and their own clinical experience. 14 patients with unilateral testis enlargement were observed. At the first examination, mean age was 12.3±1.2 years and the

volume of the enlarged testis varied between 4 ml and 20 ml (mean volume 10±4 ml) versus 1.5 ml and 10 ml (mean volume 5±2 ml) of the contralateral testis. In 75% of cases the right testis was affected. During the ten year follow-up, the volume of the enlarged testis never exceeded 25 ml and progressive reduction of the difference between the two testes was demonstrated. Therefore, they propose another clinical condition defined as transitory unilateral testis enlargement of puberty.

Key words: Testicular growth, testis volume, testis enlargement, children, adolescents.

РЕЗЮМЕ

ОДНОСТОРОННЕЕ БЕССИМПТОМНОЕ УВЕЛИЧЕНИЕ ЯИЧЕК У ДЕТЕЙ И ПОДРОСТКОВ

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В литературе нет четкого определения одностороннего бессимптомного увеличения яичка. Поэтому, педиатр должен установить причину увеличения яичка, т.е. определить яичко увеличено в результате опухоли, хирургического вмешательства, эндокринных болезней, или яичко находится в пределах физиологической нормы, но выглядит увеличенным по сравнению с уменьшенным яичком из-за предыдущей или текущей болезни. Некоторое различие в величинах яичек в пубертатном периоде нередко, что может быть обусловлено техникой измерения или результатом варикоцеле. Идентификация вариантов увеличения яичка важна, так как бывают случаи без явных клинических проявлений, с другой стороны, существуют болезни, которые требуют раннюю диагностику и немедленного лечения. Представлен краткий обзор литературы и собственный клинический опыт.

რეზიუმე

სათესლეების ცალმხრივი ასიმპტომური გადიდება ბავშვებსა და მოზარდებში

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ლიტერატურაში სათესლეების ცალმხრივი ასიმპტომური გადიდების სისტამატიზირებული განსაზღვრა არ არსებობს. ამიტომაც ასეთ შემთხვევებში პედიატრმა ან მოზარდთა მედიცინის სპეციალისტმა უნდა განახორციელოს კლინიკურ-სადიაგნოსტიკო შეფასება, რათა დაადგინოს სათესლეს გადიდება არის მეორადი - სიმსივნის, ქირურგიული ჩარევის, ენდოკრინული დაავადებების გამო,თუ სათესლე ნორმალურია და აღიქმება გადიდებულად მეორე სათესლესთან შედარებით, რომელიც შემცირებულია მანამდე (მაგალითად, კრიპტორქიზმი), ან ამჟამად არსებული დაავადების (მაგალითად,ვარიკოცელე) გამო. სქესობრივი მომწიფების პერიოდში სათესლეების მოცულობის არასითანაბრე არ არის იშვიათი. ეს სიტუაცია ზოგჯერ სათესლეს მოცულობის გაზომვის ტექნიკით არის განპირობებული,ზოგჯერ გადატანილი ვარიკოცელეს შედეგია. სათესლეს გადიდების ვარიანტების იდენტიფიკაცია მეტად მნიშვნელოვანია, ვინაიდან არსებობს შემთხვევები, როდესაც ჩარევა არის საჭირო, ზოგჯერ კი მდგომარეობა თხოულობს დროულ დიაგნოსტიკასა და გადაუდებელ მკურნალობას. ავტორები წარმოადგენენ ლიტერატურის მოკლე მიმოხილვას და მოზარდებში საკუთარ კლინიკურ გამოცდილებას.

УЛЬТРАСТРУКТУРА РЕЛЬЕФОВ И АДЕНИЛОВАЯ СИСТЕМА ЭРИТРОЦИТОВ У БОЛЬНЫХ КИСТОФИБРОЗОМ

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Кистофиброз характеризуется поражением бронхолегочной системы и желудочно-кишечного тракта. В клинической картине заболевания доминируют изменения в бронхах и легких, которые, несмотря на комплексное, а иногда и непрерывное лечение (антибиотики, ЛФК, дренаж, массаж грудной клетки, ингаляция муколитиков) у значительной части больных неуклонно прогрессируют [4,5,7,9].

Нарушения функциональной полноценности эритрона, единственного переносчика кислорода в организме, наиболее наглядно отражаются на его структуре. Поэтому значительный интерес представляет изучение рельефа поверхности и адениловой системы (АТФ-АТФ-азы) красных кровяных клеток.

Согласно работам последних лет, деформации эритроцитов обусловлены изменением энергетических процессов в клетке, так как эритроциты с дефицитом АТФ отличаются ригидностью мембран [6]. По изменениям системы АТФ-АТФ-азы эритроцитов можно судить о метаболических сдвигах и состоянии клеточной мембраны в условиях патологии [2,3].

Описаны морфологические изменения эритроцитов при различных заболеваниях [1,2]. Работы об изменениях морфологической картины эритроцитов у больных кистофиброзом единичны. Немногочисленны и исследования, посвященные нарушениям системы АТФ-АТФ-азы эритроцитов при этом заболевании [6,8]. В этой связи представляется перспективным изучение морфологической картины и энергетических процессов эритроцитов при кистофиброзе.

Целью исследования явилось определение особенностей ультраструктуры поверхности эритроцитов и системы АТФ-АТФ-азы эритроцитов у детей больных кистофиброзом.

Материал и методы. В работу включены материалы обследования 42 детей с различными формами кистофиброза в возрасте от 1 мес. до 14 лет. Мальчиков было 20, девочек - 22, по возрасту они распределились следующим образом: до года – 18 (43%)детей, 1-3 года – 12 (28,5%), 3-7 лет – 8 (19%), 7-14 лет – 4 (9,5%) больных. Критериями для установления диагноза служили анамнестические данные, характерная клинико-рентгенологическая картина и повышенное содержание хлоридов в поте.

С целью характеристики мембран эритроцитов и их энергетического метаболизма нами проведено изучение ультраструктуры поверхности эритроцитов с помощью сканирующего электронного микроскопа, а также содержания АТФ и активности АТФ-азы эритроцитов методом Любимовой М.Н. и Энгельгардта Ф.Ф. [7]. Ультраструктура, содержание АТФ и активность АТФ-азы эритроцитов изучались в Институте морфологии им. А.Н. Натишвили под руководством проф. З.Г. Цагарели и проф. Л.Е. Гогиашвили.

Контрольную группу составили 20 здоровых детей того же возраста, ранее обследованых в Институте экспериментальной морфологии.

Больные были распределены на три группы. В I группу вошли 22 больных ребенка, страдающих смешанной формой кистофиброза, во II - 8 больных легочной его формой и III группу составили 12 детей (8 - со смешанной и 4 - с легочной формой), у которых заболевание имело летальный исход. Контрольная группа включала 20 здоровых детей в возрасте от одного месяца до 14 лет.

Полученные результаты обработаны общепринятыми методами вариационной статистики с применением t-критерия Стьюдента.

Результаты и их обсуждение. Результаты исследования системы АТФ-АТФ-азы эритроцитов у больных кистофиброзом приведены в таблице 1.

Согласно данным таблицы 1, у детей I группы отмечалось достоверное снижение содержания АТФ по сравнению с контролем. Концентрация АТФ в эритроцитах составляла 716,6±10,7 мкмоль/л ($p<0,001$). Одновременно выявлено достоверное повышение активности АТФ-азы - 553,1±6,1 нмольРс-1 л ($p<0,001$).

У больных II группы наблюдались аналогичные изменения – достоверное понижение уровня АТФ - 711,6+15,4 мкмоль/л ($p<0,001$), повышение активности АТФ-азы эритроцитов - 550,0±12,5 нмольРс-1 л ($p<0,001$).

Больные III группы характеризовались более низким содержанием АТФ и высокой активностью АТФ-азы эритроцитов (соответственно, 601,0±11,4 мкмоль/л и 630,0±5,1 мкмоль/л), по сравнению с больными II и III групп.

Таблица 1. Показатели системы АТФ-АТФазы эритроцитов у больных кистофиброзом M±м

Группы наблюдения	**Кол-во детей**	**АТФ мкмоль/ л**	**p**	**АТФ-аза нмольРс-1 л-1**	**p**
I группа - больные смешанной формой	22	716,6±10,7	p<0,001	553,1±6,1	p<0,001
II группа - больные легочной формой	8	711,6±15,4	p<0,001 p_1<0,01	550,0±12,5	p<0,001
III группа - больные с летальным исходом, из них: смешанной формой легочной формой	12 8 4	 593,2±43,1 601,0±1,4	p<0,001 p_2<0,01 p_1<0,01	 575,0±8,4 630,0±5,1	p<0,001 p_2<0,00 P_3<0,01
Здоровые дети от 1 месяца до 14 лет	20	1075,8±25,5		385,9±15,2	

p - достоверность различий между данными больных кистофиброзом и здоровых детей;
p_1 - достоверность различий между данными больных I и II групп;
p_2 - достоверность различий между данными больных I и III групп;
p_3 - достоверность различий между данными больных II и III групп

Результаты исследования формы и поверхности эритроцитов периферической крови под электронным сканирующим микроскопом показало, что большинство эритроцитов у здоровых детей имеет форму двояковогнутых дисков с гладкой поверхностью. У здоровых детей количество измененных клеток не превышает 18,3%. Измененные клетки имеют форму округлых или овальных телец. Весьма редко встречаются деформированные эритроциты и малые лимфоциты.

Проведенные исследования показали, что при кистофиброзе эритроциты претерпевают серьезные изменения. Выявлено большое разнообразие их форм: наблюдались как малоизмененные эритроциты с одним или двумя выростами, так и значительно деформированные с несколькими отростками. Выявлены эритроциты в виде тутовой ягоды и куполообразные эритроциты; встречались эритроциты со сквозным отверстием в центре.

Процентное содержание различных форм эритроцитов периферической крови по их поверхностной архитектонике при различных формах кистофиброза приведено в таблице 2.

Анализ процентного соотношения эритроцитов по их поверхностной архитектонике у больных всех групп выявил снижение дискоцитов у больных всех трех групп, что касается дискоцитов с одним выростом их количество во всех группах увеличено, однако статистически достоверная разница между показателями в разных группах не выявлена.

По сравнению с контрольной группой увеличены также дискоциты с гребнем (p<0,001, p<0,05, p<0,001).

Количество дискоцитов с несколькими выростами увеличено по сравнению с контролем (p<0,001, p<0,05, p<0,001), однако статистически достоверная разница между групповыми показателями выявлена только у больных II и III групп (p<0,001).

Число микроцитов и макроцитов увеличено у всех больных по сравнению с нормой (p<0,001, p<0,05, p<0,001), разница между группами недостоверна.

Количество куполообразных эритроцитов увеличено во всех группах, разница между сравниваемыми группами достоверна (p<0,001).

По сравнению с контрольной группой у всех больных значительно увеличено количество деформированных, разрушенных и дегенеративно измененных эритроцитов, особенно у больных III группы.

При кистофиброзе выявлены эритроциты с отверстием и эритроциты сферической формы, их число особенно возрастало у больных смешанной формой с летальным исходом.

У больных всех групп, по сравнению с контрольной группой, число эритроцитов в виде тутовой ягоды увеличено. Показатели III группы превышают таковые II группы (p<0,05). Показатели II группы аналогичны данным I группы (p<0,05).

Таким образом, наши данные о том, что при кистофиброзе эритроциты претерпевают значительные изменения, согласуются с таковыми других авторов [6].

Проведенные исследования позволяют заключить, что у детей больных кистофиброзом, как при легочной, так и смешанной формах уровень АТФ-азы эритроцитов повышен, а содержание АТФ снижено.

Таблица 2. Процентное содержание различных форм эритроцитов периферической крови по их поверхностной архитектонике при кистофиброзе

Формы эритроцитов	**Здоровые дети (n=20)**	**I группа (n=22)**	**II группа (n=8)**	**III группа (n=12)**
дискоцит	81,73±0,61	50,78±0,88 p<0,001	52,56±0,97 p<0,001 p_1<0,1	37,98±0,63 p<0,001 p_2<0,01 p_3<0,1
дискоцит с одним выростом	2,3±0,11	4,97±0,93 p<0,001	4,3±0,21 p<0,05 p_1<0,01	6,27±0,23 p<0,05 p_2<0,1 p_3<0,05
дискоцит с гребнем	1,85±13	2,6±0,06 p<0,001	2,2±0,47 p<0,05 p_1<0,001	3,17±0,15 p<0,001 p_2<0,001 p_3<0,001
дискоцит с несколькими выростами	2,4±0,15	4,37±0,09 p<0,001	3,87±0,45 p<0,05 p_1<0,1	5,53±0,03 p<0,01 p_2<0,1 p_3<0,05
микроциты	2,63±0,09	6,33±0,15 p<0,001	5,6±0,3 p<0,01	8,1±0.06 p<0,001 p_2<0,01 p_3<0,5
макроциты	3,05±0,06	6,33±0,24 p<0,001	5,8±0,23 p<0,001 p_1<0,01	8,57±0,12 p<0,001 p_2<0,01 p_3<0,01
эритроциты в виде тутовой ягоды	0,35±0,06	2,53±0,1 p<0,05	2,43±0,3 p<0,05 p_1<0,001	3,67±0,19 p<0,05 p_2<0,001 p_3<0,05
куполообразные эритроциты	1,8±0,13	3,6±0,25 p<0,001	3,0±0,12 p<0,001 p_1<0,001	3,63±0,09 p<0,001 p_2<0,001 p_3<0,001
сферические эритроциты	--	2,27±0,11 p<0,001	1,7±0,06 p<0,001 p_1<0,001	2,83±0,18 p<0,001 p_2<0,001 p_3<0,05
деформированные эритроциты	1,1±0,07	3,63±0,19 p<0,001	3,17±0.03 p<0,001 p_1<0,001	4,6±0,06 p<0,001 p_2<0,001 p_3<0,05
эритроциты с отверстием	---	3,7±0,22 p<0,001	2,77±0,03 p<0,001 p_1<0,001	4,8±0,05 p<0,001 p_2<0,001 p_3<0,05
дегенеративно измененные эритроциты	2,56±0,18	13,40±0,2 p<0,01	11,54±0,47 p<0,001 p_1<0,001	10.11±0,17 p<0,01 p_2<0,001 p_3<0,05
разрушенные эритроциты	1,08±0,14	2,6±0,06 p<0,001	2,57±0,18 p<0,01 p_1<0,001	3,0±0,06 p<0,001 p_2<0,001 p_3<0,05

p - достоверность различий между данными больных кистофиброзом и здоровых детей; p_1 - достоверность различий между данными больных I и II групп; p_2 - достоверность различий между данными больных I и III групп; p_3 - достоверность различий между данными больных II и III групп

Наиболее резкое снижение АТФ, на фоне повышения АТФ-азы отмечалось у больных с летальным исходом, что является не только результатом угнетения гликолитических процессов, но и следствием истощения компенсаторно-адаптивных возможностей организма в целом.

У больных кистофиброзом наблюдаются качественные и количественные нарушения в стереоультраструктуре эритроцитов, что проявляется в статистически достоверном понижении числа дискоцитов, повышении количества всех остальных 12 типов клеток и появлении патологических форм эритроцитов. Эти изменения особенно выражены у больных смешанной формой кистофиброза, особенно, с летальным исходом.

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SUMMARY

CLINICAL VALUE OF CHANGES IN RED BLOOD CELL ULTRASTRUCTURE AND ENERGY METABOLISM IN CHILDREN WITH CYSTIC FIBROSIS

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In 42 patients of various age (from 1 month to 14 years) with cystic fibrosis were analyzed ultra structure, level of adenylnucleotides and activity ATP-ase of erythrocytes, in order to characterize their membrane and energy metabolism.

The studies revealed the changes in erythrocytes in the cases of cystic fibrosis. In the cases of broncho pulmonary form of cystic fibrosis were detected I and II row echinocytes, cone-shaped erythrocytes, also erythrocytes with reach-through hole in center.

At mixed form of cystic fibrosis were detected more changes in erythrocytes than in other forms of this disease. Both cone-shaped erythrocytes were more than in other forms of cystic fibrosis. Also there were detected erythrocytes with holes (round, polygonal) in their center.

The results of the study provide a more precise diagnosis, in time correction of disorders and a comprehensive assessment of multiple-modality treatment of cystic fibrosis.

Key words: cystic fibrosis, in children, erythrocytes, diagnosis.

РЕЗЮМЕ

УЛЬТРАСТРУКТУРА РЕЛЬЕФОВ И АДЕНИЛОВАЯ СИСТЕМА ЭРИТРОЦИТОВ У БОЛЬНЫХ КИСТОФИБРОЗОМ

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С целью характеристики мембран эритроцитов и их энергетического метаболизма проведено изучение ультраструктуры поверхности эритроцитов с помощью сканирующего электронного микроскопа, а также содержания АТФ и активности АТФ-азы эритроцитов методом Любимовой М.Н.и Энгельгардта Ф.Ф. у 42 больных кистофиброзом в возрасте от 1 месяца до 14 лет.

Проведенные исследования выявили, что у детей больных кистофиброзом, как при легочной, так и смешанной формах уровень АТФ-азы эритроцитов повышен, а содержание АТФ - понижено.

Наиболее резкое снижение АТФ, на фоне повышения АТФ-азы отмечается у больных с летальным исходом, что можно считать не только результатом угнетения гликолитических процессов, но и следствием истощения компенсаторно-адаптивных возможностей организма в целом.

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У больных кистофиброзом наблюдаются качественные и количественные нарушения в стереоультраструктуре эритроцитов, что проявляется в статистически достоверном понижении числа дискоцитов, повышении количества всех остальных 12 типов клеток и появлении патологических форм эритроцитов. Эти изменения особенно выражены при смешанной форме кистофиброза, особенно, с летальным исходом.

რეზიუმე

კისტოფიბროზით დაავადებულთა რელიეფის ულტრასტრუქტურა და ერითროციტების ადენილური სისტემა

ნ. ბადრიაშვილი, მ. ჩიქოვანი, მ. თოფუ-რიძე, ს. ღლონტი, ნ. შარიქაძე, თ. თოფურია, ყ. ფაღავა

გ. უვანიას სახ. პედიატრიული კლინიკა, თბილისი, საქართველო

კისტოფიბროზით დაავადებულთა ერითრო-ციტების მემბრანებისა და მათი ენერგეტიკული მეტაბოლიზმის დახასიათების მიზნით შესწავლილ იქნა ერითროციტების მემბრანების ულტრასტრუქტურა მასკანირებელი ელექტრონული მიკროსკოპით, ასევე ატფ-ისა და ატფ-აზის აქტივობა გ.ნ. ლიუბიმოვასა და ფ.ფ. ენგელგარდტის მეთოდით. გამოკვლევები ჩაუტარდა ერთიდან თოთხმეტ წლამდე ასაკის 42 კისტოფიბროზით დაავადებულ პაციენტს.

აღსანიშნავია,რომ როგორც ფილტვის,ასევე შერეული ფორმის კისტოფიბროზით დაავადებულებს აღენიშნებოდათ ატფ-აზის აქტივობის მატება, და ატფ-ის დაქვეითება. ატფ-ის განსაკუთრებით მკვეთრი დაქვეითება გამოვლინდა ლეტალურ შემთხვევებში,რაც განპირობებული იყო არამარტო გლიკოლიზური პროცესების დათრგუნვით, არამედ ორგანიზმის ზოგადი კომპენსატორულ - ადაპტაციური მექანიზმების გამოფიტვითაც.

კისტოფიბროზით დაავადებულ პაციენტებს აღენიშნებოდათ რაოდენობრივი და თვისობრივი ცვლილებები ერითროციტების სტერეოულტრასტრუქტურის მხრივ, რაც გამოიხატებოდა დისკოციტების რიცხვის სტატისტიკურად სარწმუნოდ დაქვეითებაში და დანარჩენი ყველა 12 ტიპის პათოლოგიური ფორმის ერითროციტების მომატებით. ეს ცვლილებები საგულიხმო იყო შერეული ფორმით დაავადებულებში, განსაკუთრებით კი ლეტალურად დასრულებულ შემთხვევებში.

ОСОБЕННОСТИ ПОЛОСТИ РТА У ПАЦИЕНТОВ С НЕСОВЕРШЕННЫМ ОСТЕОГЕНЕЗОМ

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Несовершенный остеогенез - Osteogenesis Imperfecta (OI) - редкое наследственное заболевание соединительных тканей, для которого характерна хрупкость кости и множественные беспричинные переломы. Количество переломов вариабельно (от единичных до более ста), поскольку развиваются в любом возрасте человека, даже во внутриутробном периоде. OI встречается у лиц обоего пола и любой расы [7]. На 100.000 новорожденных приходится 4-7 случаев заболевания. По официальным данным, статистика заболеваний OI следующая: в США зарегистрировано свыше 20.000 случаев, в России – 10.000 (OIF – Osteogenesis Imperfecta Foundation), а в Грузии, предположительно, 32-38 случаев, так как не известна точная суммарная цифра заболеваний, включая детей и их родителей [7].

Заболевание OI известно с незапамятных времен. Обнаруженный в древнем Египте скелет ребенка с признаками несовершенного остеогенеза по сей день хранится в "British Museum" в Лондоне. Существует почти 30 синонимов наименований этой генетической патологии, среди которых самые распространенные: стеклянные, хрустальные люди, мраморная болезнь, синдром Экмана-Лобштейна (Ekman-Lobstein), синдром Вролика (Vrolik).

Причиной развития OI является мутация одного из двух генов, синтезирующих коллаген (изменение на хромосоме COL1A1 j7 или на хромосоме COL1A2 j17). Наследование - аутосомо-доминантное, аутосомо-рецессивное или аутосомо-неомутационное. Шанс

генетического инфицирования плода равен 50%. Для заболевания характерны нарушение биосинтеза коллагена, возникновение дефектного коллагена и его количественно-качественная недостаточность [7]. Обычно кость находится в процессе ремоделирования, в котором участвуют как остеокласты, так и остеобласты. У больного нарушается баланс между формированием и резорбцией кости, преимущество на стороне остеокластов [5]. В результате у больных сокращается костная масса.

При несовершенном остеогенезе поражена не только кость, но и вся соединительная ткань организма, ввиду чего клиническая картина OI отличается широким спектром симптомов, из них следует выделить несколько: множественные переломы; нанизм; деформация костей черепа (лицо треугольной формы за счет нижней челюсти и средней трети лица); генерализированный остеопороз [3,5]; голубая или синяя склера; снижение слуха; пониженное зрение; различные патологии сердечно-сосудистой системы и др.

Как правило, у пациентов выявляются не все вышеперечисленные симптомы, а только некоторые из них. Иногда спектр клинических симптомов чрезвычайно узок.

Известно, что OI не оказывает влияния на умственно-интеллектуальные способности больных, наглядным примером чего являются: французский импрессионист Тулуз Лотрек; джаз-пианист Михаил Петручиани; немецкий актер, писатель и этик Piter Radke; британский актер Nabil Shaban; британский актер, писатель и сценарист Firdaus Kanga; американский актер Michael J.Anderson.

В многообразном клиническом спектре OI особое место уделяется таким повреждениям полости рта, как Dentinogenesis Imperfecta - несовершенный дентиногенез и патологический прикус [10,11]. Это два радикально отличающиеся положения, которые часто проявляются комбинировано, а в некоторых случаях по отдельности и требуют соответствующего лечения [11].

Dentinogenesis Imperfecta (DI, DGI) - патология зубной ткани, причиной которой является структурно несовершенное развитие дентина [13]. DI впервые было описано Barret-ом в 1882 году [цит. по 12]. В тридцатых годах XX века Skillen M., Finn, Hodges охарактеризовали это положение термином "Hereditary Opalescent Dentin" – генетически опалесцентный дентин [цит. по 9,12]. Частота распространения этой патологии среди населения 1:6000 1:8000 [1,8,12,13]. При DI поражаются как молочные, так и постоянные зубы [6]. Существует несколько типов несовершенного дентиногенеза [9] - для которых характерны идентичные повреждения.

Клинически DI характеризуется следующими особенностями: дисколоризация зуба; патологическая стираемость зубов; характерная форма коронки и корня зуба; суженная граница между коронковой и корневой частью зуба, облитерированная зубная полость, короткие и узкие корни; периапикальное повреждение корня зуба с развитием костного дефекта [2,6,8,11-13].

Целью исследования является оценка стоматологического статуса больных несовершенным остеогенезом, проживающих в Грузии.

Материал и методы. На данном этапе нашего исследования нами обследовано 14 пациентов, которые находятся на учете в Грузино-немецком центре "HBI-dent Implant". Среди пациентов 9 (64,3%) женщин и 5 (35,7%) мужчин (диаграмма 1), которые поделены нами на три возрастные группы: 2,5-6 лет, период молочного прикуса (28,6%), 6-14 лет - период сменного прикуса (35,7%) и выше 14 лет (35,7%) - период постоянного прикуса (диаграмма 2).

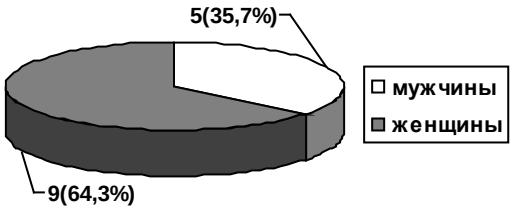

Диаграмма. 1. Процентное распределение пациентов по полу

Диаграмма. 2. Процентное распределение пациентов с учетом возраста и периода прикуса

Один из симптомов DI – дисколоризация выражается в изменении цвета зубов: зубы становятся темно-желтыми, янтарного или голубовато-серовато-коричневого оттенка. При объективном осмотре полости рта больных выявлено, что 28,5% обследованных имели дисколоризированные молочные зубы, тогда как цвет постоянных зубов не был изменен (диаграмма 3, таблица 1).

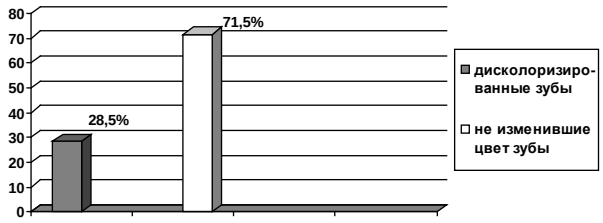

Диаграмма 3. Процентное распределение пациентов с учетом дисколоризированности зубов

Таблица 1. Деление пациентов по количеству дисколоризированных зубов с учетом различных периодов прикуса

Прикус	Дисколоризация зубов (n=4)
молочный	3
сменный	1
постоянный	-

Интересен случай одного пациента, у которого выявлены зубы одновременно темно-желтого, янтарного и серовато-коричневого цвета (рис. 1).

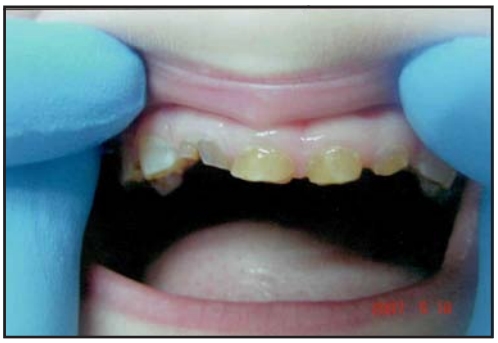

Рис. 1. Пациент Л.В., 6 л. Янтарные, серовато-коричневые зубы

Заслуживает внимания факт увеличения прозрачности дисколоризированных и некоторых не изменившихся в цвете постоянных зубов. Увеличенная опалесценция [1,3] этих зубов четко видна во время их облучения фотополимеризатором (фотополимеризатор диодического излучения фирмы «KERR DEMI», Германия) (рис. 2).

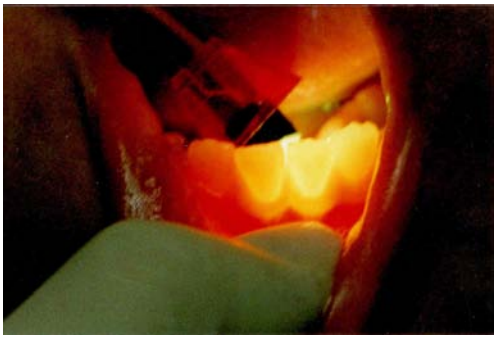

Рис. 2. Пациент К.М., 16 л. Опалесцентные зубы

Симптом DI – патологическая стираемость проявляется в преждевременной абразии резцового края, бугре коронки и утрате эмали. Такой зуб становится слабым и хрупким и даже при незначительной нагрузке, а иногда спонтанно легко ломается.

На нашем материале у 35,71% обследованных пациентов выявлена патологическая стираемость зубов. Естественно, такие зубы невелики по размеру, что влечет за собой уменьшение высоты прикуса и другие осложнения (диаграмма 4).

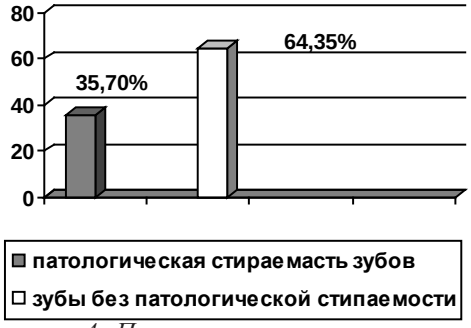

Диаграмма 4. Процентное количество пациентов, имеющих патологическую стираемость

Таблица 2. Количественное распределение пациентов с патологической стираемостью по периодам прикуса

Прикус	Патологическая стираемость зубов (n=5)
молочный	3
сменный	1 (в случае этого пациента отмечается стираемость как молочных, так и постоянных зубов)
постоянный	1

Данные таблицы 2 указывают, что патологическая стираемость молочных зубов превалирует над постоянными.

Одним из характерных радиографических симптомов DI является характерная форма коронки (в форме луковицы и лампочки) и корня (изогнугнутый, крючкообразный) зуба, которая выявлена в 21,4% случаев (диаграмма 5, рис. 3 и 4, таблица 3).

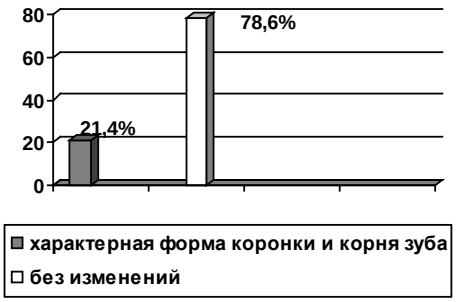

Диаграмма 5. Процентное распределение пациентов с учетом формы коронки и корня зуба

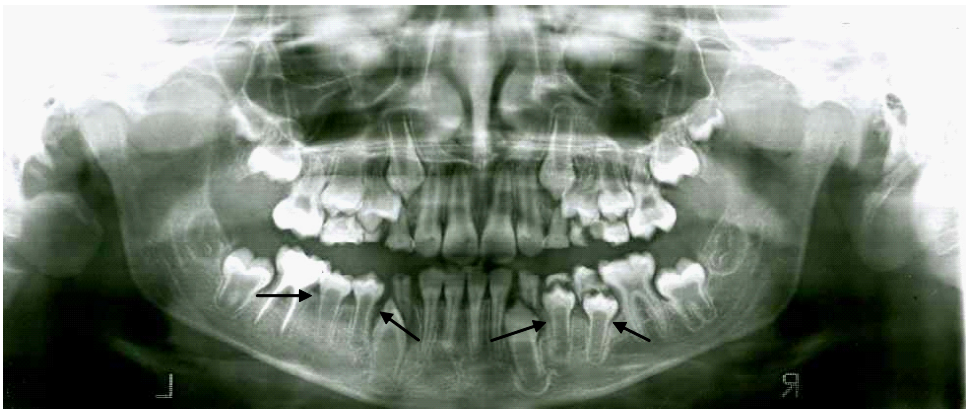

Рис. 3. Ортопантомография. Пациент А.И., 9 л. Коронки формы луковицы и лампочки

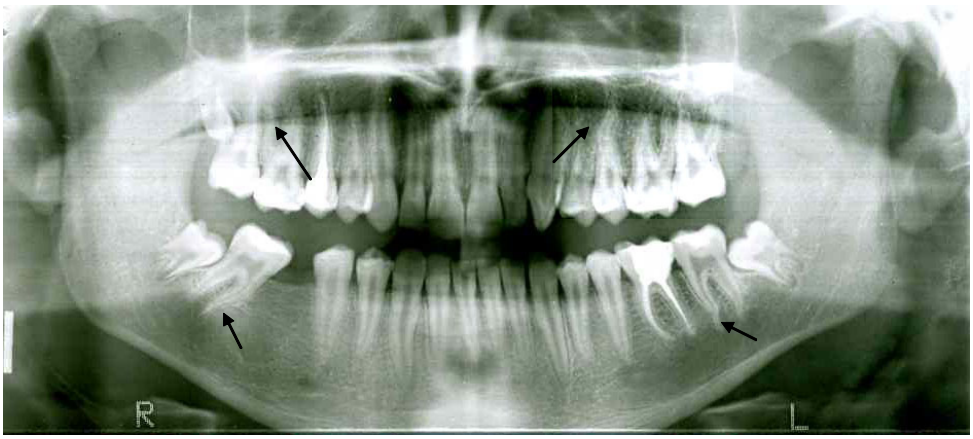

Рис. 4. Ортопантомография. Пациент К.М., 16 л. Корни зуба изогнугнутые, крючкообразные, узкие

Характерная форма коронки и корня зуба выявдена у 3 пациентов, из них характерная форма коронки - у 2, деформированный корень - у одного пациента.

Среди обследованных пациентов не были зафиксированы такие особенности DI как облитерированная полость зуба, короткие и узкие корни 0%. Наоборот, радиографически у некоторых из них была выявлена ненормально широкая коронковая и корневая пульпарная камера. По мнению некоторых исследователей [7], именно такие зубы называют “shell teeth” ввиду их ракушечной, гранатообразной формы. По утверждению Shields E.D., пульпарная камера этих зубов испытывает прогрессивную облитерацию, что в нашем материале не зафиксировано [цит. по 7]. По нашему мнению, одной из причин облитерации полости зуба может быть патологическая стираемость зубов за счет скопления вторичного и иррегулярного дентина.

Весьма интересный показатель DI, как периапикальное повреждение корня интактного зуба с наличием костного дефекта, выявлен в одном (7,1% случае) (диаграмма 6; рис. 5).

Диаграмма 6. Процентный показатель пациентов, имеющих периапикальное повреждение корня интактного зуба и костный дефект

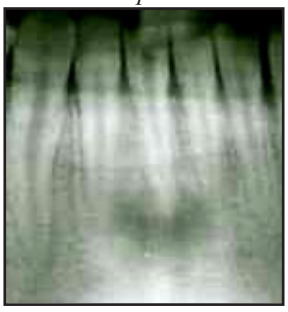

Рис. 5. Дентальная радиовизиография. Пациент К.М., 16 л. Периапикальное повреждение корня интактного зуба с наличием костного дефекта

Согласно данным исследования, из 14 обследованных пациентов с диагнозом OI, DI отмечается только в 6 (42,85%) случаях (диаграмма 7).

Диаграмма 7. Процентный показатель DI среди пациентов OI

Полученные результаты свидетельствуют, что DI вдвое чаще выявляется в молочных (66,66%), чем в постоянных (33,33%) зубах (диаграмма 8), что согласуется с мнением Shwartz S.D. [11].

Диаграмма 8. Процентное распределение DI с учетом молочных и постоянных зубов

DI более остро проявляется в тех постоянных зубах, которые зарождаются и формируются в раннем периоде (например, центральные резцы, первые моляры) [11]. Всем исследуемым пациентам было проведено радиографическое обследование – ортопантография, которая в 100% случаев выявила наследственный генерализированный вторичный остеопороз костей челюсти, развившийся на фоне генетического нарушения [6]. Прозрачность костей челюсти больных увеличена, упругость кости уменьшена, кортикальный слой утончен. Слизистая оболочка полости рта обследованных пациентов была без изменений, в пределах нормы. Среди обследованных пациентов выявлен один весьма интересный случай первично-множественно-частичной адентии (пятилетний ребенок с зачатками только 13 постоянных зубов) (рис. 6).

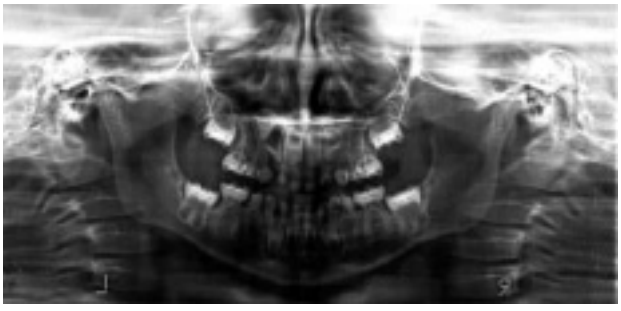

Рис. 6. Ортопантомография. Пациент Д.Г., 5 л. Первично-множественно-частичная адентия, зачатки только 13 постоянных зубов

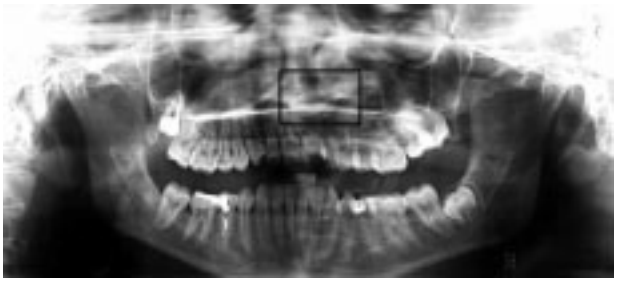

Рис. 7. Ортопантомография. Пациент К.М., 16 л. Ретенция зуба 13.

Только в случае одного пациента (6 лет) было зафиксировано наличие сверхкомплексного зуба (рис. 8).

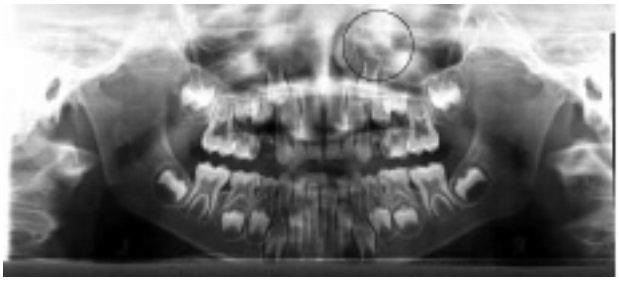

Рис. 8. Ортопантомография. Пациент Л.В., 6 л. Сверхкомплексный зуб

Находится ли в какой-либо закономерной зависимости адентия, сверхкомплексный и ретинированный зуб с OI, исходя из современных литературных данных, установить невозможно.

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SUMMARY

ORAL CAVITY FEATURES IN PATIENTS SUFFERING FROM OSTEOGENESIS IMPERFECTA

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Osteogenesis Imperfecta (OI) is a rare hereditary connective tissue disorder. This pathology is characterized by disruption of biosynthesis of Type I collagen, and production of limited amount of defective and imperfect collagens. This causes decrease in bone mass of human body, bones become fragile and brittle, resulting in unreasonable multiple fractures. Reportedly, number of patients with OI ranges between 32-38 in Georgia. However, exact number of patients, including children and their parents, is unknown.

Dentinogenesis Imperfecta (DI; DGI) and skeletal malocclusion occupy special place in varied spectrum of OI clinical symptoms. We studied 14 patients: 9 women (64.3%), 5 men (35.7%) and divided them in three age groups: I – 2.5-6 years – period of primary dentition (28.6%), II – 6-14 years - period of changing teeth dentition (35.7%) and III – above 14 years – period of permanent dentition (35.7%).

28.5% of screened patients had one of the symptoms of DI, such as tooth discoloration. Discoloration of primary teeth was revealed in 4 patients (primary dentition), while discoloration in changing and permanent dentition was equally observed in 5 – 5 patients.

Another symptom of DI, such as early abrasion, was detected in 5 patients i.e. 35.71%. This was divided in the following manner: I age group - 3 cases, II and III age groups – 1-1 cases. It was also observed that early abrasion of primary teeth prevails over permanent.

One of DI's radiographic symptoms, such as peculiar form of teeth crown and root, was revealed in 21.4% or in 3 patients, 2 of whom had bulbous crown, and the third one deformed (curved) root.

Peculiar characteristics of DI, such as increased constriction of the coronal-radicular junction, obliterated pulp chamber, short and narrow roots, were not observed in the patients examined.

Interesting characteristic of DI, such as periapical destruction of intact tooth root, was revealed in the form of bone defect in 7.1% of those examined (1 patient).

Therefore, out of examined 14 patients with OI – DI had 6 patients or 42.85% of cases. Also, interesting observation was revealed – DI is more common in primary teeth (66.66%) than in permanent (33.33%).

Radiographic examination – orthopantomography – revealed secondary osteoporosis of jaw bones in 100% of cases. Mucous tissue of examined patients is within normal range.

Among examined patients, 1 case of adenty, 1 case of retention and 1 case of overcomplex tooth were revealed. According to current literature, it is unknown whether there is a logical relationship between adenty, retention, overcomplex teeth and OI. This will be defined by future research.

Key words: osteogenesis imperfecta (OI), dentinogenesis imperfecta (DI, DGI), skeletal malocclusion, adenty, retention, overcomplex tooth.

РЕЗЮМЕ

ОСОБЕННОСТИ ПОЛОСТИ РТА У ПАЦИЕНТОВ С НЕСОВЕРШЕННЫМ ОСТЕОГЕНЕЗОМ

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Несовершенный остеогенез - Osteogenesis Imperfecta (OI) - редкое наследственное заболевание соединитель-

ных тканей. При этой патологии нарушается биосинтез коллагена тип I, возникает дефектный – количественно и качественно неполноценный коллаген. В результате уменьшается костная масса, кости становятся хрупкими и ломкими, что проявляется во множественных беспричинных переломах. Точная суммарная цифра заболеваний, включая детей и их родителей, не известна.

В многообразном клиническом спектре OI особое место уделяется таким повреждениям полости рта, как несовершенный дентиногенез (Dentinogenesis Imperfecta) и патологический прикус. Нами обследовано 14 пациентов: 9 женщин (64,3%), 5 мужчин (35,7%), в возрасте от двух до 14 лет и выше. Пациенты были подразделены на три возрастные группы: 2,5-6 лет - период молочного прикуса - 4 (28,6%), 6-14 лет - период сменного прикуса - 5 (35,7%) и выше 14 лет - период постоянного прикуса - 5 (35,7%).

Выявлено, что у 28,5% обследованных отмечался один из симптомов DI - изменение цвета зуба (зубы темно-желтые, янтарного или голубовато-сероватого-коричневого оттенка). Дисколоризация молочных зубов обнаружена у 4 пациентов, а в период сменного и постоянного прикуса распределилась поровну, по 5 в ротовой полости.

В 5 (35,71%) случаях зафиксирован очередной симптом DI – патологическая стираемость зубов: в I возрастной группе - 3, во II и III по 1 пациенту. Показано, что превалирует стираемость молочных зубов.

Из радиографических симптомов DI: характерная форма коронки и корня зуба установлены у 3 (21,4%) пациентов, из них у 2 отмечалась деформация коронки (в форме луковицы и лампочки), а у одного – деформация корня (изогнугнутый, крючкообразный).

Такие особенности DI, как суженная граница между коронковой и корневой пульпой, облитерированная пульпарная камера, короткие и узкие корни у обследованных пациентов не зафиксированы.

Весьма редкий и интересный показатель DI - периапикальное повреждение корня интактного зуба с наличием костного дефекта выявлен в одном (7,1%) случае.

Согласно полученным результатам, из 14 обследованных пациентов с диагнозом OI, DI выявлено только в 6 (42,85%) случаях. Отмечена интересная закономерность: DI вдвое чаще встречается в молочных зубах (66.66%), чем в постоянных (33.33%).

Проведенное радиографическое обследование – ортопантография, в 100% случаев выявила вторичный остеопороз костей челюсти.

Сосотояние слизистой оболочки полости рта обследованных пациентов находится в пределах нормы.

На нашем материале в одном случае выявлена вторичная адентия, в одном – ретенция и в одном случае – наличие сверхкомплексного зуба. Данных находятся ли в какой-либо взаимосвязи адентия, сверхкомплексный и ретинированный зуб с OI в литературных источниках не выявлено.

რეზიუმე

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, პაროდონტისა და პირის ღრუს ლორწოვანის დაავადებათა დეპარტამენტი; ქართულ-გერმანული იმპლანტაციის ცენტრი "HBI-dent Implant"; გენეტიკური და იშვიათი დაავადებების საქართველოს ფონდი

დაუსრულებელი ოსტეოგენეზი - Osteogenesis Imperfecta (OI) შემაერთებელი ქსოვილის იშვიათი მემკვიდრეობითი დაავადებაა. ამ პათოლოგიის დროს ირღვევა I ტიპის კოლაგენის ბიოსინთეზი, წარმოიქმნება დეფექტური – რაოდენობრივად მცირე და ხარისხობრივად არასრულფასოვანი, კოლაგენი, შედეგად ადამიანის ძვლოვანი მასა მცირდება, ძვლები მყიფე და მსხვრევადი ხდება, რაც მრავლობითი უმიზეზო მოტეხილობებით აისახება.

OI-ს კლინიკური სიმპტომების მრავალფეროვან სპექტრში განსაკუთრებული ადგილი ეთმობა პირის ღრუს ისეთ დაზიანებებს, როგორიცაა Dentinogenesis Imperfecta (DI;DGI) - დაუსრულებელი დენტინოგენეზი და პათოლოგიური თანკბილვა. ჩვენს მიერ გამოკვლეულია 14 პაციენტი: 9 ქალი (64,3%), 5 მამაკაცი (35,7%). პაციენტები დაყოფილ იქნა სამ ასაკობრივ ჯგუფად: I ჯგუფი – 2,5-6 წ. - სარძევე თანკბილვის პერიოდი - 4 (28,6%), II - 6-14 წ. - ცვლადი თანკბილვის პერიოდი - 5 (35,7%) და III – 14 წ. ზემოთ, მუდმივი თანკბილვის პერიოდი - 5 (35,7%).

დაავადებულთა პირის ღრუს ობიექტური დათვალიერებით გამოვლინდა, რომ გამოკვლეულთა 28.5% აღენიშნებოდა DI ერთ-ერთი სიმპტომი, როგორიცაა კბილის ფერის ცვლილება. სარძევე თანკბილვაში დისკოლორიზაცია აღენიშნა 4 პაციენტს, ცვლადი და მუდმივი თანკბილვის პერიოდებში კი თანაბრად განაწილდა - 5–5 პირის ღრუში.

გამოკვლეულეულთა 5 (35,71%) შემთხვევაში დაფიქსირდა DI მორიგი სიმპტომი – კბილების პათოლოგიური ცვეთა: I ასაკობრივ ჯგუფში - 3, II და III - თითო-თითო პაციენტი. ასევე გამოვლინდა, რომ კბილების პათოლოგიური ცვეთა პრევალირებს სარძევე კბილებში.

DI-ის ერთ-ერთი რადიოგრაფიული სიმპტომი, როგორიცაა კბილის გვირგვინისა და ფესვის დამახასიათებელი ფორმა აღმოჩნდა 3 (21,4%) პაციენტს, რომელთაგან 2 აღენიშნებოდა გვირგვინის (ბოლქვის, ნათურის მსგავსი), ხოლო 1 - ფესვის (მოხრილი, მოკაუჭებული) დეფორმაცია.

DI-ის ისეთი თავისებურებები, როგორებიცაა შევიწროებული საზღვარი გვირგვინოვანსა და არხოვან პულპას შორის, ობლიტირებული კბილის ღრუ, მოკლე და ვიწრო ფესვები, გამოკვლეულ პირებში არ დაფიქსირებულა.

DI ისეთი საინტერესო მახასიათებელი, როგორიცაა ინტაქტური კბილის ფესვის პერიაპიკალური დაზიანება ძვლოვანი დეფექტის არსებობით გამოვლინდა შემთხვევათა 7.1% (1 პაციენტი).

ჩატარებული კვლევის შედეგები უფლებას გვაძლევს გამოვიტანოთ შემდეგი დასკვნები: OI-ით დაავადებული 14 პაციენტიდან DI აღენიშნებოდა 6 (42,85%), გამოვლინდა საინტერესო კანონზომიერება - DI უფრო ხშირია სარძევე კბილებში (66,66%), ვიდრე მუდმივში (33,33%).

ჩატარებულმა რადიოგრაფიულმა გამოკვლევამ – ორთოპანტომოგრაფიამ, შემთხვევათა 100%-ში გამოავლინა ყბის ძვლების თანდაყოლილი, გენერალიზირებული მეორადი ოსტეოპოროზი.

ნორმის ფარგლებში აღმოჩნდა დათვალიერებული პაციენტების პირის ღრუს ლორწოვანი გარსი.

შესწავლილ პირებში გამოვლინდა მეორადი ადენტიის 1, რეტენციის 1 და ზეკომპლექსური კბილის არსებობის 1 შემთხვევა. არის თუ არა რაიმე კანონზომიერ კავშირში ადენტია, ზეკომპლექსური და რეტენირებული კბილის არსებობა OI-თან, თანამედროვე ლიტერატურული მონაცემების თანახმად უცნობია და სამომავლო კვლევების პრეროგატივად რჩება.

THE MARFAN SYNDROME - FEATURES, NATURAL HISTORY AND TREATMENT OPTIONS - OUR EXPERIENCES

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Marfan syndrome is one of the most common genetic-determined connective tissue disorders but it's still a rarely diagnosed syndrome, especially in childhood. That is the reason for a lot of patients not being diagnosed in time and losing the possibility of preventing the pathological changes' progression. Unfortunately, situations when a patient finds their disorder too late have happened, when serious symptoms have already occurred, e.g.: a young sportsman's intense chest pain during a game, which can be a result of dissection of aortic aneurysm, the most common cause of sudden deaths among young people with MFS [14] or more common injuries as a result of skeletal – arthral system changes e.g.: patella's subluxation or luxation, which affects about half the young population with MFS.

Data about MFS patients' survival and life quality, published in 1972 literature, revealed that the main risk factors were cardiovascular changes.

The aim of this research is to show our experience in diagnostic and therapeutic abilities related to Marfan syndrome.

Materials and methods. We present prospective data concerning 66 patients with clinically-diagnosed MFS who have been controlled in Department of Pediatric Cardiology and Congenital Heart Diseases Medical University in Gdansk in 2000 – 2010. Patient qualification was based on Ghent's criteria. In 6-month periods regular cardiologic, ophthalmologic and orthopedic – rehabilitation examinations have been performed.

Results and their discussion. Familial incidence of MFS was proved in 32 (48%) cases. In all 66 patients developmental abnormalities in the ocular system have been confirmed. In 51 cases (77%) it was essential progressive short-sightedness during the fast-growth period.

In the area of the motor system, in all patients different grades scoliosis were revealed; in 14 (21%) pectus excavatum coexisted with scoliosis, in 6 (9%) with pectus carinatum. In 4 situations (6%) corrective orthopedic procedures have been performed.

In the area of cardiovascular system, 29 patients (44%) had mitral valve regurgitations, 19 (29%) aneurysmal dilatation of the aorta, 13 (20%) had both these irregularities. In 7 cases (11%) diagnosis of mitral valve prolapse preceded appearance of an aneurysmal dilatation of the aortic bulb. During the observation period 11 patients (17%) underwent cardiosurgical procedures for the sake of stopping crucial progressive mitral valve dysfunction and/or aneurysmal dilatation of the aortic bulb, which threatened with a rupture of aortic aneurysm. Urgent surgery procedures were performed in 3 and on-time procedures in 8 cases. In 39 cases (59%) prophylactic treatment with beta – blockers (propranolol or metoprolol) in individual doses was administered. Physical activity was restricted in 39 patients (59) - in 19 cases (29%) because of sceletal system's changes, 11 (17%) - cardiovascular, in 9 (14%) - both systems' changes. Two of the patients died during the observation period; one because of progression the heart failure and the other because of an acute rupture of aortic aneurysm.

Marfan syndrome was first described by Antoine – Bernard Marfan in 1896 [13]. Based on forty years of observation of 150 patients, he affirmed that both sexes and sequential generations in families were affected and the typical features were: tall stature, disproportionately long, thin limbs and digits (arachnodactyly), congenital displacement of the lens (ectopia lentis) and malfunction of the mitral valve. It was very hard to define the reason of Marfan syndrome initially. The concept of the developmental defect of mesodermal tissues was presented in 1931 [23]. However on the basis of cases of aortic dilatation described many years later (first description in 1943), McKusick had started the discussion on the defect in connective tissue [16].

Today it is known that MFS in 80% of patients is caused by the mutation of the FBN 1 gene, with the locus on chromosome 15q21, which encodes the glycoprotein fibrillin – 1, a major component of the extracellular microfibrilles. In the remnant part of patients it can be de novo mutation. The small percentage of MFS, named MFS II are caused by mutations in the TGFBR2 genem, localized in 3p24.2-p25 chromosome [1]. The course of inheritance in both types is autosomal dominant and a lot of familiar features were presented.

The single mutation and the different gene's expression can lead to many clinical manifestations. These factors have an essential influence on time when disorder's first symptoms occur and their diverse clinical nature in the individual cases [18].

MFS is a disorder with a very wide range of clinical manifestations [19, 10]. In some patients, the foremost symptoms are abnormalities in skeletal system, in other - cardiovascular, respiratory or ocular systems. It causes significant difficulties in producing a diagnosis, especially in poorly-symptomatic patients of young age [17].

Subsequently, revised (Ghent) criteria were offered by De Paepe and were required for the diagnosis of MFS [6]: medical therapies in MFS should retard lesions, which deteriorate life quality and can be hazardous to life. The most frequent reasons of young people's death are cardiovascular abnormalities. A beta - adrenergic receptor blockade (usually propranolol or atenolol) is used to slow down pathologic aortic growth and decrease the risk of aortic dissection as well as enlargement of aortic aneurysms [9,12,21]. For the sake of beta blocker side effects, these drugs have limited application in chronic treatment of patients with asthma or diabetes mellitus. In such situations calcium channel blockers (verapamil) [20] and ACE – inhibitors (enalapril) [25] are administered. At present, selective AT 1 blocker (losartan) is in the process of testing [11].

The next problem is endocarditic prophylaxis. It concerns all patients with multiple cardiac valves. Abnormalities include myxomatous thickening with prolapse and regurgitation of the mitral and tricuspid valves, as well as dilatation of the aortic and pulmonic roots, with insufficiency of these valve leaflets. These patients are recommended for the administration of prophylactic antibiotics during procedures that are associated with bacteremia, such as dental, gastrointestinal, or genitourinary interventions [22,24].

The situation of many poorly - symptomatic individuals, who, because of their tall stature, are drawn to athletic activities such as volleyball and basketball, should be taken into consideration. Such people do not usually comply with the activity restrictions, such as limitations on strenuous physical exertion, competitive athletics and particularly isometric activities [3,15], which can cause an increase in the risk of vascular changes. The moderation in aerobic exertion is recommended as a means of safety for them, it does not burden them with increased risk of ophthalmologic, skeletal and vascular changes' progression.

Another method of treatment is a surgical procedure. It becomes necessary in advanced changes in ocular system, bone deformation, hemodynamic essential valvular heart disease, big aortic dilatation (>=5 cm) or aortic aneurysm [2,4]. The cardiovascular complications (mitral insuffi-

ciency, ascending aorta aneurysm with concomitant aortic insufficiency and aneurysm of other parts of aorta) are detected in 50% of patients, and if these pathologies are not treated correctly, they lead to the death in young age. In our data there were an early postoperative mortality and we have lost one patient half a year after the operation in course of dilatative cardiomyopathy. Two patients required reoperation: the first one year later because of valve reconstruction failure, the second 5 years later due to acute aortic dissection (previous surgery was for mitral valve, and during that operation aorta diameter was normal). All other patients are under echocardiographic control, and their repaired valves are working without dysfunction.

A decision to undertake a surgical procedure in individuals with MFS has to be well–thought-out. Every operation in connective tissue disorder, like MFS, brings about the risk of very serious complications, which can be more severe for patients than the basic disorder.

Summarising the therapeutic methods, the optimistic results of the newest biology treatment should be mentioned. It was proved that increased activation of and signaling by transforming growth factor beta (TGF β) lead to appearance of many manifestations of Marfan syndrome. Probably the application of anti – TGF β monoclonal antibodies can modulate manifestations of MFS [5]. There is hope that tests results, currently conducted in a murine model, could be applied to human therapy.

Several past studies have shown that Marfan syndrome diagnosis was connected with shortened survival, usually caused by cardiovascular complications. Today it is known that earlier diagnosis, prophylactic and pharmacological therapy, as well as new methods of surgical procedures, especially in cardiovascular system, results in longer life expectancy of MFS patients. The research in the 1990s showed men's life expectancy to be 53, women's – 72 years. Prognosis in individual cases must however be very careful.

Family planning in Marfan syndrome is one of the most difficult problems for parents-to-be and doctors. It is known that pregnancy can strengthen typical Marfan's symptoms, in consequences; it can lead to complications in the last period of pregnancy, during delivery and puerperium, with tragic effects. The accessory elements, which have to be noticed, are: influence of disorder and pharmacological treatment connected with it, type of prior anesthesia, cardiosurgical procedures, which are sometimes necessary in pregnancy, type of delivery and anesthesia to fetal and neonate's development.

The Marfan syndrome belongs to too late diagnosed genetic disorders because of the unclear clinical manifestation, depending of the age. The patients with the MFS should be included into multidisciplinary (cardiological, ophthalmological, orthopedic and rehabilitation) care in order to prevent pathological changes' progression. We strongly recommend it because the significant number of patients have not provide the possibility of taking up or continuing work in regular style because of advanced lesions. Therefore it is necessary to receive assistance of a psychologist and occupational adviser so that patients with Marfan syndrome can form a rightful part of the society.

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SUMMARY

THE MARFAN SYNDROME - FEATURES, NATURAL HISTORY AND TREATMENT OPTIONS - OUR EXPERIENCES

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The Marfan syndrome (MFS) is one of the most common (1:3000-1:4000) heritable connective tissue disorders. It's still a rarely diagnosed syndrome, especially in childhood. Near all cases MFS results from mutations in the fibrillin-1 (FBN1) gene on chromosome 15q21.1, which encodes for the glycoprotein fibrillin. The FBN1 gene is a large protein that can cause more than 500 mutations and molecular examinations, finally confirming the diagnosis, are conducted extremely rare.

We present prospective data concerning 66 patients with clinically-diagnosed MFS who have been controlled in Department of Pediatric Cardiology and Congenital Heart Diseases Medical University in Gdansk in 2000 – 2010.

29 patients (44%) had mitral valve regurgitations, 19 (29%) aneurysmal dilatation of the aorta, 13 (20%) had both these irregularities. In 7 cases (11%) diagnosis of mitral valve prolapse preceded appearance of an aneurysmal dilalation of the aortic bulb. During the observation 11 patients (17%) underwent cardiosurgical procedures for the sake of stopping crucial progressive mitral valve dysfunction and/or aneurysmal dilatation of the aortic bulb, which threatened with a rupture of aortic aneurysm. In 39 cases (59%) prophylactic treatment with beta – blockers was administered

The patients with MFS need a multidisciplinary system of care and the psychological supporting. The cardiosurgical treatment, which nowadays is bringing better results, due to the technological advancements is a new hope for this patient population.

Key words: Marfan syndrome, cardiovascular complications, beta-blockers.

РЕЗЮМЕ

СИНДРОМ МАРФАНА - ОСОБЕННОСТИ, ИСТОРИЯ ПРОЯВЛЕНИЯ И ВАРИАНТЫ ЛЕЧЕНИЯ - НАШ ОПЫТ

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Синдром Марфана (СМ) - часто встречаемое (1:3000-1:4000) наследственное расстройство соединительной ткани, трудно диагностируемое, особенно в детском возрасте. Почти во всех случаях СМ является результатом мутации в гене фибриллин-1 (FBN1) на хромосоме 15q21.1, который кодирует гликопротеина фибриллин.

Ген FBN1 может иметь более 500 мутаций. Молекулярные исследования, окончательно подтверждающие диагноз, проводятся чрезвычайно редко.

Нами представлены проспективные данные 68 пациентов с клинически-диагностированным СМ. Больные находились под наблюдением в департаменте педиатрической кардиологии и врожденных сердечных болезней Гданьского медицинского университета в 2000-2010 г.г.

29 (44%) пациентов имели регургитацию в области митрального клапана, 19 (29%) – аневризматическую дилатацию аорты, 13 (20%) имели обе эти патологии. В 7 (11 %) случаях диагностировался пролапс митрального клапана, который предшествовал появлению аневризматической дилатации аортальной луковицы. В процессе наблюдения 11 (17%) пациентов подверглись кардиохирургическим процедурам с целью остановки критической прогрессии дисфункции митрального клапана и/или расширения аортальной дуги с возникновением и угрозой разрыва аортальной аневризмы. В 39 случаях (59%) применяли профилактическое лечением бета - блокаторами.

Проведенные исследования позволяют заключить, что больные СМ нуждаются в междисциплинарной системе ухода и психологической поддержке. Кардиохирургическое лечение, которое в настоящее время приносит лучшие результаты благодаря технологическому прогрессу - новая надежда для этой популяции.

რეზიუმე

მარფანის სინდრომი - თავისებურებები, გამოვლინებები, მკურნალობის ვარიანტები – ჩვენი გამოცდილება

[1]ი. კვიატკოვსკა, [2]ი. ვიერჟბა, [3]რ. პავლაჩიკი, [1]ა. ვალდოხი, [1]ი. ალესცევიჩ-ბარანოვსკა

[1] გდანსკის სამედიცინო უნივერსიტეტი, პედიატრიული კარდიოლოგიისა და თანდაყოლილი გულის მანკების დეპარტამენტი; [2]საქმონო საქმის დეპარტამენტი და პედიატრიული ჰემატოლოგიის, ონკოლოგიისა და ენდოკრინოლოგიის დეპარტამენტი;
[3]გულისა და სისხლძარღვთა ქირურგიის დეპარტამენტი, პოლონეთი

მარფანის სინდრომი შემაერთებელი ქსოვილის დაზიანებით მიმდინარე დაავადებებში ერთ-ერთი ყველაზე ხშირია (1:3000-1:4000). ამასთანავე იგი ჯერ კიდევ იშვიათად დიაგნოსცირდება ბავშვთა ასაკში. თითქმის ყველა შემთხვევაში მარფანის სინდრომი ქრომოსომა 15ქ21.1-ში არსებული ფიბრილინ-1 (FBN1) გენის მუტაციის შედეგია. ამ გენს შეიძლება ჰქონდეს 500-ზე მეტი მუტაცია. მოლეკულური გამოკვლევები, რომლებმაც საბოლოოდ უნდა დაადასტუროს დიაგნოზი, ფრიად იშვიათად ტარდება.

ჩვენ წარმოვადგენთ კლინიკურად დიაგნოსცირებული მარფანის სინდრომის მქონე 68 პაციენტის პროსპექტული დაკვირვების შედეგებს. პაციენტები 2000-2010 წლებში გდანსკის სამედიცინო უნივერსიტეტის პედიატრიული კარდიოლოგიისა და თანდაყოლილი გულის მანკების დეპარტამენტში გატარდნენ.

29 პაციენტს (44%) ჰქონდა მიტრალური სარქვლის პროლაფსი, 19(29%)–ს - აორტის ანევრიზმული დილატაცია, 13 (20%)-ს აღენიშნებოდათ ორივე დარღვევა. 7 შემთხვევაში (11%) მიტრალური სარქვლის პროლაფსი წინ უსწრებდა აორტის ბოლქვის ანევრიზმულ დილატაციას. დაკვირვების პერიოდში 11 პაციენტს (17%) ჩაუტარდათ ქირურგიული ჩარევა მიტრალური სარქვლის პროგრესირაბადი დაზიანების და/ან აორტის ბოლქვის ანევრიზმული დილატაციის (რაც აორტის ანევრიზმის გასკდომის საფრთხეს ქმნიდა) შეჩერების მიზნით. 39 (59%) შემთხვევაში დაინიშნა პროფილაქტიკური მკურნალობა ბეტა-ბლოკატორებით.

მარფანის სინდრომის მქონე პაციენტებს ესაჭიროებათ მოვლის მულტიდისციპლინარული სისტემა და ფსიქოლოგიური მხარდაჭერა. კარდიოქირურგიული მკურნალობა, რომელიც ტექნიკური უსაფრთხოების დონის მატების გამო, დღეს ბევრად უფრო წარმატებულია, ამ პაციენტებისთვის ახალ იმედს წარმოადგენს.

INFLUENCE OF HALOTHANE NARCOSIS ON A CHANGE OF THE NUMBER OF GABA-POSITIVE CELLS IN THE HIPPOCAMPUS OF ADULT RATS WITH THE MIDASOLAM PREMEDICATION

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The congenital clefts of lip and palate, as is known, are accompanied by the severe disorders of respiration, speech and hearing. The inferiority of external respiration causes the receptivity of children to the inflammatory diseases of the upper respiratory tract and lungs. The congenital defects of the hard palate strongly disrupt also the natural breast feeding of infants [1,5,7]. The period and nature of surgical interference depend on the dimensions of cleft and on the degree of the decompensation of pharyngeal-palatine gate. Early rehabilitation is important not only with the medical, but also from a social point of view. The late periods of the speech restoration complicate the process of the social adaptation of child, resulting in the complex of physical and psychological inferiority [2,6]. From the above stated follows, that the treatment of children with the congenital facial pathology - one of the vital problems of children's maxilla-facial surgery, since it is caused by the increasing frequency, gravity, variety of the forms of defect and by its social significance.

Despite the fact that accumulated until today results of experimental and clinical experiments make it possible to successfully carry out the most complex surgical interventions in children, the most difficult questions of children's anesthesiology remain urgent with the surgical interventions for the purpose of the correction of the congenital maxilla-facial defects. Based on this, the selection of the method of anesthesia is extremely important task. Halothane, as the means of inhalation anesthesia is widely used among the children, including with the congenital maxilla-facial pathology. However, after halothane narcosis in the children of breast ages with the standard premedication (atropine, dimedrol) postsurgical complications (excitation, bronchitis and other) are observed [3]. On the basis of that above stated, for eliminating the postsurgical complications, is carried out pre-surgical medicamentous preparation by the drugs of the benzodiazepine group, which modulate blocked by neuromediator ionic channels activated by GABA (Gamma-Aminobutyric Acid) and GABA receptor function [8,10]. Earlier we showed that during the application of halothane as the means of narcosis and premedication by midazolam, differently changes a quantity of GAD65/67 (decarboxylase of glutamic acid) positive pyramidal cells of CA1 and CA3 fields on hippocampus [4]. It was assumed that as a consequence of an increase of the sedation degree, the reduction of postoperative complications could be result of strengthening the GABA neurosecretion.

On the basis of this assumption, the purpose of present study is to investigate a change of the quantity of GABA positive cells in the hippocampus of white adult rats under the conditions of halothane narcosis and with the premedication by midazolam.

Material and methods. Subjects of a study - 30 adult white rats with the weight of 130-140 g. Animals were subdivided into three groups. I group - intact animals; II group - false-operated rats under the conditions of halothane narcosis; III group – sham operated animals, premedicated by midazolam, under the halothane narcosis. For evaluating histo-architecture of hippocampus, the pieces of tissues after dehydration were embedded into paraffin, the cut slices were prepared with a thickness of 5-7μm. A change in the quantity of GABA positive cells was determined by the immunohistochemical method (Abcam, Rabbit Anti-GABA, dillution 1:200, detection with extravidin-peroxidase system). Light microscope "Motic series B" has been used for observation of samples. The quantity of GABA positive cells was determined by number of stained cells per 1000 cells (‰).

All data were processed by the method of standard variation statistics. The authenticity of results was evaluated according to the Student's criterion within limits of 95-99% reliability.

Results and their discussion. The results of conducted earlier by us studies revealed, that during the application of halothane as the means of narcosis, in different ways changes a quantity of GAD65/67 positive pyramidal cells of CA1 and CA3 fields on hippocampus of adult white rats. In particular, 1 hour after sham operation, considerably raises a quantity of GAD65/67 positive cells in the CA1 field of hippocampus, at the same time their number is reduced in the CA3 field. In this case in the dentate fascia of hippocampus any noticeable changes are not observed [4]. On the basis of above-mentioned it was to be expected, that correspondingly changes a quantity of GABA positive cells in the hippocampus of animals after conducting of sham operation under the conditions of halothane narcosis and with the premedication by midazolam.

As a result conducted by our investigations it is established that the halothane narcosis causes an increase in the GABA positive cells. Moreover, 1 hour after sham operation in

the CA1 field is revealed correlation between GAD65/67 positive and GABA positive cells (Fig. 1). Furthermore, as it was noted above, 1 hour after sham operation in the CA3 field of hippocampus of animals of the II group a quantity of GAD65/67 positive cells decreases. It follows from Fig. 1, that during the indicated period of the experiment, a quantity of GABA positive cells in the CA3 field of hippocampus of animals of the II group in comparison with the control group does not change. In this case during the indicated period the GABA positive cells in the dentate fascia of hippocampus of white rats also were not observed (Fig. 1).

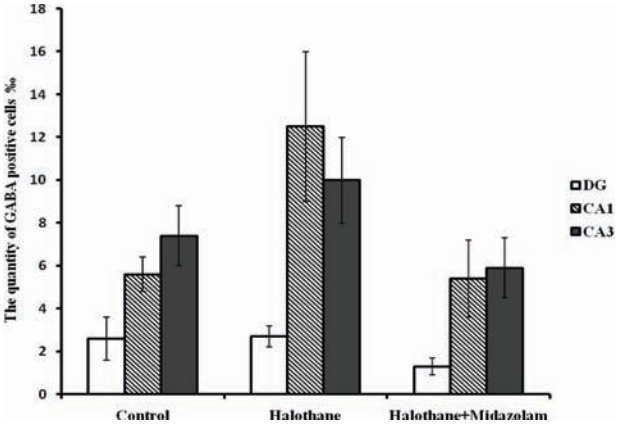

Fig. 1. Change of the number of GABA positive cells in the hippocampus of rats under the conditions of halothane narcosis with the premedication by midazolam (1 hour after sham operation)

A number of GABA positive cells in the fields of hippocampus of rats even more grow 24 hours after sham operation under the conditions of halothane narcosis. As shown in Fig.2, in the next day the number of GABA positive cells increases not only in the field CA1. In comparison with control parameters a number of GABA positive cells reliably grow also in the CA3 field of hippocampus of animals of the II group (Fig. 2).

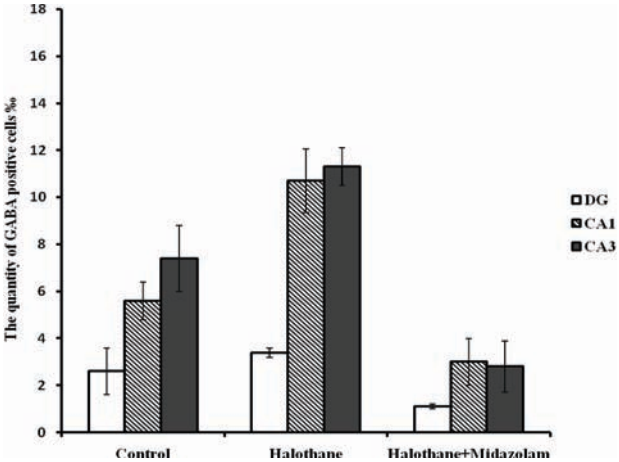

Fig. 2. Change of the number of GABA positive cells in the hippocampus of rats under the conditions of halothane narcosis with the premedication by midazolam (24 hours after sham operation)

By studies it was also shown that the changes of the number of GABA positive cells in the fields CA1 and CA3 of hippocampus of animals of the II group mentioned above are not manifested during the later periods. It follows from the analysis of the histograms, represented in Fig.3 that 168 hours after sham operation, the indices of a quantity of GABA positive cells in the fields CA1 and CA3 remain at the level of control (Fig. 3).

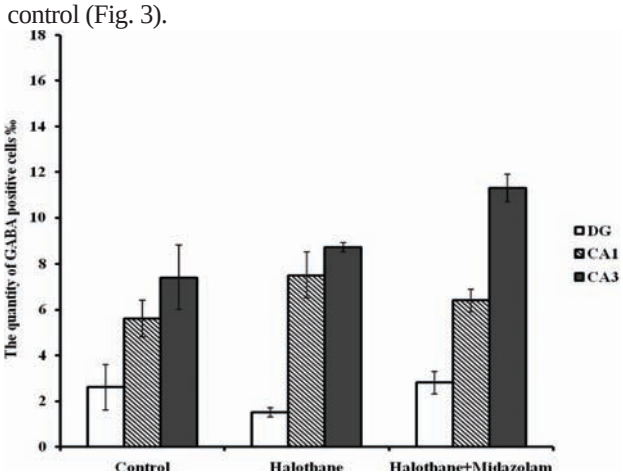

Fig. 3. Change of the number of GABA positive cells in the hippocampus of rats under the conditions of halothane narcosis with the premedication by midazolam (168th hour after sham operation)

According to literature data inhalation anesthetic halothane possesses the neuroprotective action, which is manifested in the limitation of the liberation of the exciting neuromediator (glutamate) in presynapsis and is characterized by postsynaptic action as well [11,12]. Taking into account literary, and also, obtained by us data, it is possible to conclude that a change of the number of GABA positive cells in the CA1 and CA3 fields is caused by the neuroprotective action of halothane itself as general anesthetic.

Another picture is observed in the case of sham operated animals, by which before conducting of halothane narcosis, was carried out premedication by midazolam (III group). It should be noted that a change of the number of GABA positive cells in the fields of hippocampus of animals of the III group reliably changes in comparison with the indices of control group only in a next day after conducting of sham operation (Fig. 2). It follows from the Figure that with the premedication by midazolam after 24 hours are obtained the opposite results. In particular, is observed reduction in the number of GABA positive cells in the both fields (CA1 and CA3) and in the dentate fascia of hippocampus of the III group animals (Fig. 3).

However, the week after conducting of sham operation as shown in Figure 3, a number of GABA positive cells again grow to the norm (Fig. 3). And what is more in the field CA3 and in the dentate fascia reliably exceeds corresponding indices in animals of the I and II groups (Fig. 3).

Sedative drug midazolam, as is known, interacts with the specific benzodiazepine receptors, located in the postsynaptic GABA receptor complex. In this case the frequency of opening ionic channels for the incoming currents of chlorine ions rises followed by the hyper-polarization of the membrane and suppressed neuronal activity [9]. On the basis of above-stated could be explained, why a number of GABA positive cells does not change the hour after halothane narcosis and sham operation in the CA1 field of hippocampus of III group animals (Fig. 1).

24 hours after conducting of sham operation the decrease of a number of GABA positive cells in the hippocampus of animals of the III group, occurs due to the binding of midazolam with the postsynaptic GABA receptor complex, which prevents reverse capture of GABA, contributing to its accumulation in the synaptic cleft [8]. With the accumulation of GABA, decreases its secretion (Fig. 2). Later (168 hrs) secretion of GABA is basically normalized (Fig. 3).

Fig. 4 shows the distribution of GABA positive cells in the CA1 and CA3 fields of adult rat's hippocampus within the norm and, the hour after conducting of sham operation under the conditions of halothane narcosis.

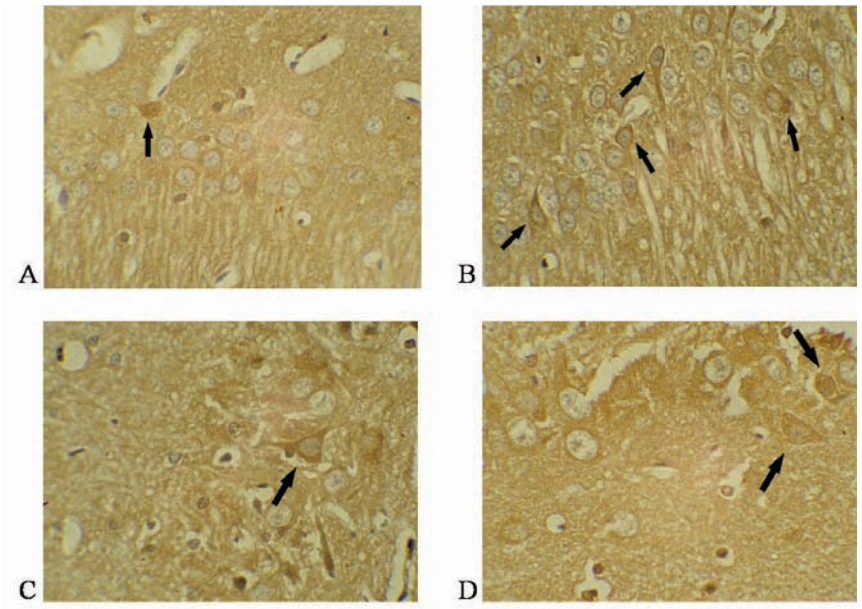

Fig. 4. Distribution of GABA positive cells in the fields CA1 (A, B) and CA3 (C, D) of hippocampus of adult rats within the norm and the hour after conducting of sham operation in the conditions of halothane narcosis (magnification 40x15). A,C – norm

On the bases of the carried out experiments was established correlation between a change in the number of GAD65/67 positive and GABA positive cells in the CA1 field of hippocampus of adult rats under the conditions of halothane narcosis. It should be noted that established correlation is observed only the hour after conducting of sham operation and is not manifested during the later periods. The study of this question is the purpose of our next investigations.

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SUMMARY

INFLUENCE OF HALOTHANE NARCOSIS ON A CHANGE OF THE NUMBER OF GABA-POSITIVE CELLS IN THE HIPPOCAMPUS OF ADULT RATS WITH THE MIDASOLAM PREMEDICATION

[1]Vadachkoria Z., [1]Dzidziguri L., [2]Bakuradze E., [2]Mosidze G., [2]Modebadze I., [2]Dzidziguri D.

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The most difficult questions in pediatric anesthesiology still remain relevant at surgeries to correct congenital maxilla-facial pathologies, accompanied by severe respiratory distress, speech and auditory sensation. For a long time the anesthetics were widely used among the neonatal and young children with extreme care due to their indicated suppressive effects on the immature organ systems. According to this fact, the choice of anesthesia is a matter of extremely importance. In addition, the study of molecular mechanisms indicating to the adverse effects induced by application of anesthesia will make it possible to develop therapeutic strategies for prevention of postoperative complications.

The purpose of present study is to investigate a change of the quantity of GABA positive cells in the hippocampus of white adult rats under the conditions of halothane narcosis and with the premedication by midazolam.

Subjects of a study - 30 adult white rats with the weight of 130-140 g. Animals were subdivided into three groups. I group - intact animals; II group - sham-operated rats under the conditions of halothane narcosis; III group - sham-operated animals, premedicated by midazolam, under the halothane narcosis. A change in the quantity of GABA positive cells was determined by the immunohistochemical method (Rabbit Anti-GABA). All data were processed by the method of standard variation statistics. The authenticity of results was evaluated according to the Student's criterion within limits of 95-99% reliability.

The results of conducted by us studies revealed, that during the application of halothane narcosis causes an increase in the GABA positive cells in the fields CA1 on hippocampus of adult white rats. In 24 hours after sham operation, at the condition of application of halothane narcosis a quantity of GABA positive cells raises in the CA3 field of hippocampus in II group animals as well. Moreover, in the CA1 field correlation between GAD65/67 positive and GABA positive cells is revealed which was not observed at later stages. The study of this question is the purpose of our next investigations.

Key words: halothane, midazolam, hippocampus, rat.

РЕЗЮМЕ

ВЛИЯНИЕ ГАЛОТАНОВОГО НАРКОЗА НА КОЛИЧЕСТВО ГАМК-ПОЗИТИВНЫХ КЛЕТОК В ГИППОКАМПЕ ПОЛОВОЗРЕЛЫХ КРЫС ПРИ ПРЕМЕДИКАЦИИ МИДАЗОЛАМОМ

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Некоторые вопросы детской анестезиологии при хирургических вмешательствах с целью коррекции врожденных челюстно-лицевых пороков, которые, как известно, сопровождаются тяжелыми расстройствами дыхания, речи и слуха по сей день остаются актуальными. Введение анестетиков новорожденным и детям младшего возраста проводится с крайней осторожностью, так как известны отрицательные эффекты этих препаратов на незрелые системы организма. Исходя из этого, выбор метода анестезии представляется чрезвычайно важной задачей. Вместе с тем, изучение молекулярных механизмов, определяющих неблагоприятные, индуцированные анестезией, эффекты, позволит разработать терапевтическую стратегию профилактики постоперационных осложнений.

Целью настоящего исследования явилось определение изменений количества ГАМК-позитивных клеток в

гиппокампе белых половозрелых крыс в условиях галотанового наркоза и при премедикации мидазоламом.

Объект исследования - 30 половозрелых белых крыс весом 130-140 г. Животные были подразделены на три группы. I группа – интактные животные; II группа – ложнооперированные крысы в условиях галотанового наркоза; III группа – ложнооперированные животные, в условиях галотанового наркоза с применением мидазолама. Изменение количества ГАМК-позитивных клеток в гиппокампе интактных и опытных групп определяли иммуногистохимическим методом (Rabbit Anti-GABA). Достоверность результатов оценивали по критерию Стьюдента в пределах 95-99% надежности.

В результате проведенных нами исследований установлено, что галотановый наркоз вызывает увеличение ГАМК-позитивных клеток в поле CA1 гиппокампа взрослых крыс. 24 часа спустя после ложной операции в условиях галотанового наркоза число ГАМК-позитивных клеток возрастает и в поле CA3 гиппокампа животных II группы. На указанных сроках в гиппокампе животных III группы изменение количества ГАМК-позитивных клеток не наблюдается. Более того, в поле CA1 выявлена корреляция между GAD65/67 положительными и ГАМК-позитивными клетками, которая не проявляется на более поздних сроках. Изучение данного вопроса является целью наших последующих исследований.

რეზიუმე

ჰალოტანის ნარკოზის ზეგავლენა ზრდასრული ვირთაგვას ჰიპოკამპში გაემ-პოზიტიური უჯრედების რაოდენობის ცვლილებაზე მიდაზოლამით პრემედიკაციის დროს

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ყბა-სახის თანდაყოლილი პათოლოგიების მქონე პაციენტებს, როგორც ცნობილია, აღენიშნებათ სუნთქვის, მეტყველებისა და სმენის მძიმე დარღვევები. აქედან გამომდინარე, ბავშვთა ანესთეზიოლოგიის ყველაზე პრობლემური საკითხები დღემდე აქტუალურია აღნიშნული პათოლოგიების კორექციის მიზნით ქირურგიული ოპერაციების დროს. გარდა ამისა, ახალშობილებსა და უმცროსი ასაკის ბავშვებში ანესთეტიკების შერჩევა და გამოყენება ხდება განსაკუთრებული სიფრთხილით, რადგან ნაჩვენებია აღნიშნული პრეპარატების დამთრგუნველი ზემოქმედება მზარდ ორგანოებსა და ქსოვილებზე. ამასთან, ანესთეზიით ინდუცირებული არახელსაყრელი ეფექტების მოლეკულური მექანიზმების შესწავლა ხელს შეუწყობს პოსტოპერაციული გართულებების პროფილაქტიკის მიზნით ახალი თერაპიული სტრატეგიების შემუშავებას.

სამუშაოს მიზანს წარმოადგენდა ჰალოტანის ნარკოზის პირობებში ზრდასრული ვირთაგვების ჰიპოკამპში გამ–პოზიტიური უჯრედების რაოდენობის ცვლილებების შესწავლა მიდაზოლამით პრემედიკაციის დროს.

კვლევის ობიექტებად გამოყენებული იყო 30 ზრდასრული ვირთაგვა (130-140გ). ცხოველები დავყავით სამ ჯგუფად: I ჯგუფი – ინტაქტური ცხოველები; II ჯგუფი – ცხოველები,რომელთაც ჰალოტანის ნარკოზის პირობებში ჩაუტარდათ ცრუ ოპერაცია; III ჯგუფი – ცხოველები,რომელთაც ჩაუტარდათ მიდაზოლამით პრემედიკაცია და ჰალოტანის ნარკოზის პირობებში ცრუ ოპერაცია. სამივე ჯგუფის ცხოველების ჰიპოკამპში გაემ–პოზიტიური უჯრედების რაოდენობის ცვლილებები შეფასებული იყო იმუნოჰისტოქიმიური მეთოდით (ბოცვერის ანტი-გაემ-ი). მონაცემების სარწმუნობის დასადგენად გამოყენებული იყო სტიუდენტის კრიტერიუმი. მონაცემების სარწმუნობა შეადგენდა 95-99%-ს.

ჩატარებული გამოკვლევებით დადგინდა, რომ ჰალოტანის ნარკოზი ზრდასრული ვირთაგვას ჰიპოკამპის CA1 ველში იწვევს გაემ–პოზიტიური უჯრედების რაოდენობის ზრდას. ცრუ ოპერაციიდან 24 საათში გაემ–პოზიტიური უჯრედების რაოდენობა მატულობს II ჯგუფის ცხოველების ჰიპოკამპის CA3 ველშიც. აღნიშნული ცვლილებები არცერთ ვადაზე არ ვლინდება III ჯგუფის ცხოველებში. დადგინდა კორელაცია გად 65/67 და გაემ–პოზიტიური უჯრედების რაოდენობას შორის, რომელიც არ ვლინდება ოპერაციიდან უფრო გვიან ვადებზე (24სთ, 168სთ). აღნიშნული საკითხის შესწავლა წარმოადგენს ჩვენი შემდგომი კვლევების მიზანს.

ENDOCRINE HISTOLOGY FINDINGS IN A PREPUBERTAL THALASSEMIC GIRL WITH MULTIPLE ENDOCRINE COMPLICATIONS SECONDARY TO IRON OVERLOAD

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Homozigous beta thalassaemia (TM) is an inherited disorder of haemoglobin resulting from an imbalance of betaglobin chain synthesis. The result is severe anaemia, increased production of erythropoietin and expansion of bone marrow of 15-30 times normal. The consequence of this is an increased in the blood volume, thinning of the bone matrix, an increased in bone deformability and fragility. The child's growth and maturation are retarded and there are very marked thalassemic features with bone deformities of the face, spine and limbs [11,27].

In the absence of diagnosis and treatment most patients with TM die before the age of five years. With recommended treatment (regular blood transfusions and iron chelation therapy) the overall prognosis is currently open ended [27].

Iron chelation therapy is essential as without this treatment the excess iron resulting from transfusions leads to endocrine disturbances, growth retardation, failure of puberty, diabetes and intractable heart failure (Table) [6-11,13,14,27].

Table. Endocrine abnormalities experienced by thalassaemic patients in different countries

Endocrinological abnormalities (% in both sexes)	Cyprus	Greece	Italy	Jordan	Iran	Turkey
Hypogonadism	37,67	42	78	51	21,3*	39** 30,7-47**
Diabetes mellitus	7,52	5	4,2	-	2,76**	4,3*
Glucose tolerance test	1,88	30,5	-	9	6,29**	-
Hypothyroidism	5,9	9	5,6	13	1,7*	16-37
Hypoparathyroidism	1,2	5	2,5	16	-	1,8

** and ** - denote the results are taken from different studies*

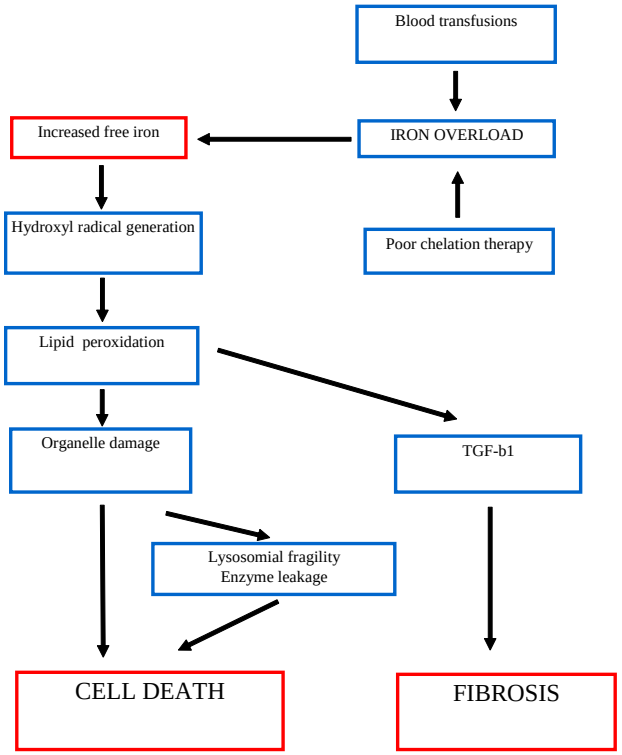

Fig. Consequences of iron-mediated toxicity in thalassaemia

Iron is normally stored intracellularly in the form of ferritin, a protein whose synthesis is induced upon influx of iron, When the storage capacity of ferritin is exceeded, pathological quantities of metabolically active iron are released intracellularly in the form of hemosiderin and free iron within and expanded labile poor. This metabolically active iron catalyzes the formation of free radicals, which damage membrane lipids and other macromolecules, leading to cell death and eventually organ failure (Fig.). The heart and pituitary are very sensitive to the toxicity of free iron [11,13,13,27].

An additional factor is the effect of L-type Ca^{2+} channels (LTCCs). These channels play a role in the excitation-secretion coupling properties of osteoblasts, pancreatic β-cells, thyrotrophs, corticotrophs and parathyroid hormone producing cells [20]. LTCCs cause a membrane depolarization, thereby mediating the opening of LTCCs which allow iron to pass in the cell membrane of endocrine glands [20].

Material and methods. We report a prepubertal thalassaemic girl with multiple endocrine complications secondary to iron overload.The endocrine gland histology is reported because the patient died at the age of 13 years from cardiac failure.

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Case report. A poorly iron chelated prepubertal girl with short stature (cm.143,4; <3° centile) due to growth hormone deficiency, delayed puberty (Tanner's stage B 1, PH 1), normal tyroid function, normal calcium metabolism and impaired glucose tolerance, died at the age of 13 years because of acute cardiac failure.

Her compliance to chelation therapy was poor and serum ferritin level was high (3580 ng/ml; normal values <150 ng/ml).

The histology post-mortem report included the following organs:
Heart: myocardial hypertrophy with mild haemosiderin deposition in the myocardial cells.
Liver: haemosiderin deposition (grade 3). Increased fibrosis. No evidence of cirrhosis or chronic viral hepatitis.
Pancreas: extensive atrophy of exocrine elements with fatty replacements and fibrosis. Normal number of islets. Haemosiderosis in the islets and surviving exocrine acini.
Pituitary: diffuse hemosiderin deposition in both pars anterior and intermedia .
Ovary: marked reduction in both primary and primordial follicles.

Results and their discussion. Our patient was followed from the age of 9 to 13 years in our pediatric endocrinology outpatient clinic for short stature,impaired glucose tolerance and delayed puberty .At the age of 13 years she died in the Cardiology Unit for heart failure. Mortality from cardiac disease remains the main cause of death in transfusion-induced iron-overloaded patients during the second decade of life.Miocarditis occurs relatively early in life,often is fatal and appears to be mediated by predominanly immunological mechanisms.

Iron-overloaded TM children, of both sexes, show reduction in growth velocity around the age of 10 to 11 years and by the time of adulthood

In developing countries short stature is mainly attributable to nutritional factors, chronic anaemia and iron overload which are the results of economic circumstances and of the late onset of chelation therapy. In Europe and North America poor compliance to the chelation therapy is the major problem causing endocrine complications[11].Our patient was treated with rechGH for growth hormone deficiency since the age of 12 years. The growth velocity/ year in our patient before treatment with rechGH was 2.7 cm and after one year of treatment was 5.8 cm.

Several mechanisms have been suggested as causing disorders of GH secretion:
Neurosecretory dysfunction [26]
Hypothalamic GH-releasing hormone deficiency [12]
Pituitary GH deficiency [12]
Increased somatostatin activity [5]
Partial GH resistance [28].

Delayed puberty and hypogonadism are the major and most obvious clinical consequences of the endocrine abnormalities (Table) [1].

Failure of pubertal development has been observed in 53 % of females and 57% of males iron overloaded patients [8]. In some patients, this was thought to be primary-gonadal in origin, whereas in other it was postulated to be secondary to pituitary insufficiency or to a combination of both primary and secondary hypogonadism [12,19,22]. Other possible causes of hypogonadism in TM patients include liver disorders, chronic hypoxia and associated endocrine complications [12].

The anterior pituitary gland is particularly sensitive to free radical oxidative stresses. Magnetic resonance imaging (MRI) shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function [2,21].

Using R2 relaxivity, Argyropoulou et al [2] studied 37 patients with β thalassemia major. Pituitary T2 showed a significant correlation between pituitary gland height and serum ferritin. The relationship between gland siderosis and function was investigated by Lam et al [21] in 50 thalassemia major patients using a T2-weighted signal intensity sequence. There was significant correlation of the pituitary signal with IGF-1 and IGFBP-3 and the history of hypogonadism (P: 0.001).

Histologically a reduced number of cells and moderate siderosis of the parenchymal cells of the anterior pituitary have been found in these patients.

The ovaries show tickened stroma with occasional iron-containing macrophages and a reduced number of primordial follicles [19,22].

The pituitary damage is rarely reversible and the treatment of pubertal disorders consists of hormone replacement therapy with sex steroids. Successful induction of ovulation has been reported after hormonal stimulation with gonadotrophins [7].

Impaired glucose tolerance and progression into diabetes mellitus is another serious complication that usually emerges during adolescence [4,8,12,23]. The incidence of impaired glucose tolerance (IGT) and diabetes mellitus is 2-30% (Table) increasing with age, and both sexes are equally affected. The pathophysiology and clinical behavior of diabetes mellitus in iron overload differ from those of type I diabetes.

The initial pathogenic mechanism of glucose intolerance seems to be insulin resistance due to liver damage subsequent to iron deposition and infectious hepatitis. Overt diabetes is probably a later event, occurring when sufficient damage to pancreatic cells has occurred and hyperinsulinemia cannot be sustained [8,12,23]. Increased glucagon

secretion in patients with impaired glucose tolerance and overt diabetes has also been found in one laboratory [6].

Au et al provided fundamental information on iron measurement in the pancreas and relationship to diabetes in thalassaemia. [3] The investigators completed pancreatic MRI-R2* in 72 patients with TM (21 diabetic, 51 normoglycemic). The two groups were comparable for ferritin and MRI-T2* heart, liver and pancreas althought diabetic patients were significantly older (P<0,0001) and had smaller pancreas volume (P<0,0001). In normoglycemic patients, log-pancreatic T2* values correlated with homeostatic model assessments HOMA-B (beta cell reserve), HOMA-IR (insulin resistance) and fastin insulin/C-peptide levels. The length of exposure to an elevated iron level had an important influence on the clinical status, not the pancreatic iron alone.

Ketoacidosis, retinopathy, peripheral neuropathy and renal impairment are rare in TM patients. The renal glucose threshold is high and there is no human leukocyte antigen (HLA) association. Furthermore, there is evidence that, if IGT is diagnosed early and treated, the development of insulin-dependent diabetes may be prevented [8,17-20,24].

In TM, metabolic control can be difficult to achieve; patients require very high doses of insulin, in particular those who are grossly iron overloaded or suffer from liver cirrhosis. Glucose metabolic control is by serum fructosamine levels [11].

In the pancreas, iron deposition in the interstitial cells results in excess collagen deposition and defective microcirculation [15,16]. Impaired oxygen supply eventually leads to insulin deficiency.

Insulin, glucagon, somatostatin and pancreatic polypeptide cells were quantified after immunoperoxidase staining in sections of pancreases abtained from nine control subjects and seven diabetic patients with primary or secondary iron overload [25].

The whole pancreas was studied, taking into account the heterogeneous distribution of the endocrine cells. In the diabetic patients, the weight of the pancreas tended to be lower. Iron overload predominated in the exocrine tissue, whereas in islets iron concentration was quite variable from case to case. The histological appearance of the islets was normal, their shape and size being unchanged; amyloid deposits were absent, as were atrophic islets. Immunoperoxidase staining revealed a secere reduction in the number of immunoreactive B cells in the four diabetic patients [25].

The electron microscopic examination, performed in four cases, reveales that the iron deposits were restricted to B cells and associated with progressive loss of their endocrine granules. This study constitutes a further argument for a specific role of iron in the pathogeny of diabetes in haemochromatotic patients [25].

In conclusion, a excess iron accumulation from transfusions leads to endocrine disturbance, heart failure and growth retardation. Variations in severity of the disease and therapeutic regimens may result in different incidence and types of complications .Currently, patients who started chelation therapy early in childhood live long enough to show that early and effective chelation can prevent death from cardiac disease. Therefore it is imperative an adequate compliance to iron chelation therapy to protect endocrine glands from haemosiderosis.

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SUMMARY

ENDOCRINE HISTOLOGY FINDINGS IN A PREPUBERTAL THALASSEMIC GIRL WITH MULTIPLE ENDOCRINE COMPLICATIONS SECONDARY TO IRON OVERLOAD

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β-thalassaemia major (TM) is an inherited disorder of erythropoiesis requiring regular blood transfusions and chelation therapy for the iron overload resulting from transfusions and increased gastrointestinal absorption. Endocrine dysfunctions are common in older children with TM and has been attributed to iron deposition in endocrine glands. The Authors report the clinical and histological findings of endocrine glands in a prepubertal girl with multiple endocrine complications secondary to iron overloadn died from cardiac failure. Variations in severity of the disease and therapeutic regimens may result in different incidence and types of complications It is emphasized the importance of chelating therapy to protect endocrine glands from haemosiderosis.

Key words: thalassaemia, iron overload, histology, endocrine complications.

РЕЗЮМЕ

ГИСТОЛОГИЧЕСКИЕ ПОКАЗАТЕЛИ ЭНДОКРИННОЙ СИСТЕМЫ У ДЕВУШКИ ПРЕПУБЕРТАТНОГО ВОЗРАСТА С ТАЛАССЕМИЕЙ И МНОЖЕСТВЕННЫМИ ЭНДОКРИННЫМИ ОСЛОЖНЕНИЯМИ ВТОРИЧНОЙ ПЕРЕГРУЗКИ ЖЕЛЕЗОМ

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Большая β-талассемия - наследственное расстройство эритропоеза, требующее регулярных переливаний крови и хелатной терапии перегрузки железом, развивающееся в результате переливаний и повышенной абсорбции железа в желудочно-кишечном тракте. Эндокринные нарушения обычны у старших детей, с талассемией, что объясняется накапливанием железа в эндокринных железах. Авторы сообщают о клинических и патогистологических изменениях эндокринных желез у девочки препубертатного воз-

раста с множественными эндокринными осложнениями, вторичными к отягощению железом, умершей от сердечной недостаточности. Различия тяжести болезни и терапевтических режимов обуславливают неодинаковую частоту и характер осложнений. Подчеркивается значимость хелатной терапии для предотвращения гемосидероза эндокринных желез.

რეზიუმე

რკინის სიჭარბით განპირობებული მრავლობითი ენდოკრინული გართულებებით მიმდინარე თალასემიის მქონე პრეპუბერტატული ასაკის გოგონას ენდოკრინული ორგანოების ჰისტოლოგიური მონაცემები

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დიდი ბეტა-თალასემია არის ერითროპოეზის მემკვიდრული დარღვევა, რომელიც მოითხოვს სისხლის რეგულარულ გადასხმებს და ხელატურ თერაპიას რკინის ზედმეტად დაგროვების თავიდან ასაცილებლად,რაც,თავის მხრივ,სისხლის გადასხმისა და გასტროინტესტინალურ სისტემაში რკინის მომატებული აბსორბციით არის განპირობებული. დიდი თალასემიის მქონე უფროსი ასაკის ბავშვებში ხშირია დარღვევები ენდოკრინულ ორგანოებში, რაც ამ ორგანოებში რკინის ჩალაგებითაა გამოწვეული. ავტორები წარმოადგენენ ენდოკრინული სისტემის კლინიკურ პათოჰისტოლოგიურ ცვლილებებს პრეპუბერტატული ასაკის გოგონაში დიდი თალასემიით, რომელსაც ჰქონდა მრავლობითი ენდოკრინული გართულებები რკინის დაგროვების გამო. გოგონა გარდაიცვალა გულის უკმარისობით. დაავადების სიმძიმე და სამკურნალო რეჟიმის თავისებურებები განპირობებულია გართულებების სხვადასხვა სიხშირითა და ტიპით. ხაზგასმულია ხელატური თერაპიის მნიშვნელობა ენდოკრინული ჯირკვლების ჰემოსიდეროზისაგან დასაცავად.

A NOVEL HEPATOCYTE NUCLEAR FACTOR-1B (MODY 5) GENE MUTATION IN A ROMANIAN BOY WITH PANCREATIC CALCIFICATIONS, RENAL AND HEPATIC DYSFUNCTION

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Maturity-onset diabetes of the young (MODY) is caused by a genetic mutation that reduces insulin production and raises the blood sugar level. Most subjects with MODY become diabetic before the age of 25 years [8].

Several types of MODY are caused by different gene mutations. The severity of the diabetes and the associated complications depend on the type of MODY [5].

In this report we describe a prepubertal boy with a novel hepatocyte nuclear factor-1 (HNF-1) gene mutation [7].

Material and methods. Case report. The patient, a 12 years old Romanian boy who had one year history of insulin-dependent diabetes (DM) and renal disease, came to our observation for a glucose decompensation.

Familial history was negative for DM and renal diseases. His clinical and laboratory data at our presentation are shown in table 1.

Table 1. Clinical and laboratory data in our patient

-Chronological age at presentation: 12 years
-Height: 150 cm (50°-75° percentile), weight 50.5 Kg (90°-97° percentile)
-Tanner's stage: 2-3
-Testicular volume: 3-4 ml bilaterally
-Blood pressure 125/80 mmHg
-HbA1c: 12.1% (nv <5.5%)
-C-peptide: 0.93 ng /ml (nv 0.4-2.2 ng/ml)
-Fructosamine: 4 mg / dl (nv < 2.8 mg/dl)
-BUN:83 mg /dl (nv :17-43 mg / dl)
-Creatinine:1.6 mg/dl (nv :0,5-1 mg / dl)
-Clearance of creatinine: 55 ml/min (nv 100-150 ml/min)
-Urine analysis: pH 5, urine concentration capacity 1023, glucose concentration 1000 mg/dl, absence of proteinuria
-ALT: 168 U/l (nv:8-35 U/l), AST: 65 U/l (nv:21-45 U/l), γGT: 351 U/l (nv:4-17 U/l)
-Immunologic islet cell autoantibodies (IAA, GADA, IA2-A): negative
-HLA typing:DQB1 * 0202 * 0604
- Serum calcium, serum phosphate and PTH: in the normal range.

Renal ultrasonography (US) revealed a kidney size smaller than normal (length 8 cm, normal values 9-10 cm), loss of cortico-medullary differentiation of the right kidney, increased echo density and presence of bilateral cortical cysts (up to 1 cm in diameter).

A 0.5 cm gallstone formation in the right kidney and an intraparenchymal arterial resistance, probably due to renal malformation, were also observed.
Liver US abnormalities were not found and an absent visualization of the pancreas was reported in the medical report.

Renal scintigraphy showed an uniformly distributed absorption of the radioisotope without well recognized cortical scars.

The early appearance of diabetes, liver dysfunction, renal cysts and renal insufficiency were compatible with the clinical suspect of MODY 5 [3-5].

A molecular genetic analysis from the peripheral white blood cells was requested. DNA amplification and sequence analysis of the HNF-1β gene, using sequence-specific primers, revealed the presence of a de novo heterozygous mutation in the coding regions of exon 3 of the HFN-1β gene (c.715 G>C; p.G239R). (Fig. 1).

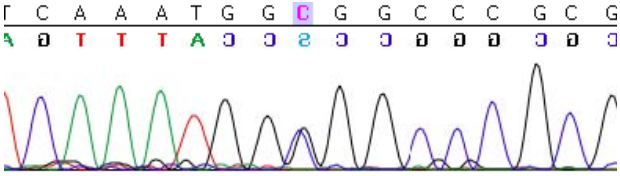

Fig. 1. Electropherogram of HNF-1β gene mutation c.715 G>C;p.G239R in exon 3 in our patient with MODY 5

During the follow-up, an abdominal MRI was performed and a hypoplasia of pancreas associated to absence of body and tail were observed.

The MRI of kidneys showed numerous small cortical and subcapsular cysts (Fig. 2).

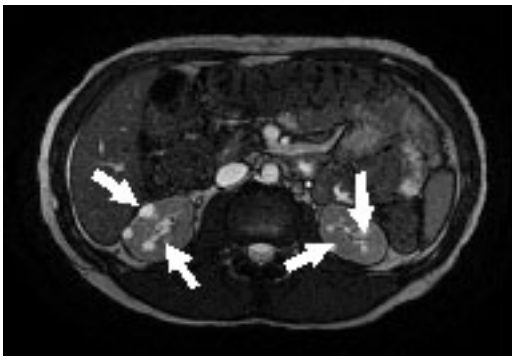

Fig. 2. MRI of abdomen in our patient showing multiple bilateral kidney cysts

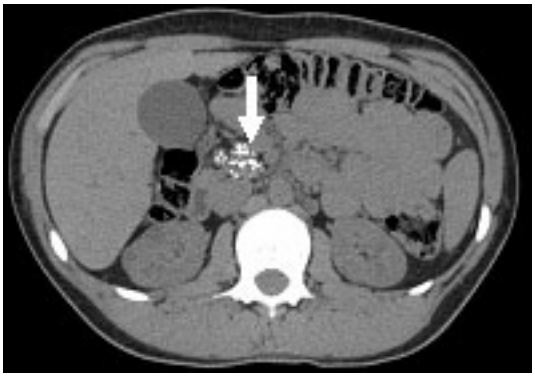

Fig. 3. Contrast-enhanced CT-scan of abdomen in our patient showing hypoplasia and calcifications of pancreas

The descriptions of liver and bile ducts, after cholangiography were reported as normal.

The abdominal CT scan confirmed the reduction of pancreas size, the absence of body and tail segments with a regular representation of the pancreas cephalic region and the presence of bilateral calcifications. A bigger than normal development of the uncinate structure and the presence of numerous micronodular calcifications in the pancreas structure were also reported. These findings have not been reported before in literature in subjects with MODY 5.

Three years after the onset of disease, the patient continues to present a poor metabolic control (glycated haemoglobin 11.5 mg/dl), a persistent increase of liver enzymes (ALT:225 U/l; AST:171 U/l;γGT:482 U/l) and a progression of renal insufficiency (serum creatinine:1.81 mg/dl, clearance of creatinine 15 ml/min, proteinuria 227,0 mg/dl/24 hours).

At present he is receiving 4 insulin injections per day. The compliance to treatment is poor.

Results and their discussion. MODY syndrome is characterized by a non-ketotic type II diabetes mellitus. Its results from a primary defect of insulin secretion. Usually MODY develops at childhood, adolescence or young adulthood [5,7,8].

It is estimated that MODY could account for 1-2% of cases in the US and can result from mutations of any of six different genes that are expressed in the β cells of pancreas [8].

Among 748 Italian subjects aged 1-18 years with incidental hyperglycemia, minimal diagnostic criteria for MODY were met by 172 families. Mutational analyses of the glucokinase (85GCK) were identified in 109 probands and hepatocyte nuclear factor 1alpha (HNF1A) genes were found in 12 probands [9].

One of these genes encode the glycolytic enzyme glucokinase (MODY 2) and the other five ones encode the transcription factors hepatocyte nuclear factor (HNF) 4α (MODY 1), HNF-1α (MODY 3), HNF-1β (MODY 5), insulin promoter factor 1 (IPF-1) (MODY 4) and neurogenic differentiation factor-1 (Neuro D1) (MODY 6) (Table 1).

The clinical presentation of the different MODY subtypes differ particularly in the severity, the course of the insulin secretion defect and the risk of microvascular complications of diabetes [8,5,9].

In patients with MODY 5, due to mutations in HNF-1β, diabetes is associated with pancreatic atrophy, abnormalities of renal morphology and function, liver tests and genital tracts abnormalities [4-10].

The HNF-1β gene is essential for kidney development and function, and it plays a partial role in epithelial differentiation [2]; it is also expressed in embryonic gall bladder, intrahepatic bile ducts and adult liver [6]. Therefore, the product induced by this gene has important physiological roles in organs such as the pancreas, liver and kidneys.

More than 6 different mutations have been identified as far [1,5].

Bellannè-Chantelot et al [1] recruited 13 patients from 8 unrelated families who had HNF-1 mutations, from 4 medical departments, with several different types of mutations of the HNF-1 gene.

Ten of the 13 patients (76%) were diabetic, but half of them had no diabetic symptoms at diagnosis. Six patients (46%) required insulin treatment. Most had kidney that were small or contained cysts, and most had kidney failure. About half had small withered pancreases. Five patients had abnormal genital organs, and 5 patients had abnormal liver function tests (38%).

The clinical spectrum of MODY is wider than initially described, and might include multi-organ involvement in addition to diabetes (Table 2).

Table 2. Characteristics of MODY subtypes (Ref.10, mod.)

	MODY 1	**MODY 2**	**MODY 3**	**MODY 4**	**MODY 5**	**MODY 6**
Mutated gene	**HNF-4α**	**GCK**	**HNF-1α**	**IPF-1**	**HNF-1β**	**Neuro D1**
Frequency (% family with MODY)	Rare	10-65%	20-75%	Rare	Rare	10-20%
Hyperglycemia	Progressive	Mild	Progressive	Progressive	Mild/ Progressive	Progressive
Affected organs	Pancreas/liver	Pancreas/liver	Pancreas/ kidney/ other?	Pancreas/ other?	Pancreas/ kidney/ other?	Pancreas/ heterogeneous?
Age at diagnosis	Prepubertal	Childhood	Prepubertal	Neonatal (homozygous) Young adult (heterozygous)	2nd decade	Not defined
Treatment	Diet/oral hypogl./insulin	Diet	Oral hypogl./ insulin	Insulin(homoz.) Diet (heteroz.)	Insulin	Insulin
Vascular complications	Frequent	Rare	Frequent	Rare	Rare	Not defined

Table 3 and 4 report the renal and non-renal phenotype of subjects with HNF-1β mutations reported in literature [3].

Table 3. Renal features reported in subjects with HNF-1β mutations (from Bingham et al, Ref 3-mod.)

Clinical features	% of affected subjects (number)
Renal cysts	66% (36/55)
Renal histology	2% Oligomeganephronia (1) 4% Cystic renal dysplasia (2) 7% Glomerulocystic kidney disease (4) 4% Non-specific (2)
Morphological renal abnormalities	2% Horseshoe kidney (1) 2% Single kidney (1)
Renal function	86% Renal impairment (47) 15% Dialysis/transplanted (8) 6% Normal renal function (3) 9% Non reported (5)

Table 4. Non-renal features reported in subjects with HNF-1β mutations (from Bingham et al, Ref 3-mod.)

Clinical features	% of affected subjects (number)
Diabetes	58% (32/55) Mean age of diagnosis: 25.8 years
Uterine malformations	14% (5)
Male genital tract malformations	5% (1)
Hyperuricaemia	20% (11)
Abnormal liver function tests	13% (7)
Other features	2% Pyloric stenosis (1) 4% Prognathism (2) 2% Learning difficulties (1) 2% Ligament laxity (1) 2% Hearing loss (1)

MODY 5 often needs a variety of treatments because it may cause other medical problems unrelated to the blood glucose levels.

In this paper we report a novel mutation of the HNF-1β gene in a Romanian boy with diabetes mellitus, renal insufficiency, hepatic dysfunction and renal cysts. In addition, this is the first report of a HFN-1β gene mutation who presented pancreatic calcifications.

Due to rarity of patients with HNF-1β mutation, the clinical manifestations and its correlation with gene mutations are not well understood.

However, we believe that the early onset of disease, the severity of symptoms and organ injuries may be the consequence of an early and widespread expression of the mutation which may led to an adverse prognosis.

In conclusion, MODY 5 is an uncommon disease that has diverse clinical and genetic findings.

The importance of molecular diagnosis of MODY patients is reinforced and the need for a careful follow-up is stressed in order to monitor the progression of clinical manifestations and its correlation with the gene mutation.

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SUMMARY

A NOVEL HEPATOCYTE NUCLEAR FACTOR-1B (MODY 5) GENE MUTATION IN A ROMANIAN BOY WITH PANCREATIC CALCIFICATIONS, RENAL AND HEPATIC DYSFUNCTION

[1]Banin P., [2]Giovannini M., [3]Raimondi F., [4]D'Annunzio G., [5]Sala S., [6]Salina A., [6]Aloi C., [7]De Sanctis V.

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We report a 12-years-old Romanian boy with a diagnosis of diabetes and renal insufficiency.

Mutations in homeodomain-containing transcription factor hepatocyte nuclear factor (HNF-1β) have been reported in association with maturity-onset diabetes of the young (MODY 5) and early maturity-onset diabetes, progressive non-diabetic renal dysfunction and bilateral renal cysts.

We found a new heterozygous mutation in HFN-1β located in the exon 3 (c.715 G>C; p.239R) associated to pancreatic calcifications.

The importance of molecular diagnosis of MODY patients is reinforced and the need for a careful follow-up is stressed in order to monitor the progression of clinical manifestations and its correlation with the gene mutation.

Key words: MODY 5, HNF-1β gene mutation, pancreatic calcifications, adolescent.

РЕЗЮМЕ

НОВАЯ МУТАЦИЯ В ГЕНЕ HNF-1b, КОДИРУЮЩЕМ ГЕПАТОЦИТАРНЫЙ ЯДЕРНЫЙ ФАКТОР-1β (MODY 5) У РУМЫНСКОГО МАЛЬЧИКА С ПАНКРЕАТИЧЕСКИМИ КАЛЬЦИФИКАТАМИ, ПОЧЕЧНОЙ И ПЕЧЕНОЧНОЙ ДИСФУНКЦИЕЙ

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Описан редкий случай диабета юношеского инсулинонезависимого сахарного диабета - MODY 5 у 12-летнего румынского мальчика с панкреатическими кальцификатами, почечной и печёночной дисфункцией. В литературе сообщалось о мутациях в гомеодомен-содержащей транскрипционной регуляции гепатоцитарного ядерного фактора (HNF-1 β) при MODY 5, раннем юношеском инсулинонезависимом сахарном диабете, прогрессирующей недиабетической почечной дисфункции и двусторонними почечными кистами. Выявлена, связанная с наличием панкреатических кальцификатов, новая гетерозиготная мутация в гене HFN-1β, расположенном в экзоне 3 (c.715 G> C; p.239R). Делается заключение о необходимости молекулярной диагностики при MODY; под-

черкивается необходимость последующего наблюдения больного с целью мониторинга прогрессирования клинических проявлений болезни и выявления носительства мутации гена.

რეზიუმე

ჰეპატოციტური ნუკლეარული ფაქტორის-1β (MODY 5) ახალი გენური მუტაცია რუმინელ ვაჟში კალციფიკატებით პანკრეასში, თირკმლისა და ღვიძლის დისფუნქციით

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ჩვენ წარმოვადგენთ 12 წლის რუმინელ ვაჟის ავადმყოფობის ისტორიას დიაგნოზით დიაბეტი და თირკმლის უკმარისობა. არსებობს ცნობები ჰომეოდომეინში არსებული ჰეპატოციტური ბირთვის ტრანსკრიპციის ფაქტორის (HNF-1b) მუტაციების შესახებ MODY 5 და ადრეულ MOD-თან, თირკმლის პროგრესირებად არადიაბეტურ დისფუნქციასა და თირკმლის ორმხრივ კისტებთან ასოციაციაში. ჩვენ გამოვავლინეთ ახალი ჰეტეროზიგოტური მუტაცია HNF-1b-ში (ექსონი 3, c.715 G> C; p.239R), ასოცირებული პანკრეასში კალციფიკატების განვითარებასთან.

დადასტურდა მოლეკულური დიაგნოსტიკის მნიშვნელობა MODY-ის მქონე პაციენტებში. ხაზგასმულია გულდასმითი დაკვირვების მნიშვნელობა დაავადების კლინიკური გამოვლინებების პროგრესირებისა და მათი გენურ მუტაციასთან კორელაციის მონიტორინგის მიზნით.

THE COURSE OF THE DILATED CARDIOMYOPATHY IN THREE SIBLINGS - A RARE CASE OF FAMILIAL NON-COMPACT LEFT VENTRICLE

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For the last thirty years we have noticed a great progress in diagnostics, interventional and cardio-surgical treatment resulting in decrease in the number of deaths caused by the congenital heart diseases. However, the dilated cardiomyopathy still remains a big problem in infant's cardiology [3,10]. Although the knowledge regarding both the etiology and the treatment is getting deeper and deeper the cardiomyopathy prognosis is still uncertain. Almost a third of patients with this diagnosis die in infancy, 30% will suffer from the chronic heart failure that forces constant treatment or/and heart transplantations, and in remaining 30% we notice improvement during infancy [10].

The goal of this work is to show the clinical view and progress of dilated cardiomyopathy based on the case of three siblings.

Material and methds. Case report. A six-month-old boy was admitted to hospital because of the loss of appetite, slow body weight increase, cough and failure to thrive.

It was the first child of healthy non-consanguineous parents (mother 25 years old and father 29 years old at the time of conception). The family history is non-contributory. The pregnancy course was normal. The condition of the newborn was estimated to be 8 points in Apgar scale, birth weight was 3,5 kg.

On the physical examination at the age of 6th months tachycardia, the gallop rhythm, systolic murmur above the heart apex, dyspnoea, wheezing and hepatomegaly were noted. The thorax x-ray disclosed great cardiomegaly. The electrocardiography examination indicated a sinus rhythm that accelerated to 160/minute, a normal heart axis deviation, deep Q wave in III femoral lead, high QRS voltage in the left pre-cordial leads and diffuse re-polarization abnormalities. The echocardiographical examination revealed a heart shilouette with a significant dilatation of the left ventricle and left atrium, a spherical left ventricle with global wall hypokinesis. The ejection fraction of left ventricle (LV) was 12%. The pronounced trabeculation of LV endocardium, mainly of the free wall and apex with the lack of increase of the ventricular thickness during contraction were also discovered. There were no pathological masses in cardiac cavities. Coronary arteries were arising properly from Valsalva sinuses. A Doppler examination showed a massive mitral insufficiency, up to the apex of the left atrium with a retrograde flow in pulmonary arteries. Mild tricuspid incompetence was also observed; the pressure in the right heart ventricle was elevated. The diagnosis of non compacted left ventricle was established.

The viral serology data which we obtained such as Epstein-Barr and coxsackie B viral antibodies were negative. The mass tandem spectrometry examination orientated towards metabolic diseases did not reveal any specific metabolic disorders. Then the coronarography was executed and it excluded coronary vessel pathology. After 30 days of the heart failure treatment, the child was discharged home, with recommendation to visit the Paediatric Cardiac Outpatient Clinic every 7-14 days. During nine months of follow-up the child's condition remained quite stable.

At the age of 16th months, a viral infection with an intensified heart failure occurred. Parents arrived at the hospital with the child in terminal condition. Despite of the treatment in the intensive care unit, the child died due to the cardiac standstill. Parents did not agree to perform autopsy.

One year later, the mother, being in the 30th week of gestation age, visited our department to perform a fetus echocardiography. The echo examination excluded any congenital heart diseases. The repeated echo examinations after the birth did not reveal any heart pathologies. In the third month of life, the girl was hospitalized in our department because of the insignificant rise of transminases level. The general child's condition was estimated to be good; apart from a slight hepatomegaly, no other abnormalities were found. Performed laboratory examinations ruled out cytomegaly, toxoplasmosis and urinary system infections. The echocardiography (ECHO) examination showed no abnormalities in the circulatory system.

Two months later mother noticed that the child's weight gain was slow. The echo examination revealed a typical picture for non-compact left ventricle, with decreased ejection fraction to 27%, with slight mitral and tricuspid valve incompetence and pressure in right ventricle about 43 mmHg. The child was admitted urgently to our department. The child's condition was estimated to be mediocre; during a physical examination the shortness of breath, tachycardia, systolic murmur above apex and hepatomegaly were observed. The thorax x-ray showed a significantly large heart silhouette, electrocardiography record was identical to the record of the dead brother. After eight days of hospitalisation the child was discharged home. Digoxin, captopril, carvedilol, diuretics, acetylsalicylic acid were prescribed. Since then the child has been systematically controlled in the outpatient clinic. After four months of follow-up the child's state stabilised; electrocardiography records showed positive T waves in left ventricular precordial leads and ECHO examination revealed ejection fraction about 40%. Currently, the girl is 7 years old and does not show any signs of heart failure, she is physically active. The ECHO examination revealed slight widening of left ventricle, ejection fraction raised to 47%; there are no signs of pulmonary hypertension or dysfunction of mitral valve.

Then the mother was pregnant for the third time. The pregnancy was unremarkable. The girl was born in 40th week of gestation, birth weight 3200 g and the condition of the newborn was estimated to be 10 points in Apgar scale. At the age of 4th months the echo examination revealed presence of a typical picture for non-compact left ventricle with decrease ejection fraction of the left ventricle (EF 30%) but with no signs of the heart failure.

Results and their discussion. The frequency of dilated cardiomyopathy (DCM) is hard to ascertain due to the lack of screening examinations and a diverse course of disease. Strauss et al. [10] estimate the frequency of DCM to be between 1,13 and 1,24 for 100 000 children in the USA, where more than 50% of diagnosis are set in the first year of life. In our case the clinical symptoms of DCM were first noticed also in the first year of life.

Thanks to the popularisation of fetus echocardiography [9] DCM is diagnosed in intrauterine life. Analyzing a fetus echo Sivarsankaran [9] asserted the high probability of a fetus intrauterine necrobiosis and high probability of death during the newborn period because of DCM. In presented cases the fetus echocardiography and a few echo examinations after the girl's birth did not reveal any cardiac pathology.

The DCM etiology is still not thoroughly explained [3,10]. There are experimental and clinical data on animals and humans suggesting that genetic, viral, and immune factors contribute to the pathophysiology of DCM. A familial DCM occurrence is estimated for between 8 and 30% of all cases. In the last twenty years there have been found more than 30 different genes, which can be responsible for DCM. Dilated cardiomyopathy can also develop as a consequence of metabolic disorders such as fatty acid beta-oxidation disorders,

amino acids metabolism disorders and others. In the described siblings the tandem spectrometry examinations for metabolic diseases excluded the metabolic background of DCM and a normal view of the coronary arteries ruled out the secondary DCM to abnormality in the coronary circulation.

Based on the echo examination in the siblings noncompacted left ventricle (NCLV) was diagnosed [2,5]. Its clinical course does not differ from others and this type of cardiomyopathy may occur in the same family.

Dilated cardiomyopathy is one of the most common causes of heart failure in childhood; in most cases it has a progressive course, despite the treatment. Specific treatments are not available for most patients with DCM. Therefore, the primary aims of treatment are to control symptoms of heart failure, to prevent disease progression and complications such as thrombosis and embolism and to treat arrhythmia.

In order to lower afterload, vasodilating drug such as angiotensin converting enzyme inhibitors was included in the treatment. Another medicine that was used was carvedilol [1,8] belonging to nonselective beta-andrenolitics, blocking alfa 1 and beta 1 receptors in heart, protecting against reflex tachycardia and beat of rennin system- hypertension. The beneficial effects of the ß-blocker carvedilol on left ventricular function, mass, and neurohormonal dysfunction in an infant with NCLV have been described. Profitable therapeutic action of carvedilol results from lowering the oxygen requirement by heart muscle. Apart from that, it lowers the influence of adrenergic stimulation on cardiac performance, preload and afterload, as well as it lowers concentration of noradrenalin in heart and peripheral vascular resistance. Strong antioxidation and antiprofileriate drug action cannot be forgotten. In presented cases, the treatment was extended by the use of acetylsalicylic acid as a prevention for thrombosis and clots [6].

In case of heart failure we face number of neurohumoral disturbances, including growth hormones [4]. In bibliography, one can find records of including growth hormone, infused subcutaneously, into the conventional treatment. Mc Elheineyb et al [7] proved not only the improvement of left-ventricular contractility but also the improvement of physical development of children with DCM who apart from the conventional treatment were treated with growth hormone.

The heart dysfunction caused by the course of DCM in some cases, despite of the intensive treatment, requires heart transplantation or ends with lethal outcome. Despite of long and intensive treatment the boy died in the course of the heart failure. In our country heart transplantations for patients in this age practically do not exist.

Signs of the heart failure in infants are nonspecific. Especially, diagnostic vigilance must be shown in the cases of positive familial history. Cardiomyopathy can manifest in various age, beginning during intrauretine life and ending at any age.

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SUMMARY

THE COURSE OF THE DILATED CARDIOMYOPATHY IN THREE SIBLINGS - A RARE CASE OF FAMILIAL NON-COMPACT LEFT VENTRICLE

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The dilated cardiomyopathy still remains a big problem in infant's cardiology. Almost a third of patients with this

diagnosis die in infancy, 30% will suffer from the chronic heart failure that forces constant treatment or/and heart transplantations, and in remaining 30% we notice improvement during infancy. We presented the clinical course and progress of dilated cardiomyopathy based on the case of three siblings. Signs of the heart failure were nonspecific. Concluding: diagnostic vigilance must be shown in the cases of positive familial history.

Key words: familiar carsiomyopathy, infant.

РЕЗЮМЕ

ДИЛАТАЦИОННАЯ КАРДИОМИОПАТИЯ У ТРЕХ БРАТЬЕВ - РЕДКИЙ СЛУЧАЙ СЕМЕЙНОЙ АНОМАЛИИ ЛЕВОГО ЖЕЛУДОЧКА

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Дилатационная кардиомиопатия по сей день остается нерешенной проблемой в кардиологии младенцев. Почти треть пациентов с этим диагнозом умирает в младенчестве, 30% страдают хронической сердечной недостаточностью, что требует постоянную терапию или/и трансплантацию сердца. В оставшихся 30% наблюдается улучшение в младенческом возрасте. В работе описывается клиническое течение дилатационной кардиомиопатии у трех родных братьев. Признаки сердечной недостаточности были неспецифическими. Заключение: необходима диагностическая бдительность в случаях положительного семейного анамнеза.

რეზიუმე

დილატაციური კარდიომიოპათიის მიმდინარეობა სამ ძმაში - მარცხენა პარკუჭის იშვიათი ანომალიის ოჯახური შემთხვევა

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დილატაციური კარდიომიოპათია კვლავ რჩება ჩვილ ბავშვთა კარდიოლოგიის მნიშვნელოვან პრობლემად. ამ დიაგნოზის მქონე პაციენტების თითქმის ერთი მესამედი კვდება ჩვილობის პერიოდში, 30%-ს აქვს გულის ქრონიკული უკმარისობა და საჭიროებს მუდმივ მკურნალობას ან/და გულის გადანერგვას, დარჩენილ 30%-ში აღინიშნება გაუმჯობესება ჩვილობის ასაკშივე. ჩვენ წარმოვადგენთ დილატაციური კარდიომიოპათიის მიმდინარეობას სამ ძმაში. გულის უკმარისობის ნიშნები არ იყო სპეციფიური.

დასკვნა: დატვირთული ოჯახური ანამნეზის შემთხვევაში საჭიროა განსაკუთრებული სადიაგნოსტიკო სიფრთხილე.

HYPERPARATHYROIDISM DUE TO AUTOIMMUNOLOGICAL MALABSORPTION IN AN AFRICAN GIRL

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Vitamin D deficiency can be seen in a long lasting celiac disease. Gluten induced subtotal villous atrophy of the small intestine is responsible for malabsorption of calcium ions and vitamin D precursors, which have to be activated in the skin by ultraviolet (UV) rays of the sun light. If one of these steps fails, serum-calcium is in danger to decrease. In order to prevent too low serum-calcium, parathormone increases and is mobilizing calcium out of the bones by activating osteoclasts. By this mechanism a normal serum-calcium is maintained by the costs of decreasing bone mass. In adults such a long lasting process will cause osteoporosis, children will develop small stature and they will suffer from pain in their bones and their joints. Supply of highly dosed vitamin D in combination with calcium is necessary to stop the symptoms.

Material and methods. Case report. A twelve year old African girl (born on Febr. 6th, 1993, fig. 1) was blood sampled because of abdominal pain and joint aches. Low values of serum calcium and of phosphate (fig. 2) as well as elevated alkaline phosphatase was indicating vitamin D-deficiency, which was proven by low vitamin D25 (Colecalciferol) and high parathormone (table 1). Immigrant rickets was the assumed diagnosis because of the dark skin and the Gambian background of the child. Sun light in the north of Europe contains not enough UV-rays to activate sufficient amounts of vitamin D. But this diagnosis could not explain abdominal pain, joint aches and additionally found iron deficiency with hypochrome anaemia and short stature (fig. 3). Immunological tests for celiac disease (gliadin- and endomysium-antibodies type IgA and IgG) were highly positive (fig. 4), and a biopsy of the intestine mucosa demonstrated a subtotal villous atrophy of Mash grade III B (table 2). Lambliasis was ruled out by no finding of flagellates in the bioptic gut material. She was treated by a gluten-free diet, by a depot-vitamin D injection of 15.000 IU (colecalciferol) and by an oral calcium supply of 500 mg twice a day.

Table 1. Disorders in blood values during joint aches: pathological low values (except elevated alkaline phosphatase - AP and parathormone - PTH) in the left, normal findings in the right panel

Pathological and normal values during joint aches	
Pathological	Normal
Hb - 8,1g/dl	CRP
Fe – 17 µg/dl	Rheumafactors
Ferr – 3,4 ng/ml	ASL
AP – 1304 U/l	Total protein
Ca – 2,1 mmol/l	Electrophoresis
PO4 – 0,7 mmol/l	Hb-E'phoresis
Vit. D25 - <17,5 nmol/l	PO4 in urine
PTH – 51,4 pmol/l	Ca in urine

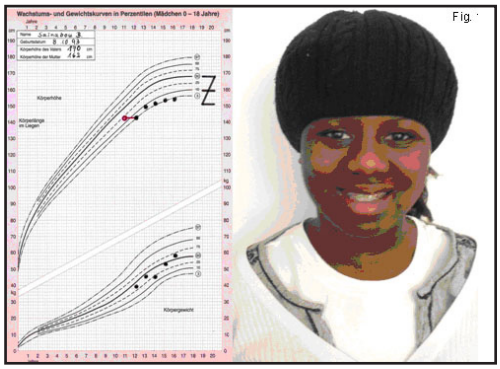

Fig. 1. Growth-chart with the patient at the age of 13 years: stunted growth due to celiac disease, no significant weight loss (no diarrhoea), but joint pain

Table 2. Symptoms of celiac disease leading to the diagnosis, which is proven by histology in mucosal tissue of small intestine

Suspicion of Celiac Disease
• Hypochrome Anaemia (iron deficiency) • Short Stature, Retarded Puberty and BA • (Diarrhoea and Weight Loss) • Vit. D-Deficiency – Elevated Parathormone • Positive IGA- and IGG-Celiac-Antibodies • Mucosa-Biopsie: Subtotal Villous-Atrophy • (Mash Grade III B)

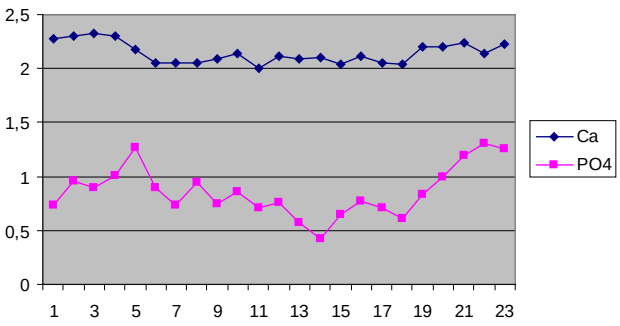

Fig. 2. Calcium and phosphate in serum: follow up over a period of 5 years. During the last months low calcium is slightly and phosphate is significantly increasing by the treatment with depot-vitamin D injections

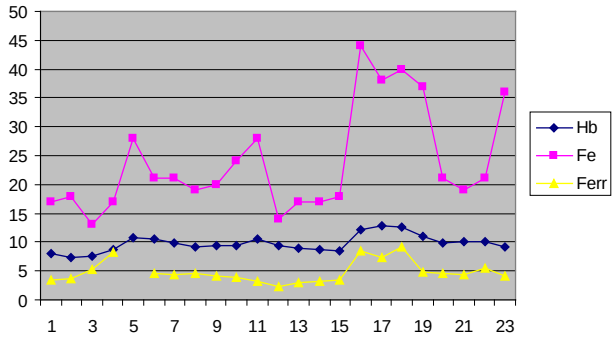

Fig. 3. Hypochrome anaemia with a low Hb (middle line) around 10 g/dl caused by iron-deficiency (upper line) and by decreased ferritin (lower line). There was significant and no long lasting increment of Hb by gluten-free diet or by additional oral iron intake

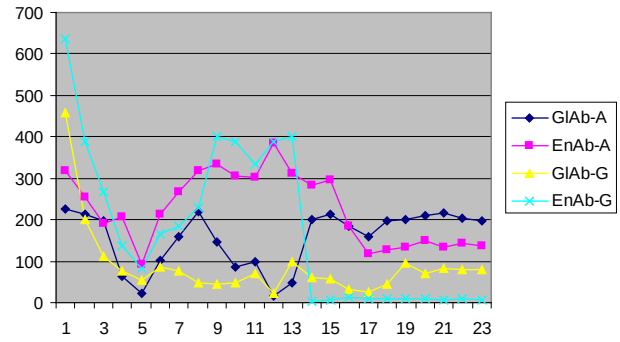

Fig. 4. IGA- and IGG-anti-gliadin Gl) and anti-endomysium (En)-antibodies (anti-tissue-transglutaminase-antibodies) did initially react to gluten-free diet after the 5th period of 3 monts, but returned to elevated levels thereafter

All pathological data tended to turn to normal, but after some months celiac antibodies and parathormone levels continued to increase, the iron deficiency and the hypochrome anaemia remained, and the abdominal pain and joint aches became more severe. Antistreptolysin-titer, rheumatic factores, and phospholipid-antibodies were low and normal, anti-nuclear-antibodies increased up to a titer of 1:160 (but not higher). Pediatric-rheumatologists diagnosed a chronic juvenile arthritis without any positive inflammation reactions like blood sedimentation rate (BSR), C-reactive protein (CRP) or leukocytes. Joint aches were treated with ibuprofen, naproxen or paracetamol, if nessesary.

Abdominal pain was fitting to a poor diet compliance. The family was trained during a six months summer camp for better and more accurate gluten-free diet. However, there was no decrease of celiac antibodies, of parathormone, of pains and aches (fig. 3).

But after parenteral (i.m.) depot-vitamin D (colecalciferol 100.000 IU) was injected every 3 months, parathormone decreased slowly but significantly (fig. 5); vitamin D25 levels increased at the same time.

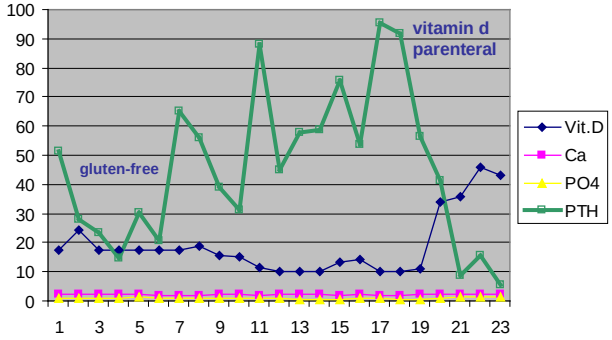

Fig. 5. Parathormone and vitamin D levels after 5 years of a gluten-free diet and after depot-vitamin D injections. Note the increment of vitamin D followed by a decrease of parathormone down to normal accompanied by vanishing joint pain

All joint aches diminished and the patient did not need analgetica anylonger. Celiac antibodies remained high and there are still abdominal pain attacks, but no diarrhoea, no weight loss, but obesity signalling wrong eating habits inducing again and again celiac antibodies and pathological painful bowel movements.

Results and their discussion. The following lab-data are given in detail according to the gluten-free diet and the treatment with 1,25OH-colecalcifirol (Rocaltrol) with calcium and iron for substitution for the observation period of 5 years. The data are also illustrated in the graphs (figs. 2-4).

Parathormone elevation up to 96 pmol/l was the main finding, it decreased down to normal (lower than 7,7 pmol/) after colecalcifirol injections every 3 months (fig. 5).

Vitamin D25 (Vit.D25: colecalciferol = 25-OH-Vitamin D) deficiency was absolutely diagnostic at the repeatingly low levels under 20 nmol/l. It increased following vitamin D injections up to 46 nmol/l (normal).

Calcium levels in the serum were always subnormal but never significantly decreased. They stabilized after vitamin D injections up to 2,2 mmol/l.

Phosphate wasting was inducing low serum levels lower than 0,5 mmol/l. Parenteral vitamin D was giving the impuls for the increment up to 1,3,mmol/l (fig. 2).

Alkaline phosphatase (AP) was elevated up to 1700 U/l as it highest and decreased to normal (lower than 180 U/l) after parenteral vitamin D supply.

Bone specific AP paralleled with AP and was giving no specific information, since there was no liver disease and no disturbing factor of its normal fluctuation.

IgA- and IgG-endomysium- antibody (AB) are specific for celiac disease and were initially very high up to 300 and 640 U/ml, respectively. They decreased by the initiation of gluten-free diet, but increased again despite the same diet, causing abdominal pain (fig. 4).

IgA- and IgG-gliadin-AB are somewhat more unspecific, but they were also elevated during all the 5 years of observation.

Iron, ferritin and haemoglobin were always low by malabsorption of iron despite of treatment with an oral iron supply (fig. 3).

This case description gives the differential diagnosis of hyperparathyroidism and vitamin D deficiency. Dark skin is a natural protection against sun and its UV-rays causing sun burn and D-hypervitaminosis if reacting too long and too intensive [9]. In northern Europe sun light is too weak [4] to stimulate vitamin D sufficiently in people with dark skin. They are at risk to develop vitamin D deficiency, if they do not change their eating habits (vitamin D intake) and their sun light avoiding customs used to practice in their home countries [4]. This kind of vitamin D deficiency is called immigrant's rickets in children and has to be treated with additional oral vitamin and calcium supply [7]. More serious diseases are renal failure with wasting of phosphate or calcium, which is also treated with a combination of calcium and vitamin D. Finally there are well known malabsorptions of calcium and vitamin D leading to so called intestinal rickets [5]. Mainly they are caused by severe celiac disease, an autoimmunological gluten induced condition at the intestine mucosal tissue [3]. All cereals (except corn) contain a special protein, gluten (=gliadin), able to induce in some genetically determed patients a gluten (gliadin) intolerance, a malabsorption due to a subtotal villous atrophy in the small gut. Leading clinical symptoms are diarrhoea, failure to thrive, hypochromic anaemia, short stature and sometimes abdominal pain [6].

Vitamin D deficiency followed by hyperparathyroidism and joint or bone aches are rare symptoms and were misinterpreted initially as rheumatic joint pain in the described case. This is comprehensible, since celiac disease and juvenile rheumatism is sometimes induced in parallel: both diseases are of immunological origin like Hashimoto thyroiditis [8] or type-1-diabetes mellitus [10] induced by autoantibodies against cells of the own body. Especially in Down [2] and Turner's syndrome [1] these overlapping sister diseases are well known.

But in the described case the black skin of the child with Gambian origin was not the inductor of the symptoms and there was no second disease like juvenile rheumatism. All the symptoms can be explained by celiac disease, not well controlled due to diet mistakes (diet compliance), demonstrated by elevated gliadin- and endomysium-antibodies over 5 years. The destroyed intestinal mucosa (villous atrophy) is not able to absorb enough calcium, phosphate and vitamin D. To prevent low serum-calcium levels parathormone increases in order to mobilize calcium out of the bone in favour of normal calcium in the blood. As long as there is a damage to the intestinal mucosa, it is not possible to normalize vitamin D levels despite the oral given activated vitamin D as Rocaltrol (Calcitriol). Because of the persisting severe malabsorption in the small bowel, the vitamin D has to be substituted by a non-oral rout. If given by i.m. injections as a depot preparation the vitamin D25 concentration in blood as a marker of a normal vitamin D content could be increased.

Vitamin D is necessary to enable a normal mucosa absorption in the bowel, serum-calcium tends to increase and can be used by the organism to build up normal bone structures by stimulated osteoblasts. Normal calcium levels are signalling the parathyroid gland to lower its activities in stopping secretion of parathormon, which stepwise decreases down to normal (fig. 4). If this healing process comes early enough and is long lasting, younger children will show a catch-up growth and will normalize their bone defects including the disappearance of bone aches and joint pains.

These effects happened in the Gambian child when treated with depot vitamin D injections. There is only one symptom persisting, which is abdominal pain. It is caused by mucosa irritating immunological actions of gluten or by gluten induced autoantibodies stimulating irregular bowel movements.

Severe and long lasting celiac disease is difficult to treat by a strict gluten-free diet alone. Small mistakes in food intake (containing tiny amounts of gluten) may induce damage to the mucosa of the small gut followed by malabsorption. It is a cause for iron deficiency, for vitamin D depletion (especially in the case of dark skin and weak sun shine), for low serum calcium, and in response for elevated parathormone levels in the serum. Parathormone stimulates osteoclasts to shift calcium from the bone into the serum in order to stabilize calcium levels in the circulation. If this process is not stopped, reduced bone mass becomes responsible for bone and for joint aches mimicking chronic juvenile arthritis. The causal treatment is parenteral vitamin D supply by intramuscular injections of a highly dosed depot preparation (100.000 IU/3 mo.) in combination with oral calcium intake. It normalizes vitamin D content in the serum followed by decreasing parathormone levels and normal calcium and phosphate levels as shown in fig. 5. Early during this healing process the symptoms of "juvenile arthritis" (arthralgia) are vanishing and there is no need for longer application of different analgetica.

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SUMMARY

HYPERPARATHYROIDISM DUE TO AUTO-IMMUNOLOGICAL MALABSORPTION IN AN AFRICAN GIRL

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Hyperparathyroidism is a rare finding in children. It is a typical sign of vitamin D-deficiency caused by different reasons. It may also be due to calcium wasting syndromes, and it can rarely be induced by adenomas of the parathyroid glands and in parathormone receptor mutations (pseudohyperparathyroidism).

A 12-year old Gambian girl living in Hamburg, Germany, was developing abdominal and joint pain. Serum analysis revealed low serum-calcium, significantly elevated parathormone and decreased vitamin D. Immigrant rickets was assumed. Because of abdominal pain and iron deficiency, lambliasis was ruled out. Celiac disease was demonstrated by gliadin and endomysium antibodies as well as by intestinal mucosa biopsy. Despite of a gluten-free diet the joint pains persisted. They were declared by rheumatologists to be caused by a chronic juvenile arthritis (sister disease of celiac disease). However, there were no positive inflammation signals and no clear elevated rheuma-immunology.

Follow up: Gluten-free diet and additional treatment with calcium and active vitamin D did not stop increasing parathormone levels, did not stop abdominal and joint pain, and did not stop increment of positive celiac disease antibodies. Assuming compliance problems the patient was then treated with vitamin D injections, which caused decreasing parathormone levels and vanishing joint pain.

Celiac disease can cause intestinal rickets with elevated parathomone levels mimicking chronic juvenile arthritis, if gluten-free diet is not strictly performed by compliance problems.

Key words: Celiac disease, autoimmunology, parathormone, vitamin D, rheumatology, anaemia, iron deficiency, short stature, gliadin antibodies, endomysium antibodies, tissue-transglutaminase-antibodies, gluten-diet.

РЕЗЮМЕ

ГИПЕРПАРАТИРЕОИДИЗМ У ДЕВОЧКИ АФРИКАНСКОГО ПРОИСХОЖДЕНИЯ, ВЫЗВАННЫЙ АУТОИММУННОЙ МАЛАБСОРБЦИЕЙ

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Гиперпаратиреоидизм, как характерный признак недостатка витамина D, обусловленного различными причинами, среди детей встречается редко. Причиной может быть синдром потери кальция, аденома паращитовидной железы, или мутация рецепторов паратгормона (псевдогиперпаратиреоидизм).

12-летняя девочка из Гамбии, проживающая в Гамбурге (Германия), с жалобами на боли в животе и суставах. Анализ крови показал низкое содержание кальция в сыворотке, заметное увеличение уровня паратгормона и пониженный уровень витамина D. Предполагалось также наличие рахита. По причине болей в животе и дефицита железа лямблиоз был исключен. Заболевание целиакия было выявлено путем детекции специфических антител против глиадина и тканевой трансглютаминазы при биопсии слизи ки-

шечника. Несмотря на глютен-несодержащую диету, боли в суставах продолжались, что ревматологами было расценено, как хронический ювенильный артрит (родственное целиакии заболевание), хотя не отмечалось ни признаков воспаления, ни четко выраженных ревматоидно-иммунологических изменений.

Глютен-несодержащая диета и дополнительное лечение кальцием и витамином D не приостановили повышение уровня паратгормона; не удалось уменьшить боли в животе и в суставах. Не прекращался также и рост титра целиакия-положительных аутоантител.

С целью предотвращения возможных проблем было проведено лечение пациента инъекциями витамина D, в результате чего последовало снижение уровня паратгормона и исчезновение боли в суставах.

Если глютен-несодержащая диета не будет строго соблюдаться, целиакия, по причине сопутствующих проблем, может вызвать кишечный рахит с повышенным уровнем паратгормона, который выражается также в виде скрытого хронического ювенильного артрита.

რეზიუმე

ჰიპერპარათირეოიდიზმი აფრიკელ გოგონაში, გამოწვეული აუტოიმუნური მალაბსორბციით

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ჰიპერპარათირეოიდიზმი იშვიათად გვხვდება ბავშვებში. ეს არის სხვადასხვა მიზეზით გამოწვეული D ვიტამინის დეფიციტის დამახასიათებელი ნიშანი. შესაძლოა მიზეზი იყოს კალციუმის დაკარგვის სინდრომი; ასევე იშვიათად შეიძლება გამოწვეული იყოს პარაფარისებრი ჯირკვლის ადენომით და პარათჰორმონის რეცეპტორთა მუტაციით (ფსევდოჰიპერპარათირეოიდიზმი).

პაციენტი და დაავადების მიდინარეობა: ჰამბურგში (გერმანია) მცხოვრები 12 წლის გამბიელი გოგონა, მუცლის ღრუსა და სახსრების ტკივილით. სისხლის ანალიზმა გამოავლინა შრატში კალციუმის დაბალი შემცველობა, პარათჰორმონის დონის შესამჩნევი მატება და D ვიტამინის დაქვეითებული დონე. საჭარაუდო იყო რაქიტიც. ლამბლიოზი გამოირიცხა მუცლის ტკივილისა და რკინის დეფიციტის გამო. ცელიაკიის დაავადება გამოვლენილი იქნა ნაწლავის ლორწოს ბიოფსიისას გლიადინისა და ქსოვილოვანი ტრანსგლუტამინაზის მიმართ ანტისხეულების დეტექციით. მიუხედავად გლუტენთავისუფალი დიეტისა,სახსრების ტკივილი გრძელდებოდა, რაც რევმატოლოგების მიერ შეფასებულ იქნა როგორც ქრონიკული იუვენილური ართრიტი (ცელიაკიის მონათესავე დაავადება), თუმცა არც ანთების ნიშნები და არც ნათლად გამოხატული რევმატოიდულ-იმუნოლოგიური ძვრები არ აღინიშნებოდა.

მკურნალობის შედეგები: გლუტენ-თავისუფალმა დიეტამ და კალციუმითა და ვიტამინ D-თი დამატებითმა მკურნალობამ ვერ შეაჩერა პარათჰორმონის დონის მატება და ვერ შეამცირა სახსრებისა და მუცლის ტკივილი. ცელიაკია-პოზიტიური აუტოანტისხეულების ტიტრის მატებაც არ შეჩერებულა.

შესაბამისი მოსალოდნელი პრობლემების თავიდან ასაცილებლად, პაციენტს მკურნალობა ჩაუტარდა D ვიტამინის ინექციებით,რამაც გამოიწვია პარათჰორმონის დონის დაწევა და სახსრების ტკივილის გაქრობა.

თუკი გლუტენ-თავისუფალი დიეტა არ იქნება მკაცრად დაცული, ცელიაკიამ, თანმდევი პრობლემების გამო,შესაძლოა გამოიწვიოს ნაწლავური რაქიტი, პარათჰორმონის მაღალი დონით, რაც გამოიხატება ფარული ქრონიკული იუვენილური ართრიტითაც.

SOMATOSTATIN - THERAPEUTIC OPTION FOR CHYLOTHORAX IN PRETERM NEONATES. REPORT ON TWO PATIENTS AND REVIEW OF THE LITERATURE

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Chylothorax is a comparatively rare disease in childhood. It may arise as a serious complication of thoracic surgery with an incidence of around 1-4% in pediatric cardiac surgery [37], but even spontaneous and neonatal occurrence of chylothorax in pre- and full-term newborns is described in literature [38,41]. Through the pleural effusion of chyle-fluid severe symptoms like respiratory insufficiency, loss of protein, clotting factors, and antibodies, as well as immunodeficiency and fluid imbalance may be induced [7,29]. Current treatment strategies vary in different clinical centers and are usually "adapted" to the individual situation of the patient. It is well accepted that conservative methods should be used first line in patients with no mechanical obstacle of chyle flow, e.g. a tumor, as primary cause of the chylothorax. The standard therapeutic approach is aimed at reducing the production of lymphatic fluid. This may be achieved through an oral diet with medium chain triglycerides, free of long chain triglycerides, or through total parenteral nutrition [3,4]. Both regimes are reported to be equally effective [4], but may fail to succeed in particular cases.

Alternative approaches, such as nitric oxide, high PEEP- (positive-end expiratory pressure) ventilation and Etilefrine have been described. There are only few reports about these therapeutic options which are so far experimental. All are rather invasive treatments and are associated with a reported high incidence of side-effects.

In contrast to these alternative treatment regimens several reports identify somatostatin, and its long-acting synthetic analogue octreotide, as a new therapeutic option in older pediatric patients and adults, with comparatively small risk for severe adverse effects [5].

Preterm infants might have a special benefit from somatostatin treatment because they are particularly vulnerable to invasive surgical procedures and to the impact of prolonged withdrawal of oral food intake, which interferes with appropriate nurturing of the gut mucosal cell and the integrity of the immature gastrointestinal tract, and might predispose the infant to develop necrotising enterocolitis.

It seems therefore advisable to find alternative strategies to delimit the time span when total parenteral nutrition is needed for reduction of the triglyceride content of the chyle and of the lymphatic flow through the thoracic duct.

In this paper we report the use of somatostatin in the treatment of persistent chylothorax in two preterm neonates. One was the first preterm infant reported in literature that has been treated with somatostatin with intent to cure post-surgical chylothorax [6]. Aim of this article is to discuss those cases on base of the current literature on treatment of chylothorax with somatostatin in infants born preterm.

Table 1. Course of treated patients

	Patient 1	**Patient 2**
Diagnosis Chylothorax (weeks, corrected gestational age)	34	35
Maximal volume of pleural effusion (ml/d)	312	40
Days on total parenteral nutrition or on enteral nutrition* until start of somatostatin therapy (d)	11	60
Somatostatin trade name	Somatostatin 3 mg Ferring®	Stilamin®
Lenght of somatostatin treatment (d)	29	18
Maximal dose of somatostatin (micg/kg bw/day)	360	218
Observed side effects	Slight fluctuations of blood glucose levels	None

** - fat free formula supplemented with medium chain triglycerides micg/kg bw/d=micg/kilogram body weight/day*

Patient reports (Table 1):
Patient 1 (Greifswald): A preterm appropriate for gestational age (AGA) neonate born after 30+3/7 gestational weeks, birth weight 1270g, underwent surgery for the correction of an esophageal atresia type IIIb on day 23 post partum (weight 1500g). 7 days after the intervention a chylothorax developed on the right side and a pleural drainage via a thoracic tube was performed, with chylous fluid volumes up to 310 ml/d. The conservative treatment with an enteral MCT-fat based diet, free of long chain fatty acids (16 days) and successive total parenteral nutrition (26 days) were ineffective. Before the start of surgical intervention a continuous intravenous application of somatostatin (Somatostatin Ferring ®) was performed to treat the chylothorax, starting with a dose of 3,3 micg/kg bodyweight/hour and gradually increasing the dose to a maximum of 15 micg/kg body weight/hour over a period of 6 days. During the first 6 days of somatostatin treatment no abnormal changes of blood glucose levels (2,3-9,8 mmol/l) or other side-effects were observed. Somatostatin was given for a total period of 29 days. In combination with total parenteral nutrition the treatment was successful and the chest drain could be removed after a total of 42 days. The neonate was discharged on day 102 with a body weight of 2485g.

Patient 2 (Freiburg): A preterm small for gestational age (SGA) neonate was born after 25+2/7 gestational weeks with a birth weight of 450 g. On day 36 post partum the neonate developed a thrombosis of the vena cava superior in association with a central line. A thrombolytic therapy with heparin (500 IU/kg bodyweight/day) and urokinase (4000 IU/kg bodyweight/hour) was started but had to be discontinued later because of thrombocytopenia and low serum fibrinogen. On day 74 post partum, a chylothorax was diagnosed. The symptomatic therapy of the chylothorax, in accordance with the local rules of treatment in the department (parenteral nutrition, enteral diet with MCT-fat free of long chain fatty acids, chest tubes for continuous evacuation or serial puncture) had to be repeated several times, decreased the volume of the chylous pleural effusion only for a short time, without final success. From day 134 post partum continuous somatostatin treatment was applied via an intravenous line (Stilamin ®, Serono). The starting dose was 1,5 micg/kg bodyweight/hour increased to the maximum dose of 9,1 micg/kg bodyweight/hour. After 18 days of somatostatin treatment the chylothorax disappeared. No side effects (e.g. blood glucose changes, disturbances of the gastrointestinal tract) of the somatostatin treatment were observed. The patient showed a normal weight gain and was discharged on day 205 without further complications (bodyweight: 2830g).

Results and their discussion. The rationale for our decision to apply somatostatin in the cases of two preterm infants with persistent chylothorax was that these children are high risk patients for side effects of the chylothorax, surgical interventions [3] or other treatment options. Surgical interventions of the chylothorax usually are advocated after a period of 3-4 weeks of unsuccessful conservative treatment, but do not always attain satisfactory results [37].

In both medical centers the attempt to use somatostatin as an additional conservative therapy option was induced by the good results that had to that date been published about somatostatin treatment both in adults, as well as in older pediatric patients [7,8,11,16,31,32,37,39,41,44].

Table 2. Physiological effects of endogenous somatostatin in healthy subjects [7,26-28]

Target organs of endogenous somatostatin:	Major inhibiatory effects:
Pituitary Gland	Growth hormone (GH) Thyreotropin (TSH)
Thyroid Gland	Thyroxin (T4) Calcitonin secretion
Pancreas	Insulin Glucagon Somatostatin (self inhibitory effect) Exocrine function of pancreas (bicarbonate)
Kidney	Renin secretion Aldosteron secretion
Gastrointestinal Tract	Gastric-acid Gastrin Pepsin Intrisic factor Secretin Transit-time Absorption of nutrients like triglycerides, aminoacids, electrolytes, and water
Hemodynamic effects	Blood flow of the splanchnic area Pressure of the venae portae Blood flow to liver

Somatostatin was first described by Brazeau et al. 1973 [7]. Its main mechanisms of action arise from the inhibitory effect on the endo-, para- and exocrine secretion of hormones (Table 2). The hormone is in use in the therapy of so different diseases like acromegaly, intractable diarrhoea [8] severe gastrointestinal bleeding [9], pancreatitis, metastatic carcinoids and tumors secreting vasoactive intestinal peptides [10]. It is used in the treatment of gastrointestinal fistulae [43] and neonatal hyperinsulinism. In adults it is mostly applied intravenously. Its longer acting form octreotide can also be given subcutaneously or intramuscularly.

There are two different somatostatin molecules identified in the human organism, composed of 14 or 28 aminoacids. The key regions of both forms are identical. The major amount of somatostatin is secreted from neurones of the central nervous system (CNS), and different tissues of the gastrointestinal system (D-cells of the pancreas, different cells of the gut), C-cells of the thyroid gland, various cells in the kidney, prostate and placental tissue. Currently the mechanisms of action of endogenous somatostatin are not known in every detail. The dominating inhibitory effects of somatostatin are signalled via corresponding somatostatin receptors (5 subtypes) located frequently in the CNS (pituitary gland, meninges) and in different tissues of the gastrointestinal tract. The genes are located on different chromosomes. This possibly implies distinct receptor functions.

The mechanisms of action underlying the somatostatin effects on chyle effusion in patients with chylothorax are not fully established. It is assumed that somatostatin acts through vasoconstriction of the lymphatic vessels via vascular somatostatin receptors. This reduces lymph fluid excretion [12] because lymph flow in the thoracic duct depends, amongst other factors, on the state of splanchnic circulation and gastrointestinal motility [13]. Indeed, it has been shown that somatostatin reduces splanchnic, hepatic, and portal blood flow and inhibits intestinal motility [14]. Apart from reducing the chyle output, somatostatin reduces the ratio of triglyceride levels of the lymph as compared to that of serum. This was shown in a study in dogs, suggesting that the reduction of chylomicron synthesis and transport into the lymphatic duct occurs through perturbation in the splanchnic circulation[13].

In addition to the reported vasoconstriction of the vessels in the splanchnic area it may be speculated that the lymphatic vessels are equipped with somatostatin receptors like the ones found in blood vessels of the splanchnic area.

From this assumption concerns may arise that externally supplied somatostatin could be a possible trigger for necrotising enterocolitis in preterm infants. Currently the incidence of such side effects on the vulnerable immature gastrointestinal tract in preterm infants is not fully evaluated. In a recent review on the use of somatostatin and octreotide in young children singular cases of strangulation-ileus and necrotising enterocolitis were reported during the treatment of persistent chylothorax with somatostatin, and octreotide respectively [38]. Those severe adverse effects occurred in patients with considerable comorbidity and a specific predisposition for vascular insults, one child having asplenia syndrome [25] and the other newborn suffering from congenital aortic coarctation [27]. Our case reports showed no adverse effects of that kind. But the transmitted cases of possibly therapy-related serious side effects on the gastrointestinal tract should induce caution, particularly regarding the treatment of patients vulnerable to vascular compromise.

Due to the known influences of the hormone on the endocrine system, symptoms of endocrinologic adverse effects must be carefully observed during therapy. Somatostatin derivates have been shown to inhibit the secretion of thyroid stimulating hormone, possibly resulting in hypothyroidism in the course of somatostatin treatment. Two independent case reports describe the occurrence of hypothyroidism during or following somatostatin therapy in two newborns with congenital chylothorax, one of whom had been a preterm baby [24,30] (Table 3). Those changes in thyroid function turned out to be transient and were treatable sufficiently with the substitution of L-thyroxine.

Though being a potent inhibitor of growth hormone, also, long term effects resulting in growth restriction due to somatostatin treatment have not been published so far.

Apparent clinical side-effects of somatostatin treatment are primarily related to suppressive actions on gastrointestinal motility and secretion. They include loose stools, malabsorption, nausea, and flatulence. Hypoglycaemia and liver dysfunction have been described but are usually transient[11]. Disturbance of biliary secretion and cholelithiasis had been reported during long-time treatment with somatostatin in children with congenital hyperinsulinism [13,33], but not in short-period application.

We carefully monitored the application of somatostatin in our patients in order to detect potential side effects early (clinical observation, stool frequency and consistency, fluid balance, blood glucose, liver enzymes, bilirubin), but no such adverse effects were detected during the course of treatment.

We used short-acting somatostatin preparations (somatostatin Ferring ® /Stilamin ®, Serono) and applied them continuously via an intravenous line. The starting dose was chosen in accordance with data from previous publications [15]. Because this therapy is still experimental and side effects are described, as mentioned above, we chose to increase the doses gradually. Buettiker et al. [16] published that bile production ceases at a dose of 10micg/kg/h.

Octreotide is a longer acting analogue of endogenous somatostatin which is known to be effective also after

subcutaneous application in neonates [17]. In our cases the decision to use somatostatin rather than octreotide was influenced by considerations of being able to stop therapy quickly in case of any major side-effects (shorter clearance time of somatostatin). Different analogues of somatostatin may have a different affinity to specific receptor sub-types. For pediatric patients no data are available, showing that one specific somatostatin derivate has a specific effect on the receptors which are predominant in the gastrointestinal tract.

Table 3. Overview on published cases of preterm neonates treated with somatostatin or octreotide for chylothorax

Ref	GA	Chylothorax	Therapy Start (day of life)	Treatment	Duration of therapy	Doses (micg/kg bw/d)	Side effects	Success
(15)	26+0	Spontaneous	36	OCT	3 days	7,2	None	Stop of drainage flow
(2)	36	Post-surgical	POD 33	OCT	7 days	- 84	None	Stop of thoracic output within 4 days
(34)	34	Congenital	32	OCT	10 days	7,2	None	Respiratory stabilization
(23)	24	Spontaneous	103	OCT	4 days	7	None	n.r.
(42)	36	Post-surgical	POD 8	OCT	4 days	72-120	None	Reduction of chyle drainage within 16 h
(41)	34	Congenital	22	OCT	10 days	-84	None	Regression of chyle drainage from 3rd day of therapy
(10)	26	Spontaneous	103	OCT	42 days	4-24	Transient hyperglycemia, nausea	Prolongated regression of chyle drainage
(40)	33	Congenital	15	OCT	10 days	12-240	None	Resp. stabilization after therapy start, decrease of chyle flow
(9)	31	Post-surgical	POD 12	SST	14 days	24	None	decrease of chyle volume within 24 h, ceasing of chyle drainage after 5 days
(24)	32-34	Congenital	n. r.	SST	n. r.	n. r.	Transient hypothyroidism	n. r.
(14)	26	Post-surgical	100	SST	5 days	-24	Pneumothorax	Prompt response to treatment
	34	Post-surgical	10	SST	8 days	-84	None	Decrease of thoracic effusion after increasing of dose day 5
	33	Congenital	1	SST	22 days	-240	None	Decrease of thoracic effusion after increasing of dose day 9

GA - gestational age; n.r. - not related; micg/kg bw/d - micg/kilogram body weight / day; SST - somatostatin; OCT - octreotide; POD - postoperative day

Up to the present day various case reports, only few reviews and scarce meta-analyses regarding the use of somatostatin and octreotide as a treatment option for persistent chylothorax in infants and preterm neonates have been published (Table 3). But to date no conclusive recommendations can be made on starting dose and on the rate of dosage titration during somatostatin therapy, because the form of application (intravenous, subcutaneous) and the applied doses vary considerably between publications, reaching from 2 to 360 micg/kg bodyweight/day for somatostatin and from 4 to 240 micg/kg bodyweight/day for octreotide (Table 3). Usually treatment was initiated after unsuccessful nutritional treatment strategies, beginning with lower starting doses and slowly titrating up the dosage until clinical effectiveness established.

Further evaluations of possible side-effects, the determination of recommendable doses and treatment algorithms, and the identification of target groups in whom an early introduction of additional somatostatin therapy might be indicated, still need to be established. Until now there is no data available from controlled randomized trials that might elicit the actual benefits deriving from additional somatostatin therapy in the treatment of neonatal chylothorax.

In the light of a variety of reports over the successful use of somatostatin or octreotide in the treatment of chylothorax there seem to be strong indications for a beneficial effect of the drug when used as an add-on therapy in preterm neonates, whenever conservative treatment alone failed to induce cessation of thoracic effusion (Table 3). This impression has been reflected by the courses of disease in the two individual cases depicted in this article.

From our case reports and the results of various cases published so far there is reason to call for more elaborate evaluation of somatostatin as an additional therapeutic option in the treatment of refractory chylothorax in preterm infants (after failure of the classical non-invasive methods). If efficient, the incidence of complications, surgical interventions, and the time of hospitalisation probably might be reduced. There is strong need for more conclusive evidence in the treatment of chylothorax in preterm infants, reaching beyond the level of single case description or reports on case series.

However, randomized controlled trials might be difficult to perform, because of the rareness of the disease in infancy and the difficulty to gain parental consent to a placebo-controlled design in clinical situations that often seem critical for the child.

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SUMMARY

SOMATOSTATIN - THERAPEUTIC OPTION FOR CHYLOTHORAX IN PRETERM NEONATES. REPORT ON TWO PATIENTS AND REVIEW OF THE LITERATURE

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We report the use of somatostatin in two preterm neonates with chylothorax and discuss those cases in the light of current literature on the treatment of chylothorax in infants born preterm.

Chylothorax, a severe complication in thorax surgery, is also a symptom of different diseases and may even occur spontaneously. Treatment is difficult, especially in preterm neonates with co-morbidities. The standard therapeutic strategy with non-invasive procedures (e.g. enteral diet free of long chain triglycerides or parenteral nutrition) is not always effective. Surgical interventions, like pleurodesis, ligation of the ductus thoracicus, or pleuroperitoneal shunt may be of considerable risk in preterm infants and must be carefully evaluated. Somatostatin is a new non-invasive therapeutic option for the treatment of chylothorax in adults and older pediatric patients. Case reports demonstrate the

effectiveness of the somatostatin treatment, mostly in adult patients and in adolescents. There are only few case reports describing the use of somatostatin in preterm neonates.

One VLBW (very low birth weight) and one hypotrophic ELBW (extremely low birth weight) neonate (gestational ages of 30+3/7, and 25+2/7 weeks; birth weights of 1270g, and 450g respectively) were treated for chylothorax with continuous infusion of somatostatin in addition to the dietary treatment.

The chylothorax disappeared after start of somatostatin. No major side-effects of the somatostatin treatment were observed.

As reported in other published pediatric cases, somatostatin seems to be a therapeutic option for the treatment of chylothorax in preterm neonates. In review of the literature we identified another eleven case reports on the treatment of persistent chylothorax with somatostatin or octreotide in preterm neonates. Further observations are needed before somatostatin can be recommended as a standard first-line treatment procedure for chylothorax in infants.

Key words: MCT-fat, medium chain triglycerides, Nutrition, Octreotide, Infants, preterm neonate, chylothorax.

РЕЗЮМЕ

СОМАТОСТАТИН - МЕТОД ВЫБОРА ПРИ ТЕРАПЕВТИЧЕСКОМ ЛЕЧЕНИИ ХИЛОТОРАКСА НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ. СООБЩЕНИЕ О ДВУХ СЛУЧАЯХ ИЗ ПРАКТИКИ И ОБЗОР ЛИТЕРАТУРЫ

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Сообщается об использовании соматостатина у двух недоношенных новорождённых с хилотораксом. Обсуждаются эти случаи в свете текущей литературы по лечению хилоторакса у недоношенных.

Хилоторакс, серьезное осложнение в хирургии грудной клетки, является также признаком различных болезней; в некоторых случаях развивается спонтанно. Лечение затруднительно, особенно у недоношенных новорожденных с сопутствующими заболеваниями. Стандартная терапевтическая стратегия с неинвазивными процедурами (диета без триглицеридов с длинными цепями или парентеральное питание) не всегда эффективна. Проведение различных хирургических вмешательств у недоношенных сопровождается значительным риском и их целесообразность должна быть тщательно оценена. Соматостатин - новый неинвазионный терапевтический выбор для лечения хилоторакса у взрослых и старших педиатрических пациентов. Имеются лишь единичные случаи его использования у недоношенных новорожденных.

Пациенты: один новорожденный с очень низким весом при рождении (VLBW), второй - гипотрофик с чрезвычайно низким весом при рождении (ELBW) в гестационном возрасте 30+3/7 и 25+2/7 недель, вес при рождении - 1270 г и 450 г, соответственно, лечились по поводу хилоторакса непрерывной инфузией соматостатина в дополнение к диетическому лечению.

После начала лечения соматостатином хилоторакс исчез. Побочных эффектов лечения не выявлено.

Как сообщалось, соматостатин, по всей вероятности, является терапевтическим выбором для лечения хилоторакса у недоношенных новорожденных. В обзоре литературы мы идентифицировали еще одиннадцать сообщений относительно лечения перманентного хилоторакса у недоношенных новорожденных соматостатином или октреотидом. Необходимы дальнейшие наблюдения для окончательного решения о целесообразности применения соматостатина в качестве стандартной первоочередной лечебной процедуры у младенцев с хилотораксом.

რეზიუმე

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[1]პედიატრიული განყოფილება, შპანდაუს ევანგელური ტყის საავადმყოფო, ბერლინი, გერმანია; [2]ახალშობილთა განყოფილება, საუნივერსიტეტო ბავშვთა საავადმყოფო, ფრაიბურგი, გერმანია; [3]ახალშობილთა და პედიატრიული ინტენსიური თერაპიის განყოფილება, საუნივერსიტეტო ბავშვთა საავადმყოფო, გრაიფსვალდი, გერმანია; ამჟამად: პედიატრიის დეპარტამენტი, ჰამილტონის მაკმასტერის უნივერსიტეტი, ონტარიო, კანადა

განხილულია სომატოსტატინის გამოყენების ორი შემთხვევა ქილოთორაქსის მქონე დღენაკლ ახალშობილში.

ქილოთორაქსი გულმკერდის ქირურგიაში მძიმე გართულებაა. ის, აგრეთვე, სხვადასხვა დაავადების სიმპტომია, შეიძლება სპონტანურადაც განვითარდეს. მკურნალობა რთულია, განსაკუთრებით დღენაკლ ახალშობილებში თანმხლები დაავადებებით. სტანდარტული თერაპიული სტრატეგია არაინვაზიური პროცედურებით (დიეტა გრძელჯაჭვიანი ტრიგლიცერიდების გარეშე ან პარენტერალური კვება) ყოველთვის არ არის ეფექტური. ქირურგიული ჩარევები დღენაკლ ჩვილებში შეიძლება საკმაო რისკს წარმოადგენს, ამიტომ მისი გამოყენების მიზანშეწონილობა სიფრთხილით უნდა შეფასდეს. სომატოსტატინის გამოყენება ქილოთორაქსის დროს წარმოადგენს მკურნალობის ახალ არაინვაზიურ მეთოდს. მოზრდილებსა და უფროსი ასაკის ბავშვებში სომატოსტატინით ქილოთორაქსის მკურნალობის შესახებ ლიტერატურული მონაცემები საკმარისად არის წარმოდგენილი. რაც შეეხება სომატოსტატინის გამოყენებას დღენაკლულ ახალშობილებში, მხოლოდ რამდენიმე შემთხვევაა აღწერილი.

პაციენტები: ერთი ავადმყოფი ძალიან დაბალი დაბადების წონით (VLBW), ხოლო მეორე ავადმყოფი ჰიპოტროფიით უკიდურესად დაბალი დაბადების წონით (ELBW)-გესტაციური ასაკი -30+3/7 და 25+2/7 კვირა, დაბადების წონა - 1270 გ და 450 გ, შესაბამისად. ორივე ახალშობილს ქილოთორაქსის გამო დიეტურ მკურნალობასთან ერთად უტარდებოდათ სომატოსტატინის უწყვეტი პერფუზია.

ქილოთორაქსი გაქრა მკურნალობის დაწყებისთანავე. რაიმე მნიშვნელოვან გვერდით რეაქციას ადგილი არ ჰქონია.

როგორც ეს ლიტერატურაშიცაა აღნიშნული, სომატოსტატინის გამოყენება ქილოთორაქსის დროს დღენაკლ ახალშობილებში საკმარისად ეფექტურია. ლიტერატურულ წყაროებიდან დღენაკლ ახალშობილებში პერსისტული ქილოთორაქსის დროს სომატოსტატინით ან ოქტრეოტიდით მკურნალობის თერთმეტი შემთხვევა არის ცნობილი. საჭიროა შემდგომი დაკვირვებები, რათა ჩვილებში ქილოთორაქსის დროს პირველი რიგის სამკურნალო პროცედურად სომატოსტატინის დანიშვნა იყოს აღიარებული.

HALLERMANN-STREIFF SYNDROME: A CASE REPORT FROM GEORGIA

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Hallermann-Streiff syndrome (HSS) was first described minutely by Hallermann in 1948 and then by Streiff in 1950 [13]. The syndrome is also known by alternative designations, which are based on the characteristic clinical signs like dyscephalia and ocular alterations, or as “Francois dyscephalic syndrome” or “Hallermann-Streiff-Francois syndrome” [7,9,10,13].

The HSS (MIM ID #234100) is a rare congenital disorder. By 1981 only up to 150 cases had been published worldwide [10]. Several tens more have been reported since then; the literature devoted to some of them has been reviewed recently [2,3,5,17].

The HSS is primarily characterized by dyscephaly; hypotrichosis and atrophy of skin (paricularly in the facial area); “bird-like” face with mandibular hypoplasia and beaked nose; dental abnormalities; various ocular anomalies like microphthalmia, cataracts and glaucoma; proportionate short stature [3,5,17]. According to Francois [8] the seven essential features of this syndrome (valid as diagnostic criteria) are as follows: dyscephaly with birdface, dental anomalies, proportionate short stature, hypotrichosis, atrophy of skin, bilateral microphthalmos, and cataract.

The HSS inheritance pattern is still unknown, and most of the clinical cases seem to constitute sporadic mutations [3,5]. It was postulated that GJA1 homozygous hypomorphic mutations on chromosome 6q may result in a phenotype in the HSS/Oculodentodigital dysplasia spectrum [19]. On the assumption of the above-stated, there is no definitive test (e.g. genetic analysis) for confirming the clinical suspicion of the HSS; the diagnosis is established on the basis of the clinical criteria.

Since the HSS is extremely rare, it seems to be rational to collect as much information about the patients with this diagnosis as possible. Our work is devoted to reporting the first Georgian case of the HSS and discussing some pertinent issues.

Material and methods. *Case Report.* A 9 years and 5 months old boy was referred to the Pediatric Endocrinology Unit of the G. Zhvania Pediatric Hospital (Tbilisi, Georgia) by a pediatrician for the general endocrine status evaluation.

Complaints: The patient has been complaining of impaired vision and recurrent upper respiratory tract infections.

History: The patient has lived in the rural area, in satisfactory living conditions in terms of nutrition and accommodation.

He was born by normal delivery following the 39-40 weeks of eventless pregnancy. The birth weight and height were "normal" (the mother failed to provide the precise data). Reportedly, teeth eruption started at the age of 6 months, psychomotor development was normal. He started speaking by the age of 1 year, and was speaking with 2-3 word phrases by the age of 2.

Reportedly, the patient had an acute respiratory illness at the age of 1 year 6 months which resulted in respiratory failure. The patient was admitted to the local hospital and was treated with oxygen. Later on the patient had frequent respiratory infections. He underwent the tonsillectomy and adenoidectomy operation which led to the decrease in the frequency of the respiratory infections. Nevertheless, the patient has still reportedly been snoring and even has had episodes of apnoea while sleeping. On the other hand, he has had no somnolence or heavy breathing in the daytime anymore.

The patient has easily got tired with an extended physical activity.

His academic performance at school was as follows: 5 out of 10 scores in mathematics, 10 out of 10 in Georgian language (objectivity of the assessment questionable). The mother rationalized patient's uneven successes by the overcrowdedness of the classrooms (up to 50-60 children in the same premises). Social adaptation seemingly satisfactory so far: He has played football, and has had friends.

Reportedly the patient has also had night enuresis, which ceased after the therapy course with Imipramine.

Clinical examination: Height 128 cm (~20th percentile of the national growth chart), target height 168.3 cm (~20th percentile of the national growth chart).

No evident clinical signs of the endocrine pathology apart from the laterally thinned eyebrows (Fig. 1). The following additional physical signs were noted (Fig. 2): Beaked nose; microstomia; prognathism with hypoplasia of the mandible; high palate; mild dental anomalies; proliferation of the nasopharyngeal lymphoid tissue; microphtalmia; specific (parrot-like) facial gestalt (according to patient's mother, he looked like his father; the latter did not show up for clinical examination).

Fig. 1. Laterally thinned eyebrows

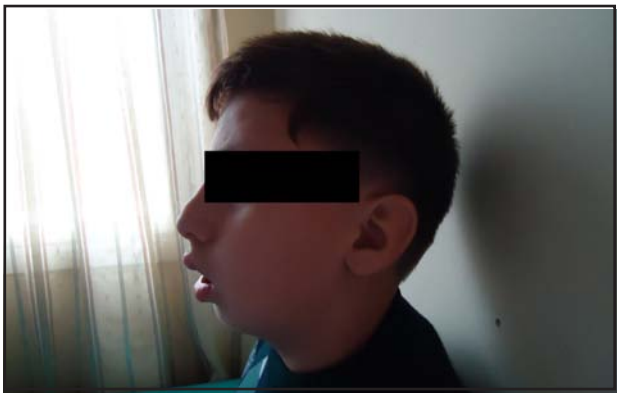

Fig. 2. Typical facies: beaked nose; microstomia; prognathism with hypoplasia of the mandible; microphtalmia; specific (parrot-like) facial gestal

Genitals and sex development were normal. No cardiac (clinical or ECG) anomalies were detected.

Ophtalmologic examination revealed the following: VOD=0.4, VOS=0.4, binocular vision. Bilateral bidimensional +2.0 refraction anomaly. Light-refracting structures of the eye opaque, fundus could not be examined. The diagnosis of bilateral congenital cataract and allergic conjunctivitis was established.

Clinically mild mental retardation and attention deficit were suspected. No specific neurologic complaints were voiced except for the occasional night enuresis. Head circumference 51 cm. Patellar reflexes were torpid bilaterally. Muscle strength in extremeties was preserved. Left-side equinovarus and friedreich's foot were detected. The patient was unsteady while performing the coordination tests, and swayed while performing the Romberg's manouver. The poverty of skilled movements was evident. Hyperhidrosis but dry palms were detected.

Thoracal and Pelvic X-ray investigation was performed (Fig.

3), which yielded the following: Spina bifida of S1 vertebra, narrowing of the intervertebral spaces at Th4-5 level. No evidence for the osteoporotic alterations in the vertebrae. Thinning of the ilium apophyses. Craniogram (Figs. 4,5): The mandible made up by a thin plate, nasal septum curved, cranial bones thinned in the parietal and occipital areas. Sella turcica dimensions ~10 mm sagittal (normal value) and ~6.5 mm vertical (normal value ~8.4 mm).

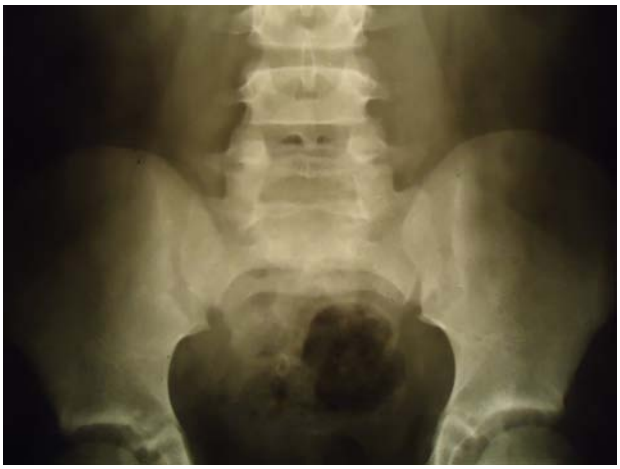

Fig. 3. Spina bifida of S1 vertebra, no evidence for the osteoporotic alterations in the vertebrae; thinning of the ilium apophyses

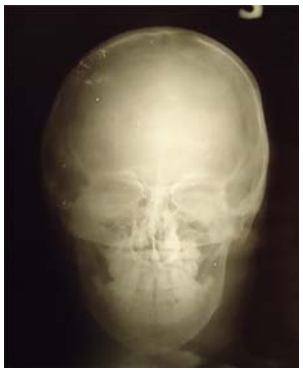

Fig. 4. Craniogram: The mandible made up by a thin plate, nasal septum curved

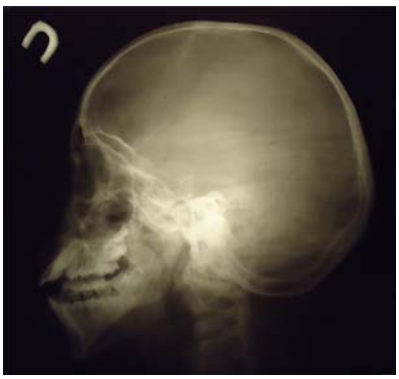

Fig. 5. Craniogram: The mandible made up by a thin plate; cranial bones thinned in the parietal and occipital areas; altered sella turcica dimensions (~10 mm sagittal (normal value) and ~6.5 mm vertical (normal value ~8.4 mm).

Lab analyses: Thyroid panel results were normal.

Diagnosis: Patient's facial gestalt was quite remarkable and promoted the clinical suspicion for the Hallermann-Streiff syndrome immediately. The history data and results of the further clinical examination (including the specialized studies) confirmed the diagnosis of Hallermann-Streiff syndrome, non-lethal form.

Recommendations: There is no definitive cure for the Hallermann-Streiff syndrome. The management of this disorder implies the symptomatic therapy (with an emphasis on respiration and vision) and continuous monitoring of the patient's development and vital functions, as well as specialized training in case of the mental retardation.

The patient was referred to ophtalmologist, neurologist, orthopaedist, otorhinolaryngologist (for re-excision of the lymphoid tissue); monitoring of the sleep breathing and referral to surgeon with relevant expertise to evaluate the facial dysostosis responsible for the narrowing of the upper respiratory tract was recommended. Endocrine monitoring of the growth and sex development was initiated.

The mother was informed about the nature of the disorder and potential future risks like apnoea; also the significance of the upper respiratory tract narrowing when / if operated. The genetic consultation was provided as well.

Results and their discussion. Currently, there is no consensus on the diagnostic criteria of the HSS, and the clinical picture of this disorder seems to be variable. For instance, there seemed to be a clear (though relatively mild) intellectual deficit in our case, whereas mental retardation was considered to be present only in a minority of cases [11], and some authors even postulated that the absence of the neuropsychological deficit distinguished this condition from other related conditions [18]. Moreover, only 2 out of 7 criteria established by Francois [8] were clearly manifested in our case: The patient had no short stature, no skin atrophy or marked hypotrichosis (just sparse eyebrow hair bilaterally), only moderate microphtalmos and only moderate dental anomalies. However, the dyscephaly with definite bird-like (parrot-like?) appearance and cataract was pronounced and let establish the diagnosis. It is remarkable that this very clinical signs were particularly emphasized by the first researchers of the syndrome – Hallermann and Streiff had designated the syndrome which was named after them later as "Vogelgesicht und Cataracta congenita" (Bird-face and congenital cataract) and "Dysmorphie mandibulo-faciale (tete d'oiseau) et alterations oculaires" (Mandibular and facial dysmorphism (bird-head) and ocular alterations) [13]. In our opinion these criteria may be 'heavier', i.e. more characteristic for the HSS, and therefore it might be expedient to assign to them more significance when dealing with the differential diagnosis for the HSS-like disorder (incl. by means of the expert system). It was already shown,

that the presence of microcephaly in infants with bilateral cataracts was strongly suggestive of a syndromic cause, with the HSS constituting 20% of cases in the 5-patient sample [12]. Generally speaking, taking into consideration the absence of the reliable diagnosis confirmation tool, facial gestalt evaluation seems to be quite efficient in primary diagnostics of the HSS and similar disorders. On the other hand, the variability of the HSS clinical picture and lack of the standard diagnostic criteria make any meta-analysis subject to selection flaws.

The short stature which is commonly attributable to the HSS (but nonexistent in our case), should be related to the GH and IGF-1 deficiency, as verified in some cases [4,14]. Remarkably, there was a report of a unique case of the HSS association with hemihypertrophy [6]. Hypothyroidism may be present as well [14]; however, it is unclear, whether it is specific for the HSS. Impairment of the thyroid function seems to be relatively rare, and not necessarily related to the syndrome proper, but may constitute a mere coincision due to the high overall prevalence of the thyroid disorders. However, there may be a certain overlap between the HSS related hypotrichosis and diffuse or focal alopecia which is sometimes present in case of hypothyroidism (an autoimmune process involving the thyroid gland). It is noteworthy, that our patient had a pronounced thinning of the outer half of the eyebrows (Fig. 1) (Sign of Hertoghe or Queen Anne's sign, usually attributable to hypothyroidism), but normal thyroid function. It is remarkable, that the diagnosis of the HSS was established by the endocrinologist in our case; this points out the significance and benefits of the interdisciplinary approach to the patients with equivocal clinical picture.

X-ray study of our patient yielded some specific data. It seems that the HSS is associated with a specific constellation of radiological findings [2]. Being a readily available and relatively inexpensive diagnostic tool, it may be quite useful when performing the differential diagnosis of the HSS-like disorders.

The long-term management of the non-lethal (i.e. relatively mild) form of the HSS should focus on the potentially life-threatening dyscephalic narrowing of the upper airways and treatment of congenital cataract. The former is related to many potential complications [3]; narrowness of the upper respiratory tract raises particular concerns with regard to the anaesthetic management of a child with the HSS [1,7,16,21]. The frequency of the spontaneous lens absorption in the HSS seems to be quite high; this is an argument in favour of postponing the surgical intervention, particularly when the cataract is combined with considerable microphthalmia [20].

The rarity of the HSS stipulates for the creation of a worldwide register of all the reported cases, ideally within the framework of an online hub. The accumulation of the available information would imply the publishing of all the diagnosed cases. To our knowledge, no cases of the HSS from Caucasus area have been published so far (Turkish and Iranian cases have been reported [6,15,17]). The present publication would hopefully contribute to the study of the rare disorders in Georgia and particularly to the further research of the HSS.

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SUMMARY

HALLERMANN-STREIFF SYNDROME: A CASE REPORT FROM GEORGIA

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We report a 9 years and 6 month old boy with the Hallermann-Streiff syndrome (HSS). The patient was referred by a pediatrician. The diagnosis was established by endocrinologist based on the presence of specific facial gestalt (bird-like face) and bilateral congenital cataracts. The patient was not short, but had mild mental retardation; hypotrichosis was represented by Sign of Hertoghe (Queen Anne's sign) only. Thyroid function was normal. X-ray study yielded valuable data. The night apnoea (secondary to the dyscephalic narrowing of the upper airways) constituted the major concern.

We also discuss diagnostic criteria for the HSS along with significance of various clinical signs. Combination of specific facial gestalt and ocular abnormalities should be particularly alarming. Endocrine aspects of the HSS are reviewed. X-ray study is recommended as an inexpensive and readily available but informative tool.

Key words: Hallermann-Streiff syndrome, facial gestalt, bird-face, congenital cataract, short stature, narrow airways, sign of Hertoghe, Queen Anne's sign, IGF-1, GH.

РЕЗЮМЕ

СИНДРОМ ХАЛЛЕРМАННА-ШТРАЙФА – КЛИНИЧЕСКИЙ СЛУЧАЙ В ГРУЗИИ

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Описан клинический случай мальчика в возрасте 9 лет и 6 месяцев, которому был поставлен диагноз синдрома Халлерманна-Штрайфа (Hallermann-Streiff). Пациент был направлен педиатром, диагноз установлен эндокринологом на основе наличия комбинации специфического лицевого гештальта (птичье лицо) и двухсторонней врожденной катаракты. Пациент не страдал низкорослостью, однако отмечалась задержка умственного развития. Гипотрихоз был представлен симптомом Гертога (Королевы Анны). Тиреоидная функция была в норме. Рентгенографическое исследование оказалось высокоинформативным. Основной клинической проблемой являлось ночное апноэ (по причине сужения верхних дыхательных путей).

Обсуждаются диагностические критерии синдрома Халлерманна-Штрайфа, а также значение отдельных клинических признаков. Необходимо особо заострять внимание на комбинации специфического лицевого гештальта и глазных аномалиях. Рассматриваются эндокринологические аспекты синдромаХаллерманна-Штрайфа. Рекомендуется проводить рентгенографию как недорогое, доступное и информативное исследование.

რეზიუმე

ჰალერმან-შტრაიფის სინდრომი – კლინიკური შემთხვევის აღწერილობა საქართველოში

მ. გორდელაძე, ი.ფაღავა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, შინაგანი მედიცინის დეპარტამენტი, ენდოკრინოლოგიის მიმართულება; პედიატრიის დეპარტამენტი; გ. ჟვანიას სახ. პედიატრიული კლინიკა, პედიატრიული ენდოკრინოლოგიის განყოფილება, თბილისი, საქართველო

აღწერილია 9 წლისა და 6 თვის ასაკის ბიჭის კლინიკური შემთხვევა, რომელსაც დაესვა ჰალერმან-შტრაიფის (Hallermann-Streiff) სინდრომის დიაგნოზი. დიაგნოზი დაისვა ენდოკრინოლოგის მიერ სპეციფიური (ჩიტის-მაგვარი) იერ-სახის (გეშთალთის) და ორმხრივი თანდაყოლილი კატარაქტის კომბინაციის არსებობის საფუძველზე. პაციენტი არ გამოირჩეოდა ტანდაბლობით,მაგრამ აღენიშნებოდა მსუბუქი გონებრივი ჩამორჩენილობა; ჰიპოტრიქოზი წარმოდგენილი იყო მხოლოდ ჰერთოგის (დედოფალ ანას) ნიშნით. თირეოიდული ფუნქცია ნორმალური იყო. რენტგენოგრაფია მეტად ინფორმატიული გამოდგა. ძირითად კლინიკურ გამოწვევას წარმოადგენდა ღამის აპნოე (ზედა სასუნთქი გზების დისცეფალური შევიწროების შედეგად). განხილულია ჰალერმან-შტრაიფის სინდრომის სადიაგნოსტიკო კრიტერიუმები და სხვადასხვა კლინიკური ნიშნის მნიშვნელობა. დიაგნოზის დასმის დროს აუცილებელია განსაკუთრებული ყურადღების გამოჩენა სპეციფიური გეშთალთისა და ოკულური ანომალიების კომბინაციის მიმართ. დახასიათებულია ჰალერმან-შტრაიფის სინდრომის ენდოკრინოლოგიური ასპექტები. რეკომენდებულია რენტგენოგრაფია, როგორც იაფი და ადვილად ხელმისაწვდომი და, ამასთანავე, ინფორმატიული კვლევის მეთოდი.

НАСЛЕДСТВЕННАЯ ПАРЦИАЛЬНАЯ ЭРИТРОБЛАСТОПЕНИЯ - АНЕМИЯ ДАЙЕМОНДА-БЛЕКФЕНА

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Апластические анемии (АА) – гетерогенная группа заболеваний, характеризуются депрессией всех 3 или одного (эритроидного) ростков кроветворения. Различают приобретённые и наследственные формы АА. Среди последних особое место занимает анемия Дайемонда-Блекфена. Это конституциональная эритробластопения, которую впервые описал H. Josephs в 1936 г., а затем L. Diamond и K. Blackfan в 1938 г. подробно охарактеризовали клинико-гематологическую картину заболевания. Это редкая и тяжелая анемия, которая носит аутосомно-рецессивный тип наследования. В литературе, до настоящего времени, описано около 500 случаев заболевания [4,5]. Инциндентность болезни Дайемонда-Блекфена составляет 4-7 случаев на 1 млн. живых новорожденных [1,2,8]. Она встречается во всех этнических группах с одинаковой частотой у лиц обоих полов (соотношение мальчики: девочки 1,04:1). 75% случаев болезни носят спорадический характер, хотя описаны единичные семейные случаи [3,6]. У 25% больных обнаружены мутации гена RPS19, характеризующиеся транслокациями t(X;19)(p21;q13), делецией 19q. [9]. Мутация была выявлена как при спорадических, так и семейных случаях болезни, что, по всей вероятности, указывает на генетическую природу заболевания [6,9]. При этом в эритроидных клетках повышается активность аденозиндезаминазы (АДА), которая снижает чувствительность клеток предшественников красного ряда к эритропоэтину, IL-3, IL-6, что приводит к нарушению регуляции эритроидных предшественников [10]. У родителей и сибсов больных могут отмечаться биологические аномалии в виде увеличения содержания HbF, макроцитоза эритроцитов, повышения активности АДА, при отсутствии у них анемии. Кариотип у больных нормальный [9]. Этиология анемии Дайемонда-Блекфена не установлена.

По современным данным, в основе анемии Дайемонда-Блекфена лежит дефект созревания эритроидных гемопоэтических клеток предшественников и их микроокружения, однако эти клетки морфологически и

фенотипически остаются нормальными [9]. В костном мозге отмечается супрессия эритропоэза и наличие гуморальных ингибиторов. Эритроидные клетки в костном мозге гибнут, в основном, путем апоптоза [2,4].

В 25% случаев анемия Дайемонда-Блекфена диагностируется в период новорожденности, в первые 6 месяцев жизни - у 60%, к одному году - у 90%. Характерны бледность, адинамия и отставание в физическом развитии. Мертворождение отмечается у 25,4% [3,4,7]. У 25-40% больных, наряду с гематологическими нарушениями, наблюдаются конституциональные аномалии. К их числу относятся: черепно-лицевой дисморфизм (гипертелоризм, микроцефалия, врожденная глаукома, аномалии развития нёба), задержка роста и увеличение массы тела, нарушение развития большого пальца, синостоз лучевой и локтевой костей, гипогонадизм, ретинопатия, аномалии головы, шеи, моче-половой системы, сердца, костей, суставов и др. Волосы иногда двухцветные. Причинно-следственная связь между врожденными аномалиями и нарушением эритропоэза не установлена. Спустя 5-6 лет после начала заболевания кожа становится темной, с сероватым оттенком (признаки вторичного гемосидероза) [9]. Переферические лимфоузлы не увеличены. “Костный возраст “ на 4-5 лет отстает от “паспортного возраста“ [3,10].

При анемии Дайемонда-Блекфена лабораторные данные таковы: анемия нормо- или гиперхромная, гипо- или арегенераторная, объем эритроцитов (MCV) в норме или повышен, количество ретикулоцитов снижено (0-10$^{0}/_{00}$). В эритроморфограмме: анизоцитоз, микроцитоз, незначительный лейкоцитоз. Количество лейко-тромбоцитов в норме. В костном мозге выявляется аплазия эритроидного роста, соотношение миелоидных и эритроидных клеток 50-200:1 (N - 3-4 :1). Отмечается резкое повышение АДА в эритроцитах. Повышены показатели i антигена и HbF [2,6,8].

Основными диагностическими критериями анемии Дайемонда-Блекфена являются: возникновение анемии до 2-летнего возраста, исключение инфекции, вызванной парвовирусом В-19, а также низкое содержание ретикулоцитов в переферической крови и стойкое снижение количества или полное отсутствие эритробластов в костном мозге. Количество эритрокариоцитов ≤5% [1,6,8].

При анемии Дайемонда-Блекфена дифференциальный диагноз проводят с анемией Фанкони, детской транзиторной эритробластопенией, приобретенной эритробластопенией (вызванной, в основном, инфицированием парвовирусом B_{19}), острой лейкемией и другими опухолевыми заболеваниями.

Ответ на лечение анемии Дайемонда-Блекфена может быть:
- полный (количество ретикулоцитов повышено, нет необходимости в гемотрансфузии);
- частичный (количество ретикулоцитов повышено, снижена необходимость в гемотрансфузии);
- плохой частичный (необходимо проводить гемотрансфузию каждые 3-6 недель);
- ответа нет (регулярные трансфузии).

Течение болезни - хроническое, с периодическими обострениями.

Основным методом лечения анемии Дайемонда-Блекфена является кортикостероидная терапия преимущественно преднизолоном или метипредом в больших дозах (1-3 мг/кг/сут), (положительный ответ отмечается в 66-72%) [2,6], а также трансфузии эритроцитарной массы. В случае отсутствия эффекта, проводится иммуносупрессивная терапия, трансплантация костного мозга и стволовых клеток, полученных из пуповинной крови. Имеются данные по клиническому использованию рекомбинантного интерлейкина-1 и интерлейкина -3. Спленэктомия не эффективна.

Прогноз серьёзен. Большинство больных не достигает пубертатного возраста. Высок риск трансформации заболевания в острую лейкемию, миелодиспластический синдром, лимфогранулематоз и другие опухолевые заболевания. По данным литературы [5,8] на основании наблюдения 200 детей с анемией Дайемонда-Блекфена у 17% больных наблюдали спонтанную ремиссию, 34% стали кортикстероид-зависимыми, 28% - транфузиязависимыми, у 21% исход был летальным.

На протяжении 25 лет в гематологическом отделении педиатрической клиники им. Г. Жвания у нас была возможность наблюдать 5 пациентов с анемией Дайемонда-Блекфена:
а) больной, в настоящее время ему 22 года, находится в полной клинико-гематологической ремисси (однако, он является носителем вирусов гепатита В и С);
б) больная умерла в возрасте 2 лет от острой кишечной инфекции;
в) больному в настоящее время 10 лет, нуждается в периодических гемотрансфузиях [7];
г) больному 1 год и 9 мес., он находится на регулярных трансфузиях.

В 2010 г. нами был выявлен новый случай анемии Дайемонда-Блекфена. Приводим краткую выписку из амбулаторной истории 5-го больного (ист.№8081). Больной мальчик А.Ш. (житель Сачхерского района) в возрасте одного месяца был доставлен на амбулаторную консультацию 08.10.2010 по поводу анемии неизвестной этиологии.

Со слов матери ребенок болен с рождения. В однодневном возрасте он был переведен из роддома в реанимационное отделение детской больницы «Республика» в тяжелом состоянии с Hb – 60 г/л. На следующий день уровень гемоглобина понизился до 40 г/л, в связи с чем дважды была произведена трансфузия эритроцитарной массы, проводилась интенсивная терапия. Состояние мальчика улучшилось и с уровнем Hb – 115 г/л в возрасте двух недель он был выписан. Ребенок до 3-х недель находился на смешанном вскармливании, затем был переведен на искусственное.

При осмотре больного привлекали внимание бледность кожных покровов и слизистых, относительная худоба мальчика (масса тела 3650 г) и короткая статура (длина 48 см). Со стороны внутренних органов: тоны сердца приглушены, на верхушке прослушивался систолический шум средней интенсивности, живот мягкий, печень выступала из под края рёберной дуги по мамилярной линии на 2 см, селезенка не пальпировалась, мочеиспускание нормальное, отмечалась тенденция к запорам. Ребенок был активен, психо-моторное развитие соответствовало возрасту.

Из анамнеза следует, что ребенок от первой беременности. На втором месяце беременности в связи с обострением желчекаменной болезни, матери (под общим наркозом) была произведена холецистэктомия. Мать является носителем вируса гепатита В. При ультрасонографии во время беременности отмечали помутнение околоплодных вод и чрезвычайно активное движение плода, что послужило поводом для проведения кесарева сечения на 37-й неделе гестации. Ребенок родился с массой тела 3200 гр, длиной 48 см. в асфиксии. Матери больного 35 лет, отцу – 42 года, они практически здоровы. Родственники I и II степеней заболеваний крови не отмечают.

Амбулаторно больному были проведены лабораторно-инструментальные исследования (таблица 1).

Таблица 1. Общий анализ крови больного А.Ш. (08.10.2010)

Hb-90г/л Эр-3.32 х 10^{12}/л Fi-0.8 Рет.-8$^{0}/_{00}$ Лейк.-8.9 х 10 ^{9}/л Тр.-199 х 10 ^{9}/л СОЭ -5мм/ч	Нейтрофилы: п-2% с-31% Э – 4% М – 7% Л – 56%
Морфоэритрограмма: нормохромия, нормо-, макроцитоз, встречаются единичные пойкилоциты	

Средний диаметр эритроцитов- 7,9 мкм, MCV – 91 мкм^3.
Реакция Кумбса (11.10.2010) прямая и непрямая – отрицательны.
Биохимический анализ крови (11.10.2010). Билирубин общий – 16,9 мкмоль/л, непрямой – 14,5 мкмоль/л, трансаминазы в норме, общий белок – 67,1 г/л, сывороточное железо – 13,9 мкмоль/л.
Общий анализ кала - в норме, реакция на скрытое кровотечение – отрицательная.
Общий анализ мочи – без особенностей.
Ультрасонография органов брюшной полости и нейросоноскопия головного мозга патологических изменений не выявили.
Эхокардиография – открытое овальное отверстие (необходимо повторное обследование в возрасте 6 мес.).
Антитела против первовируса $B-_{19}$ и гепатита В не выявлены (13.10.2010).
Анализы периферической крови родителей в пределах нормы.
На фоне симптоматического лечения (витамины «С», «Е», фолиевая кислота) повторно проконтролированы показатели красной крови (таблица 2).

Таблица 2. Показатели красной крови больного А.Ш. (15.10.2010)

Hb-72 г/л Эр-2,5 х 10^{12}/л Fi-0.8 Рет.-5 $^{0}/_{00}$	Морфоэритрограмма: нормохромия, нормо-, макроцитоз

С согласия родителей 15.10.2010 была проведена пункция костного мозга. Медулограмма: костный мозг сравнительно беден клеточными элементами, он миелоидный, резко снижено количество эритрокариоцитов (5%), отмечаются качественные изменения эритропоэза, встречаются 2-ядерные эритробласты, пикноз ядер, сужение цитоплазмы. Грануло- и мегакариоцитарный ростки в пределах нормы, увеличено количество лимфоцитов.

Определение i антигена и АДА по техническим причинам не удалось.

Полученные данные позволили исключить постгеморагическую, гемолитическую анемии и заболевания, протекающие с аплазией костного мозга. На основании анализа анамнестических, клинических и параклинических данных: в частности, рождение ребенка от тяжелой беременности, наличие анемического синдрома с рождения, малоэффективность трансфузионной терапии, в переферической крови стойкая, прогрес-

сирующая, макроцитарная, гипорегенераторная анемия, в костном мозге резкое сужение эритроидного ростка на фоне сохранения лейко-тромбоцитопоэза, нормальные эритрометрические показатели, отрицательная реакция на скрытое кровотечение, нормальные показатели билирубина, трансаминаз, общего белка, сывороточного железа, отрицательная реакция Кумбса, отсутствие антител против вируса гепатита В и первовируса- $B_{19,}$ нормальные показатели периферической крови родителей – позволили предположить наличие эритробластопенической формы АА – анемии Дайемонда-Блекфена.

Было проведено лечение преднизолоном (1,5 мг/кг/сут), витаминами («С»,«Е», фолиевая кислота). На 6 день после начала стероидной терапии картина красной крови резко улучшилась (таблица 3).

Таблица 3. Показатели красной крови больного А.Ш. (22.10.2010)

Hb-82 г/л Эр-2,72 х 10^{12}/л Fi-0.87 Рет.-52 $^{0}/_{00}$	Морфоэритрограмма: нормохромия, нормо-, макроцитоз, встречаются единичные пойкилоциты

Наблюдая больного в динамике, отмечалось значительное улучшение общего состояния, он стал хорошо прибавлять в весе (меньше в длину). Месяц спустя после начала преднизолонотерапии стали снижать дозу гормона. Несмотря на наслоившуюся респираторную инфекцию и отит (пришлось подключить антибиотик), картина красной крови не ухудшилась.

Таблица 4. Общий анализ крови больного А.Ш. (19.11.2010)

Hb-90г/л Эр-3.14 х 10^{12}/л Fi-0.8 Рет.-$32^{0}/_{00}$ Лейк.-6,1 х 10^{9}/л Тр.-252 х 10^{9}/л СОЭ -11 мм/ч	Нейтрофилы: п-9% с-40,5% М –13% Э –3,0% Л – 34% Б – 0,5%
Морфоэритрограмма: анизоцитоз, за счет микро- нормо-макроцитов, пойкилоцитоз	

В связи с активацией эритропоэза и появлением на морфоэритрограмме микроцитов и пойкилоцитов, сочли необходимым повторно проконтролировать уровень сывороточного железа – оно оказалось пониженным (8,4 мкомоль/л), поэтому был подключен препарат железа (таблица 5).

Таблица 5. Общий анализ крови больного А.Ш. (02.12.2010)

Hb-90г/л Эр-3.5 х 10^{12}/л Fi-0.8 Рет.-$26^{0}/_{00}$ Лейк.-5,6 х 10^{9}/л Тр.-212 х 10^{9}/л СОЭ -9 мм/ч	Нейтрофилы: п-5% с-50% Э –5,0% М –7,5% Л – 32,5%
Морфоэритрограмма: нормохромия, нормо-, макроцитоз	

В динамике показатели периферической крови имели тенденцию к улучшению. Поэтому суточную дозу преднизолона снизили до 1 мг. Показатели красной крови спустя 6 недель приведены в таблице 6.

Таблица 6. Показатели красной крови больного А.Ш. (13.01.2011)

Hb-108 г/л Эр-4,02 х 10^{12}/л Fi-0.8 Рет.-19 $^{0}/_{00}$	Морфоэритрограмма: нормохромия, нормо-, макроцитоз, встречаются единичные микроциты и пойкилоциты.

В настоящее время больной получает 1 мг преднизолона 2 раза в неделю. Он находится в клинической и неполной лабораторной ремиссии (таблица 7). Наблюдение продолжается.

Таблица 7. Общий анализ крови больного А.Ш. (07.02.2011)

Hb-110г/л Эр-4,02 х 10^{12}/л Fi-0.8 Рет.-$12^{0}/_{00}$ Лейк.-6 х 10^{9}/л Тр.-300 х 10^{9}/л СОЭ -4 мм/ч	Нейтрофилы: п-1% с-42% М –11% Э –4% Л –41%
Морфоэритрограмма: нормохромия, нормо-, макроцитоз	

Таким образом, этот случай интересен в том плане, что в неонатальном периоде причиной анемического синдрома, правда редко, может быть АА. Поэтому, у новорожденных и детей раннего возраста, для установления истинных причин анемии, следует заострить внимание на показателе ретикулоцитов и при необходимости исследовать количественные и качественные показатели костного мозга.

Выражение признательности. Работа была выполнена в рамках проекта GNSF #460, при поддержке Грузинского национального научного фонда им. Ш. Руставели.

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SUMMARY

THE CONGENITAL PARCIAL ERITHROBLASTOPENIA - DIAMOND-BLACKFAN ANEMIA

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The article presents twenty-five year observation on 5 patients with Diamond-Blackfan anemia. In 2010 the new case of this pathology in neonate was diagnosed. Research suggests that rarely, the Diamond-Blackfan anemia may be may be the result of an aplastic anemia. To find out what the real cause of anemia is the number of reticulocytes and qualitative and quantitative indicators bone marrow should be investigated in newborns and infants.

Key words: Diamond-Blackfan congenital aplastic anemia.

РЕЗЮМЕ

НАСЛЕДСТВЕННАЯ ПАРЦИАЛЬНАЯ ЭРИТРОБЛАСТОПЕНИЯ - АНЕМИЯ ДАЙЕМОНДА-БЛЕКФЕНА

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Приведены результаты клнического наблюдения в течение 25 лет за 5 случаями наследственной парциальной эритробластопении – анемии Деймонда-Блекфена. В 2010 г. был выявлен новый случай у новорожденного, который интересен в том плане, что в неонатальном периоде причиной анемического синдрома, правда редко, может быть апластические анемии. Поэтому, у новорожденных и детей раннего возраста, для установления истинных причин анемии, следует заострить внимание на показателе ретикулоцитов и при необходимости исследовать количественные и качественные показатели костного мозга.

რეზიუმე

მემკვიდრეობითი პარციალური ერითრობლასტოპენია – დაიემონდ-ბლეკფენის ანემია

მ. კვეზერელი-კოპაძე. ყ. ფაღავა, ი. კორინთელი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

შრომაში მოყვანილია 25-წლიანი დაკვირვების შედეგები დაიემონდ-ბლეკფენის მემკვიდრეობითი აპლაზიური ანემიით დაავადებულ 5 პაციენტზე. 2010 წ. ჩვენ გვქონდა საშუალება გამოგვევლინა ამ პათოლოგიის ახალი შემთხვევა ახალშობილობის პერიოდში.

ТРОМБОЦИТОПЕНИЯ С АПЛАЗИЕЙ ЛУЧЕВОЙ КОСТИ – TAR-СИНДРОМ

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В последние годы значительно увеличилось число наследственных заболеваний среди неонатальной патологии. По данным ВОЗ наследственная патология выявляется у новорожденных [4,6].

Тромбоцитопения с аплазией лучевой кости – TAR-синдром является редким наследственным заболеванием, при котором тромбоцитопения ассоциируется с двухсторонней аплазией лучевой кости. TAR-синдром впервые был описан Г. Гроссом и соавт. в 1956 году. Главным диагностическим критерием является тромбоцитопения, которая выявляется в первые четыре месяца жизни практически в 100% случаев, а также двухсторонняя аплазия или гипоплазия лучевой кости. С возрастом число тромбоцитов увеличивается, однако их агрегация нарушена, уменшена продолжительность жизни. Мегакариоциты не выявляются в 66% случаев, а в 12% их количество снижается. Тромбоцитопенический криз может провоцировать стресс, инфекцию, хирургическое вмешательство и т.д. У 60-70% больных на первом году жизни отмечается лейкемоидная реакция, особенно в периоде кровотечений. В это время тромбоцитопения усугубляется и выявляется гепатоспленомегалия. Основной скелетной аномалией TAR-синдрома считается двухсторонняя аплазия или гипоплазия лучевой кости (100%), которая часто ассоциируется с аномалией кисти (ограничение выпрамления, радиальная девиация, гипоплазия костей пясти и фалангов, хотя сохранен первый палец), укорочена и деформирована локтевая кость. В единичных случаях отмечается ограничение движении в коленном суставе. В 30% случаев имеется врожденный порок сердца, чаще тетрада фалло и дефект предсердней перегородки, редко выявляется почечная патология, дивертикул меккеля, со стороны глаз - косоглазие, глаукома. В случае TAR-синдрома возможна умственная отсталость (ввиду мозгового кровоизлияния), в 35-40% случаев больные погибают от кровотечения [1-3,5].

Популяционная частота болезни не известна. Генетическим департаментом Университета Джона Гопкинса проанализировано 40 (27 по литературным данным и 13 собственных) случаев гипомегакариоцитной тромбоцитопении и двухсторонней аплазии или гипоплазии лучевой кости. В частности, гематологические осложнения обычно выявляются сразу после рождения или в неонатальном периоде. Тромбоцитопения может быть эпизодичной или сопровождаться лейкемоидной реакцией или эозинофилией. Изучение костного мозга показывает увеличенные или аномальные мегакариоциты. Прогноз благоприятный, если больной выживает к одному году жизни. Болезнь наследуется аутосомно-рецессивным путем. Соотношение полов 1:1. TAR-синдром, описанный С. Эдельбергом и соавт. значителен тем, что тромбоцитопения и аномалия верхних конечностей у девочки выявились с рождения, хотя она развивалась нормально и геморрагии не отмечались. В семейном анамнезе – брат скончался в возрасте 3 месяцев от тяжелой тромбоцитопении и пороков развития, в частности, аномалий костей. У 10-летней двоюродной сестры с двухсторонней аплазией лучевой кости гематологических изменений не отмечались.

Приводим короткое описание истории болезни новорожденного с диагнозом - тромбоцитопения с двухсторонней аплазией радиальной кости - TAR-синдром.

Больной Г., (ист. №3711) в 30-дневнем возрасте поступил в клинику с диагнозом: сепсис, некротический энтероколит. Со слов матери ребенок болеет с двухнедельного возраста. Заболевание началось кровяной рвотой, дегтеобразным стулом, сыпью на лице (видимо из-за геморрагии). Ребенок был госпитализирован в г. Батуми, лечение проводилось антибиотиками, гемотрансфузиями, симптоматическими средствами. Ввиду того, что состояние не улучшалось был переведен в г. Тбилиси. Ребенок от четвертой беременности и первых родов. Первые три беременности закончились естественным выкидышем. Мать лечилась по поводу хламидиоза. Наш больной родился в срок, с массой 3500, длиной 50 см, без асфиксии. Сразу же после рождения внимание привлекли аномалии конечностей (рис. 1).

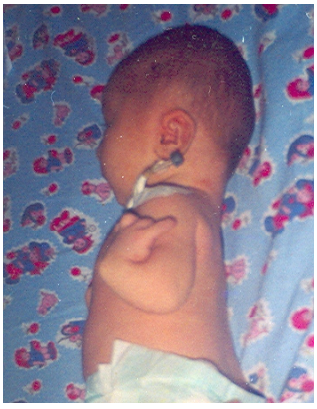

Рис. 1. Новорожденный с аномалией конечностей

При поступлении общее состояние тяжелое: ребенок адинамичный, бледный. На языке, твердом небе, деснах,

лице, ягодицах отмечались кровоизлияния. На туловище единичные петехии, а также кровотечение из желудка, мест инекций. На рентгенограмме верхних конечностей - двухсторонняя аплазия лучевой кости, деформированная и укороченная локтевая кость (рис. 2, 3).

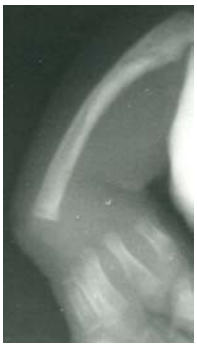

Рис. 2. Рентгенограмма верхних конечностей

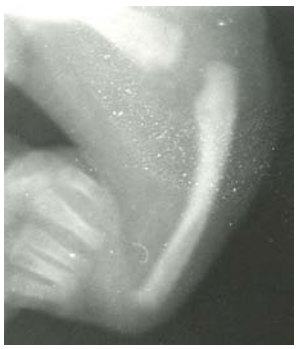

Рис. 3. Рентгенограмма верхних конечностей

Общий анализ крови выявил анемию, лейкоцитоз, тромбоцитопению, учащенное СОЭ. Со стороны внутренних органов патология не отмечалась. Ультрасонографическое исследование показало гипоксическо-ишемическое поражение мозга, единичные точечные геморрагии. Больной несколько раз был консультирован гематологом, генетиком. На фоне лечения состояние постепенно улучшилось, исчезли геморрагии, кровотечение прекратилось, пациент начал прибавлять в весе. Картина крови также улучшилась. Психо-моторное развитие ребенка соответствовало возрасту.

Таким образом, анамнестическими, клиническими, лабораторными, радиологическими и др. исследованиями, а также фенотипическим изучением пробанда был подтвержден диагноз моногенного синдрома с аутосомно-рецессивным типом наследования - тромбоцитопения с аплазией лучевой кости – TAR-синдром.

Выражение признательности. Работа была выполнена в рамках проекта GNSF #460, при поддержке Грузинского национального научного фонда им. Ш. Руставели.

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SUMMARY

THROMBOCYTOPENIA-ABSENT RADIUS – TAR-SYNDROME

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Thrombocytopenia-absent radius - TAR-syndrome is a rare condition in which thrombocytopenia is associated with bilateral radial aplasia. TAR syndrome was first described in 1956 by H. Cross et al. An autosomal recessive inheritance pattern was proposed because TAR affected more than one member of some families. The disease varies and includes abnormalities in the skeletal, hematological, cardiac, gastrointestinal and other systems. In article the 30 day infant with thrombocytopenia-absent radius - TAR-syndrome is described. The diagnose was confirmed by clinical, laboratory, radiological, genetic etc. investigations.

Key words: Thrombocytopenia-absent radius (TAR) syndrome.

РЕЗЮМЕ

ТРОМБОЦИТОПЕНИЯ С АПЛАЗИЕЙ ЛУЧЕВОЙ КОСТИ – TAR-СИНДРОМ

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Тромбоцитопения с аплазией лучевой кости - TAR-синдром, является редким наследственным заболева-

нием, при котором тромбоцитопения ассоциируется с двухсторонней аплазией лучевой кости. TAR-синдром впервые был описан Г. Гроссом и соавт. в 1956 году. Болезнь наследуется аутосомно-рецессивным путем. Симптоматика включает патологические изменения со стороны скелета, крови, сердечно-сосудистой, желудочно-кишечной и других систем. В статье описан случай TAR- синдрома у 30-дневнего ребенка. Диагноз был подтвержден анамнестическими, клиническими, лабораторными, радиологическими и другими исследованиями.

რეზიუმე

თრომბოციტოპენია სხივის ძვლის აპლაზიით - TAR-სინდრომი

ი. ფავლენიშვილი, ნ. მჭედლიშვილი, თ. გოთუა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი;
მ. იაშვილის სახ. ბავშვთა ცენტრალური კლინიკური საავადმყოფო, თბილისი, საქართველო

თრომბოციტოპენია სხივის ძვლის აპლაზიით - TAR-სინდრომი, ერთ-ერთი იშვიათი მემკვიდრეობითი დაავადებაა, რომლის დროსაც აღინიშნება თრომბოციტოპენია ასოცირებული სხივის ძვლის ორმხრივ აპლაზიასთან. TAR-სინდრომი პირველად აღწერა ჰ. გროსმა და თანაავტ. 1956 წელს. ამ აუტოსომურ-რეცესიული და მემკვიდრეობითი მონოგენური სინდრომის ძირითადი დიაგნოსტიკური სიმპტომატიკა მოიცავს ჰემატოლოგიურ, ძვლოვან, გასტრო-ინტესტინალურ გულ-სისხლძარღვთა და სხვა სისტემების პათოლოგიურ ცვლილებებს. აღწერილია 30 დღის ასაკის TAR-სინდრომით დაავადებული ბავშვი, რომელსაც ანამნეზური, კლინიკური, ლაბორატორიული, რადიოლოგიური და სხვა კვლევებით დაუდგინდა ეს იშვიათი დაავადება.

A CASE OF DiGEORGE SYNDROME IN GEORGIA

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DiGeorge syndrome or 22q11.2 deletion syndrome is an autosomal dominant syndrome resulting in defective development of the third and fourth pharyngeal pouches. There is considerable variability in phenotype based on the location and extent of microdelition.Overlapping syndromes includes velo-cardio-facial syndrome and Shprintzen syndrome [1-4].

The incidence is about 1: 4000 births and abnormal chromosome is usually inherited form mother [5]. The associated immunodeficiency is secondary to the plastic or hypo plastic thymus, where T-lymphocyte maturation occurs. Most patients have no or only mild immune defects. The term partial Disgorge syndrome is commonly applied to these patients with impaired rather than absent thymus function.

Clinical characteristics include congenital heart defects, hypocalcaemia due to hypoparathyroidism,distinctive craniofacial features,renal anomalies, and thyme hypoplasia. Presetation usually results from cardiac failure, or from hypocalcemia.Some signs and symptoms of DiGeorge syndrome can vary significantly in type and severityThey may be apparent at birth, but others may not appear while later in infancy or early childhood.Signs and symptoms may include some combination of the following:
-bluish skin due to poor circulation;
wakness or tiring easily;
failure to gain weight;
poor muscle tone;
twitching or spasms around the mouth, hands or throat;
fequent infections;
delayed development;
low set ears,wide-set eyes,narrow groove in the upper lip.etc.

Laboratory findings: laboratory evaluation typically reveals normal or decreased numbers of T lymphcytes with preserved T lymphocyte function.in the rare patient with absent or dysfunctional T lymphocytes, B lymphocyte

function may be abnormal as well.Diagnosis is confirmed via fluorescence in situ hybridization chromosomal analysis for the microdeletion on chromosome 22.

Materials and methods. Patient: 6 yy old boy was admitted to the clinic with following complaints: fever (39 C) for last 4 days, recurrent abdominal pain, cough. On presentation –child has development of 75 percentiles, high and broad nasal bridges, narrow palpebral fissures, small teeth. From previous history –child had surgery for cleft palate; recurrent otitis; two episodes of sezuires.

Results and their discussion. CT hyperplasia of mediastenal limph nodes, bilateral pleural effusions,right II and posterior basilar lung segments, VI –X left lung segments are showing inflammation, peritoneal effusions.

Heart ultrasound-VSD-14-17mm, slight dilatation of right atrium and ventricle.

Peritoneal effusion:1,5 L/per day from drainage, opaque,yellowish,proteins-33%,leucocytes-10-15 hpf, erythrocytes many in hpf, PMN-43%.MMN-57%.

Morphology-purulent inflammation.
Pleural exudate: xantochromic,proteins 9,9%, leucocytes-20-25 in hpf,PMN-29%,MMN-71%.
PCR for m.Tuberculosis-neg.

C-Xray- "wet" lung, low pneumatization, hypoplasia of thymus.
CBC:Hb 104 m/L, leucocytes-11x 10,9, bands-14-%,plt-63%,ESr-38mm/hr,CRP-20,Total protein-41,4;AST39(<59),ALT 28(39),creatinine-79mcm/L, hypocalcemia.
HCV-neg,HIV-neg,HBsAg-neg.
BC-neg.

Microbiological study of pleural effusion was positive for *Serratia spp*.

Preleminary diagnosis DiGeorge syndrome had to be confirmed by comprehensive immunological study. Total number of T lymphocytes was decreased. Further genetical study was positive for 22q11.2 deletion. The diagnosis of DiGeorge syndrome was confirmed. Patient was treated with broad spectrum antibiotics and was discharged home.

Conclusions :The immune deficiencies of childhood comprise numerous rare disorders that have been well characterized by a combination of clinical patterns,immunologic laboratory evidence. Immune deficiencies should be considered when infections are severe, persistent, resistant to standart treatment, or caused by opportunistic organisms. Clinical patterns and recurring infections with certain types of microbes are indicative of specific immune deficiencies.

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SUMMARY

A CASE OF DiGEORGE SYNDROME IN GEORGIA

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Patient 6 - year- old boy, with history of recurrent otitis, cleft palate, was admitted to the hospital for fever, abdominal pain; He had high ESR,CRP, low T lymphocytes, VSD. Peritoneal fluid was positive for pseudomona aeroginoza. Diagnosis of DiGeorge syndrome was confirmed by further genetical study. Immune deficiencies should be considered when infections are severe, persistent resistant to standard treatment, or caused by opportunistic organisms. Treatments can often correct many of the critical and immediate problems associated with DiGeorge syndrome such as heart defects, calcium defects, poor immune system functions and cleft palate. People who had poor immune function as children due to small or missing thymus, may have an increased risk of autoimmune disorders, such as a rheumatoid arthritis and Graves disease. Because DiGeorge syndrome can result in so many disorders, a number of specialists should be involved in diagnosing specific conditions, recommending treatments and providing care.

Key words: DiGeorge syndrome, immunodeficiency, congenital anomaly.

РЕЗЮМЕეფშы

КЛИНИЧЕСКИЙ СЛУЧАЙ СИНДРОМА ДиДЖОРДЖИ В ГРУЗИИ

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Пациент – мальчик, 6 лет поступил в клинику с высокой температурой, абдоминальной болью. Лабораторные данные - высокое СОЕ, С-реактивный белок, лимфопения, дефект межжелудочковой перегородки, перитонеальная жидкость дала положительный результат на *Serratia spp*. Множественные стигмы, расщелины неба; частые отиты подтверждали иммунодефицитное состояние, в частности, синдром ДиДжорджи, что в последствии было подтверждено генетическим обследованием. Иммунодефицитные состояния должны приниматься во внимание при рецидивирующих (особенно оппортунистических) инфекциях.

რეზიუმე

დიჯორჯის სინდრომის კლინიკური შემთხვევა საქართველოში

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[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ბავშვთა და მოზარდთა მედიცინის მიმართულება, [2]ყბა-სახის ქირურგიის დეპარტამენტი, საქართველო

პაციენტი – მამრობითი სქესის,6 წლის,კლინიკაში შემოვიდა ჩივილებით მაღალ ტემპერატურაზე, აბდომინალური ტკივილით, მრავლობითი დიზმორფული გამოვლინებები (ჰიპერტელორიზმი, ჰიპოგნათია, ყურის ნიჟარების არასტანდარტული დოგმა), ლაბორატორიული მონაცემები: მაღალი ედს, C-რეაქტიული ცილა, ლიმფოპენია, პარკუჭთა შუა ძგიდის დეფექტი, პერიტონეალური სითხის დადებითი შედეგი *Serratia spp*-ზე. ადრეული ანამნეზიდან საყურადღებოა 2 კრუნჩხვითი ეპიზოდი, სასის ნაპრალის გამო ჩატარებული ოპერაცია, ხშირი ოტიტი. ყოველივე ზემოთ აღნიშნული მიუთითებს იმუნოდეფიციტური პათოლოგიის, კერძოდ, დიჯორჯის სინდრომის არსებობაზე, რაც შემდგომში დადასტურდა გენეტიკური კვლევით.

მორეციდივე,განსაკუთრებით კი ოპორტუნისტული ინფექციის შემთხვევაში აუცილებელია გათვალისწინებულ იქნას იმუნოდეფიციტის არსებობა.

PEDIATRIC DRUG INDUCED HYPERSENSITIVITY SYNDROME: CASE REPORT

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Drug induced hypersensitivity syndrome (DIHS) is a rare but potentially life-threatening adverse drug reaction particularly associated with the anticonvulsant drugs. It has been estimated to occur in between 1 in 1000 and 1 in 10 000 exposures with antiepileptic drugs. Mortality is approximately 10% and is primarily associated with systemic organ involvement [2,3].

The clinical features of this syndrome include the stepwise development of multiorgan failure and frequent deterioration of clinical signs, such as fever, skin rashes and liver or renal dysfunction, occurring even other discontinuation of the causative drug. DIHS has been reported to occur in all age groups, but this multisystem disorder has not been emphasized in the pediatric literature. However, accurate and timely diagnosis in the pediatric patient may be particularly challenging as 2 salient features of the syndrome, fever and rash, are common nonspecific signs of illness in children. An infectious cause, particularly viral illness, frequently is the initial diagnosis and may delay the discontinuation

of the responsible medication. Mortality is approximately 10% and is primarily associated with systemic organ involvement, such as liver dysfunction, renal impairment, and interstitial pneumonitis [1,4].

No controlled trials have demonstrated effectiveness of any modality of treatment in patients with DHS. There are several reports describing improvement in patients with DHS during treatment with systemic glucocorticoids [5].

Aim: We describe the case of a patient who suffered from DHS caused by valproic acid. Our experience suggests glucocorticoids (GC) may be of benefit to children with severe DHS.

Materials and methods. A 10 year old girl presented 45 days after initiation of valproic acid therapy with a 3-day history of fever. She treated with ampicillin, after 2 days, her primary care physician discontinue the ampicillin because rash over most at her body, and was given ceftriaxone. He was hospitalized 3 days later because fever, worsening rash, arthralgia. Discontinued ceftriaxone, but did not discontinue valproic acid. After 6 days he was hospitalized in our clinic because a generalized rash, fever, diffuse swelling, arthralgia, limpadenopaty, oliguria, hepatosplenomegaly.

Abnormal laboratory studies included white blood cell count was 25×10^9 leukocytes/L, 26% eosinopilia, alanine aminotransferase of 335 (normal 0-43 U/L), aspartate aminotransferase of 380 (normal 0-37 U/L), direct bilirubin 62,2 (4,3 mcmole/L), indirect bilirubin 31,5. Blood urea nitrogen and creatinine was normal.

Titers were negative for hepatitis A, B, C, Epstein-Barr virus, human immunodeficiency virus, cytomegalovirus. Throat, blood, stool, urine, and intravenous line catheter cultures all were negative for pathogens.ANA, ds DNA, SMA, ANF, LKM, C3, C4 complement were negative. A diagnosis of DIHS was made 4 days after hospitalizations.

During the remainder hospitalization patient had worsening hepatitis. alanine aminotransferase of 876 (normal 0-43 U/L), aspartate aminotransferase of 504 (normal 0-37 U/L) , lactate dehydrogenase of 2551 (normal 225-450 unit/L), direct bilirubin 80.9 (4,3 mcmole/L), indirect bilirubin 44.4 .Aptt- 66 (normal 23.8-36.6), PT- 19,8" (normal 8"-14"), prothrombin index - 45% (normal 70-110%), INR- 1,82 (normal < 1.2).

Results and their discussion. On the first hospital day oral prednizolone therapy at 40 mg/day was started, and on the second day valproic acid therapy was discontinued. The fever resolved and she showed overall clinical improvement. Over the ensuring 6 days, the dermatitis worsened, cervical lymph node became enlarged, but prednizolone was continued in a same dose. After 8 days she showed clinical improvement.

After 18 days, the patient no evidence of rash mucosal involvement, edema, eosinophilia, hepatic function remained normal. She was discharged on a very gradual steroid taper. Alternative antiepileptics were not instituted.

We are observing the patient in course of disease. Clinical-laboratory remission has been reached. We are reducing the prednizolone.

Prompt recognition of DIHS and immediate discontinuation of the causative drug is of utmost importance in the treatment of these patients to prevent or minimize more serious sequel involving other organs. Timely diagnosis and discontinuation of the medication undoubtedly will reduce the morbidity of DIHS. Our experience suggests glucocorticoids may be of benefit to children with severe DIHS.

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SUMMARY

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Drug induced hypersensitivity syndrome (DIHS) is a rare but potentially life-threatening adverse drug reaction particularly associated with anticonvulsant drugs.

We describe the case of a patient who suffered from DIHS caused by anticonvulsant. Our experience suggests glucocorticoids (GC) may be of benefit to children with severe DIHS.

Key words: drug induced hypersensitivity syndrome, hypersensitivity syndrome, antiepileptic hypersensitivity syndrome, drug reaction.

РЕЗЮМЕ

ЛЕКАРСТВЕННО ИНДУЦИРОВАННЫЙ ГИПЕРСЕНСИТИВНИЙ СИНДРОМ

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Лекарственно индуцированный гиперсенситивный синдром (ЛИГС) - редкое заболевание, является одним из потенциально жизнеугрожающих состояний, которое развивается, в основном, при потреблении антиконвульсантов. Клиническое проявление этого синдрома включает в себя постепенное развитие недостаточности внутренних органов.

Болезнь проявляется в виде повышения температуры, кожной сыпи, почечной и печеночной недостаточности.

ЛИГС описан во всех возрастных группах, в том числе и детском возрасте. Своевременное установление точного диагноза весьма затруднительно, так как жар и кожная сыпь являются частым неспецифическим проявлением многих заболеваний в педиатрии. Смертность при ЛИГС достигает 10%, в основном, за счет системного поражения органов, что проявляется в почечной и печеночной недостаточности, интерстициальном пневмоните. Контролированных исследований, относительно схемы лечения ЛИГС не проведено, имеются данные об эффективности системных глюкокортикоидов при данном синдроме.

У нас была возможность наблюдать 10-летнюю девочку, у которой после приема вальпроевой кислоты развился ЛИГС. Наш опыт показал эффективность глюкокортикоидов при лекарственно индуцированном гиперсенситивном синдроме.

რეზიუმე

წამლით ინდუცირებული ჰიპერსენსიტიური სინდრომი

მ. იოსელიანი, მ. ლეკიშვილი

მ. იაშვილის სახ. ბავშვთა ცენტრალური საავადმყოფო, თბილისი, საქართველო

წამლით ინდუცირებული ჰიპერსენსიტიური სინდრომი (წიჰს) განეკუთვნება იშვიათ, სიცოცხლისთვის საშიშ დაავადებათა ჯგუფს, იგი ძირითადად ვითარდება ანტიკონვულსანტების გამოყენების ფონზე.

წიჰს სინდრომის ძირითადი კლინიკური გამოვლინებებია: ცხელება, გამონაყარი კანზე, ღვიძლისა და თირკმლის უკმარისობა.

წიჰს აღწერილია სხვადასხვა ასაკობრივ ჯგუფებში, მათ შორის ბავშვებშიც. ამ დაავადების დროული დიაგნოსტიკა ზედმიწევნით რთულია, ვინაიდან ცხელება და გამონაყარი რამდენიმე ათეული დაავადების ხშირი და არასპეციფიური გამოვლინებაა. სიკვდილობა დაახლოებით 10%-ს აღწევს. იგი ძირითადად შინაგანი ორგანოების სისტემური დაზიანებით-ინტერსტიციული პნევმონიტით, თირკმლისა და ღვიძლის უკმარისობით არის განპირობებული.

არ არსებობს წიჰს მკურნალობის დაზუსტებული სქემა. დაავადების გამომწვევი პრეპარატის დაუყოვნებელი მოხსნა და მკურნალობის დროული დაწყება საგრძნობლად აუმჯობესებს დაავადების გამოსავალს. არსებობს მონაცემები გლუკოკორტიკოიდების გამოყენების ეფექტურობის შესახებ.

ჩვენ წარმოგიდგენთ 10 წლის გოგონას, რომელსაც ვალპროატის მჟავის გამოყენების ფონზე განუვითარდა წიჰს. აღნიშნულმა შემთხვევამ დაადასტურა გლუკოკორტიკოიდების გამოყენების ეფექტურობა აღნიშნული დაავადების დროს.

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RARE TUBULOPATHY - PRIMARY HYPOPHOSPHATEMIC RICKETS (CASE REPORT)

[1]Tsanava M., [1]Abuladze T., [1]Zenaishvili B., [2]Kvaratskhelia E., [3]Pagava K.

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[2]Center For Endocrinology, Metabology and Nutrition, Tbilisi;
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Primary, the same as Hereditary, Hypophasphatemic Rickets (HHR) (phosphatdiabetes) were originally described by Albright et al. as rickets resistant to vitamin D therapy. HHR include X-linked, autosomal dominant (ADHR) and autosomal recessive (ARHR) disease, as well as hypophosphatemic rickets with hypercalciuria (HHRH). The X-linked form is most common, with incidence approximately one case per 20000 live births; the other forms are rare, with fewer than 100 reported case.In some cases it appears to arise by spontaneous mutation. The pathogenesis of X-linked hypophosphatemic rickets is not fully understood. A number of functional studies indicate that the tubular defect in patients with XLH and in the corresponding mouse model (Hyp mouse) is caused by one or more circulating factors (eg. fibroblast growth factor 23 (FGF23) that causes renal phosphate wasting and is a common final pathway). The gene responsible for XLH was identified on chromosome Xp22.1 and named PHEX. PHEX is expressed predominantly in bone and teeth. Mutations in PHEX (in bone tissue) indirectly alter the degradation and production of FGF23,wich inhibit phosphate reabsorption. Elevated levels of FGF23 also appear an important common pathway for other forms of hereditary hypophosphatemic rickets, as well as tumor-induced osteomalacia. ADHR rickets results from activating mutations in the fibroblast growth factor 23 (FGF23) gene on chromosome 12p13 when ARHR is caused by inactivating mutations in the DMP1 gene, which encodes Dentin matrix protein 1 and results in increased FGF23 expression and defective osteocyte maturation.

HHR usually manifested in infancy and childhood by stunting of growth, deformities of the lower limb. Patients have hypophosphatemia, normocalcemia,normal levels of parathyroid hormone and an elevated serum alkaline phosphatase activity. Clinical features also include coxa vara, genu valgum and pelvic deformities. The corresponding radiological findings are rickets in the epiphysis and metaphysis with a widening of the bone shaft and a loose reticular pattern of bone trabuculae. Enamel formation of the teeth is normal, but dentin formation (intraglobular dent) is defective. Serum P is very low, ranges between 1,0-2,5mg/dl (0,32-0,86 mmol/l). Serum Ca usually is in the low normal range. Urinary Ca excretion is low, urinary P excretion is high. Despite hypophosphatemia the reabsorption of P in relation to glomerular filtration rate (GFR) is low, as reflected by a TmPO4/GFR ration of <1,8mg/100 ml in comparison to normal childhood values of 4, 5 to 8, 0. Normal plasma calcidiol concentration and normal or slightly reduced plasma calcitriol concentration suggests that calcitriol synthesis is abnormal in HHR because calcitriol is expected to be elevated in the presence of hypophosphatemia. The defect appears to be at the level of translation of the 25(OH)D-1alpha-hydroxylase mRNA . The fecal concentration of both Ca and P is elevated. Despite a reduction in intestinal calcium absorption, the circulating values of iPTH are normal and rise after oral P therapy**.** The current therapy for HHR has been used for more than 20 years and consists of the oral administration of phosphate and calcitriol. Calcitriol is administered in two doses per day (10 to 20 ng/kg per dose). Phosphorus is administered in four to five doses that are equally spaced throughout the 24-hour period; the starting dose is 40 mg of elemental phosphorus/kg per day. A nighttime dose is important to achieve satisfactory results. Some catch-up growth should be noticeable within the first year of therapy. If this does not occur despite good compliance, the daily phosphorus dose should be increased in steps of 250 mg to 500 mg up to a maximum of 3500 mg/day. Slow growth and persistently elevated alkaline phosphatase activity indicate inadequate dose of phosphorus or compliance with therapy. Since the aim of treatment is to achieve normal growth, therapy is maintained as long as the growth plates are open (usually up to the age of 15 to 17 y).

Case report: Female patient, 12 years old, was presented to the nephrology department of Tbilisi Jvania pediatric clinic at the age of 2 with deformation of legs and difficulties with walking.

Patient was born to healthy parents, at 41 weeks of gestation by normal delivery and had a normal birth weight and length. She had one healthy sibling (male).

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Table. The diagnosis of primary hypophosphatemic rickets was based on the following biochemical data

Investigations	Results (before treatment)	Normal Values
Serum CA	2,39	(2,1-2,7) mmol/l
Serum Phosphate	0,68	(1,05-,8)mmol/l
Serum alkaline phosphatase	1169	(<300) U/l
Serum PTH	68, 31	(16-62,0) ng/ml
24-hr urine Ca	2,5	(<6,2)mmol/l24h
24-hr urine phosphate	15	(< 15-35) mmol/24hr
Renal Phosphate clearance	18,32	< 10 ml/min
Phosphate Tubular Reabsortion (PTR)	52%	> 80%
Phosphate Clearance/Cr Clearance=	0,52	N< 0,15
TmP/GFR	0,25	(0,8-1,35) mmol/l

Treatment was started with inorganic phosphate (50-100 mg/kg/d) and calcitriol 40-50 ng/kg/d.

Follow-up. Now she is almost 12 years old, her height SDS is -3,78, bone age is approximately 8 years (Greulich & Pyle), her predicted height is much less than Target height (Fig. 1.2), she has multiple skeletal deformities (Fig. 3,4). Resulats of several biochemical investigations are shown in Fig. 5-6.

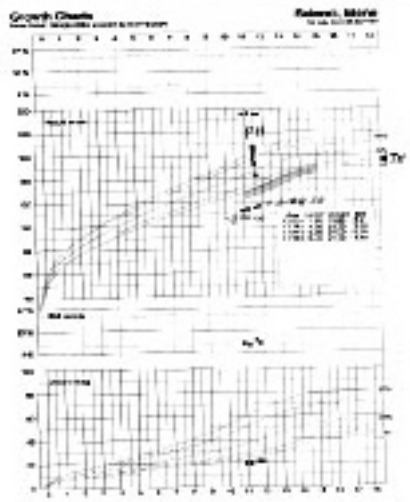

Fig.1 Physical development (Growth Chart) of the patient

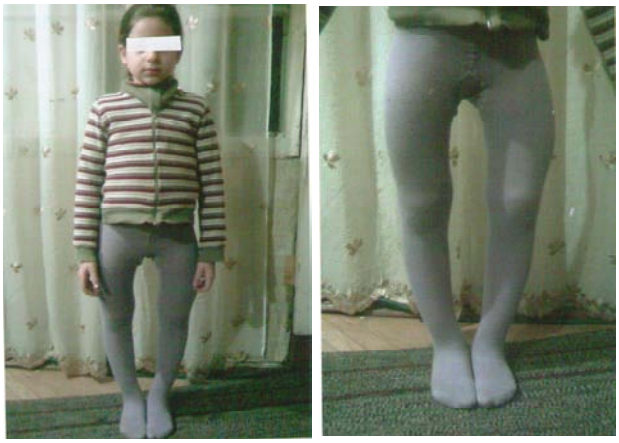

Fig. 2. Current appearance of the patient (age 10 years)

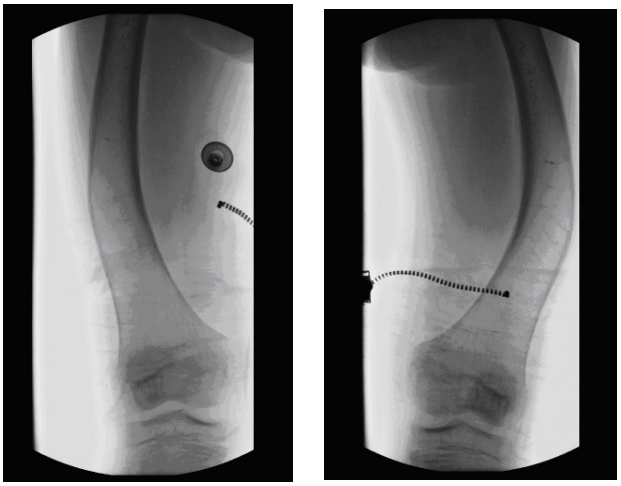

Fig. 3. Deformities of legs

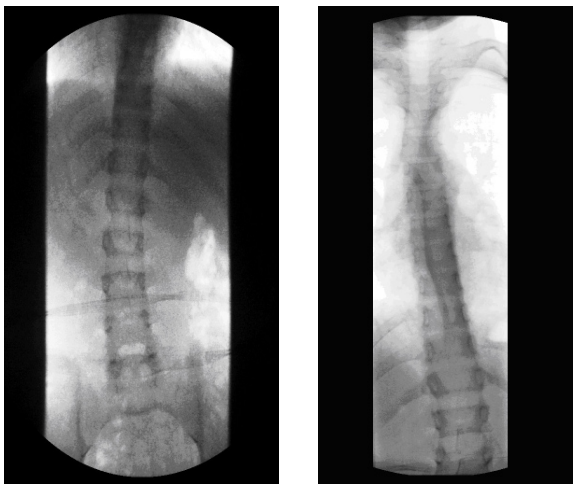

Fig. 4. Skeletal deformities

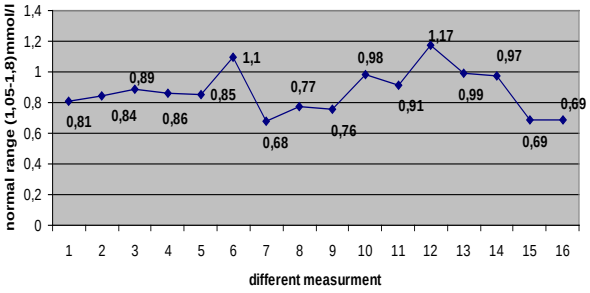

Fig. 5. Serum Phosphor concentration before and during treatment

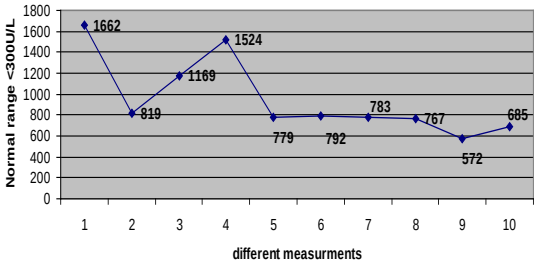

Fig. 6. Alkaline Phosphatase concentration before and under the trearment

Our patient has hypophosphatemic rickets characterized by growth retardation, leg and skeletal deformities, persistant hypophosphatemia and some other tubular abnormalities(glucosuria, proteinuria). Supposedly, in this case we have to deal with the sporadic version of the disease. We also plan to undergo a genetic analysis of our patient. After long-term P and calcitriol therapy some clinical signs were improved such as walking abilities, leg deformities, but auxological parameters still remain under the normal ranges, O-legs are still remarkable and biochemical markers stay still abnormal. At this stage of the disease, the question of referring to the growth hormone therapy is being considered aimed to improve the growth tendencies. It is possible that orthopedic surgery is also needed in the future.

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SUMMARY

RARE TUBULOPATHY - PRIMARY HYPOPHOSPHATEMIC RICKETS (CASE REPORT)

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[1]G. Zhvania Pediatric Clinic, Department of nephrology, Tbilisi; [2]Center For Endocrinology, Metabology and Nutrition, Tbilisi; [3]Tbilisi State Medical University, Georgia

Primary hypophosphatemic rickets is a rare disorder caused by inborn defect of renal tubular reabsorbtion and usually manifested in childhood and infancy with stunted growth and deformities of lower limbs.

Patient 12 years old, female, was born to healthy parents, at 41 weeks of gestation by normal delivery and had a normal birth weight and length. She had one healthy sibling (male).

Psychomotor development until the age of 2 years was normal. Since the age of 2 years deformation of legs and difficulties with walking have been observed. The Patient was consulted by Pediatric Orthopedist, Nephrologists and Endocrinologist. The blood biochemical findings revealed normal pH, normal calcium (CA), potassium (K), sodium (Na) concentrations, very low phosphate (P) with markedly elevated alkaline phosphatase (AP) and slightly elevated parathyroid hormone (PTH) concentration; urine test indicated impaired tubular function: mild glucosuria, proteinuria, and markedly increased phosphaturia. Phosphate tubular reabsorbtion (PTR) was 52%, phosphate/creatinine clearance 0,52, renal threshold phosphate concentration (TmP/GFR) 0,25 mmol/l. Genetic tests results not available yet. Results: the diagnosis of phosphate diabetes made on the basis of clinical-laboratory data. The therapy with Inorganic phosphate (50-100mg/kg/d)

and 1,25(OH)D3 40-50 ng/kg/d had been started. Childs walking abilities improved with treatment, the deformation of legs decreased, but O-legs and other skeletal deformations are still remarkable. Auxological parameters are not satisfactory.

Physical growth is below the normal range (height SDS -3,78); the patient's predicted height less than target height. Biochemical monitoring performed regularly under the treatment, serum phosphate remains below normal, serum ALP is still elevated. Conclusion: This case is in line with other publications and indicates the difficulty to achieve normal phosphate levels and normal growth without an additional treatment with growth hormone. At this stage of the disease, the question of referring to the growth hormone therapy is being considered aimed to improve the growth tendencies. It is possible that orthopedic surgery is also needed in the future.

Key words: primary hypophosphatemic rickets, biochemical monitoring, growth hormone therapy.

РЕЗЮМЕ

РЕДКАЯ ТУБУЛОПАТИЯ – ПЕРВИЧНЫЙ ГИПОФОСФАТЕМИЧЕСКИЙ РАХИТ (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Первичный гипофосфатемический рахит (фосфатдиабет) редкое наследственное, рахитоподобное заболевание, при котором нарушена реабсорбция фосфора в канальцах почек.

Пациент 12 лет, девочка, родилась от здоровых родителей, в срок, с нормальным весом и ростом. До 2 лет развивалась хорошо. После 2 лет появились проблемы с ходьбой, деформации нижних конечностей. Девочка была консультирована детским ортопедом, нефрологом, эндокринологом. Биохимические исследования крови выявили нормальный уровень PH, кальция, натрия, калия, весьма низкий уровень фосфора - 0,68 ммоль/л, очень высокий щелочной фосфатазы - 1169 е/л. Незначительно была увеличена концентрация паратиреоидного гормона. На нарушение тубулярных функций почек указывала глюкозурия, протеинурия, резко выраженная фосфатурия. Канальцевая реабсорбция фосфора составляла 52%, почечный порог концентрации фосфора - 0,25 ммоль/л. Диагноз был поставлен на основании вышеуказанных клинико-лабораторных данных.

Пациенту назначено лечение неорганическим фосфатом (50-100 мг/кг/в сутки) и 1,25(OH)D3 (кальцитриол) - 40-50 нг/кг/в сутки. На фоне лечения уменьшилась деформация нижних конечностей, улучшилась двигательная функция. Физическое развитие отстает от возраста (SDS роста - 3,78). Мониторинг биохимических данных постоянно выявляет низкий уровень фосфора и высокий уровень щелочной фосфатазы.

Данный клинический пример доказывает, что, несмотря на лечение фосфатдиабета фосфатами и кальцитриолом, невозможно обеспечить нормальный уровень фосфора в крови и нормальное физическое развитие ребенка. На данном этапе дискутируется вопрос о применении гормона роста в комплексе лечения. Не исключается необходимость в ортопедической операции.

რეზიუმე

იშვიათი ტუბულოპათიის - პირველადი ჰიპოფოსფატემიური რაქიტის კლინიკური შემთხვევა

[1]მ. ცანავა, [1]თ. აბულაძე,[1]ბ. ზენაიშვილი,[2]ე. კვარაცხელია,[3]ყ. ფაღავა

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პირველადი ჰიპოფოსფატემიური რაქიტი (ფოსფატდიაბეტი) იშვიათი მემკვიდრეობითი დაავადებაა, ხასიათდება თირკმლის მილაკში ფოსფორის რეაბსორბციის დარღვევით და ქვედა კიდურების დეფორმაციით.

პაციენტი - 12 წლის გოგონა, დაიბადა დროული, ნორმალური წონის და სიგრძის. ჰყავს ჯანმრთელი მშობლები და ძმა. 2 წლამდე ვითარდებოდა კარგად. 2 წლის შემდეგ დაეწყო კიდურების დეფორმაცია, გაუძნელდა სიარული, რის გამოც იგი კონსულტირებული იყო ბავშვთა ორთოპედის, ნეფროლოგისა და ენდოკრინოლოგის მიერ. სისხლის ბიოქიმიურმა კვლევამ გამოავლინა: სისხლის PH-ის, კალციუმის, კალიუმის, ნატრიუმის ნორმალური კონცენტრაცია, ფოსფორის ძალიან დაბალი დონე სისხლში - 0,68 მმოლ/ლ, ძალიან მაღალი ტუტე ფოსფატაზა - 1169ე/ლ,მცირედ მომატებული პარათირეოიდული ჰორმონის კონცენტრაცია. შარდის ანალიზით - ზოგიერთი ტუბულარული ფუნქციის დაქვეითება ზომიერი გლუკოზურიის, პროტეინურიისა

და მნიშვნელოვანად მომატებული ფოსფატურიის სახით. ფოსფორის მილაკოვანმა რეაბსორბციამ შეადგინა 52%,ფოსფორის/კრეატინინის კლირენსი - 0,52, ფოსფორის კონცენტრაციის თირკმლის-მიერი ზღურბლი - 0,25 მმოლ/ლ. დიაგნოზი დაისვა ზემოაღწერილი კლინიკურ-ლაბორატორული მონაცემების საფუძველზე.

პაციენტს ჩაუტარდება მკურნალობა არაორგანული ფოსფატით (50-100 მგ/კგ/დღე-ღამეში), 1,25(OH)D3 (კალციტრიოლი)-ით - 40-50ნგ/კგ/დღე-ღამეში მკურნალობის ფონზე გაუმჯობესდა მოძრაობა, შემცირდა ქვედა კიდურების დეფორმაციის ხარისხი, თუმცა რჩება 0-ის მაგვარი ფეხები და ჩონჩხის სხვა დეფორმაციები. ფიზიკური განვითარება ჩამორჩება ასაკს (სიმაღლის SDS -3,78), ბიოქიმიური მაჩვენებლების მონიტორინგი მუდმივად ავლენს ჰიპოფოსფატემიას და მაღალ ტუტე ფოსფატაზას.

აღწერილი კლინიკური შემთხვევა ადასტურებს, რომ, მიუხედავად ფოსფატებითა და კალციტრიოლით ხანგრძლივი მკურნალობისა, შეუძლებელია სისხლში ფოსფორის ნორმალური დონის და ბავშვის ნორმალური ფიზიკური განვითარების უზრუნველყოფა, რაც მკურნალობაში ჰორმონის ჩართვის აუცილებლობის საკითხს სვამს. დისკუსია ამ საკითხზე მიმდინარეობს. არ არის გამორიცხული მომავალში ორთოპედიული ოპერაციის ჩატარების საჭიროებაც.

ENCEPHALOCELE AND SKELETAL MALFORMATIONS (CASE REPORT)

[1]Ghonghadze T., [1]Lekiashvili M., [1]Gogatishvili T., [2]Pagava K.

[1]G. Zhvania Pediatric Clinic; [2]Tbilisi State Medical University, Georgia

Encephalocele – meningoencephalocele - is a herniation of the brain and/or the meninges through a defect in the skull (cranium bifidum). The mechanism is uncertain, although it involves defective closure of the anterior neural tube. Lesions are thought to result from defective separation of neural and surface ectoderm at the site of final closure of the rostral neuropore. The protruding sac may be pedunculated or sessile. Its size can range from a small nubbin of tissue to larger than the cranium. Encephaloceles are generally classified as nasofrontal, nasoethmoidal, or naso-orbital, however, there can be some overlap in the type of encephalocele. If the bulging portion contains only cerebrospinal fluid and the overlaying membrane, it may be called a meningocele. If brain tissue is present, it may be referred to as an encephalomeningocele. The sac may be completely covered by skin or only a thin parchment-like membrane. Vascular abnormalities of the scalp may be adjacent to or overlying the mass. If the defect consists only of a simple hole in the cranium, without protrusion of meninges or brain, it is known as cranium bifidum occultum [1].

Epidemiology. Its incidence has been estimated as 0.8 to 5 per 10,000 live births [1]. Encephaloceles occur rarely, at a rate of one per 5,000 live births worldwide. Encephaloceles of the back of the head are more common in Europe and North America, while encephaloceles on the front of the head more frequently occur in Southeast Asia, Africa, Malaysia, and Russia [2,3]. Classification – occipital (75%), fronto-ethmoidal (13-15%), parietal (10-12%), sphenoidal, nazo-frontal, nazo-ethmoidal, nazo-orbital (1.3%).

Risk Factors: family history of Spina bifida or anencephaly (other neural tube defects), Folic acid deficiency [5-8]. Ethnic, genetic, and environmental factors, teratogens, parental age, can all affect the likelihood of encephaloceles.

Postnatal symptoms depend mainly on the defect size and its content. Encephaloceles are often accompanied by craniofacial abnormalities or other brain malformations. Symptoms may include neurologic problems, hydrocephalus (cerebrospinal fluid accumulated in the brain), spastic quadriplegia (paralysis of the limbs), microcephaly (an abnormally small head), ataxia (uncoordinated muscle movement), developmental delay, vision problems, mental and growth retardation, and seizures. Malformations and chromosome anomalies are described in 60% of cases [9-11].

Early Antenatal ultrasonogrphy is a valuable diagnostic tool. Encephaloceles have been diagnosed on ultrasound from about 13 weeks. With ultrasonography (US) scanning, the diagnosis is based on the herniation of a spherical, fluid-filled structure, more correctly diagnosed as a meningocele or brain parenchyma (encephalocele) beyond the calvarial confines. Increased level of alpha-fetoprotein in mothers serum (gestation age 16-18 weeks) is seen in only in 3%, because the defect is covered by skin [9-11].

Only 20% of fetuses with encephalocele are able to be born alive and only half of them are viable. The only effective treatment for encephaloceles is reparative surgery, generally performed during infancy. The extent to which it can be corrected depends on the location and size of the encephaloceles. Only 3% of patients have chance to survive [4]. Existence of brain tissue within the hernia sac greatly decreases survival chance.

Recovery is difficult to predict prior to surgery, and depends on the type of brain tissue involved and location of the encephaloceles. If surgery is successful, and developmental delays have not occurred, a patient can develop normally.

Prognoses: depends on the content and size of encephalocele. Outcome depends on accompanying illnesses.

Folic acid (400mkg daily until pregnancy and during first 2 months) has been shown in order to reduce the risk of having a child with Neural tube defects, although the mechanism is not well understood [5-8].

We document a case of a huge fronto-ethmoidal encephalocele of the patient V.K, born on 22.04.2009 – who was diagnosed with bronchogenic pneumonia and was under treatment in the infant therapeutic department. As the co-existing illnesses, there were multiple developmental anomalies - encephalocele, amniotic knots, foot deformity, sindactilia, cleft palate. The pregnancy was presumably undesirable, because other important ethiological factors couldn't be displayed from anamnesis due to the parent's deprivation. From clinical signs there was depicted tumorous formation in the middle area of the forehead (Fig. 1-4). Amniotic knots on lower third of both shins, foot deformity (which might have been developed due to that), sindactilia of left hand - the bone form, sindactilia on the right hand - the skin form.

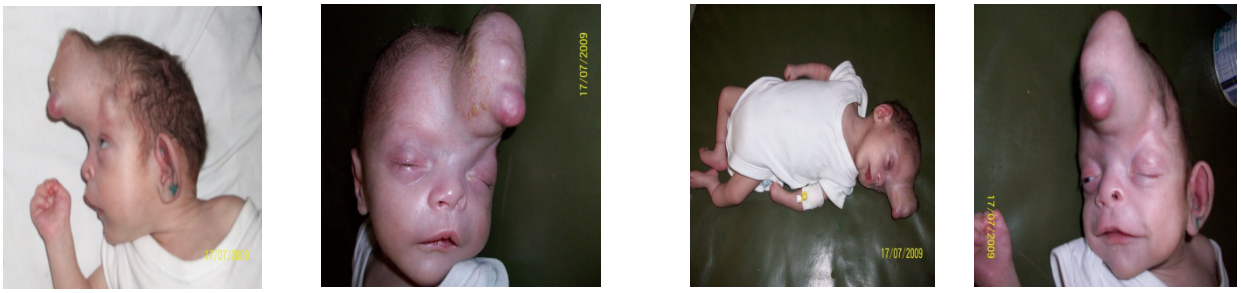

Fig. 1-4. Patient V.K, 3 months old, with huge fronto-ethmoidal encephalocele

Differential diagnose was made with Meckel-Gruber syndrome – it is a congenital disorder characterized by encephalocele, microphthalmy, microcephaly, polydactyly, cleft palate/lip and polycystic kidneys**.**

Examinations: On craniogram – sliding of skull bones. Homogeneous soft tissue formation on fronto-sincipital area.

Neurosonography with ultrasonography (US) scanning revealed increased echogenicity of the brain tissue. The diagnosis was based on the herniation of a spherical, fluid-filled structure, slight asymmetry of side ventricles, moderate dilatation and preserved liquor dynamics. Scanning of timorous formation reflected brain parenchyma (Fig. 5-8).

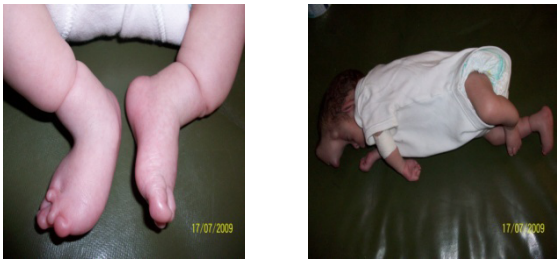

Fig. 5,6. Patient V.K, 3 months old, lower extremities, amniotic knots, sindactilia

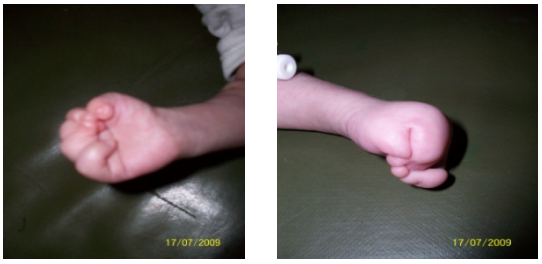

Fig. 7,8. Patient V.K, 3 months old, upper extremities, sindactilia

Radiological analysis displayed some backwardness of phalanges of both feet, existence of callosity under the bones of both shins. Straight view of both forearms revealed membranous syndactilia on the left, phalanges could not be visualized because of deformation. And finally, recommendations to women of reproductive age: in order to prevent development of neural tube anomalies, according to their pregnancy plan, there must be necessity of folic acid intake and monitoring of pregnancy course.

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SUMMARY

ENCEPHALOCELE AND SKELETAL MALFORMATIONS (CASE REPORT)

[1]Ghonghadze T., [1]Lekiashvili M., [1]Gogatishvili T., [2]Pagava K.

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Encephalocele is a herniation of the brain (cranium bifidum, cephalocele, craniocele), formed during embryonic development, because of the incomplete closure of Neural Tube. It is a rare skull defect, with the incidence of 0.8 to 5 per 10,000 live births. The article presents the medical history of a four month old patient, with frontoethmoidal encephalocele and multiple skeletal anomalies, such as amniotic knots on limbs, foot deformity, sindactilia and cleft palate.

Key words: encephalocele, sindactily, cleft palate, amniotic knots, foot deformities.

РЕЗЮМЕ

ЭНЦЕФАЛОЦЕЛЕ И МАЛЬФОРМАЦИИ КОСТНОЙ СИСТЕМЫ (СЛУЧАЙ ИЗ ПРАКТИКИ)

[1]Гонгадзе Т.В., [1]Лекиашвили М.М., [1]Гогатишвили Т.О., [2]Пагава К.И.

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Энцефалоцеле - энцефаломиелоцеле – врожденная черепно-мозговая грыжа, редкий порок, является следствием нарушения развития костей черепа и головного мозга в ранних стадиях эмбриогенеза; распространение – 0,8-5 случаев на 10000 живого новорожденного. В работе представлена история болезни 4-месячного пациента с фронто-этмоидальной энцефалоцеле и множественными аномалиями костно-суставной системы - амниотические перетяжки нижней части голеней, косолапость, синдактилия (костная и кожная) и незаращение неба.

რეზიუმე

ენცეფალოცელე და ძვლოვანი სისტემის მალფორმაციები (კლინიკური შემთხვევა)

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[1]გ. ჟვანიას სახ. პედიატრიული კლინიკა; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ენცეფალოცელე – ენცეფალომენინგოცელე - თავის ტვინის თიაქარი (cranium bifidum, cephalocele, craniocele) ვითარდება ემბრიონული განვითარების დროს ნერვული ღეროს არასრული დახურვის შედეგად. ეს არის ქალა–ტვინის იშვიათი ანომალია. ინციდენტე - 0.8-5 შემთხვევა 10000 ცოცხლადშობილ ბავშვზე. სტატიაში წარმოდგენილია 4 თვის პაციენტის ავადმყოფობის ისტორია,რომელსაც აღენიშნებოდა ფრონტოეთმოიდალური ენცეფალოცელე და ძვალსახსროვანი სისტემის მრავლობითი ანომალია - კიდურებზე ამნიოტური გადანაჭდევები, ტერფმრუდობა, სინდაქტილია და სასის ნაპრალი.

Conference review

"INTERNATIONAL CONFERENCE ON RARE DISEASES IN TBILISI, 2010"

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The "International Conference on Rare Diseases" took place in Tbilisi, Georgia on September 10-11, 2010. It happened so that it became the first one dedicated to this topic in Southern Caucasus.

The conference was organized by the Georgian Foundation for Genetic and Rare Diseases, JSC Traumatologist and Tbilisi State Medical University, namely, Department of Child & Adolescent Medicine. The event enjoyed a substantial backing rendered by the Charity-Humanitarian-Foundation "SOCO", and its director and founder Sandra Elisabeth Roelofs, the First Lady of Georgia, within the framework of the "SOCO" project "Alliance for Rare Diseases". The following institutions and organizations provided valuable organizational and financial support as well: National Center for Disease Control and Public Health; Health & Social Program Agency; Georgian Association of Dermatovenerologists; I. Paghava Scientific Research Institute of Pediatrics.

The conference was co-chaired by K. Pagava, M. Chkhatarashvili, T. Chigladze.

Mrs. Sandra Elisabeth Roelofs, the First Lady of Georgia inaugurated the conference by means of a video address. Minister of labor, health and social Affairs of Georgia A. Urushadze and Rector of the Tbilisi State Medical University Z. Vadachkoria greeted the participants as well.

Besides the scholars, healthcare workers and Parent organizations representatives from Georgia, guests from 8 countries (Armenia, Azerbaijan, Bulgaria, Canada, Germany, Netherlands, Poland and Russian Federation) took part in this scientific event.

The motto of the conference was "Bridging patients & researchers". Correspondingly the conference was devoted to the diagnostics and treatment of various specific rare diseases as well as the general approaches to various modes of their nationwide management.

In all 22 communications were delivered.

The participants from various countries shared their respective national as well as international experience in dealing with the issue of the rare diseases, including defining and shaping the national priorities, legislation, data gathering and multi-institutional cooperation: "Alliance for Rare Diseases" (E. Aptsiauri, I. Bulia and N. Manjaparashvili); "Patient's influence on law-making initiatives in Bulgaria" (V. Tomov, Bulgaria); "Rare Diseases – Aspects of Management" (K. Pagava, I. Korinteli, T. Kisileva, N. Uberi, Ts. Parulava, M. Kvezereli-Kopadze, I. Pagava and M. Korinteli, Georgia); "Crossing borders for Rare Diseases" (L. Siderius, Netherlands); "Information and data gathering as a compound component of the help to people with rare illnesses and their families" (S. Karimova, Russian Federation); "Armenian Experience in the field of rare diseases" (A. Matevosyan, Armenia).

Presenting authors covered comprehensively various rare diseases and their management, including the following disorders: hemangioma (T. Kutubidze and B. Zenaishvili, Georgia); haemophilia and other coagulopathic diseases (R. Khomasuridze, Georgia); McCune-Albright syndrome (U. Seyidova, Azerbaijan); osteogenesis imperfecta (discussed by F. Fassier from Canada and T. Chigladze, M. Chkhatarashvili, a team of Georgian doctors); phenylketonuria (L. Margvelashvili, Georgia); Cornelia de Lange Syndrome (J. Wierzba and T. Wierzba, Poland); Sjogren's syndrome and associated complications (T. Chachibaia, Tbilisi); spinal muscular atrophy (E. Khmaladze and P. Imnadze, Georgia); β thalassemia major (Z. Mtvarelidze, M. Kvezereli-Kopadze and A. Kvezereli-Kopadze, Georgia).

Some of the participants devoted their presentations to the general issue of the rare diseases in the fields of the medicine that they are active in: dermatology (T. Kituashvili, O. Kvlividze and G. Galdava, Georgia), gastroenterology and abdominal surgery (K. Pachkoria, S. Kemoklidze, Georgia); pediatric rheumatology (M. Ioseliani, M. Lekishvili, Georgia); growth disorders, secondary to the rare diseases like Silver-Russell, Laron and Prader-Willi Syndromes (N. Davituliani, M. Rekhviashvili, R. Morgoshia and D. Metreveli, Georgia). The issues of osteoporosis in orthopaedics (Varto Seeid, Germany) and joints prostheses in cancer pathology (T. Katsitadze and T. Nozadze, Georgia) were also regarded.

Various aspects of healthcare system and clinical approaches to the general issue of rare diseases and their management were discussed during the culminative Round Table session (guided by G. Abesadze from Georgia and L. Siderius from the Netherlands).

It was considered to be reasonable to carry out in Tbilisi

conferences on rare diseases on the regular basis. A hope was fostered that such events would contribute its mite into alleviating the burden of the rare diseases to the humankind, by disseminating the data required for improving the clinical outcome for the millions of patients suffering from the thousands of generally neglected orphan (rare) diseases.

RARE DISEASES EPIDEMIOLOGY*, 2010 (BOOK REVIEW)

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The rare diseases number about 10 thousand individual clinical entities; and while the population occurence of the rare disease should not be less than 1 out of 2,000 the disorder to be qualified as rare, their total prevalence is millions. Despite the figure so impressive, and notwithstanding the recent upsurge in the interest for them, these clinical conditions are still virtually orphan, as both the bodies driven by commercial interest and the clinical community tend to neglect this area of clinical medicine to a considerable degree. The limited market for the medical products designed for any single rare disease obviously repels the former, while the latter have predictably limited expertise in the field.

Understandably enough, the current scantiness of the available information for the healthcare practitioners and policy-makers with regard to the rare diseases naturally validates any effort to fill in this gap. And we are happy to have at hand now a major work devoted to the epidemiological aspects of the whole area of the rare diseases now: Rare Diseases Epidemiology*, a 542 plus page book edited by Manuel Posada de la Paz, and Stephen C. Groft, with its divisions composed by many renowned figures in the field. And of no small importance is that it is quite fresh, having been published in 2010.

The book is conveniently divided into 7 parts, dealing with various dimensions of the issue, with some of the parts being subdivided further into smaller sections. The short preface is followed by the introductory Part I, vindicating the need for the trustworthy epidemiological data on the rare diseases. The Part II deals with methods and approaches, including the general principles of the evidence-based medicine and the epidemiology research in this field; this section of the book also deals thoroughly with various modes of research and data collecting and analysis, like case reports and patient registries, biobanking and genetic testing, clinical trials, population-based surveillance and geographic analysis. The Part III is discussing the incentives (including the legislative ones) for the development and marketing of the pharmaceutical products for the relatively small populations with some specific rare disorder. The Part IV goes further into the economic and social implications of the rare diseases, like financial burden for the national healthcare systems and quality of life of the humans affected. The Part V is surveying many rare diseases assembled according to some criterium or other: rare cancers, hereditary channelopathies, osteochondral diseases and fibrodysplasia ossificanc progressiva, autoimmune diseases, rare anaemias, congenital anomalies, inherited metabolic disorders, and neurodevelopmental disabilities. The Part VI dwells on policy and ethics issues, including the international (European) framework for actions, national plans and strategies (again in European countries), and ethical aspects. And, last but not least, the Part VII reviews the Patient Organizations and Advocacy Groups and their significance for the research in the field.

The book is very well written, and deals with its subject delineated above comprehensively. The compact style of the authors is particularly noteworthy; the laconic and full of content *multum in parvo* sections provide the reader with a hearty food for thought. The authors present the valuable insights by sharing their vision based on the personal hands-on expertise as well as on the extant evidence.

The section on the clinical cases (p.77-86) seems to be particularly valuable for the physician involved in the day-to-day clinical work with a potential to face the patient with some rare disorder or other at any time. While being relegated to the lowest significance level of the scientific evidence due to the obvious limitations of the methodology, the registration, analysis and publication of clinical cases still retain their value. This is particularly clear in case of the rare diseases, some of them numbering only a handful of published cases worldwide; obviously, every new case or case series would of much help.

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Somewhat Eurocentric approach of many divisions of the book when discussing the epidemiology and policy issues is perhaps apprehensible, if one takes into consideration the resources available in Europe and also the relative deficit of the relevant information from other regions of the world; however, the amount of the latter is not quite negligible, and it should have perhaps been touched upon as well.

While discussing several groups of the rare diseases (*vide supra*) within the Part V, the book is virtually silent on the myriads of others. This is fully tolerable since a single volume, multipage as it is, could not possibly comprise all of the diseases. Nevertheless, the reader has a right to know that from this viewpoint the book is not all-embracing.

But the amount of information presented is very impressive. The multitude of the data presented in the reviewed work make it indispensable for anyone potentially active in the field of the rare diseases, let alone those, who specialize in it. We believe that this volume will remain the major reference book for quite some time, and highly recommend it to the healthcare planners, general practitioners and those specializing in the field of the rare diseases alike.

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