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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობით და მისი პატრონაჟით

This special issue of the journal is dedicated to Adolescent Medicine and Physiology
Guest Editors - Vincenzo de Sanktis and Karaman Pagava

Номер журнала посвящается вопросам подростковой медицины и физиологии
Приглашенные редакторы – Винченцо де Санктис и Караман Пагава

ნომერი ეძღვნება მოზარდთა მედიცინის და ფიზიოლოგიის საკითხებს
მოწვეული რედაქტორები - ვინჩენცო დე სანქტისი და 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. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный медицинский журнал, издается 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. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო რეცენზირებადი სამედიცინო ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ, ინგლისურ და გერმანულ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები, რეცენზიები.
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В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Библиографическое описание литературы составляется на языке текста документа. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующему номеру данной работы в списке литературы.

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Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 6 pages and not exceed the limit of 15 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

6. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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8. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

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10. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: introduction, material and methods, results and conclusions) and a list of key words.

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Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx,** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის ავტორთა რაოდენობა არ უნდა აღემატებოდეს 5-ს; სტატიის მოცულობა არ უნდა შეადგენდეს 6 გვერდზე ნაკლებსა და 15 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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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.

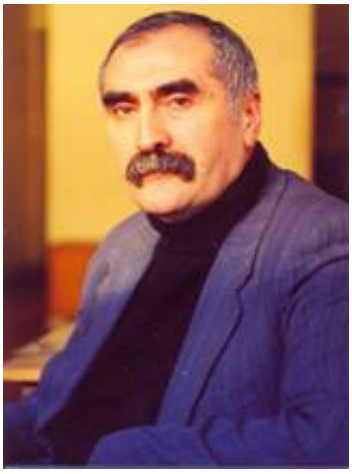
10. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: შესავალი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და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

Содержание:



ADOLESCENT MEDICINE: AN OPPORTUNITY TO OPEN OUR HORIZON

Adolescence is a period of great change physiologically, psychologically and socially. Although most adolescents make the transition to adulthood without major difficulties, it is important for the health care professional to identify problems and develop an approach to treatment for those patients who need help during this time. Therefore, adolescence is a time of exploration, experimentation and striving for independence.

Young people have significantly different health care needs compared to those of children and adults. Their needs are diverse and are affected by the physical, emotional, psychological and socio-cultural stages of adolescence. Healthy and at risk activities that affect adult morbidity often have their origins during the adolescent years. Therefore it is important not to ignore problems in teens with the excuse that the youth "will grow out of it". Moreover, it is important to identify the adolescent's strengths and support system in coping with these issues.

The American Academy of Pediatrics has recommended that pediatric health care be extended through the adolescent years and has renewed the attention of clinicians to ensure a better quality of care for youth.

In order to improve the quality and quantity of education in adolescent health for paediatricians and GPs, the Study Group of the Emilia and Romagna Region for Adolescent Health Care (SGA-ER) was established in 2010 in an effort to generate strategies and possible solutions to improve the quality and quantity of pediatricians' and GPs' knowledge of adolescent health care. In 2011 the SGA-ER received the patronage of SASIA (Sociedad Argentina de Salud Integral del Adolescente) and in 2012 the patronage of SEMA (Sociedad Española de Medicina de la Adolescencia). Since its establishment, SGA-ER, with the support of Quisisana Accredited Private Hospital of Ferrara, has organized an annual nationally accredited CME course for health professionals, and other meetings for parents.

We wish to thank the Authors of scientific papers for giving us the opportunity to prepare this adolescent issue of Georgian Medical News, the founding Members of SGA-ER for their cooperation and enthusiasm, and Dr. Bernadette Fiscina for her envaluable support and help.

We are also particularly delighted by and rejoice in the constant support which we have received from Dr. Giorgio Piacentini, President of Quisisana Hospital of Ferrara (Italy). Finally, but not at least, a special thank to Dr. Nino Mikaberidze, Editor of Georgian Medical News, for having accepted our request and for the professional editing of this adolescent issue.

We hope that increasing educational opportunities in adolescent health may accelerate the development and dissemination of new and improved therapeutic approaches for serving adolescents and also may help to attract a larger cadre of physicians to this field of practice.

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НАУКА

ADOLESCENT HEALTH CARE IN ITALY: A MINI-REVIEW

[1]De Sanctis V., [2]Filati G., [3]Fiscina B., [4]Marsciani A., [5]Piacentini G., [6]Timoncini G., [7]Reggiani L., [8]Zucchini A.

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Adolescence is a period of great change physiologically, psychologically and socially. Although most adolescents make the transition to adulthood without major difficulties, it is important for the health care professional to identify problems and develop an approach to treatment for those patients who need help during this time [2-4,10,12]. Some young people engage in risky behaviors that reflect the processes of adolescent development: experimentation and exploration, including using drugs and alcohol, sexual and other risk-taking activities that affect their physical and mental health [2-12,12].

The purpose of this mini review is to present the services available for adolescents and the National Health System in Italy and to review the most relevant data on morbidity and mortality in Italian youth.

The National Health System in Italy.
Healthcare is provided to all citizens and residents by a mixed public-private system. The public part is the national health service, Servizio Sanitario Nazionale (SSN), which is organized under the Ministry of Health and is administered on a regional basis. This system was instituted in 1978 to provide universal inexpensive health care to all residents in Italy.

The Ministry of Health is responsible for monitoring and taking measures to improve the health status of the population and assure a uniform level of services, care, and assistance to the population. It also negotiates and monitors the labor contracts of medical and paramedical NHS personnel [6,11,13].

Covered are in-patient treatments that include tests, medications, as well as surgeries during hospitalization, family doctor visits, medical assistance that is provided by pediatricians, and other specialists. The health system also provides for drugs, medicines, out-patient therapies, as well as dental treatments.

The Regions
Recent national legislation has transferred several important administrative and organizational responsibilities and authority from the central government to the 20 regions. The regions organize services that are designed to meet the needs of their specific populations, define ways to allocate financial resources within their territories, monitor health care services and activities, and assess their performance. In addition, the regions are responsible for selecting and accrediting public and private health services providers and issuing regional guidelines to assure a set of essential health care services in accordance with national laws [11].

General practitioners (GPs) and pediatricians
Primary health care in Italy is provided mainly by general practitioners (GPs) and pediatricians, and on-call physicians (Guardia Medica) for after-hour medical care and services.

Family doctors are entirely paid by the SSN, must offer visiting time at least five days a week and have a limit of 1500 patients. Patients are assigned a doctor by the SSN but if they are dissatisfied with the assigned doctor they are free to change physicians, provided the doctor they choose has free slots [11].

GPs and pediatricians act as “gatekeepers” for the system, assessing the needs of citizens, prescribing pharmaceuticals, ordering diagnostic procedures and referring patients to specialists and hospitals [11].

The family paediatrician provides care for children aged 0-6 years with the possibility of extending the age group to 14 years. Parents may request that a family paediatrician assist adolescents with chronic illness up to the age of 16 years [2-5].

There are no specific protocols for the transition to GPs for patients with chronic diseases or special health needs [2-5].

Few specific clinics for adolescents or young adults with chronic illness (e.g. thalassaemia, cystic fibrosis, diabetes, chronic renal failure) are available. The percentage of adolescents affected at least by one chronic disease is 8%, by 2 chronic diseases is 1.3% and by 3 or more is 0.3% [2,5].

However, some services for adolescents in paediatric departments or gynaecologic and obstetrics wards have been set up, mostly in large cities where university hospitals or hospital of national relevance are located.

Specific preventive services are also available, used mainly as family planning centers. These centers are basically perceived as providers of advice for gynaecologic problems in more than 80% of cases [6].

The total number of centres taking care of adolescents in Italy is 4097 (50% in the North of Italy, 20% in the Central and 20 % in the South and Islands) [2].

The Youth Health Problems in Italy

The population of Italy on January 1st, 2011 was approximately 60,477,881 (extrapolated from a population of 60,157,214 on October 27th 2009 and a population of 60,231,214 on February 8th 2010) and the number of adolescents, aged 10 to 19 years, was 6,214,000.

Injuries and poisonings are the major health problems of adolescents (27.4% of hospital admissions) and the leading cause of death in this age group. Overall rates of injury death for 15 to 24 year old males exceed those for females by as much as 3:1. Although the mortality rates of adolescent are low compared to adults, there is significant morbidity among teens [5].

In primary care, adolescents present with a large number of issues, in particular respiratory and musculoskeletal problems, pain syndromes, obesity, dermatological diseases, eating disorders, mood and somatoform disorders, school and mental health disorders (Table 1), and chronic fatigue. Many of these may require a coordinated, multidisciplinary management approach [5,8].

Table 1. Mental health disorders in a group of adolescents (aged 14-19 years) followed in Milan

Dissociative identity disorders (global and body images)	41%
Eating	18%
Behavioural disorders	18%
School related disorders	11%
Somatoform disorders	7%
Mood disorders	5%

In the community, common adolescent needs include contraception, family planning, mental health problems, and prevention of infectious diseases (vaccinations).

The percentage of adolescents utilizing pediatric emergency units is variable from 2.1% to 30%. Most adolescent visits were classified as non-urgent consultations. The main complaints were injuries, gastrointestinal disorders, respiratory infections, psychiatric and psychosocial problems [5].

Epidemiological evidence has shown that the majority of adolescents are admitted to adult wards, especially in the South of Italy (Table 2). However, data in the literature support the continued development of adolescent wards in larger general hospitals and children's hospitals and the importance of dedicated adolescent inpatient wards for improving the quality of care for young people compared to that in child or adult wards, particularly for older adolescents [1].

Table 2. Age limits to the admission of adolescents in Italian Paediatric Units

Age (Years)	North % (n=143)	Central % (n=95)	South % (n=145)	Total % (n=383)
14	18	17	49	26
15	9	8	6	8
16	20	22	26	22
17	50	46	25	39

In 2001, the main hospital discharge diagnoses in 127.247 adolescents (aged 15-17 years) were: injures and poisoning (27.4%), gastrointestinal problems (13.4%), unexplained symptoms (7,5%), respiratory illness (7.5%), musculoskeletal problems (6.9%), urinary tract disorders (5.4%), nervous system illness (4.6%), pregnancy complications (3.9%), dermatological problems (3.7%), mental health disorders 3%), oncologic diseases (2.8%), infectious diseases (2.7%), congenital malformations (2.2%), endocrine and metabolic diseases (1.9%), haematological diseases (0.7%) [5].

Conclusions

Adolescence is a time of exploration, experimentation and striving for independence. Young people have significantly different health care needs compared to those of children and adults. Their needs are diverse and are affected by the physical, emotional, psychological and socio-cultural stages of adolescence [2-5,10,12]. The American Academy of Pediatrics has recommended that pediatric health care be extended through the adolescent years and has renewed the attention of clinicians to ensure a better quality of care for youth [9].

Adolescent health in the Italy is not a distinct speciality, but is practised in some services for adolescents in paediatric departments or gynaecologic wards, mostly in large cities where University hospitals or hospital of national relevance are located.

Although young people have significantly different health care needs than those of children and adults, epidemiological evidence has shown that the majority of adolescents are admitted to adult wards.

The most frequent causes of death in adolescents are motor vehicle accidents - more than half of which are related to drug or alcohol use - followed by cancer and suicide. Many of the behaviours involved call for preventive and interventional measures.

Healthy and at-risk activities that affect adult morbidity often have their origins during the adolescent years. Therefore it is important not to ignore problems in teens with the excuse that the youth "will grow out of it". Moreover, it is important to identify the adolescent's strengths and support system in coping with these issues.

In addition, many of the gynecologic problems encountered in the adolescent population are unique to this age group. Even if the pathology is the same, the approach involves physician skills differing from those utilized with an adult population. These problems are not easily addressed by physicians with a strictly physiologic orientation, and may not even show up on the standard review of systems that physicians are taught to perform [12,13].

The estimated population with a chronic illness is 8%. There are no specific protocols to deal with the transition to GPs for patients with chronic diseases or special health needs [2-5].

Providing health care for adolescents involves a variety of medical, social and legal knowledge, and close working relationships must be established within the adolescent's network to establish an effective care system. Clinicians who are taking care of adolescents have unique opportunities to make a difference in their health and their lives by being creative, flexible and open in the care provided. Learning and using a few special techniques to communicate with youth may make this medical intervention easier and often more successful [7].

In order to improve the quality and quantity of education in adolescent health for paediatricians and GPs, the Study Group of the Emilia and Romagna Region for Adolescent Health Care (SGA-ER) is going to organize, starting in 2012, a two year educational intervention course in adolescent health.

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SUMMARY

ADOLESCENT HEALTH CARE IN ITALY: A MINI-REVIEW

[1]De Sanctis V., [2]Filati G., [3]Fiscina B., [4]Marsciani A., [5]Piacentini G., [6]Timoncini G., [7]Reggiani L., [8]Zucchini A.

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The purpose of this mini-review is to present the National Health System and services available for adolescents in Italy, and to review the most relevant data on morbidity and mortality in Italian teens.

Adolescent medicine in Italy is not a separate speciality, but there are some distinct services for adolescents in paediatric departments or gynaecologic wards, mostly in large cities where university hospitals or hospital of national relevance are located.

Primary health care in Italy is provided mainly by general practitioners (GPs) and pediatricians, and on-call physicians (Guardia Medica) for after-hours medical care and services. The number of centres providing care for adolescents in Italy is 4097 (50% of these are in the North of Italy, 20% in the Central regions and 20% in the South and Islands).

The population of Italy on January 1st 2011 was approximately 60,477,881 and the number of adolescents, aged 10 to 19 years, was 6,214,000.

The most frequent causes of death in adolescents are motor vehicle accidents - more than half of which are related to drug or alcohol use - followed by cancer and suicide. In primary care, adolescents present with a large number of issues, particularly upper respiratory infections, musculoskeletal problems, pain syndromes, obesity, eating disorders, dermatological issues, mood and somatoform disorders, school and mental health problems, and chronic fatigue, many of which require a coordinated, multidisciplinary management approach.

The estimated population with a chronic illness is 8%. There are no specific protocols for the transition to adult medicine physicians for patients with chronic diseases or special health needs.

In order to improve the quality and quantity of education in adolescent health for paediatricians and GPs, the Study Group of Emilia and Romagna Region for Adolescent Health Care (SGA-ER) is going to organize, beginning in 2012, a two year educational intervention course in adolescent health.

Keywords:adolescent health care, national health system, Italy.

РЕЗЮМЕ

ОХРАНА ЗДОРОВЬЯ ПОДРОСТКОВ В ИТАЛИИ: КРАТКИЙ ОБЗОР

[1]Де Санктис В., [2]Филати Г., [3]Фисцина Б., [4]Марсциани А., [5]Пиацентини Дж., [6]Тимончини Дж., [7]Реггиани Л., [8]Зуччини А.

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Целью обзора явился анализ наиболее значимых показатели заболеваемости и смертности среди итальянских подростков.

Подростковая медицина в Италии не является отдельной специальностью, однако в больших городах при университетских или больницах общенационального значения в составе педиатрических и гинекологических департаментов имеются службы, предназначенные для подростков.

Первичная медицинская помощь в Италии оказывается врачами общей практики и педиатрами, в нерабочее время - дежурными врачами (Guardia Medica). В Италии всего 4097 центров, оказывающих медицинскую помощь подросткам (среди них 50% - в северной Италии, по 25% - в центральной и южной Италии).

Население Италии на первое января 2011 года составляло примерно 60,477,881, среди них 6,214,000 подростков (10-19 лет).

Основными причинами смерти среди подростков являются дорожно-транспортные происшествия (в более чем половине случаев связанные с приемом алкоголя или наркотиков), за ними следуют рак и самоубийство. В первичное звено здравоохранения подростки обращаются по поводу различных причин - инфекции верхних респираторных путей, проблемы со стороны костно-мышечной системы, болевые синдромы, ожирение, нарушения пищевого поведения, дерматологические проблемы, нарушения настроения, соматоформные нарушения, школьные проблемы, проблемы умственного здоровья, хроническая усталость. Многие из перечисленных нарушений требуют координированного мультидисциплинарного подхода.

Хроническими заболеваниями страдает приблизительно 8% подростков, однако, нет специальных протоколов для перевода пациентов с хроническими заболеваниями или специальными медицинскими нуждами к врачам по медицине взрослых.

С 2012 г. с целью улучшения качества образования по подростковой медицине педиатров и врачей общей практики Группа по изучению здоровья подростков региона Эмилии и Романьи (SGA-ER) разработала план соответствующих специальных двухгодичных курсов.

რეზიუმე

მოზარდთა ჯანდაცვა იტალიაში: მცირე მიმოხილვა

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მიმოხილვის მიზანია იტალიელი მოზარდების ავადობის და სიკვდილობის ამსახველი ძირითადი მონაცემების ანალიზი.

მოზარდთა მედიცინა იტალიაში არ წარმოადგენს ცალკე დისციპლინას, თუმცა დიდ ქალაქებში საუნივერსიტეტო და ნაციონალური მნიშვნელობის კლინიკებში პედიატრიულ ან გინეკოლოგიურ დეპარტამენტებში არის სპეციალური სამსახურები მოზარდებისთვის. პირველადი სამედიცინო დახმარება იტალიაში,ძირითადად,ხორციელდება ზოგადი პრაქტიკის ექიმების ან პედიატრების მიერ, ხოლო არასამუშაო საათებში - მორიგე ექიმების მიერ (Guardia Medica). მოზარდებს სამედიცინო დახმარებას უწევს 4097 ცენტრი (ამათგან 50% ჩრდილოეთ იტალიაშია, 25-25% - ცენტრალურ და სამხრეთ იტალიაში).

იტალიის მოსახლეობა 2011 წლის პირველი იანვრისთვის შეადგენდა 60,477,881, ამათგან დაახლოებით მოზარდებისა (10-19 წლის) – 6,214,000.

მოზარდობის ასაკში სიკვდილის ყველაზე ხშირი მიზეზებია სამგზავრო უბედური შემთხვევები, რომელთაგან ნახევარი დაკავშირებულია ალკოჰოლის და ნარკოტიკების მოხმარებასთან, გარდა ამისა,სიმსივნური დაავადებები და თვითმკვლელობა. ჯანდაცვის პირველად რგოლს მოზარდები სხვადასხვა საკითხის გამო მიმართავენ, კერძოდ: ზემო სასუნთქი სისტემის ინფექციები, ძვალ-კუნთოვანი სისტემის პათოლოგია, ტკივილის სინდრომები, სიმსუქნე, კვების დარღვევები, კანის პრობლემები,გუნებ-განწყობის და სომატოფორმული დარღვევები,მენტალური პრობლემები, ქრონიკული დაღლილობა. ჩამოთვლილთაგან მრავალი მოითხოვს კოორდინირებულ, მულტიდისციპლინურ მიდგომას.

ქრონიკული დაავადებების მქონე პოპულაცია 8% შეადგენს. არ არის სპეციალური პროტოკოლები, თუ როგორ გადავიყვანოთ ქრონიკული დაავადების ან განსაკუთრებული საჭიროების მქონე მოზარდი მოზრდილთა ექიმთან. იმისთვის, რომ გაუმჯობესდეს პედიატრებისა და ზოგადი პრაქტიკის ექიმების ცოდნა მოზარდთა მედიცინაში, ემილიას და რომანიას მოზარდთა მედიცინის კვლევის ჯგუფი (SGA-ER) 2012 წლიდან იწყებს 2-წლიანი სასწავლო კურსის დანერგვას მოზარდთა მედიცინის დარგში.

THE SGA-ER EDUCATIONAL INTERVENTION IN ADOLESCENT HEALTH CARE FOR ITALIAN PHYSICIANS: GOALS, CONTENT AND INSTRUCTIONAL DESIGN

[1]De Sanctis V., [2]Clemente S., [3]Gallotta M.R., [4]Filati G., [5]Fiscina B., [6]Marsciani A., [7]Piacentini G., [8]Timoncini G., [9]Reggiani L., [10]Zucchini A., [11]Zunelli C.

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Adolescence is a period of great change physiologically, psychologically and socially. Although most adolescents make the transition to adulthood without major problems, it is important for the health care professional to identify problems and develop a treatment approach for those patients who need help during this time [1-5,8,12,13,16].

Adolescent medicine in Italy is not a distinct speciality but is practised in some services for adolescents in paediatric departments or gynaecologic wards.

Pediatricians and general practitioners (GPs) provide most of the accessible health care for youth in the Italian health care system. The family paediatrician provides care for children aged 0-6 years with the possibility of extending treatment until 14 years of age, and up to the age of 16 for adolescents with chronic diseases [1-5].

It is well known that physicians involved in adolescent care need a variety of medical, psycho-social, mental health, and legal knowledge. Because not all of these issues are readily addressed by physicians with traditional medical training, the Study Group of Adolescent Health Care of Emilia and Romagna Region (SGA-ER), in response to the identified needs of pediatricians and GPs [12], designed a two year educational course to improve knowledge, skills and self-perceived competence in adolescent health care.

This paper presents the goals, content and instructional design of SGA-ER educational intervention.

Youth Health Problems in Italy

Injuries and poisonings are the major reasons for adolescent hospitalizations in Italy (27.4% of hospital admissions) and the leading cause of death in this age group. Overall rates of injury death for 15 to 24 years old males exceed those for females by as much as 3:1. In 2001, the main hospital discharge diagnoses in 127,247 adolescents (aged 15-17 years) were (after injures and poisoning): gastrointestinal problems (13.4%), unexplained symptoms (7,5%), respiratory illness (7.5%), musculoskeletal problems (6.9%), urinary tract disorders (5.4%), nervous system illness (4.6%), pregnancy complications (3.9%), dermatological problems (3.7%), mental health disorders 3%), oncologic diseases (2.8%), infectious diseases (2.7%), congenital malformations (2.2%), endocrine and metabolic diseases (1.9%), and haematological diseases (0.7%) [5,12].

Although the mortality rates of adolescent are low compared to adults, there is a significant morbidity among teens [5].

In primary care, adolescents present with a large number of issues, in particular respiratory illnesses, musculoskeletal and pain syndromes, obesity, dermatological problems, eating disorders, mood and somatoform disorders, school and mental health issues, and chronic fatigue, many of which require a coordinated, multidisciplinary management approach [5,12].

In the community, common adolescent needs include contraception and family planning, mental health problems, and prevention of infectious diseases (vaccinations).

The utilization of pediatric emergency units is variable, ranging from 2.1% to 30% among adolescents. The main complaints were injuries, gastrointestinal disorders, respiratory infections, psychiatric and psychosocial problems [5].

Emilia and Romagna Region

Emilia-Romagna (ER) today is considered as one of the richest and most developed regions in Europe [9]. Bologna, the region's capital, has one of the world's first universities [10]. Emilia-Romagna has thirteen cities with populations above 50,000 (based on 2006 estimates): Bologna (population: 381,860 - metropolitan area 1,000,000), Modena (pop. 185,228), Parma (pop. 187,159), Reggio Emilia (pop. 170,355), Ravenna (pop. 149,084), Rimini (pop. 138,060), Ferrara (pop. 131,907), Forlì (pop. 112,477), Piacenza (pop. 99,340), Cesena (pop. 93,857), Imola (pop. 66,340), Carpi (pop. 64,517) and Faenza (pop. 54,749) [11].

SGA-ER establishment and aims

The Adolescent Health Study Group of the Emilia and Romagna Region (SGA-ER) was established in 2010 in a effort to generate strategies and possible solutions to improve the quality and quantity of pediatricians' and GPs' knowledge of adolescent health care.

The Council Board Group (CBG) consists of 1 coordinator and 5 members (all are pediatricians), 1 counsellor, 1 education specialist and 1 registered general nurse. Health professionals who have demonstrated involvement in adolescent health care are welcomed as members. The registration for SGA-ER is free of charge. The Coordinator carries out the policies that are created by the CBG and SGA-ER membership. Honorary Members as of June 2012 include pediatricians and adolescent medicine specialists Monica Borile (Argentina), Bernadette Fiscina (USA) and Daniel Hardoff (Israel).

In 2011 the SGA-ER received the patronage of SASIA (Sociedad Argentina de Salud Integral del Adolescente) and in 2012 the patronage of SEMA (Sociedad Española de Medicina de la Adolescencia).

SGA-ER has a website: http://www.sga-er-sga.blogspot.com/ and soon will have an I-Phone and I-Pad app entitled "Adolescent Planet" for health professionals, teens and parents.

Since its establishment, SGA-ER, with the support of the Quisisana Accredited Private Hospital of Ferrara, has organized an annual nationally accredited CME course (31 hours of multidisciplinary lectures and participants' case presentations) for health professionals, and other meetings for parents. Forty pediatricians and GPs have completed these courses. Except for feedback questionnaires commonly used at the end of courses, no assessment has yet been made to evaluate the impact of this training on the participants or their clinical practice.

The SGA- ER educational intervention in adolescent health care

Increasing educational opportunities in adolescent health may accelerate the development and dissemination of new and improved therapeutic approaches for serving adolescents and also may help to attract a larger cadre of physicians to this field of practice [6,7,14,15].

Other pediatric subspecialties, e.g. oncology, rheumatology and adolescent psychiatry, have developed successfully in Italy and may represent excellent models for adolescent medicine specialists to emulate.

Several methods and approaches have been implemented to improve physician skills in adolescent health care. In the first two years of SGA-ER, we followed the model favoured in the UK that consists of delivering an adolescent educational intervention course to all health professionals, rather than creating a separate specialty [17].

SGA-ER convened to identify the following steps for the course implementation:

a) Knowledge and skills required by professionals in caring for adolescents (Table 1);
b) Building the field: proposals, key objectives, topics, description, time table, national accreditation (CME) (Table 1);
c) Overall challenges in evaluating programs and strategies;
d) Staff: selection of a multidisciplinary team of experts in the following areas: adolescent medicine, counselling, dermatology, endocrinology, gynaecology and obstetrics, paediatrics, paediatric allergy, pulmonology, public health, radiology, education, health information technology (Table 2);
e) Participants' case presentations with interactive discussion;
f) Required readings;
g) Useful websites for health professionals;
h) Recommend outcome measures;
i) Measures to evaluate the impact of the training programme in adolescent health;
j) Identification of gaps in training.

Conclusions

The population of Italy on January 1st 2011 was approximately 60,477,881 and the number of adolescents, aged 10 to 19 years, was 6,214,000.

Adolescent medicine is a field dedicated to helping young people grow and thrive. In Italy, it is not a distinct speciality, but is practised in some services for adolescents in paediatric departments. The number of centres taking care of adolescents in Italy is 4097 (50 % in the north of Italy, 20% in the central regions and 20% in the south and islands) [3].

In Italy there is a growing interest among healthcare professionals to extend their knowledge in adolescent health care. Helping physicians to learn and to change their practice is the purpose of continuing medical education design. Formal training curricula and postgraduate diploma courses in adolescent medicine have been developed in United States, Canada, Australia, Israel and Switzerland [6-8,13]. The length of training courses varied among different countries and training needs of the participants.

SGA-ER was established in 2010 in an effort to generate strategies and possible solutions to improve the quality and quantity of pediatricians' and GPs' knowledge of adolescent health care. Increasing educational opportunities in adolescent health may help to accelerate the development and dissemination of new and improved therapeutic approaches for serving adolescents and may also attract a larger cadre of physicians [6,7,14,15]. During the first two years, we followed the model favoured in the UK that consists of delivering an adolescent educational intervention course to all health professionals, rather than creating a separate specialty [13], and the suggested strategies of Fox et al. [7] for enhancing training.

Table 1. Knowledge and skills required by professionals in caring for adolescents (Adapted From Kittredge D, Baldwin CD, Bar-on ME, Beach PS, Trimm RF (Eds.). (2004). APA Educational Guidelines for Pediatric Residency. Ambulatory Pediatric Association Website. [Available online: www.ambpeds.org/egweb] *and ref. 3, 6, 8,13, 14)*

1.GOAL. Improve knowledge, skill and attitude in the generic concept of adolescent health, screen for health risks, provide health promotion and appropriate management plans Intervention content 1. Be familiar with questionnaires (e.g., GAPS), trigger questions (e.g., from Bright Futures) and structured interview techniques (e.g., HEEADSSS; HEADSFIRST) 2. To perform and interpret adolescent screening according to guidelines by experts in the field (e.g., AAP, Bright Futures and GAP) 3. To evaluate immunization status 4. Conducting a physical examination 5. Psychosocial screening (e.g., school performance, mood disorders, tobacco and substance abuse, sexual risks, media use, other risk taking behaviors) and adolescent mental health screening such as depression, anxiety and related disorders. 6. Nutrition, obesity and eating disorders 7. Promoting Healthy Eating and Healthy Lifestyles according to recommended guidelines (e.g., AAP, Bright Futures and GAP) 8. Sexual and reproductive health 9. Sexuality, contraception and STD 10. Medicolegal and ethical issues that apply to adolescents. 11. Be familiar with adolescents with chronic illness and special needs 12. Enhancing compliance 13. Communication/consultation skills 14. To help adolescents to use health services appropriately during their teens and guide them in their transition to adult care
2. GOAL: Understanding normal adolescent growth, development and behaviour and recognize deviations from the norm
3. GOAL: Evaluating and managing common signs, symptoms and situations or risks in adolescents, recognizing when referral is indicated
4. GOAL: Diagnose and manage common conditions in adolescents
5. GOAL: Recognize, manage and refer adolescent conditions that generally require consultation or referral
7. GOAL: Enabling competencies, resources and contacts
8. GOAL: Offering resources to families to promote and improve the health and well-being of adolescents Pediatricians should encourage both parents to be involved in the health care, education, discipline and emotional support of their children. Physicians must be aware of family influences and dynamics that impinge on adolescent health

Table 2. Selection criteria and characteristics of a competent trainer (From: Training needs for nutrition education: Guidelines for in-service training of nutrition educators. C Hosmer, JT Dwyer, A Villarroel http://www.fao.org; modified)

1. Interested in such subjects and sensitive to concerns of adolescents
2. Graduates/post graduates in any discipline
3. Non-judgmental
4. Understands and takes into account the motivation and participation patterns of adult learners
5. Understands and provides for the needs of clinicians
6. Knows the community and its needs
7. Knows how to use various methods and techniques of teachung
8. Possesses communication and listening skills
AFTER THE SESSION
1. Summarize each session and ensure that the objectives are achieved and contents are covered
2. Carefull consider any suggestions made by participants and try to incorporate them, if possible, into subsequent sessions
3. If personal questions are asked, the facilitator uses his/her discretion in answering

Forty pediatricians and GPs have completed such courses (2010/2011). No attempt was made to assess the impact on the participants or their clinical practice. However, the feedback questionnaires commonly used at the end of courses to measure attainment of educational objectives were administered.

The effectiveness of an educational intervention in adolescent health designed for general practitioners was supported in a recent study [14]. A total of 108 self-selected general practitioners attended and completed a multifaceted educational program in the principles of adolescent health care (2.5 hours per week for 6 weeks), followed 6 weeks later by a 2-hour session of case discussion and debriefing. The design of the intervention, using evidence-based educational strategies, proved effective and expeditious in achieving sustainable and large improvements in knowledge, skill, and self-perceived competency compared with the randomly allocated control group of practitioners. The changes were generally sustained over 12 months and further improved in the independent observers' rating of competence. Almost all participants reported a change in their practice since the intervention.

In order to expose the participants to a larger array of issues that are relevant in the comprehensive health care of adolescents, a 2-year education course is in progress for 2013. We hope that the patronage and the common interests with other Societies (SASIA and SEMA) in teaching adolescent health can provide an additional opportunity for networking, interaction and exchange of ideas amongst professionals.

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SUMMARY

THE SGA-ER EDUCATIONAL INTERVENTION IN ADOLESCENT HEALTH CARE FOR ITALIAN PHYSICIANS: GOALS, CONTENT AND INSTRUCTIONAL DESIGN

[1]De Sanctis V., [2]Clemente S., [3]Gallotta M.R., [4]Filati G., [5]Fiscina B., [6]Marsciani A., [7]Piacentini G., [8]Timoncini G., [9]Reggiani L., [10]Zucchini A., [11]Zunelli C.

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Adolescent medicine is a field dedicated to helping young people grow and thrive, in relation to their particular stage of development. In Italy, adolescent medicine is not a distinct speciality, but it is practised in some services for adolescents in paediatric departments. Increasing educational opportunities in adolescent health may help to accelerate the development and dissemination of new and improved therapeutic approaches for serving youth and also attract a larger cadre of physicians. Other pediatric subspecialties, e.g. oncology, rheumatology and adolescent psychiatry, have developed successfully and may represent excellent

models for adolescent medicine specialists to emulate. The Adolescent Health Study Group of the Emilia and Romagna Region (SGA-ER) was established in 2010 in an effort to generate strategies and possible solutions to improve the quality and quantity of knowledge in adolescent health care for pediatricians and GPs. Several methods and approaches have been implemented to improve physicians' skills in adolescent health care. The authors report the goals, content and instructional design of an educational course in adolescent medicine. Alliances with other adolescent health groups may provide an additional opportunity for networking, interaction and exchange of ideas amongst professionals.

Keywords: Adolescent health care, Italy, medical education, physician needs.

РЕЗЮМЕ

ОБРАЗОВАНИЕ ВРАЧЕЙ В ИТАЛИИ В ОБЛАСТИ ЗДРАВООХРАНЕНИЯ ПОДРОСТКОВ, ОСУЩЕСТВЛЯЕМОЕ ГРУППОЙ ПО ИЗУЧЕНИЮ ЗДОРОВЬЯ ПОДРОСТКОВ РЕГИОНА ЭМИЛИИ И РОМАНЬИ: ЦЕЛИ, СОДЕРЖАНИЕ И ДИЗАЙН ИНСТРУКЦИЙ

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Целью подростковой медицины является способствовать здоровью и развитию подростков с учетом их возрастных особенностей. В Италии подростковая медицина не является отдельной дисциплиной, однако практикуется в специальных службах при педиатрических департаментах. Увеличение числа образовательных возможностей в подростковой медицине привлекательно для врачей и может способствовать развитию и внедрению новых и усовершенствованных методов и подходов в здравоохранении подростков. Такие педиатрические субспециальности, как онкология, ревматология и подростковая психиатрия, дают пример для подражания специалистам подростковой медицины. Группа по изучению здоровья подростков региона Эмилии и Романьи была создана в 2010 году как попытка разработки стратегии и возможных решений с целью улучшения знаний в области здравоохранения подростков для педиатров и врачей общего профиля. Различные методы и подходы были внедрены для улучшения врачебных навыков в этой области. В работе представлены цели, содержание и дизайн инструкций учебного курса по подростковой медицине. Связи с другими подобными группами могут способствовать созданию соответствующих рабочих сетей, сотрудничеству и обмену идеями между профессионалами.

რეზიუმე

ემილიას და რომანიას რეგიონის მოზარდთა ჯანმრთელობის ჯგუფის საგანმანათლებლო ინტერვენცია იტალიელი ექიმებისთვის მოზარდთა ჯანდაცვის გასაუმჯობესებლად: მიზნები, შინაარსი და ინსტრუქციების დიზაინი

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მოზარდთა მედიცინის მიზანია ხელი შეუწყოს მოზარდთა ჯანმრთელობას და განვითარებას ასაკობრივი თავისებურებების გათვალისწინებით. იტალიაში მოზარდთა მედიცინა ცალკე სპეციალობად არ განიხილება; აქტივობა ამ მიმართულებით ხორციელდება პედიატრიული დეპარტამენტების მოზარდებისთვის განკუთვნილ სამსახურებში. განათლების შესაძლებლობების გაფართოვება მოზარდთა მედიცინაში ექიმების ფართო წრეებისთვის ხელს შეუწყობს ახალგაზრდებში, ახალი გაუმჯობესებული სამკურნალო მეთოდების განვითარებას,სრულყოფას და დანერგვას. პედიატრიული სუბსპეციალობები, როგორიცაა ონკოლოგია, რევმატოლოგია და მოზარდთა

ფსიქიატრია წარმატებით ვითარდება და შეიძლება საუკეთესო მაგალითად ჩაითვალოს მოზარდთა მედიცინის სპეციალისტებისთვის. ემილიას და რომანიას რეგიონის მოზარდთა ჯანმრთელობის ჯგუფი 2010 წელს შეიქმნა, როგორც მცდელობა ახალი სტრატეგიების შემუშავებისა და სათანადო გადაწყვეტილებების მისაღებად პედიატრებსა და ზოგადი პრაქტიკის ექიმებში მოზარდთა ჯანდაცვის საკითხებში ცოდნის გასაუმჯობესებლად. მოზარდთა ჯანდაცვის დარგში საქმიო ჩვევების გასაუმჯობესებლად სხვადასხვა მეთოდი და მიდგომა იყო დანერგილი. ნაშრომში წარმოდგენილია მოზარდთა მედიცინის სასწავლო კურსის მიზნები, შინაარსი და ინსტრუქციების დიზაინი. სხვა მსგავს ჯგუფებთან კავშირები ხელს შეუწყობს ახალი სამუშაო ქსელების შექმნას, პროფესიონალებს შორის თანამშრომლობას და იდეების გაზიარებას.

LEGAL AND ETHICAL ISSUES IN ADOLESCENTS' HEALTH CARE

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Adolescence is a time of great physical change and maturing brain function. This leads to adolescents establishing independence and coming to terms with the implications of their own actions. The definition of maturity in adolescents depends on the developmental domain that is under consideration. Most adolescents reach physical maturity by the age of 16 [5], however only by the middle of the third decade of life young people are expected to be psychologically and cognitively mature [29]. The World Health Organization has defined adolescents as individuals within the age range of 10 to 19 years, and young people as individuals within the age range of 10 to 24 years. The legal age (age of majority) is the age at which a person may by law assume the rights and responsibilities of an adult [38]. The vast majority of countries set the legal age at 18, but ages as low as 14 and as high as 21 also exist. The British 14th century "Rule of Sevens" has been used by US courts, stating that "a child less than 7 years of age has no capacity to formulate criminal intent and thus could not be guilty of a crime. A child between the ages of 7 and 14 years is presumed not to have the capacity to form criminal intent, and a child older than 14 years of age is presumed to have such capacity, although evidence could be introduced to disprove these presumptions" [35]. This Rule of Sevens was adopted, for example, to determine a minor's maturity for refusal to medical treatment [40]. The adaptations of the rigid laws related to the capacity of children and adolescents to be involved in the decision processes regarding their health, were possible following several declarations of children's rights: "The opinion of the child shall be considered as an increasingly crucial with the increasing age and maturity" [39]; "In all actions the interest of the child shall be a primary consideration" [41]; and "Children and adolescents have the right to be listened to on all matters affecting them" [42]. The mature minor doctrine (MMD) that was developed in the US is the common-law rule that allows a mature adolescent to give consent for medical care [35]. This doctrine emphasizes that from the age of 14 years adolescents become increasingly autonomous and their capability for medical decision-making may be considered already similar to adult capacity [24]. MMD encourages early self-care and facilitates a better transition into the adult medical system [36].

The following discussion will focus on three major issues related to legal and ethical aspects in adolescents' health care: confidentiality, consent to health care, and research involving adolescents.

Confidentiality

Confidentiality refers to the "privileged and private nature of information provided during the health care transaction" [6]. Confidentiality protection is essential in the development of independence that includes the gradual assumption of responsibility for personal health, health behaviors, and medical decisions [6,19]. Adolescents are more likely to seek health care if their provider assures that the information discussed during the visit will be kept confidential [13,14,16,43]. Concerns regarding lack of confidentiality protection may cause some adolescents to go without health care [21]. Parents, as the legal guardians of their adolescent child, have the privilege to receive all information concerning their child's health. However, confidentiality keeping becomes complex when the needs and wishes of the adolescent conflict with the opinions and preferences of the parents [9]. In providing confidential care, it is therefore important to balance the needs of the patient, parents, and provider [13]. Confidentiality should be discussed at the beginning of the adolescent-provider relationship, explicitly defining the circumstances under which confidentiality

is "conditional". Disclosure is required by law in situations such as abuse, suicidal or homicidal ideations, as well as in certain sexually transmitted infections (STIs) that require reporting to public health departments [27]. In addition, a serious threat to patient safety may warrant disclosure [2]. For example, when an adolescent patient discloses consensual sexual relationship with a family member, person of authority, or member of the clergy; or when the sexual relationship involves violence or coercion [2]. Whenever breaching of confidentiality is indicated, clinicians should allow the adolescent's participation in the decision to whom the information should be delivered [3]. Privacy concerns affect adolescents' choices of provider, and may lead young people to forgo care entirely resulting in negative outcomes. For example, forgoing contraceptive care may lead to unplanned pregnancy and STIs [28]. When an adolescent is at risk for harming himself or herself, confidentiality must be breached [34], as well as when risky behavior is discovered and is assessed by the clinician as threat to the safety of the patient or to others [30].

Unfortunately, there are more laws in place that protect confidentiality in the context of the physician-patient or health care professional-patient relationship than in the context of billing and insurance claims. In both contexts there are multiple ways in which confidentiality can be breached, sometimes as a result of policies that dictate disclosure of confidential information. Thus, there is no guarantee that the billing and insurance claims process will not divulge private information to a parent or guardian [28]. Confidentiality of adolescent patients may be inadvertently breached through documentation of their health care visits, followed by parents' request for copies of the medical record [44]. This is particularly true when documenting sexual health, mental health, and behavioral issues [31]. Pharmacists may refuse to fill a prescription for contraception for a minor without parental consent, even if the prescription was legally provided [7].

Consent to health care

Informed consent may be defined as the autonomous act by a patient or research subject to expressly permit a professional person to perform a medical action on the patient or to include a person in a research project [26]. Obtaining true informed consent consists of a number of critical elements: disclosure of the pertinent medical facts and alternative courses of action; ensuring patient capacity to understand the decision to be made; ensuring patient understanding of the medical information; the absence of coercion or manipulation; and the ability to consent [12]. Whenever minors are the subjects for medical intervention, consent for the procedure is required from the patient's parent or guardian, since in many countries, including the United States, Britain, and Greece, laws deem adolescents incompetent to give valid informed consent [4,23].

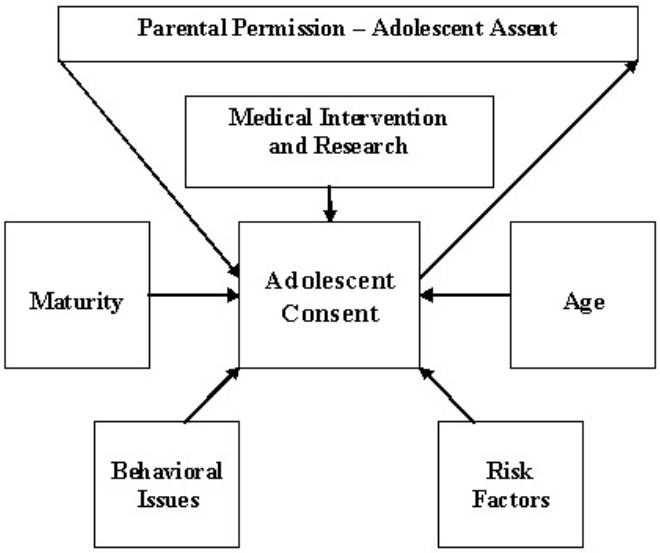

Fig. A multi-factorial model regarding consent to medical treatment and research in adolescents

The need to balance appropriate standards for decision making capacity with the individual rights of the pediatric patient, has given rise to the concept of assent in clinical decision-making. A 1995 policy statement by the American Academy of Pediatrics (AAP) defined assent as having four essential elements: helping patients achieve a developmentally appropriate awareness of the nature of their condition; telling patients what they can expect with tests and treatment(s); making a clinical assessment of the patients' understanding of the situation and the factors influencing how they respond; and soliciting an expression of patients' willingness to accept the proposed care [11]. The international Convention on the Rights of the Child limits parental powers and duties, by "adolescents' evolving capacities" for self-determination. There is usually no chronological "age of consent" for medical care, but a condition of consent, meaning capacity for understanding. Minors may grant or even deny assent to

treatment for which guardians provide consent [8]. Regarding sexual health for example, modern legal systems recognize that sufficiently mature adolescents can decide not only to request care for contraception, abortion and STIs, but also whether and when their parents should be informed [10]. Laws developed over the past half century have significantly improved adolescents' access to essential sexual and reproductive health care. Special considerations apply to consent and confidentiality questions pertaining to family planning, contraception, and pregnancy-related care for minors [20]. Moreover, there is no evidence that abortion during adolescence causes negative psychological consequences, decreased fertility, or increased risk in future pregnancies [17]. In Israel, physicians may confidentially prescribe contraceptive pills to female adolescents. This is based on the regulation that any activities that are common among minors are permitted even without their guardians' consent. Pregnant adolescents in Israel may legally consent for termination of pregnancy without parental involvement. Confidentiality is allowed to be kept following a decision of a specific committee that includes a gynecologist and a social worker.

Cancer treatment in adolescents is another example of the complex issues around the role the adolescent patient plays in the decision-making process. It is clear that educating adolescent cancer patients and involving them in their treatment provides the groundwork for the clear and supportive communication with the patient. However, there continues to be some controversy regarding what constitutes appropriate assent, particularly with regard to seeking the patient's permission to proceed with treatment [1].

The same considerations apply to adolescents consenting to other medical treatment issues, such as adolescents' consent for primary health care and emergency room interventions, psychiatric evaluation, and eating disorder treatment. Once again an assessment of the developmental capabilities of the individual patient is an essential component of the assent process [15].

Research

Participation by specific populations in health research is critical in order for those populations to receive the full benefits of research. Protection of adolescents in research should be based on understanding of their developing capabilities and a careful assessment of the risks and benefits of including adolescents in research projects. The basis for clinical research regulation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research – the Belmont report – was established in 1979 [25]. It proposed for the first time a clear separation between research and standard health care practice. The purpose of medical practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge. The Belmont Report provides the moral foundation for the ethical principles in the conduct of research: respect for persons, beneficence, and justice. Respect for persons means treating a person as an autonomous being and not as a means to an end; Beneficence is the ethical obligation to do good and to avoid harm, and in research it means maximizing benefits and minimizing harm; Justice entails a fair distribution of the benefits and burdens of research, with a specific notion that vulnerable persons should be protected from the burdens of research.

When adolescents are the subjects of research these three ethical principles require development related considerations [37]: Respect means balancing between the emerging capacity of an adolescent for independent decision-making and the need for continued special protections; Beneficence applies not only to benefits to individual adolescents, but also to benefits of adolescents as a group as well. Indeed, the principal threats to adolescent health and well-being are mostly social and behavioral, and behavioral research generally presents little risk and may provide benefit to the individual adolescent or adolescents as a group [45]; Justice interests demand that adolescents are not exploited for the benefits of others, but also that adolescents are not excluded from participation in research that may have direct or indirect benefit [37]. Owing to uncertainty about the legal and ethical status of adolescent involvement in research, adolescents are frequently excluded from research that is needed to improve adolescent health care. Regulatory procedures, while protecting adolescents, increase the potential for the neglect of important research needs of adolescents. A balance between the need for research in children and adolescents and its regulation is necessary [33]. There are differences in adolescent and parents understanding and appreciation of research risks and procedures, as well as in opinions about decision-making authority for research participation [18]. Children are capable of assent when they become able to understand the research in question. While development varies across individual children, existing data suggest that most children develop this ability by approximately age 14. Until instruments are developed to assess the assent capacity of individual children, this age should be used as the threshold for assent [32].

The requirement for permission by the parent or guardian may be waived in two circumstances: if the minor is "emancipated" and if the institutional review board (IRB) finds that permission is not a reasonable requirement (e.g., studies of abused or neglected children). Many IRBs recognize legitimate circumstances in which the requirement for permission may be waived: Research on diseases or conditions for which adolescents may obtain treatment without parental permission; Research involving "mature minors," which presents no more than minimal risk; Research designed to meet the needs of children designated by their parents as "in need of supervision"; and research

involving children whose parents are legally or functionally incompetent [22].

Conclusions

Focusing on confidentiality, consent to health care, and research in adolescents several points are emphasized:

- From the age of 14 years adolescents become increasingly autonomous and their capability for decision-making already becomes similar to adult capacity.
- Adolescents are more likely to seek health care if their provider assures confidentiality.
- In providing confidential care a balance should be considered between the needs of the adolescent patient, parents, and provider.
- There is no chronological age of consent, but a condition of consent that takes into consideration the adolescent's capacity for understanding.
- Adolescent's assent for both medical treatment and research is always mandatory.
- Involving adolescents in research should be based on understanding of their developing capabilities and a careful assessment of risks and benefits.

Figure 1 summarizes the multi-factorial model regarding consent to medical treatment and research in adolescents.

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SUMMARY

LEGAL AND ETHICAL ISSUES IN ADOLESCENTS' HEALTH CARE

Hardoff D.

Adolescent Medicine Services of the Clalit Health Services, Israel and Reuth-Open-Door of the Israel Planned Parenthood Association

This review examines confidentiality, consent to health care and research involving adolescents in regard to legal and ethical aspects. Adolescents are more likely to seek health care if their provider assures confidentiality, but in providing confidential care a balance should be considered between the needs of the adolescent patient, parents, and provider. The vast majority of countries set the legal age at 18, but from the age of 14 years adolescents' capability for medical decision-making may be considered already similar to adult capacity. Instead of chronological age of consent, permission for consent must take into consideration the adolescent's capacity for understanding the medical treatment or the research in which the adolescent is requested to be involved. At all circumstances adolescent's assent for both medical treatment and research is always mandatory. Involving adolescents in research should be based on a careful assessment of risks and benefits together with understanding of the developing capabilities of the adolescent.

Keywords: Adolescents. Legal issues, Ethics, Confidentiality, Consent, Research.

РЕЗЮМЕ

ПРАВОВЫЕ И ЭТИЧЕСКИЕ ВОПРОСЫ ОХРАНЫ ЗДОРОВЬЯ ПОДРОСТКОВ

Хардоф Д.

Медицинское обслуживание подростков Службы медицинских услуг «Клалит», Израиль и Центр "Открытая Дверь" Израильской Ассоциации планирования семьи

В обзоре рассматриваются правовые и этические аспекты включения подростков в исследование с учетом их согласия на проведение медицинских вмешательств и конфиденциальности. При оказании конфиденциальной медицинской помощи следует учитывать баланс нужд пациента-подростка, родителей и провайдера. В большинстве стран правовая дееспособность наступает с 18 лет, однако с 14 лет способность подростков участвовать в принятии медицинского решения можно сравнить с таковой у взрослых. Вместо хронологического возраста при взятии разрешения на согласие при проведении медицинских вмешательств или исследования

следует учитывать насколько подросток понимает в чем заключается лечение или исследование, в которое его/ее включают. При всех обстоятельствах согласие подростка как на лечение так и проведение исследования обязательно. Включение подростка в исследование должно базироваться на тщательной оценке рисков и пользы при учете уровня развития.

რეზიუმე

მოზარდთა ჯანდაცვის სამართლებრივი და ეთიკური საკითხები

დ. ჰარდოფი

ოჯახის დაგეგმვის ასოციაცია და კლელიტის ჯანდაცვის სამსახურის მოზარდთა მედიცინის სამსახური, ისრაელი

მიმოხილვაში გაანალიზაბულია მოზარდების კვლე-ვაში ჩართვის სამართლებრივი და ეთიკური ასპექტები მათი თანხმობის გათვალისწინებით. მოზარდები იმ შემთხვევაში მიმართავენ ჯანდაცვის დაწესებულებებს,როცა დარწმუნებულნი არიან კონფიდენციალობაში. კონფიდენციალური სამედიცინო დახმარების გაწევისას გათვალისწინებული უნდა იქნას მხოლოდ მოზარდი პაციენტის, მშობლების და პროვაიდერის საჭიროებათა ბალანსი. ქვეყნების დიდ უმრავლესობაში იურიდიული უფლებამოსილება, ძირითადად, 18 წლის ასაკიდან იწყება, თუმცა 14 წლის ასაკიდან მოზარდების უნარი, მონაწილეობა მიიღონ სამედიცინო გადაწყვეტილების მიღებაში უკვე შეიძლება განხილულ იქნას მოზრდილის უფლებამოსილების მსგავსად. ქრონოლოგიური ასაკის გარდა,თანხმობის ნებართვის მიღება უნდა ემყარებოდეს მოზარდის უნარს, ჩაწვდეს სამედიცინო მკურნალობის ან კვლევის არსს. ყველა გარემოებაში მკურნალობასა ან კვლევაზე მოზარდის თანხმობა სავალდებულოა. მოზარდის კვლევაში ჩართვა უნდა ემყარებოდეს რისკებისა და სარგებლის გულდასმით შეფასებას მისი განვითარების დონის გათვალიწინებით.

SEXUALITY IN YOUNG PEOPLE WITH PHYSICAL DISABILITIES: THEORY AND PRACTICE

Hardoff D.

Reuth-Open-Door of the Israel Planned Parenthood Association and Adolescent Medicine Services of the Clalit Health Services, Israel

Persons with disabilities are identified as those who have long-term physical, mental, intellectual, or sensory impairments which, in interaction with various barriers, may hinder their full and effective participation in society on an equal basis with others.

The United Nations General Assembly adopted the Convention on the Rights of Persons with Disabilities on December 2006. The Convention stated that persons with disabilities and their family members should receive protection and assistance, so that families can contribute towards the full and equal fulfillment of the rights of persons with disabilities [19]. Sexuality and sexual function are just as important to persons with disabilities as they are to their able-bodied counterparts [11,22,24]. Despite the call for universal access to reproductive health at the 4th International Conference on Population and Development in Cairo in 1994 [20], sexual and reproductive health was omitted from the Millennium Development Goals and remains neglected [6]. Indeed, young people with physical disabilities and their parents often admit that they have inadequate knowledge about sexual and reproductive health (SRH) [18]. Schools provide sex education that is unrelated to sexuality and disability [4], and even when sexuality is discussed with a health professional, frequently it is not applied to the specific disability [17]. Therefore, young people with physical disabilities and their parents frequently receive their sex education from friends and the media [5], and refrain from discussing sexuality issues with a health care provider unless these issues are raised by the professional [18].

Adolescents and young adults with physical disabilities have been shown to be less active socially, and to have difficulties in developing intimate relationships as well as in gaining sexual experience as compared to their able-bodied age mates [25,26]. These barriers may be associated with psychological maladjustment and low sexual self-esteem due to parental overprotection and negative attitudes of other people around [28]. Moreover, individuals with acquired disabilities due to accidents or illnesses during or after puberty often do not see themselves as members of the disability community. Thus, they frequently lack the social support that people who have grown up with disabilities rely upon [22]. Social isolation has been demonstrated in younger adolescents with cerebral palsy and spina bifida, where only 14.7% and 28.3% respectively indicated that they had ever been on a date [3]. Still, sexual activity has been reported in up to 47% of patients with spina bifida [21].

While persons with disabilities have the same needs for SRH services as everyone else, all too often, the SRH of persons with disabilities has been overlooked by both the disability community and professionals who work in SRH services [22]. Moreover, persons with disabilities probably have greater needs for SRH education and service delivery than persons without disabilities due to multiple reasons, including lack of accessibility to SRH services and relevant information, and increased vulnerability to abuse [22]. The recommendation that adolescents and young adults with disabilities should be provided with more help in independence skills, and that personal counseling services should be made available is not new [10,27] and intervention models have already been proposed [1,9,28]. Collaboration of professional staff with families and peers of young people with disabilities may indeed foster more informed decisions regarding their social and sexual lives [2]. However, professionals often have limited experience regarding sexuality issues when working with adolescents and young people in medical settings [8,12,14], and parents often have difficulties in discussing sexual issues with their adolescent children [15]. Therefore, young people with disabilities deserve SRH services that address their unique needs and are run by professionals who are both sensitive to and familiar with these needs. Comprehensive sexuality education was recommended as vital for normal growth and development of adolescents with developmental disabilities [7], while dedicated services regarding sexuality and physical disabilities are scantly reported [13].

In 2004 the Israel Family Planning Association in collaboration with the Reuth Medical Center for rehabilitation in Tel Aviv established a comprehensive multi-professional counseling service - "Reuth Open-Door" (ROD) - dedicated to young people, aged 12 to 35 years, with physical and sensory disabilities and to their families, targeting at social relations, sexual relationships and SRH issues. Beside individual and group counseling, ROD also provides consultations and organizes workshops for professionals who encounter young people with physical and sensory disabilities regarding SRH issues. ROD's core team includes a rehabilitation psychologist, a rehabilitation social worker, and a consultant physician specializing in adolescent medicine with special experience in adolescents and young adults' sexuality and disability issues. Further consultation is available at the sexual rehabilitation clinic of the Reuth Medical Center. The utilization of ROD by young people with physical disabilities between 2006 and 2009 was recently published [16], reporting that out of 1203 people contacting the service, 301 were invited for intake and 74 patients actually arrived for intake at the service. Among the patients who showed up for intake (62% males), 59% were in their third decade of life, 30% were older than 30 years and 12% were younger than 20 years. Neurological disorders were the most frequent (76%) causes for disabilities among the ROD's patients, including cerebral palsy in 28% and spina bifida in 10%. Muscular dystrophy was present in 8% of the patients [16]. Regarding relationships, similar to previous reports [25,26], while 82% of the ROD's patients were engaged in social relationships, just 54% had ever dated and only16% reported having experience in sexual relations [16]. This may be associated with psychological maladjustment and low sexual self-esteem due to parental overprotection and negative attitudes of other people around [28]. The main reasons for consultation request at ROD were engagement in relationships with a partner in 42% of the patients, sexual functioning in 23%, and socialization skills in 14% [16]. Two thirds of ROD's patients resided with their parents and only nine per cent lived with a partner, demonstrating their social isolation, as had been previously reported in a younger group of patients [3].

The reasons for the limited utilization of the ROD service were difficulties in transportation to the clinic and in finding escort for aid in accessibility to public transportation [16]. Indeed, according to a recent WHO report, the main barriers to approaching health services for people with disabilities are affordability of health services and transportation [23]. SRH services are often inaccessible to persons with disabilities for a number of reasons, such as physical barriers, lack of disability-related clinical services, stigma and discrimination. Physical barriers to health services include limited transportation to clinics, lack of ramps and examination tables, as well as lack of information and communication materials (e.g. materials either in Braille or large print, use of simple language, self-explanatory pictures, sign language interpreters etc.). Additionally, inadequate coordination among health care providers and lack of funding contribute to the inaccessibility to SRH services [22].

In order to overcome transportation barriers for SRH services in Israel, the Israel Family Planning Association has established a service similar to ROD for young people with

disabilities in the North of Israel in 2010, and is planning to establish another such facility in the Southern region of the country.

In summary, sexuality and sexual function are just as important to persons with disabilities as they are to their able-bodied counterparts, and SRH services for young people with disabilities are just as necessary as they are for the general population. Even the limited number of existing SRH services are underutilized, mainly due to barriers in accessibility. Health authorities should therefore provide the resources for the development of accessible comprehensive multidisciplinary SRH services dedicated to young people with disabilities, and thus fulfill the United Nations General Assembly declaration on the rights of persons with disabilities.

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SUMMARY

SEXUALITY IN YOUNG PEOPLE WITH PHYSICAL DISABILITIES: THEORY AND PRACTICE

Hardoff D.

Reuth-Open-Door of the Israel Planned Parenthood Association and Adolescent Medicine Services of the Clalit Health Services, Israel

Sexuality and sexual function are important to persons with disabilities just as they are to their able-bodied counterparts, but knowledge about sexual and reproductive health (SRH) among persons with disabilities is frequently inadequate. Adolescents and young adults with physical disabilities are less active socially, and have difficulties in developing intimate relationships. Thus, despite greater needs for SRH education and service delivery than persons without disabilities, dedicated services regarding sexuality and physical disabilities are scantly reported. Together with a literature survey on sexuality and disability in adolescents, a unique comprehensive SRH service for young people with physical disabilities is described in this review. Despite being interdisciplinary, the utilization of the service was limited due to difficulties in transportation to the clinic and in finding escort for aid in accessibility to public transportation. Health authorities should provide the resources for the development of accessible comprehensive multidisciplinary SRH services dedicated to young people with disabilities, and thus fulfill the United Nations General Assembly declaration on the rights of persons with disabilities.

Keywords: Adolescents, physical disabilities, sexuality, sexual and reproductive health, rights of persons with disabilities.

РЕЗЮМЕ

СЕКСУАЛЬНАЯ ЖИЗНЬ МОЛОДЫХ ЛЮДЕЙ С ОГРАНИЧЕННЫМИ ФИЗИЧЕСКИМИ СПОСОБНОСТЯМИ: ТЕОРИЯ И ПРАКТИКА

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Центр "Открытая Дверь" Израильской Ассоциации планирования семьи и Медицинское обслуживание подростков Службы медицинских услуг «Клалит», Израиль

Сексуальная жизнь и сексуальная функция также важны для лиц с ограниченными физическими способностями (ОФС), как и для здоровых, однако достаточных знаний о сексуальном и репродуктивном здоровье (СРЗ) у лиц с ОФС не имеется. Подростки и молодые люди с ОФС социально менее активны и имеют трудности в налаживании интимных взаимоотношений. Однако, несмотря на потребность в образовании в сфере СРЗ и оказании соответствующих услуг лицам с ОФС, достаточных сведений о специальных службах, занимающихся сексуальными вопросами лиц с ОФС не имеется. В представленной работе, наряду с обзором соответствующей литературы, описывается специальная служба, оказывающая необходимую помощь лицам с ОФС. Однако использование этой службы весьма ограничено ввиду трудностей в транспортировке и сопровождении этих лиц в клинику. Анализ литературы выявил необходимость выполнения решения декларации Генеральной Ассамблеи ООН о правах лиц с ограниченными способностями, которая обязывает руководство системы здравоохранения обеспечить необходимыми ресурсами мультидистиплинарную службу СРЗ для лиц с ОФС.

რეზიუმე

ფიზიკური უნარშეზღუდულობის მქონე ახალგაზრდების სექსუალობა: თეორია და პრაქტიკა

დ. ჰარდოფი

ოჯახის დაგეგმვის ასოციაცია და კლელიტის ჯანდაცვის სამსახურის მოზარდთა მედიცინის სამსახური, ისრაელი

სექსუალური ცხოვრება და სექსუალური ფუნქცია უნარშეზღუდული პირებისათვის ისევე მნიშვნელოვანია, როგორც ჯანმრთელებისთვის, თუმცა უნარშეზღუდულთა სექსუალური და რეპროდუქციული ჯანმრთელობის (სრჯ) შესახებ ცოდნა მეტად მწირია, გამომდინარე იქიდან, რომ ფიზიკური უნარშეზღუდულობის (ფუ) მქონე მოზარდები და ახალგაზრდები სოციალურად ნაკლებად აქტიურები არიან,მოცემულ ნაშრომში, უნარშეზღუდული მოზარდების სექსუალური ცხოვრების შესახებ ლიტერატურის მონაცემების მიმოხილვასთან ერთად, აღწერილია მათთვის განკუთვნილი უნიკალური სრჯ-ის ყოვლისმომცველი სამსახურის საქმიანობა. მიუხედავად იმისა, რომ სამსახური ინტერდისციპლინურია,მისი გამოყენება შეზღუდულია, ვინაიდან ძნელია ახალგაზრდების კლინიკაში ტრანსპორტირების განხორციელება და თანმხლები პირების პოვნა. რეტროსპექტული და მიმდინარე ლიტერატურის განხილვამ გამოავლინა გაერთიანებული ერების ორგანიზაციის გენერალური ასამბლეის მიერ უნარშეზღუდულ პირთა უფლებების შესახებ მიღებული დადგენილების შესრულების აუცილებლობა, რომლის მიხედვით ჯანდაცვის მესვეურებმა უნდა უზრუნველჰყონ სათანადო რესურსებით სრჯ-ის სამსახურები.

ADOLESCENT IMMUNIZATION

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National Immunization Programs (NIPs) in children were implemented worldwide during the twentieth century. During the last decades immunization programs were modified to cover adolescents and adults as well. The extension of pediatric immunization program was imposed when it was realized that there was a relatively high prevalence of certain vaccine preventable diseases in adolescents, associated either to incomplete immunization or to waning of vaccine induced immunity like pertussis, diphtheria and others. In addition the production of new vaccines for severe diseases, predominating in adolescents as human papillomavirus and meningococcal infections, favored the extension of pediatric immunization programs to adolescence and adulthood.

To emphasize the role and essential need for this modification the Committee of Infectious Diseases of the American Academy of Pediatrics changed the definition of "The standards for Pediatric Immunization Practices" to "Standards for Child and Adolescence Immunization Practices" [10].

The recent National Immunization Programs for children, adolescents and adults have two main goals. The "immediate", which aims to the prevention of a severe disease in vaccinated individuals and the "ultimate" which aims to eradicate the disease in a particular population and in long term worldwide.

In this review some general issues of active immunization, common to pediatric and adolescent immunization are discussed in brief and adolescent immunization in detail.

Evolution of immunization programs.
The rapid evolution in the implementation of national immunization programs occurred during the second half of the 20th century. In 1962, when available vaccines were few and massive immunization programs had just started in developed countries it was predicted that "Never in the history of human progress has a better and cheaper method of preventing illness has been developed, that immunization at its best" [7].

These predictions were confirmed after prolonged and systematic implementation of immunization in infants and children in developed countries. At present it is generally accepted that vaccination is the most effective, applicable and cheap method to prevent infectious diseases [1]. The statement is confirmed from data on the morbidity prior and after prolonged implementation of immunization programs for preventable diseases in UK and USA; both countries have high vaccine coverage and accurate surveillance data. In England the morbidity for 9 vaccine preventable diseases was compared prior and in 1997. The overall reduction for the 9 diseases exceeded - 99%.The total annual number of 1,639,000 patients prior to immunization was reduced to 6,600 in 1997.Poliomyelitis was completely eradicated, reduction of other diseases exceeded - 99% with the exception of tetanus - 97%, and pertussis - 98%. Similar data were reported in US for 2001and for 10 preventable diseases. Smallpox and poliomyelitis were also eradicated, reduction of diphtheria, measles, mumps, rubella (including congenital), hemophilus influenza exceeded - 99%, of tetanus - 97% and pertussis - 95% [2,3].

National immunization programs for children were universally implemented in developed countries in the second half of the last century. During this period there was a persistent and increasing alertness and improvement in immunization practices due to a number of factors as the continuous accumulation of experience on vaccines' effectiveness and the type, incidence, severity and management of adverse reactions, the improvement of efficacy of old vaccines and the production of new vaccines for common severe diseases.

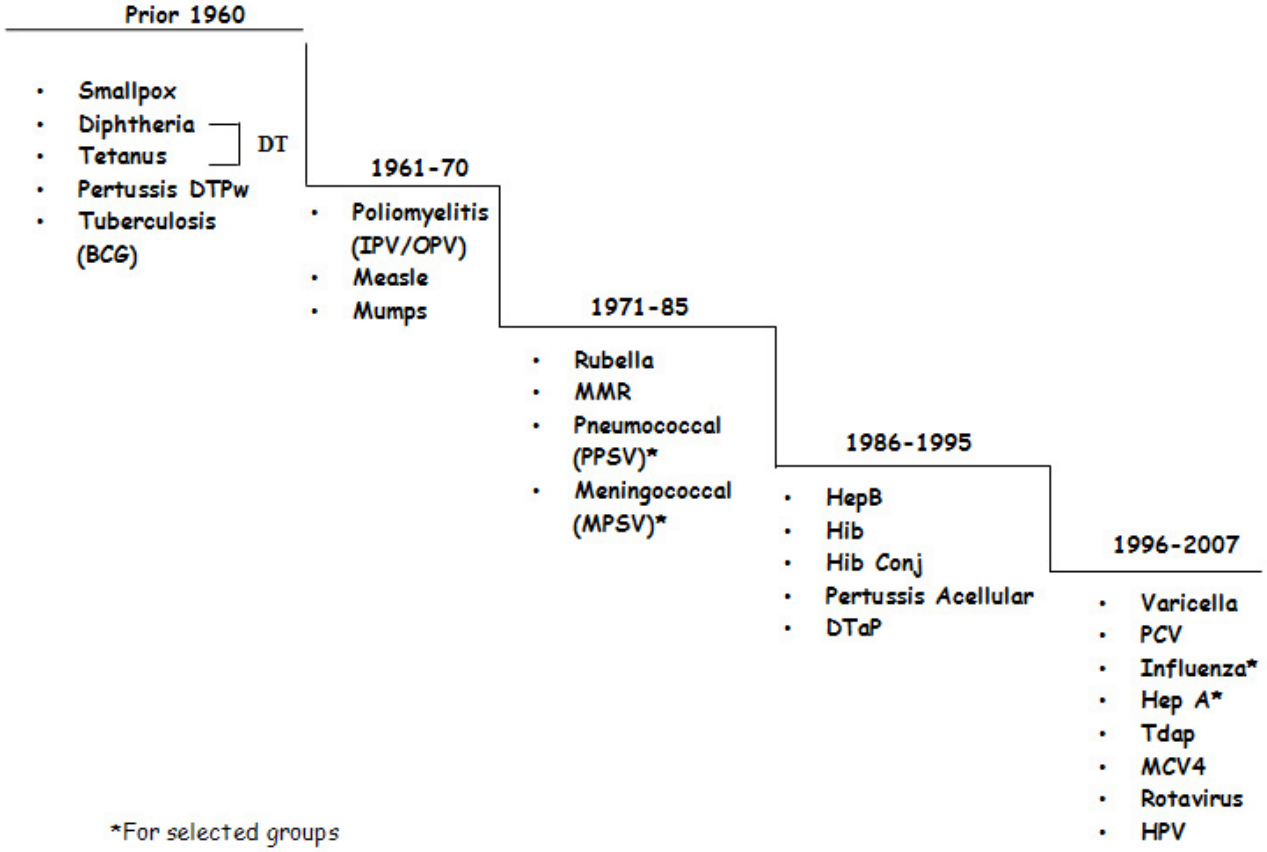
The evolution and enrichment of NIPs with new vaccines in developed countries is summarized in table 1.

Prior to1960, 3-5 vaccines were available for use (smallpox, BCG, DTPw, DT and pertussis).Gradually the number of vaccines increased to more than 25. Prior to 1985 production of new vaccines and improvement of old, were slow as was the rate of changes of NIPs. Since 1985, there were rapid advances in the development of new vaccines and improvement of old ones. It was unfortunate that a number of new vaccines were too expensive to be included in the national programs of many countries. The NIPs are formulated, as a rule, by scientific national committees having as guidelines: i) the structure, capability and funding of the national health system;
ii) the rate of morbidity and mortality of the disease in the population and
iii) the socio-economic status of the country [1,3]. This explains the existing heterogeneity in the practices of pediatric and adolescent immunization within developed countries, and much more with the WHO Expanded Program of Immunization (EPI) for undeveloped countries.

WHO EPI program started in 1974 covering only tuberculosis, diphtheria, tetanus, pertussis, polio and measles, with a minimum number of five doses, injections and visits. Later hepatitis B and hemophilus influenza type b infections were added to the EPI in the majority of undeveloped countries

[18]. In developed countries immunization practices vary in regard to the number of diseases covered, the type of vaccines, the number of visits and injections, the interval between doses and others.

Table 1. Evolution of vaccines for immunization programs



To relieve children from the discomfort of injections and parents from frequent medical visits, new combined polyvalent vaccine have been manufactured and licensed. The advantages of the new combined vaccines as compared to common mono and polyvalent vaccines are: improved efficacy, lower incidence of side effects, better compliance because of reduced number of injections and minimization of discomfort, reduction of medical visits and lower cost. The more commonly used new combined polyvalent vaccines are those based on acellular pertussis DT vaccine (DTaP). The more popular combination in the market is shown in table 2.

Table 2. Combined Polyvalent vaccines incorporated with DTaP

■ **DTaP**	■ **DTaP-HBV**
■ **DTaP-IPV**	■ **DTaP-Hib-HBV**
■ **DTaP-Hib**	■ **DTaP-IPV-HBV**
■ **DTaP-Hib-IPV**	■ **DTaP-IPV-Hib-HBV**

Adolescent Immunization: Prerequisites

For adolescent immunization a major prerequisite is the precise assessment of the immune status, preferably at the preadolescent period of 8-10 years or at early adolescence at 11-12 years. The assessment of immune state is based mainly on the immunization records kept usually by parents; these data are supplemented with information from parents as regard vaccine administration, physical immunization after viral infection of measles, mumps, rubella, chickenpox, hepatitis A and B. In case of doubt, immunity is assessed by antibody detection [1,10].

Detection of antibody or antibodies is the best method to confirm the presence of immunity. The procedure is expensive, time consuming and not easily applicable. Individuals with un-clarified immune state are considered non-immune and follow the standard immunization practices for the respective disease and age group.

Assessment of immune state identifies three groups of adolescents:

I) Individuals who completed the pediatric immunization program and are ready to proceed to the adolescent program.

II) Adolescents inadequately vaccinated for one or more diseases skipping one or more vaccine doses. They have to catch up pediatric immunization prior or parallel to adolescent immunization. III) Adolescents that are at high risk for

certain vaccine preventable infectious diseases [11].

Compliance with national pediatric immunization programs varies from country to country, and is best reflected by the proportion of immune adolescents to pediatric vaccines. At present a major activity of adolescent immunization covers the catch up process of pediatric vaccination.

Recommendations for Adolescent Immunization Practices
National Immunization Program (NIP) of US and developed Europeans countries include recommendations for immunization of the three age groups, children, adolescents and adults. In US the recommendations for immunization practices for the three age groups is the product of careful review of all aspects of vaccines by the Advisory Committee of Immunization Practices (ACIP) and adoption of the committee's recommendations by the Centers for Disease Control and prevention (CDC), in collaboration with the American Academy of Pediatrics, American Academy of Family Physicians and other professional organizations [1,10]. The recommendations and schedule of immunization are annually revised, are considered the more advanced and are used as prototype for immunization practices by the majority of pediatricians and health providers worldwide.

The adolescent immunization schedule, as part of the whole NIP is formulated to cover all three groups of immune state of adolescents. Vaccines covering the needs of adolescents are classified in three groups based on the immune state of the individuals (Table 3). The first group includes vaccines for routine administration to all adolescents, immune for preventable diseases covered by childhood immunization program. The second group includes vaccines for catch up vaccination of not fully immunized adolescents. The third group consists of vaccines recommended for high risk adolescents.

Table 3. Classification of vaccines in adolescent immunization program

1. Vaccines for Adolescents
• Influenza (TIV or LAIV)
• Human papillomavirus (HPV2 or HPV4)
• Meningoccocal conjugated (MCV4)
• Tetanus-diphtheria-acellular pertussis (Tdap)
2. Catch up vaccines for not fully immunized adolescents
• Hepatitis B (HepB)
• Inactivated polio (IPV)
• Measles, mumps and rubella (MMR)
• Varicella (Var)
3. Vaccines for certain high risk adolescents
• Hepatitis A (HepA)
• Pneumococcal polysaccharide (PPSV)

The update, mildly modified, schedule of adolescent immunization recommended by AAP and CDC for 2012 in US is illustrated, in Figure. The modifications cover mainly the discrepancies in the definition of adolescence in regard to cutoffs ages. The adolescent immunization schedule utilizes four vaccines for routine administration to all immune adolescents to pediatric vaccines.

Fig. Recommended adolescent immunization schedule for 2012 in U.S (Modified, Pediatrics 2012;129(2):385-6)

Adolescence age (years) / Vaccines	Pre- 9-10	Early 11-12	Early 13-14	Mid 15-18	Late 19-21
Tetanus -Diphtheria Pertussis (Tdap)	1 dose**	1 dose*	1 dose (if indicated)**		
Human Papillomavirus #(HPV2/HPV4)		3 doses*	Complete 3 dose series**		
Meningococcal (MCV4)		1 dose*		Booster at 16 yrs**	
Influenza (TIV or LAIV)	YEARLY*				
Hepatitis B (Hep B)	Complete 3- dose series**				
Poliomyelitis (IPV)	Complete 3- dose series**				
Measles - Mumps - Rubella (MMR)	Complete 2- dose series**				
Varicella (Var)	Complete 2- dose series**				
Hepatitis A (Hep A)	Complete 2- dose series***				
Pneumococcal (PCS or PPSV)	1 dose***				

** - Range of recommended ages: for all adolescents #HPV2 or HPV4 for females, HPV4 for males; ** - Range of recommended ages for catch-up immunization; *** - Range of recommended ages for certain high risk groups*

These are: i) The trivalent inactivated influenza vaccine (TIV), or the live attenuated influenza vaccine (LAIV); the vaccine it is recommended annually for all adolescents up to the age of 21 years. In a number of European countries is recommended only for high risk groups with chronic diseases mainly of respiratory system.
ii) The human papillomavirus vaccine (HPV) .Two vaccines are licensed for use for females; the bivalent HPV2 and quadrivalent HPV4. The last one is also recommended for males. Ideally HPV vaccines should be administered before potential exposure to papillomavirus through sexual activity. In females routine vaccination with either HPV2 or HPV4 in a 3 dose series is recommended at the age of 11-12; and for the not vaccinated at ages 13-26 years.
iii) The meningococcal conjugated quadrivalent vaccine with serotypes A, C, W and Y (MCV4). A single dose is recommended at the age of 11-12 years with a booster dose at the age of 16yrs. For unvaccinated adolescents a single dose is also recommended from 13 to 21 years.
iv)The adult type of tetanus-diphtheria-acellular pertussis vaccine Tdap. The vaccine is similar to TDaP (used in children) but with reduced dose of diphtheria toxoid and acellular antigenic components of pertussis. Tdap is recommended as a booster dose for adolescents aged 11-12 years, repeated in 10 years [13,15].

For the inadequately vaccinated group of adolescents the catch up procedures use the vaccines of pediatric immunization: IPV, HepB, MMR, and Var. and for the high risk groups of adolescents the PPSV, HepA and MCV4 vaccines. Of major importance for the adolescent immunization program is the compliance with the catch up procedures that have to be completed preferably in early adolescent period. The procedures depend on the type of missing vaccines, the skipped number of doses and the age of initial vaccination. Information for the catch up procedures are analytically provided by CDC and AAP in the recommendations for adolescent immunization practices [13,15]. Information can be modified and adjusted to the NIP of each country.

Vaccines for treatment
Certain vaccines are used to treat non-immune adolescents exposed to infectious diseases that are prevented by vaccines. Diseases with a beneficial outcome are:
i) measles; vaccine administered within 72 hours from exposure prevents clinical manifestation and within 3-5 days ameliorates clinical signs;
ii) Chickenpox; varicella vaccine could be effective within 72 hours from exposure; it is contraindicated for immunosuppressed patients for whom hyper immune globulin is indicated;
iii) hepatitis B: in case of exposure to HBV ,HepB vaccine preferable in combination with hyper immune globulin is most effective to prevent clinical and biochemical findings of disease. This is the common practice to treat neonates born to HBsAg positive mothers and other non-immune individuals at high risk of HBV infection. iv) hepatitis A. HepA vaccine prevents disease if given within 5-7 days of exposure and is recommended as alternative to gamma globulin [1,13,15].

Adolescent Immunization Background and Perspectives
During the last decades NIPs are in a continuous revise targeting to extend universal immunization programs to adolescents and adults, to formulate precise recommendations for old and new vaccines and to evaluate the prevention cost effectiveness and safety of novel vaccines. Extension of universal immunization programs to older ages is expected to prolong immunity throughout life, maximize vaccines' prevention efficacy minimizing morbidity and mortality rates for vaccine preventable diseases in the population. Informative are the results of a recent survey in U.S. comparing morbidity and mortality rates prior and after implementation of NIP for 13 vaccine preventable diseases for the year 2006 for morbidity and 2004 for mortality. A greater than 92% decline in morbidity and a 99% or greater decline in death, were found for diphtheria, mumps, pertussis and tetanus. An endemic transmission of poliomyelitis, measles, rubella and smallpox viruses has been eliminated. Declines of 80% or greater were reported for cases and deaths for most vaccine preventable diseases targeted since 1980 including hepatitis A, acute hepatitis B, Hemophilus influenza b, and varicella . Decline in cases and deaths for invasive S pneumonia were 34% and 25% respectively [14].

Contemporary NIPs for adolescents recommend vaccines exclusively addressed to adolescents and vaccines common for all ages. These vaccines, as a rule, protect from serious diseases with a high morbidity, considerable mortality and chronic sequels. In US, human papillomavirus affects annually more than 6 million adolescents; nearly three in four females aged 15-24 years. While most of HPV infections clear on their own, infection may have a chronic process with serious consequences. Chronic HPV in females can lead to cervical cancer, the second leading cause of cancer deaths among women; about 500,000 new cases are diagnosed annually worldwide. Seventy percent of cervical cancer is related to chronic infections with the oncogenic types 16 and 18 of HPV. For the protection of HPV infection, two vaccines were recently licensed: the HPV2 (with types 16 and 18) and HPV4 (with types 6,11,16 and 18). Both are recommended for adolescent girls as a three dose series at 0,2,and 6 months, at 11-12 year of age, and 13 through26 years to provide protection against HPV type cervical cancer, cervical cancer precursors, vaginal and vulvar precursors and anogenital warts. HPV4 is recently recommended for adolescent boys for protection against anogenital warts and the rare anal, penile and oropharengeal cancers related to HPV [9]. The third vaccine exclusively prepared for adolescents and adults is the adult type of diphtheria - tetanus - pertussis vaccine. Universal implementation of DT initially and DTwP or DTaP in childhood immunization reduced considerably morbidity and mortal-

ity in US and other developed countries. Diphtheria became extremely rare; recently an increasing number of isolated cases were reported in European countries in adolescents exposed to diphtheria bacillus imported by immigrants. Tetanus on the other hand still affect inadequately vaccinated adolescents as tetanus bacteria are ubiquitous. To minimize further morbidity and mortality of the two diseases a booster dose of Td at the age of 11-12 years, repeated in 10 years throughout life, is recommended.

Pertussis is the least well controlled vaccine preventable bacterial disease in developed countries. Whole and acellular pertussis vaccines (single or in combination with tetanus and diphtheria) took a very long time to be accepted for universal use because of serious adverse reactions. In developed countries vaccination of infants and toddlers with four doses of DTwP or DTaP vaccine reduced morbidity for more than 95 percent. On this schedule vaccine induced immunity wanes in 4-6 years compared to 12-15 years of natural immunity, while epidemiological studies demonstrated a continuous trend of increasing morbidity in adolescents. Though the precise incidence of pertussis is difficult to assess because of substantial underreporting, data from US, UK and France estimate the annual incidence of pertussis between 300-500 cases per 100.000 populations. Pertussis causes nearly 300,000 deaths annually worldwide [6]. Whether disease is subclinical, mild or severe, infected (diagnosed or undiagnosed) adolescents may serve as an important reservoir of infection for neonates and other individuals at higher risk for serious illness or pertussis related death. To prolong the efficacy of pertussis vaccination and vaccine induced immunity a booster dose of the novel Tdap vaccine is recommended at the age of 11-12 years, repeated every 10 years lifelong. European countries chose the administration of Tdap for all adolescents and young adults with or without selective vaccination for groups of adults, as parents, childcare and healthcare workers and elders at risk of severe pertussis disease [5,8].

Compliance with adolescent immunization program is expected to achieve further improvement in the control of vaccine preventable diseases and their serious sequels as are liver and cervical cancers.

Comment and Conclusion

The successful implementation of infants and children immunization to achieve and maintain high coverage levels throughout childhood resulted in a considerable reduction of morbidity and mortality of vaccine preventable diseases. The overall benefits of vaccines is difficult to assess as they are influenced by a number of factors, most of which change during the span of NIP implementation. Crucial factors for this assessment are the precise follow of vaccine coverage, which is directly related to the compliance of immunization process combined with precise surveillance of vaccine preventable diseases.

At present the major issue is the low compliance of vaccination program of adolescents. Surveys on adolescent vaccines coverage and disease surveillance in US and other countries showed a gradual increase, which is still well below the desirable level for effective prevention. This is the case not only for the novel but also for the old vaccines of adolescent immunization. In US, a recent study among adolescents aged 13-17 years disclosed for 2010, 68.7% coverage for Tdap, 62.7% for MCV4 and only 32% for the 3 doses HPV2 or HPV4 for females. Coverage for catch up vaccines (MMR, HepB and Var) was also below the desirable level of 90%. A most interesting finding was the wide variation of coverage among states [4].

Increase of immunization rate is suspended by a number of barriers. An important one is the lack of special units within the health system to provide health services for adolescents. Based on the structure of health system adolescents are under the care of pediatricians, family physicians or general practitioners who, as a rule are not familiar to the unique needs of adolescent health care. Recently units of adolescent medicine were organized within the university departments of pediatrics in US and few developed European countries and WHO promoted the development of youth friendly health services units in Europe and worldwide. These units are open to primary health care visits, including preventive [16,17]. To promote immunization a comprehensive health care visit for all adolescents at the age of 11-12 years that includes evaluation and implementation of immunization program is recommended.

Another barrier is the changing behavior among adolescents and their parents or guardians. While children have no control over healthcare decision adolescents play as a rule a key role in decision making for their own health. It is therefore important to educate adolescents, parents and guardians about the benefits of vaccines and seriousness of preventable diseases. In addition healthcare providers must be familiar to the recommendation of adolescent immunization practices, follow the instructions for vaccines administration and provide requested data on disease surveillance and vaccine coverage.

In conclusion, vaccines are one of the greatest achievements of biomedical science and public health. Continued efforts to improve efficacy and safety of vaccines and vaccine coverage among all age groups will provide overall public health benefit. Adolescent immunization programs are still below the desirable immunization rates critical for the program's diseases prevention. A major immediate challenge for adolescent immunization is to improve compliance for achievement and maintenance of high vaccination rates for this age group.

Abbreviations for vaccines

DT: diphtheria - tetanus toxoids (pediatric); **DTaP:** diphtheria –tetanus toxoids and acellular pertussis; **HepA**:

hepatitis A; **HepB**: hepatitis B ; **HPV2/HPV4**:human papillomavirus bivalent and quadrivalent; **IPV**: Inactivated poliovirus; **LAIV**: Live attenuated influenza; **MCV4**: quadrivalent meningococcal conjugate; **OPV**: oral poliovirus; **PCV:** Peunococcal conjugate; **PPSV**: Peunococcal polysaccharide; **Td**: adult tetanus and diphtheria toxoid; **Tdap**: tetanus and reduced diphtheria toxoids and acellular pertussis(adult type); **TIV**: Trivalent inactivated influenza; **VAR**: varicella.

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SUMMARY

ADOLESCENT IMMUNIZATION

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During the last century National Immunization Program (NIP) were implemented worldwide. The program started with a small number of vaccines for universal administration to infants and young children. In the second half of the century an evolution (slow in the start and rapid later) occurred in the structure of NIPs especially in developed countries. NIPs were enriched with new and more effective vaccines and expanded to adolescents and adults. The Adolescent Immunization Program (AIP) developed its own instructions and schedule that are continuously revised to improve further its efficacy. AIP composes of three main parts: a) the administration of novel vaccines produced for exclusive use in adolescents, b) the catch up process to supplement incomplete pediatric immunization schedule and c) the coverage of high risk groups with the appropriate vaccines.

The novel vaccines for adolescent immunization are: the human papillomavirus (HPV2 and HPV4), the conjugated meningococcal with serotypes A, C, Wand Y, (MCV4), and the adult type of tetanus – diphtheria-pertussis (Tdap).

Even in developed countries adolescent immunization is still below the desirable rates, critical for the prevention of diseases covered by the program. Thus at present a major challenge for adolescent immunization programs of developed countries is improvement of compliance to achieve and maintain high vaccination rates, for this age group, to provide an overall public health benefit.

Keywords: adolescent immunization, national immunization schedules.

РЕЗЮМЕ

ИММУНИЗАЦИЯ ПОДРОСТКОВ

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В течение последнего столетия весь мир был охвачен Программой всеобщей иммунизации. На начальном этапе в программу вакцинации младенцев и детей дошкольного возраста были включены вакцины ограниченного числа болезней. Во второй половине столетия в структуру национальных календарей прививок, в особенности в развитых странах, внесены определенные коррективы. Они были дополнены новыми и более эффективными вакцинами и распространены на подростков и взрослых. Для программы иммунизации подростков (ПИП) были разработаны соответствующие инструкции и календарь, которые постоянно пересматриваются с целью их усовершенствования. ПИП состоит из трех основных частей: а) назначение новых вакцин, разработанных исключительно для подростков; б) процесс наверстания – дополнение неполных педиатрических программ; в) обеспечение групп с высоким риском соответствующими вакцинами.

Новыми вакцинами для иммунизации подростков являются вакцина против вируса папилломы человека (HPV2 and HPV4), конъюгированная менингококковая вакцина с серотипами A, C, Wand Y (MCV4) и вакцина против столбняка-коклюша-дифтерии для взрослых (Tdap).

Даже в развитых странах охват подростков прививками ниже желаемых показателей, необходимых для превенции соответствующих инфекций. Следовательно, основным вызовом в ПИП в развитых странах является улучшение комплайенса с целью достижения и сохранения высоких показателей вакцинации для этой возрастной группы, что будет способствовать улучшению общественного здравоохранения в целом.

რეზიუმე

მოზარდთა იმუნიზაცია

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ათენის უნივერსიტეტი, პირველი პედიატრიული დეპარტამენტი; აია სოფიას ბავშვთა ჰოსპიტალი, ათენი, საბერძნეთი

უკანასკნელი ასწლეულის განმავლობაში საყოველთაო იმუნიზაციის პროგრამამ მოიცვა მთელი მსოფლიო. პროგრამის დასაწყისში გარკვეულ დაავადებათა ვაქცინებით ხდებოდა ჩვილი და უმცროსი ასაკის ბავშვების საყოველთაო იმუნიზაცია. საუკუნის მეორე ნახევარში იმუნიზაციის ნაციონალური პროგრამების სტრუქტურამ (ინპ), განსაკუთრებით განვითარებულ ქვეყნებში, ევოლუცია განიცადა. ინპ გამდიდრდა ახალი და უფრო ეფექტური ვაქცინებით და გავრცელდა მოზარდებსა და მოზრდილებში.

მოზარდთა იმუნიზაციის პროგრამისთვის (მიპ) შემუშავდა სპეციალური ინსტრუქციები და კალენდარი, რაც პერიოდულად გადაიხედება ეფექტურობის ასამაღლებლად. მიპ მოიცავს სამ ძირითად ნაწილს: ა) ახალი ვაქცინების დანიშვნა, რაც მოწოდებულია უშუალოდ მოზარდებისთვის, ბ) დაწევის პროცესი არასრული პედიატრიული აცრების შესავსებად და გ) მაღალი რისკის მქონე ჯგუფების სრული უზრუნველყოფა სათანადო ვაქცინებით. მოზარდების იმუნიზაციისთვის ახალ ვაქცინებს მიეკუთვნება ადამიანის პაპილომავირუსის საწინააღმდეგო ვაქცინა (HPV2 and HPV4), კონიუგირებული მენინგოკოკური ვაქცინა A, C, Wand Y სეროტიპებით (MCV4) და ტეტანუსი-დიფტერია-ყივანახველას ვაქცინა მოზრდილებისთვის (Tdap). განვითარებულ ქვეყნებშიც კი მოზარდთა იმუნიზაცია არ აღწევს შესაბამისი ინფექციების პრევენციისთვის სასურველ მაჩვენებლებს. აქედან გამომდინარე, მიპის ძირითადი გამოწვევაა კომპლაიენსის გაუმჯობესება, რათა მიღწეული და შენარჩუნებული იქნას ამ ასაკობრივი ჯგუფისთვის აცრებით უზრუნველყოფის მაღალი მაჩვენებლები, რაც ხელს შეუწყობს საზოგადოებრივი ჯანდაცვის გაუმჯობესებას.

EFFECTS OF GROWTH HORMONE ON HEART STRUCTURE AND FUNCTION IN ADOLESCENCE

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Growth hormone (GH) is secreted by the somatotrope cells of the anterior pituitary gland. In the circulation, various molecular forms of GH exist, the majority of which are bound to the carrier proteins corresponding to the extracellular domain of the GH receptor (GHR) [3]. GH stimulates hepatic production of Insulin Growth Factor 1 (IGF-1) in the presence of sufficient nutrient intake. IGF-1 is critical on promoting the anabolic effects of GH on the target tissues such as bone, muscle and fat (Fig. 1). The secretion of GH is maximal at mid-puberty, accompanied by very high circulating IGF-1 levels in addition with the concomitant increase of insulin resistance [36]. On the contrary a gradual decline of GH and IGF-1 secretion characterizes adulthood. In adolescence, where the most anabolic effects and cardiac performance reach a zenith, GH-IGF-1 system plays a crucial role.

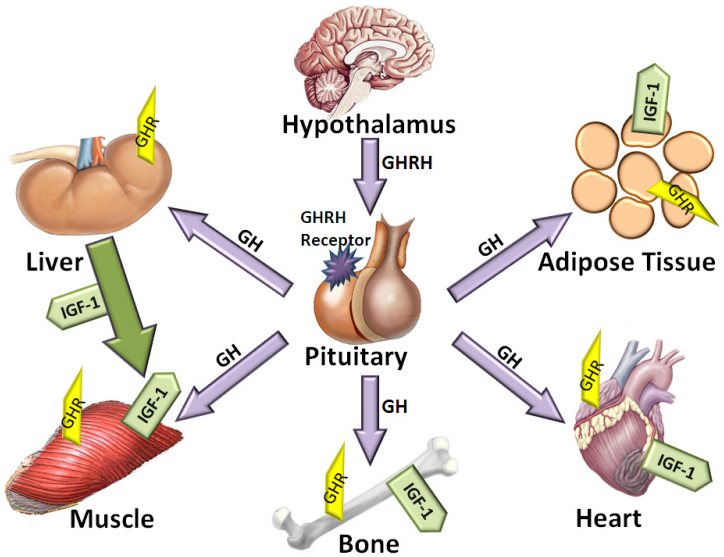

Fig. 1. GHRH-GH-IGF1 axis effects on target tissues. GH (Growth Hormone), GHRH (Growth Hormone Releasing Hormone), IGF-1 (Insulin like Growth Factor -1), GHR (Growth Hormone Receptor)

Heart as a target organ for the GH-IGF-1 axis

Both GH and IGF-1 receptors are expressed in cardiac myocytes *in vitro* and *in vivo* [21]. IGF-1 causes hypertrophy of cultured rat cardiomyocytes [28]. Experimental studies proved the anti-apoptotic effect of IGF-1 on the cardiomyocyte [9]. In addition, GH and IGF-1 enhance the role of calcium in the myocardial contractility. Intracellular calcium content and calcium sensitivity of myofilaments in cardiomyocytes increase by the direct action of both GH and IGF-1 [10,25].

Studies on rats showed that exogenous administration of GH and IGF-1 induce cardiac hypertrophy without development of significant fibrosis. Cardiac performance increases both *in vivo* and in the isolated heart. Additionally GH excess produced by a GH-secreting tumor in rats have yielded conflicting measures of cardiac function *in vivo* with either increased or decreased contractility. IGF-1 has been postulated to initiate, mediate, or modulate cardiac hypertrophy either per se or in response to several stimuli; including pressure and volume overload [11].

The exact mechanism of the GH-IGF-1 axis and other interfering factors on the physiology of the cardiovascular system is complicated. Apart from GH and IGF-1 system, other hormonal and biochemical factors are implicated. Such important factors for example are GH secretagogues (GHS) and ghrelin. Ghrelin not only promotes GH secretion and regulates appetite and metabolism, but also exerts a number of effects on the cardiovascular system. The main cardiovascular actions of GHS are possible inotropic effects, vasodilation, cardioprotective effects against ischemia, and *in vitro* effects on cardiomyocytes involving cell proliferation and anti-apoptotic actions. Interestingly GHS may be expressed directly on the heart and vasculature

rather than being mediated by GH. Evidence to suggest this feature is the GHS binding sites on cardiomyocytes and the fact that some of the effects of GHS can be expressed also in the absence of GH [27].

The ability of GH to trigger cardiac muscle growth plays a pivotal role in the physiology of the heart. Specifically GH has both direct and indirect actions on the cardiovascular system. GH acts directly on the cardiac muscle and augments cardiac contractility, independent of myocardial growth. It also improves myocardial energetics and mechanical efficiency. Among the indirect effects of GH on the heart, the most consistently found is the decrease of Peripheral Vascular Resistance. GH may also raise Preload through its sodium-retaining action. Its interference with the hormonal system that regulates water and electrolyte metabolism leads to expansion of blood volume and to increase of glomerular filtration rate. Particularly important is the effect of GH on skeletal muscle mass which together with the enhanced respiratory muscle activity contributes to the better function and performance of the cardiovascular system.

Heart function in Growth Hormone Deficient adolescents

The existence of a relationship between GH-IGF-1 and the cardiovascular system has also been suggested by clinical studies. The majority of these studies report an increased risk for cardiovascular morbidity and mortality in patients with GH deficiency (GHD) either with adulthood or childhood onset. A limited number of studies involve adolescents and children (Table 1). GH deficient patients have a reduced life expectancy, with approximately a twofold higher risk of death from cardiovascular disease compared with healthy controls [9,23,38]. This is likely related to the direct and indirect adverse consequences of GHD on the cardiovascular system; hypercoagulability, abdominal obesity, insulin resistance, impairment in lipid profile, atherosclerosis, endothelial dysfunction, reduction of pulmonary function and muscle performance [5,12]. Specifically, GHD patients were reported to perform a reduction in the thickness of the left ventricular (LV) posterior wall, interventricular septum, LV internal diameter and LV mass (LVM) index [1,33]. Such findings are not established in adolescents with GHD. A recent study in GHD children and adolescents showed no significant differences in parameters of cardiac systolic function and LVM in comparison with controls. However, significantly higher Isovolumetric Relaxation Time (IVRT) values and elevated IMT values in the common carotid artery were observed in adolescents with GHD [43].

Table 1. Main studies on the heart function and structure in children and adolescents

Reference	Diagnosis	Patients	Age (y)	GH tx duration (y)	Cardiac Changes
Stamoyiannou 2000 [26]	GHD	42	4.3-16.7	3	No change
Colao 2002 [23]	GHD	15	17-20	Treated until FH, then stopped, and re-instituted for ½ yrs	LV mass normal during tx, decreased during discontinuation, increased again with re-institution
Shulman 2003 [28]	GHD	10	10	1	LV mass and SF increased
Lanes 2005 [24]	GHD	10	14	½	LV mass increased
Salerno 2006 [27]	GHD	30	8	2	LV mass increased
Barton 1992 [35]	ISS	18	6	1	No change
Daubeney 1995 [34]	ISS	15	7.8	4	No change
Matura 2007 [41]	TS	67	16.5	4.5	No change

Abbreviations: GHD- Growth Hormone Deficiency; ISS-Idiopathic Short Stature; TS - Turner Syndrome; LV- Left Ventricular; FH- Final height; SF- Systolic Fraction

Growth Hormone Replacement Therapy and the Heart in GHD adolescents

Current practice in GHD adolescents is to discontinue GH replacement therapy at final height. The persistence of GHD should be then reevaluated by appropriate GH testing because one third to one half of patients with GHD during childhood do not have persistence of the disease in adulthood. The rest show persistent GHD causing deleterious consequences in adulthood as mentioned above. Continuation of GH treatment after final height may have beneficial effect on the cardiovascular system in GHD patients.

Growth hormone replacement therapy in GHD adult patients showed to have positive effects on their heart structure and function [6]. Amato et al, showed that GH replacement induces an increase in the LVM index by 26% in GHD adults [1]. These effects disappeared after 6 months of GH discontinuation. In another cohort of 20 young adult GHD patients, with either childhood onset disease or adult onset disease, there was a significant increase in the LVM during the 12 months of GH replacement [13]. Importantly, it was shown that the hypertrophic effect of GH replacement subsided during treatment and was not detectable 2

years after therapy continuation; cardiac mass was similar to pre-treatment values after 10 years of replacement [44]. Additionally, the effects on cardiac mass are strictly GH dependent as it was observed in a group of patients with GHD receiving GH replacement therapy [14].

A number of studies on GH treatment of GH deficient adolescents showed no adverse effects on the heart. On the contrary, some of them presented the beneficial role of GH substitution in the cardiovascular system generally. Johannsson *et al.* reported that the discontinuation of GH treatment in GHD adolescents, results in the accumulation of relevant cardiovascular risk factors like increase of body and abdominal fat and total and LDL cholesterol concentrations [29]. In another study, a decrease in the LVM index was found in adolescents with GHD when GH treatment was discontinued. The LVM index returned to normal levels 6 months after treatment was re-instituted [15]. Lanes *et al.* in a cross sectional study including GH-treated and untreated GHD adolescents and controls reported abnormal lipid and lipoprotein-a concentrations in the untreated group [30]. However, there was no abnormality in cardiac mass and function.

More limited are the studies in children. A few studies on the effect of GH on the cardiovascular system in children with GHD, showed no significant alterations during GH therapy [3,4,8,16-18,20,24,34,37,39,41,42]. On the contrary, Shulman et al found that LVM indexed for Body Surface Area (BSA) increases with GH treatment in severely GHD children [41]. The increase rate of LVM was greater than the increase rate of BSA, suggesting that GH could be a trophic factor for the heart [41].

Growth Hormone excess and the Heart in adolescence

GH excess may affect heart morphology and performance in acromegalic patients [16]. Chronic GH excess in acromegaly induces a specific cardiomyopathy, characterized by concentric hypertrophy in the theoretical absence of other cardiomyopathy [16]. This condition is rarely found in adolescents. However, young patients with early-onset acromegaly have increased LV mass, improved cardiac performance at rest, reduced exercise capacity and duration, with normal or mild abnormalities of diastolic ventricular filling, leading only to a decrease in cardiac performance on effort [17,24,34]. Cardiomyopathy can be asymptomatic for years before clinical and instrumental signs of cardiac involvement are noted. In cases of GH hypersecretion, the suppression of GH should start as early as noted in order to arrest the adverse effects of GH excess on the cardiac morphology and performance in acromegalic patients [18].

There are little data assessing cardiac structure and function in non GHD children and adolescents (Table 1). GH therapy has not yet been demonstrated to cause any adverse cardiac effects and any early signs of cardiomyopathy have not been reported. In short, normal children, LV size and function were reported to remain within the normal range even after 4 years of GH treatment [20] or when high doses of GH were used [2]. However, early detection and early normalization of GH and IGF-1 levels is essential to arrest cardiovascular disease later in life [4,8].

Growth Hormone Effect in Other Conditions

In adolescents with Noonan (NS) or Turner syndrome (TS), the effect of GH treatment on the heart has been studied with controversial findings. Some of the studies in adolescents with NS or TS treated with GH showed no signs of LV hypertrophy [19,26,31,40]. However some other studies, have reported an increased risk for adverse events of GH treatment like diabetes which may have a negative indirect effect on their cardiovascular system later in life [37]. There is no evidence that GH treatment in these patients might be related to adverse effects on the structure and function of the heart or the main vessels. The National Cooperative Growth Study (NCGS) has collected efficacy and safety data for 5220 TS children treated with GH. From this large population cohort, it was concluded that the aortic dissection/rupture incidence reflects the higher baseline risk for lethal events in TS which seemed to be unrelated to GH treatment [7]. On the contrary, GH replacement therapy may even have beneficial effects on the mechanical properties of the arterial wall, particularly in distensibility [22,45].

Growth hormone treatment has been shown to be beneficial, in adolescents with chronic heart failure secondary to dilated cardiomyopathy. Cardiovascular effects of GH treatment, included a trend towards the improvement of LV ejection fraction in these patients [32]. Additionally, GH is safe and effective in treating growth failure in children after cardiac transplantation [35]. GH therapy among anthracycline treated survivors of childhood cancer increased LV wall thickness, but the effect was lost after therapy was discontinued [31].

In conclusion GH-IGF-1 system plays a crucial role on the structure and function of the cardiovascular system in adolescence via its direct and indirect effects. Nevertheless GH treatment may have favorable and unfavorable effects on the heart depending on the condition, dose and duration of treatment. Thus, it should be closely regulated with a thorough follow up of the patients in adolescence in order to avoid complications on the cardiovascular system later in life.

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SUMMARY

EFFECTS OF GROWTH HORMONE ON HEART STRUCTURE AND FUNCTION IN ADOLESCENCE

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Until recently, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were considered to control only linear growth. Apart from growth effect, GH has additional important physiological functions in the human body influencing several metabolic processes, body composition, muscle strength, and bone mineral density. In adolescence, where the majority of these physiological functions reach a zenith, GH plays a crucial role.

The ability of GH to trigger cardiac muscle growth by direct and indirect effects plays a pivotal role in the physiology of the heart. Patients with childhood or adulthood onset of GH deficiency are exposed to increased risk for cardiovascular morbidity. GH treatment may have beneficial effect on the cardiovascular system in GH deficient adolescents. On the other hand discontinuation of GH treatment in these patients may result in the accumulation of relevant cardiovascular risk factors such as increase in body and abdominal fat and LDL and total cholesterol concentrations.

No potential adverse cardiac effects of GH therapy have been so far demonstrated in short stature patients with normal GH secretion. Nevertheless, no evidence of heart hypertrophy or cardiomypathy has been documented in adolescents with GH excess has been reported in adults. Nonetheless, normalization of GH and IGF-1 levels in

such patients is essential in order to arrest cardiovascular disease later in life.

Keywords: Growth Hormone, IGF-1, Heart, Left Ventricular Mass.

РЕЗЮМЕ

ЭФФЕКТЫ ВОЗДЕЙСТВИЯ ГОРМОНА РОСТА НА СТРУКТУРУ И ФУНКЦИИ СЕРДЦА В ПОДРОСТКОВОМ ПЕРИОДЕ (ОБЗОР)

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По сей день считали, что гормон роста (ГР) и инсулиноподобный фактор роста 1 (ИФР-1) контролируют лишь линейный рост. Однако, помимо воздействия на рост, ГР выполняет значимые физиологические функции в организме человека. В частности, он влияет на различные метаболические процессы, мышечную силу, минеральную плотность костей. В подростковом периоде, когда большинство этих физиологических функций достигает своего зенита, ГР играет решающую роль.

Исходя из изложенного, целью обзора явился анализ ретроспективной и текущей научной литературы о влиянии гормона роста на структуру и функции сердца в подростковом периоде.

Анализ литературы выявил, что способность ГР быть триггером роста сердечной массы посредством прямого и непрямого воздействия играет значительную роль в физиологии сердца. Пациенты с начальной стадией недостаточности ГР в детском или подростковом возрасте подвержены повышенному риску развития сердечно-сосудистых заболеваний. Поэтому лечение ГР положительно влияет на сердечно-сосудистую систему (ССС). Прекращение лечения ГР у подобных больных часто способствует увеличению ожирения, концентрации липидов низкой плотности и общего холестерина.

По сегодняшний день, потенциальных побочных эффектов лечения ГР на ССС больных с гипостатурой с нормальной секрецией ГР не выявлено. В литературе не обнаружено также данных о развитии гипертрофии сердца и кардиомиопатии у взрослых с избытком ГР в подростковом периоде. Результаты анализа ретроспективной и современной научной литературы по вышеуказанному вопросу диктуют необходимость проведения соответствующих мер по нормализации уровней ГР и ИФР-1 у подростков с дефицитом ГР с целью превенции кардиоваскулярных заболеваний.

რეზიუმე

ზრდის ჰორმონის ზემოქმედება გულის სტრუქტურასა და ფუნქციებზე მოზარდობის პერიოდში (მიმოხილვა)

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ზჰ-ის უნარს - პირდაპირი და არაპირდაპირი გზით შეასრულოს ტრიგერის როლი გულის კუნთის ზრდაში მნიშვნელოვანი როლი ენიჭება გულის ფიზიოლოგიაში. პაციენტებს,რომელთაც ბავშვობის ან მოზარდობის ასაკში გამოუვლინდათ ზჰ-ის დეფიციტი, აღენიშნებათ გულ-სისხლძარღვთა დაავადებების მომატებული რისკი. აქედან გამომდინარე, ზჰ-ის დეფიციტის მქონე მოზარდებში ზჰ-ით მკურნალობამ შეიძლება სასარგებლო ზემოქმედება მოახდინოს გულ-სისხლძარღვთა სისტემაზე. მეორე მხრივ, ამ პაციენტებში ზჰ-ით მკურნალობის შეწყვეტამ შეიძლება განაპირობოს მნიშვნელოვანი კარდიოვასკულური რისკ-ფაქტორების დაგროვება,როგორიცაა სხეულის და მუცლის ცხიმის,დაბალი სიმკვრივის ლიპიდებისა და საერთო ქოლესტერინის კონცენტრაციის მატება.

ზჰ-ის ნორმული სეკრეციით მიმდინარე ჰიპოსტატურის მქონე პაციენტებში, ზჰ-ით მკურნალობის პირობებში რაიმე პოტენციური გვერდითი ზემოქმედება გულზე დღემდე არ გამოვლენილა. ასევე,არ არის დოკუმენტირებული გულის ჰიპერტროფიის ან კარდიომიოპათიის განვითარების ფაქტი მოზრდილებში, რომელთაც მოზარდობის პერიოდში ზჰ-ის სიჭარბე აღენიშნებოდა. მიუხედავად ამისა,შემდგომში გულ-სისხლძარღვთა დაავადებების განვითარების პრევენციის მიზნით ფრიად მნიშვნელოვანია ზჰ და იმზფ1 დონის დროული ნორმალიზება.

GENETIC DEFECTS IN THE CYP21A2 GENE IN HETEROZYGOUS GIRLS WITH PREMATURE ADRENARCHE AND ADOLESCENT FEMALES WITH HYPERANDROGENEMIA

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Congenital adrenal hyperplasia (CAH) is a recessively inherited disorder which is caused by the loss or severe decrease in the activity of one of the enzymatic steps required for cortisol biosynthesis in the adrenal cortex. The most common form of CAH (95% of all cases) is due to 21-hydroxylase deficiency (21-OHD) resulting from molecular defect in the steroid 21-hydroxylase (*CYP21A2*) gene, with an overall estimated incidence of 1:10,000 to 1:15,000 for the severe classic form and 1:500 to 1:100 live births for the non classic form (NC-CAH) [19,27,28,39].

As expected from the prevalence of CAH and NC-CAH, the frequency of heterozygotes in the population for 21-OHD is quite common and varies considerably, ranging from 1 in 10 to 1 in 60 in certain populations and ethnic groups [8,10,30,40], and in some cases it may affect as 1 in 3 of Askenazi Jews [51].

The incidence of the genetic defects of 21-OHD has been extensively studied and ethnic specific distribution of mutations has been reported [1,9,13,15,16,22,37,38,45,49]. Approximately 95% of the mutated *CYP21A2* alleles is the result of recombination events between the homologous *CYP21A2P* pseudogene and the active *CYP21A2* gene, while the remaining 5% represent new mutations [14,20]. In population studies with a large number of non-classical patients, the percentage of alleles with identified mutations is variable, ranging from 80% to 100% [7,12,48], signifying the necessity to evaluate the *CYP21A2* regulatory regions. Several studies in the Mediterranean region, including studies from our group have reported as the most prevalent genetic defects, the mutations IVS2-13A/C>G, p.Q318X, p.V281L, c.329_336del (8bpdelE3) [29,37,38].

Compared to normal female individuals, female carriers for 21-OHD frequently demonstrate an exaggerated secretion of the 21-OH precursors 17-hydroxyprogesterone (17-OHP) and progesterone (P4) [24,47] and lower levels of 11-deoxycorticosterone [34] and aldosterone [33] after ACTH administration. In fact, between 50-80% of carriers exhibit a 17-OHP level after ACTH stimulation that is above the 95th percentile of the control value [34].

In this study, we investigated a cohort of 17 Cypriot girls with premature adrenarche and 17 adolescent females with hyperandrogenemia and determined whether heterozygous mutations of the *CYP21A2* gene are responsible for phenotypic and metabolic abnormalities. To test this hypothesis the hormonal response to ACTH was evaluated in the 34 females with clinical signs of hyperandrogenism along with direct DNA sequencing and MLPA analysis for mutations in the *CYP21A2* gene.

Material and methods. *Biochemical and Clinical Evaluation.* Thirty four unrelated Greek Cypriot female patients were studied. Of these 34 females, 17 were girls, who presented with premature adrenarche before the age of 8 years and 17 adolescents, who had signs of hyperandrogenemia (severe acne or hirsutism, with or without menstrual disorders and complete lack of virilization). Informed consent for this study was obtained from the parents or guardians of the minors. Patients were characterized on the basis of clinical and an elevated plasma 17-OHP [2,10]. Serum 17-OHP concentrations were measured with the commercial RIA method (Beckman Coulter).

Amplification of the CYP21A2 gene

The *CYP21A2* genes of all patients were analysed using genomic DNA isolated from peripheral blood samples. Molecular analysis was performed according to a cascade strategy as previously described [29,37,38]. The primers P1-P48 [47] were used to amplify the fragment containing the -370 bp *CYP21A2* promoter, the 5' untranslated region of the *CYP21A2* gene that is mainly located in the first 167 nucleotides upstream the ATG codon and the 3' untranslated region that is 536 nucleotides downstream the TGA stop codon of the *CYP21A2* gene [26].

MLPA Analysis

DNA from the 34 female patients in this study analyzed by direct sequencing was also examined with the multiplex ligation-dependent probe amplification (MLPA) technique (MRC Holland, Amsterdam, Netherlands). MLPA was employed to investigate any possible large gene deletions and large gene conversions in the *CYP21A2* gene.

The kit detects mutations for exons 1, 3, 4, 6 and 8; among these are 8bpdelE3, p.I172N, Cluster E6 and p.Q318stop mutations. Furthermore, this kit contains 3 *CYP21A1P*-specific probes, 3 *TNXB* probes, 1 *C4A* probe, 1 *C4B* probe and 1 probe for the *CREBL1* gene located q-telomeric of

TNXB. In addition, 2 other probes located on chromosome 6p21.3, 1 Y-chromosome specific gene (*UTY*) and 16 reference probes are included. Briefly, 50-200 ng DNA was denatured and hybridized overnight at 60 °C with the SALSA probe mix. Samples were then treated with Ligase-65 enzyme for 15 min at 54 °C, the reactions were stopped by incubation at 98 °C for 5 min. Finally, PCR amplification was carried out using BigDye terminator v1.1, cycle sequencing kit (Applied Biosystems, Foster City, CA, USA). Amplification products were run on an automated Applied Biosystems 3130*xl* Genetic Analyzer. The raw data were analyzed by using Coffalyzer 9.4 Software (MRC Holland, Amsterdam, Netherlands). The size of migration of exon-specific peaks was identified according to their migration relative to Gene Scan 600 LIZ size standard (Applied Biosystems, Foster City, CA, USA).

Results and their discussion. *Characteristics of the 34 females*

The overall frequency of the molecular defects detected in the pool of these females is shown in Table 1. The most frequent mutation within the 34 unrelated alleles was p.V281L (52.9%), followed by p.Q318stop (20.6%), p.V304M (8.9%), p.P482S (5.9%), p.P453S (5.9%), large deletion/conversion exons 1-4 (2.9%) and large deletion/conversion exons 6-8 (2.9%).

Table 1. Mutation frequency of affected alleles from 34 unrelated heterozygote girls and adolescent females with hyperandrogenemia

***CYP21A2* mutations**	**Number of alleles**	**% of alleles**
p.V281L	18	52.9
p.Q318stop	7	20.6
p.V304M	3	8.9
p.P482S	2	5.9
p.P453S	2	5.9
Deletion/conversion exons 1-4	1	2.9
Deletion/conversion exons 6-8	1	2.9

The clinical phenotype and hormonal characteristics of the patients are as follow. Seventeen of the *CYP21A2* heterozygote female patients presented premature adrenarche and were diagnosed in childhood (Table 2). The remaining seventeen *CYP21A2* heterozygote female patients were diagnosed in adolescence with clinical signs of hyperandrogenemia (Table 3). Among the seventeen *CYP21A2* heterozygote adolescent patients, irregular menses with or without PCOS was the most common presenting symptom (11/17), followed by hirsutism (as determined by a Ferriman Gallway score more than 8) with or without acne in 8 out of 17.

Table 2. Clinical features, basal and adrenocorticotropic hormone (ACTH) stimulated 17-OHP levels in 17 CYP21A2 heterozygote girls who presented with premature adrenarche before the age of 8 years

No.	**Age of diagnosis**	**Genotype**	**17-OHP, nmol/L, Basal**	**17-OHP, nmol/L ACTH Stimulated 60'**	**Polymorphism**
1 2	7 7	Large del 1-4 p.P453S/X	2.4 3.9	14.5 32	p.N493S
3	7	p.V281L/X	3.5	23.5	
4	7	p.V281L/X	3.2	25.4	
5	7	p.P453S/X	2.2	14.7	
6	7	p.V304M/X	8.3	13.7	
7	8	p.V281L/X	7.7	20.2	
8	8	p.V281L/X	7.7	24.2	
9	8	p.V281L/X	6.6	20.0	
10	8	p.V281L/X	4.1	12.6	
11	8	p.V281L/X	5.9	23.6	
12	9	p. V281L/X	2.1	21.3	
13	9	p.Q318stop/X	2.7	12.0	
14 15	9 3	p. V281L/X p.Q318stop/X	4.4 15.6	22.8 27	
16	9	Del EX6-8/X	6.5	11.7	p.N493S
17	9	p.V281L/X	4.3	18.2	

Table 3. Clinical features, basal and adrenocorticotropic hormone (ACTH) stimulated 17-OHP levels in 17 CYP21A2 heterozygote adolescent females with hyperandrogenemia

No	Age of diagnosis	Genotype	17-OHP, nmol/L, Basal	17-OHP, nmol/L ACTH Stimulated 60'	Clinical Presentation	Polymorphism
1	14	p.Q318stop/X	4.7	10.3	PA, A, H	
2	14	p.V281L/X	2.6	21.0	PA, A, H	
3	15	p.V281L/X	5.2	28	PCOS	p.N493S
4	17	p.P482S/X	6.7	14.7	IM	p.N493S
5	16	p.V281L/X	4	22.8	IM, A, H	p.N493S
6	15	p.Q318stop/X	4.8	17.7	A, H	
7	16	p.P482S/X	3.5	37.1	IM, H, PCOS	
8	15	p.V281L/X	5.7	26.4	IM	
9	16	p.V281L/X	7.1	19.4	A, H	
10	17	p.V304M/X	2.4	9.6	IM	
11	17	p.V281L/X	12.4	22.2	IM, A	
12	16	p.V281L/X	5.7	26.3	A, H	
13	16	p.Q318stop/X	9.2	10.5	IM, H	p.N493S
14	17	p.V281L/X	5.1	15.7	A, H, PCOS	
15	17	p.V304M/X	5.1	11.8	IM, A, PCOS	
16	16	p.Q318stop/X	6.7	19.6	IM, A, H,	p.N493S
17	15	p.Q318stop/X	4.2	14.3	IM	

PCOS = Polycystic ovary syndrome; IM = irregular menses; A = acne; H = hirsutism; PA = premature adrenarche

The relationship between the severity of the mutation and the biochemical data in carrier hyperandrogenic females is also presented in Tables 2 and 3. Mean plasma basal 17-OHP (nmol/L) level in the girls with premature adrenarche was 5.4±3.3 (mean ± SD, range 2.1 -15.6) and rose to 19.9±6.0 (mean ± SD, range 11.7-25.4) after ACTH stimulation. Mean plasma basal 17-OHP (nmol/L) level in the adolescent females with hyperandrogenemia was 6.0±2.4 (mean ± SD, range 2.4-12.4) and rose to 19.3±7.4 (mean ± SD, range 37.1-9.6) after ACTH stimulation. Higher mean plasma values of 17-OHP after 60 minutes of ACTH stimulation were exhibited in female carriers of the p.V281L mutation when compared to the mean values observed in female carriers of other *CYP21A2* mutations (21.9 nmol/L *vs* 17.0 nmol/L).

Numeral of investigators have suggested that mild 21-OHD plays a role in the development of hyperandrogenic disorders, including premature adrenarche, hirsutism, acne, irregular menses, androgenic alopecia and polycystic ovary syndrome [3,43]. In the present study all females with hyperandrogenemia exhibited a significant 17-OHP elevation with values above the normal range after 60 minutes of ACTH stimulation. This finding was indicative of carrier status for 21-OHD and was further confirmed by molecular analysis of the *CYP21A2* gene.

All 17 girls and 17 adolescent females had identifiable heterozygote mutations in the *CYP21A2* gene. The most frequent mutation identified was p.V281L (52.9%), followed by p.Q318stop (20.6%), p.V304M (8.9%), p.P482S (5.9%), p.P453S (5.9%), large deletion/conversion exons 1-4 (2.9%) and large deletion/conversion exons 6-8 (2.9%). In the past, several studies have demonstrated a high prevalence of heterozygous *CYP21A2* mutations to be associated with an increased risk of hyperandrogenism [2,8,9,25,31]. Recently, a high prevalence of heterozygous mutations was reported in a cohort of French Mediterranean girls with isolated premature pubarche. In a similar manner as in the case of our patients, the French girls with premature pubarche were found to exhibit high 17-OHP levels [32].

We are not aware of the incidence of NC-CAH in our population, however the classical form seems to be rare in Cyprus since we had only ten cases (6 males, 4 females) diagnosed over the past 30 years (1980 - 2010). Given the total number of births during this period which is 310.000 (*www.mof.gov.cy*), the incidence of classical CAH in live births is 1:30000, much less than expected [19,27,43].

The most prevalent mutation in the present study was the mild missense mutation p.V281L and it was observed in 18/34 patients or 52.9% of the alleles as in

most populations studied [4,11,13,15,16,18,35,41]. The overall frequency of p.V281L is however one of the highest found for this mutation both in Greek [10] and other populations in Europe and the Mediterranean area [1,6,9,13,17,18,22,36,45]. This mutation is quite common in our population [37,38]and in a random screening of healthy individuals, often used as controls in our laboratory, p.V281L was determined in 26 out of 600 alleles or 1/23 [unpublished data].

The higher ACTH stimulated 17-OHP mean values exhibited in the female carriers of the p.V281L mutation when compared to the mean values observed in female carriers of other *CYP21A2* mutations (21.9 nmol/L vs 17.0 nmol/L) suggest increased exposures to androgens and point to more severe impairment of 21-OHD in the symptomatic p.V281L carriers. As observed by other studies as well, the missense p.V281L although a mild mutation when inherited in the heterozygote state may exhibit higher ACTH-stimulated 17-OHP levels and higher rates of either PCOS [2], irregular menses or hirsutism [5]. It is speculated that the impairment of enzymatic activity in the symptomatic p.V281L carriers is caused by a dominant-negative effect of this particular mutant allele on the wild type and that is reducing drastically its activity. The mutant enzyme may interfere or compete with the wild type for the conversion of 17-OHP to 11-deoxycortisol [2].

The rare missense p.V304M was first found in a 7 year old girl with premature adrenarche and in 2 adolescent females with irregular menses and PCOS. The large deletion/conversion of exons 1-4 and large deletion/conversion of exons 6-8 were respectively found in two young girls at the age of 7 and 9 years, both diagnosed with mild NC-CAH and premature adrenarche. We highlight that p.V304M is a mild and rare mutation and after expression in *COS-1* cells the mutated enzyme was found to have residual activity of 46% for conversion of 17-OHP and 26% for conversion of progesterone compared with the normal enzyme [23]. To our knowledge p.V304M missense mutation was reported only by our group in Cypriot patients with the NC-CAH form [29] and in a female patient of Asian origin who presented hirsutism, acne and alopecia at the age of 24 [23]. The p.V304M missense mutation is located at a region suggested to be involved in substrate interaction in a model of the protein [21,51].

In the present report all children presented with premature pubarche as expected and most of the adolescent females presented with irregular menses and to a lesser extent with PCOS. No association could be found between presenting symptoms in adolescents and the type of molecular defect.

In conclusion this study demonstrates that the frequency of the underlying genetic defect in heterozygote patients with NC-CAH is similar to that observed in other populations. Although the clinical expression of NC-CAH is not solely depended on the genotype, discrimination between mild and severe alleles should be made and the systematic evaluation of 17-OHP values after synacthen stimulation testing should be performed in all girls with premature adrenarche. Knowing the genetic defect is of immense help in detecting heterozygote carriers in antenatal diagnosis and genetic counselling.

Conflict of interests. There is none to declare.

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Abbreviations: Congenital adrenal hyperplasia (CAH), Non Classical Adrenal Hyperplasia (NC-CAH), 17-hydroxyprogesterone (17-OHP), 21-hydroxylase (21-OHD).

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SUMMARY

GENETIC DEFECTS IN THE CYP21A2 GENE IN HETEROZYGOUS GIRLS WITH PREMATURE ADRENARCHE AND ADOLESCENT FEMALES WITH HYPERANDROGENEMIA

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Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disorder primarily caused by mutants in the CYP21A2 gene.

Heterozygosity for CYP21A2 mutations in females increases their risk of clinically manifesting hyperandrogenism and the present study was designed to seek evidence on the prevalence and consequences of heterozygous CYP21A2 mutations in children with premature adrenarche and adolescents with hyperandrogenemia.

The hormonal response to ACTH was evaluated in 17 girls with clinical signs of premature adrenarche and 17 adolescent females with hyperandrogenemia, along with direct DNA sequencing and MLPA analysis for mutations in the

CYP21A2 gene. The suspicion of heterozygote state was based on the median plasma 17-OHP before and 60 minutes after ACTH stimulation. All 34 patients were identified as carriers of CYP21A2 mutations. The most frequent mutations among this cohort of carriers were the mild p.V281L (52.9%), followed by p.Q318stop (20.6%), p.V304M (8.9%), p.P482S (5.9%), p.P453S (5.9%), large deletion/conversion exons 1-4 (2.9%) and large deletion/conversion exons 6-8 (2.9%). Higher values of stimulated 17-OHP levels were found in the carriers of the p.V281L mutation compared with carriers of other mutations (mean=21.9 nmol/L vs 17.0 nmol/L). This finding supports the already identified notion that carriers of the mild p.V281L are at higher risk for hyperandrogenism than carriers of severe mutations.

In conclusion: a. Females with premature adrenarche and hyperandrogenemia are likely to bear heterozygous CYP21A2 mutations, therefore systematic evaluation of 17-OHP values in combination with the molecular testing of CYP21A2 gene is beneficial, b. carriers of the mild p.V281L, are at higher risk of androgen excess compared to carriers of other types of mutations.

Key words: NC-CAH, CYP21A2, 17-OHP.

РЕЗЮМЕ

МУТАЦИИ ГЕНА CYP21A2 У ГЕТЕРОЗИГОТНЫХ ДЕВОЧЕК С РАННИМ АДРЕНАРХЕ И ДЕВОЧЕК-ПОДРОСТКОВ С ГИПЕРАНДРОГЕНЕМИЕЙ

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Врожденная гиперплазия надпочечников частое аутосомно-рецессивное заболевание, в основном, обусловленное мутациями в CYP21A2 гене. Гетерозиготность по CYP21A2 мутациям у женщин повышает риск клинически манифестированной гиперандрогении.

Целью настоящего исследования явилось определение частоты носительства CYP21A2 мутаций у детей с ранним адренархе и подростков с гиперандрогенемией.

Гормональный ответ на адрено-кортикотропный гормон (ACTH) определялся у 17 девочек и 17 девочек-подростков с гиперандрогенемией. У всех проводилось также прямое секвенирование ДНК и анализ амплификации проб (MLPA) с целью выявления мутаций в гене CYP21A2). Подозрение на наличие гетерозиготного состояния основывалось на показателях 17-гидроксипрогестерона (17-OHP) до и 60 минут спустя после стимуляции ACTH. Все 34 пациента были идентифицированы как носители CYP21A2 мутаций.

Частота мутаций в этой когорте была следующей: легкая p.V281L (52.9%), p.Q318stop (20.6%), p.V304M (8.9%), p.P482S (5.9%), p.P453S (5.9%), большая делеция экзонов 1-4 (2.9%), большая делеция экзонов 6-8 (2.9%). При стимуляции у носителей p.V281L мутации отмечался более высокий уровень 17-OHP по сравнению с носителями других мутаций (средняя = 21.9 nmol/L *vs* 17.0 nmol/L). Эти данные подтверждают ранее высказанное мнение о том, что носители мутации p.V281L находятся под более высоким риском развития гиперандрогении, чем носители других мутаций.

რეზიუმე

CYP21A2 გენის დეფექტების შესწავლა ნაადრევი ადრენარქეს მქონე ჰეტეროზიგოტულ გოგონებში და ჰიპერანდროგენემიის მქონე მოზარდ გოგონებში

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თანდაყოლილი ადრენალური ჰიპერპლაზია (თაჰ) წარმოადგენს საკმაოდ ხშირ ავტოსომურ-რეცესიულ დაავადებას, რაც განპირობებულია CYP21A2 გენის მრავლობითი მუტაციით. CYP21A2

გენის მუტაციების ჰეტეროზიგოტულობა ქალებში ზრდის ჰიპერანდროგენურობის კლინიკური მანიფესტაციის რისკს.

კვლევის მიზანია ჰეტეროზიგოტული CYP21A2 გენის მუტაციების სიხშირის დადგენა ნაადრევი ადრენარქეს მქონე გოგონებსა და ჰიპერანდროგენემიის მქონე მოზარდ გოგონებში.

ჰორმონული პასუხი ადრენოკორტიკოტროპულ ჰორმონზე (ACTH) ფასდებოდა, შესაბამისად, 17 გოგონასა და 17 მოზარდ გოგონებში, ამასთანავე მათ უტარდებოდა დნმ-ს სეკვენირება და MLPA სინჯის ამპლიფიკაცია CYP21A2 გენში მუტაციების დასადგენად. ეჭვი ჰეტეროზიგოტულ მდგომარეობაზე ემყარებოდა 17-ჰიდროქსიპროგესტერონის (17-OHP) მაჩვენებლებს სტიმულაციამდე და სტიმულაციიდან 60 წთ-ის შემდეგ. ყველა 34 პაციენტი იდენტიფიცირებული იქნა, როგორც CYP21A2 მუტაციის მატარებელი.

ამ კოჰორტაში მუტაციების სიხშირე იყო შემდეგი: მსუბუქი,(p.V281L (52.9%), p.Q318stop (20.6%), p.V304M (8.9%), p.P482S (5.9%), p.P453S (5.9%), 1-4 ეგზონების დიდი დელეცია (2.9%) 6-8 ეგზონების დიდი დელეცია (2.9%). p.V281 მუტაციის მატარებლებში სტიმულაციის შემდგომი 17-OHP-ის დონე იყო უფრო მაღალი, ვიდრე სხვა მუტაციების მატარებლებში (საშუალო = 21.9 nmol/L *vs* 17.0 nmol/L). ეს მონაცემები ადასტურებს ადრე გამოთქმულ მოსაზრებას იმის თაობაზე, რომ p.V281L მუტაციის მატარებლებს ჰიპერანდროგენიის უფრო მაღალი რისკი გააჩნიათ, ვიდრე სხვა მუტაციების მატარებლებს.

CONTINUOUS GLUCOSE MONITORING, ORAL GLUCOSE TOLERANCE, AND INSULIN – GLUCOSE PARAMETERS IN ADOLESCENTS WITH SIMPLE OBESITY

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The prevalence of obesity in children and adolescents has reached an epidemic proportion in developed countries in the last three decades [11,23]. This has led to a striking worldwide increase in the rate of glucose metabolism alterations in this age group [1,4]. Obesity causes various degrees of insulin resistance which in turn increases, by various mechanisms, insulin secretion, witnessed by the high circulating insulin concentrations found in patients with obesity. Pancreatic beta-cells may or may not be able to cope with the sustained overload imposed by insulin resistance. Over time, if the function of strained beta-cell declines, hyperglycemia or even type 2 diabetes (T2DM) may ensue [8].

Standard oral glucose tolerance test (OGTT) is currently used by measuring fasting, 30, 60, 90 and 120-minute blood glucose levels (capillary or vein samples) [9,20,26] or only by measuring fasting and 120- minute levels [25,35]. It has the potential to miss the diagnosis of many glycemic abnormalities because of possible missing of the glucose peak. More frequent measurement of glucose is often not readily accepted by parents or patients [2]. Continuous glucose measurement of interstitial fluid (ISF) is now possible. Interstitial fluid (ISF) glucose equilibrates with blood glucose concentration and can be measured by automatic sampling from a simply implanted subcutaneous sensor. The continuous glucose monitoring system (CGMS) has been shown to detect rapid changes and trends in blood glucose concentrations during real life food intake and activities [6,7,27].The objective of the current study was to assess

oral glucose tolerance, 72-h continuous blood glucose concentrations by CGMS, calculate homeostatic model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) in children and adolescents with simple obesity.

Material and methods. The study was conducted on thirteen adolescents, aged 13.9±2.2 years, who were obese (BMI >2 SD for age and sex), BMI-SDS: 4±1.06. Fasting-08:00 AM cortisol, thyroid function (FT4 and TSH) levels were normal in all subjects: 255.6±141 mmol/L, 13.5±1.9 pmol/L, and 2.7±1.8 mIU/L, respectively.

A standard OGTT was performed (1.75 g of glucose solution per kilogram of body weight to a maximum of 75 g). Plasma samples were collected at 0 and after 2 hours for determination of glucose and insulin concentration.

Impaired fasting glucose (IFG) was defined, as a fasting plasma glucose level of 100–125 mg/dL (5.5-6.9 mmol/L); IGT was defined as 2-h post- OGTT plasma glucose level of 140-199 mg/dl (7.8-11.1 mmol/L); and T2DM was defined as a fasting glucose level of 126 mg/dL (7 mmol/L) or higher or 2-h plasma glucose level of more than 200 mg/dL (11.1 mmol/L) [3].

The CGMS sensor (Medtronic MiniMed, Minnesota, USA) was inserted subcutaneously and interstitial fluid (ISF) glucose levels were measured for 24 hours covering the time for OGTT. Glucose levels were measured by the glucose oxidase reaction in ISF by the CGMS. The sensor was inserted on the anterior abdominal wall, avoiding any abnormal areas of skin. The CGMS functioned for 24 hours and automatically measured ISF glucose levels every 5 minutes over the complete study period. There was an additional calibration requirement to align the device with two capillary glucose readings, which were measured by one touch ultra.

Insulin resistance was estimated by homeostatic model assessment of insulin resistance (HOMA-IR) [21]. The estimate obtained with HOMA-IR correlates well with measures of insulin resistance obtained from obese children and adolescents with the use of the euglycemic-hyperinsulinemic clamp technique [29,31]. QUIKI (quantitative insulin sensitivity check index is calculated using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose: 1 / (log (fasting insulin μU/mL) + log (fasting glucose mg/dL) [15].

Statistical analysis: A logistic regression analysis was performed with the presence/absence of glucose values above 200 mg/dl at follow-up as the dependent variable. Linear regression equations were used to investigate correlations between the different variables including: age, BMI, insulin, C-peptide, and glucose data measured by the two methods (OGTT and CGMS). Data were presented as mean ±SD and significance was accepted at $p<0.05$. Excel version 2007 was used for all analysis.

Results and their discussion. Using OGTT, the mean fasting and 2h glucose concentrations were 5.02±0.73mmol/L and 6.8±1.56 mmol/L, respectively. OGTT revealed 3 cases (23%) with IFG (>5.6 mmol/L), 4 cases (30%) with IGT (>7.8 <11.1 mmol/L) (Table 1).

Table 1. Glycemic abnormalities detected by different methods in obese adolescents

	Normal	IF	IGT	T2DM	Hypoglycemia
OGTT	47%	27%	30%	0	0
CGMS	16.4%	36%	69%	7.6%	38%
HbA1C%	100%	0	0	0	NA

OGTT = Oral glucose tolerance; CGMS = continuous glucose monitoring system; HbA1C= glycated hemoglobin; IF = impaired fasting glucose; IGT= impaired glucose tolerance; T2DM = type 2 diabetes mellitus

Using the CGMS supported with the multiple blood glucose monitoring (glucometer) (3-4 times/day), IFG was detected in four cases, two of them were detected with the OGTT as well, the maximum BG (2h or more after meal) were >7.8 and <11.1 mmol/L (IGT) in 9 children (69%) and >11.1 mmol/L (diabetic) in one case (7.6%). Five cases had a minimum BG recorded of < 2.7 mmol/L (hypoglycemia). Measuring HbA1C % (mean levels 5.7±0.3%) detected no abnormality (none >6.5%) (Table 2).

The mean values of HOMA and QUICKI were 6.93±8.06 and 0.34±0.126, respectively. Eleven patients out of thirteen had HOMA values >2.6 and QUICKI values <0.35 denoting insulin resistance. Beta cell mass percent was 200±94.8% and insulin sensitivity was 50.4±45.5% denoting insulin resistances with hyper-insulinemia and preserved beta cell mass (Table 3).

There were no significant correlations between the HOMA and the QUICKI with the BMI, fasting blood glucose concentrations, or the age (r: <0.2 , $p>0.05$). The age was positively correlated with the BMI (r: 0.82, $p<0.001$). Triglycerides concentrations were positively correlated with the BMI and the average glucose concentrations detected with the CGMS (r: 0.48, $p<0.01$ and 0.54, $p<0.01$, respectively) while it was negatively correlated with the QUICKI (r=-0.75, $p<0.001$). The BMI was negatively correlated with the QUICKI (r:-0.47, $p<0.01$).

Table 2. Glycemic data in our obese adolescents

Gender	OGTT (Time 0')	OGTT (Time 120')	Average G-CGMS	Minimal G-CGMS	Maximum G-CGMS	HbA1C
F	5.1	8.4	5.2	3.5	7.8	5.7
M	6	6.3	4.7	2.3	7	5.8
F	4.5	4.2	6.3	2.5	10.2	5.8
M	4.7	6.3	7.8	4.8	22.2	5.6
F	4.5	7.8	6.7	2.2	8.5	5.5
F	4	8.1	5.5	2.2	10.8	5.9
F	6.3	6.2	5.9	3.3	8.1	6.1
M	6.2	9.6	5.6	2.2	8	6.4
M	5.3	7.6	6	4.4	8.2	5.2
F	4.8	5.5	5.1	3.1	8.7	5.7
F	4.6	6.7	5.8	4.17	11.05	5.8
Mean	5.07	6.99	5.87	3.15	10.05	5.73
SD	0.73	1.5	0.85	0.96	4.23	0.31

OGTT = Oral glucose tolerance; 0 = fasting – 2h = 2 hours after oral glucose load;
CGMS = continuous glucose monitoring system; G = glucose; HbA1C= glycated hemoglobin

Table 3. Degree of obesity and insulin-glucose indices in our adolescent subjects

Gender	Age (yrs)	BMI SDS	QUICKI	HOMA
F	18	3.17	0.293523049	6.30
M	11	6.6	0.317725885	3.47
F	16	3.36	0.401477284	0.76
M	12	3.7	0.756304196	4.48
F	14	4.1	0.321274302	3.20
F	13	3.4	0.258471204	18.26
F	14	3.6	0.267676393	13.44
M	13	1.68	0.295536939	5.97
M	17	3.12	0.309839702	4.24
F	12	2.83	0.304976941	4.69
F	13	----	0.24549719	29.24
Mean	13.9	3.5509	0.343000936	6.874
SD	2.2	1.1847	0.122267105	7.7732

Oral glucose tolerance test is usually used to identify IGT, T2DM, insulin sensitivity and insulin secretion. However, the glucose peak in OGTT and the diagnosis of glucose excursion changes and trends might be missed. In our obese adolescents, OGTT diagnosed 3 cases (23%) with IFG (> 5.6 mmol/L), 4 cases (30%) with IGT (> 7.8 < 11.1 mmol/L), and no case with diabetes. Using OGTT, Sinha et al (20) reported an high percentage of IGT in obese children and adolescents (25% and 22%, respectively), irrespective of ethnic group. Sun et al [34] observed an IGT in 9.6% and DM in 2% of their obese children. Wiegand et al (22) found an IGT in 36% and DM in 5.9% out of 102 obese children. They diagnosed IFG in (2%) 12 of 491 obese children. Using the screening algorithm for DM as advocated by the American Diabetes Association, high percentage of patients with IGT and DM would have been missed if FBG was used alone [37].

The use of the CGMS gives potential insights both into overall glucose levels, mean glucose, and variability of the full 24-hour period [38]. The CGMS has been validated as a reliable and accurate measure of blood glucose in adults [6,7,16].Studies have shown that ISF glucose levels generally follow venous blood glucose levels, and finger stick measured capillary glucose levels[5,14,32].

We used CGMS in 13 obese adolescents with randomly selected and compared the results obtained with those detected by performing OGTT. In the present study, using CGMS has detected significantly more glycaemic abnormalities (76.6%) (IGT and diabetes) compared to the standard OGTT (53%). These findings denoted the presence of high prevalence of glycaemic abnormalities in our obese children and adolescents.

In consistence with our findings, Kestilä et al [17] found CGMS superior to the self monitoring of blood glucose in pregnant women and detected 31% who required treatment versus only 8% detected by self monitoring.

In cystic fibrosis patients, Martin-Frias et al [19] reported that CGMS allows a better detection of glucose disorders than OGTT as only one patient was diagnosed with DM using OGGT and 7/13 (53.8%) with CGMS.

Eleven patients out of our 13 obese adolescents had HOMA values >2.6 and QUICKI values <0.35 denoting insulin resistance. The mean values of HOMA and QUICKI were 6.93±8.06 and 0.34±0.126, respectively. Beta cell mass percent was 200±94.8% and insulin sensitivity was 50.4±45.5% denoting insulin resistance with hyperinsulinaemia and preserved beta cell mass. Consistent with our findings, Sinha et al [30] found that impaired oral glucose tolerance was associated with insulin resistance while beta-cell function was still relatively preserved.

In our adolescents triglycerides (TG) concentration was negatively correlated with the QUICKI suggesting its contribution to the insulin resistance state. This can be explained by the increased free fatty acid flux resulting from increased lipolysis secondary to adipose-tissue insulin resistance which induces or aggravates insulin resistance in liver and muscle through direct or indirect generation of metabolites, altering the insulin signalling pathway [13].

Five of our patients had a minimum BG recorded of <2.7 mmol/L (hypoglycemia). The timing of nocturnal hypoglycaemia was variable. Zou et al [38] noted both nocturnal hypoglycemia and hyperglycemia in some obese children of unknown reason. Veldhuis et al [36] reported that both GH secretion and burst frequency were negatively correlated with the degree of obesity (ponderal index). An impaired GH response to hypoglycaemia and a failure of glucose load to inhibit spontaneous and stimulated GH release are documented in obese patients; furthermore, drugs able to block lipolysis and thus to lower serum free fatty acids (NEFA) significantly improve GH secretion in obesity. Elevated free fatty acid (FFA), increased secretion of leptin, low spontaneous GHRH secretion, high somatostatin secretion, and increased negative feedback of IGF-I were previously considered as possible causes of the blunted GH secretion in obese subjects. Caloric restriction and weight loss are followed by the restoration of a normal spontaneous and stimulated GH release. On the whole, hypothalamic, pituitary and peripheral factors appear to be involved in the GH hyposecretion of obesity. This defective nocturnal secretion of GH may relatively decrease the insulin resistance in obese subject making them liable to hypoglycemia at night [10,12,18,24].

In conclusion, in obese children and adolescents, CGMS is superior to OGTT and HbA1C in detecting glycemic abnormalities, which appears to be secondary to insulin resistance.

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SUMMARY

CONTINUOUS GLUCOSE MONITORING, ORAL GLUCOSE TOLERANCE, AND INSULIN - GLUCOSE PARAMETERS IN ADOLESCENTS WITH SIMPLE OBESITY

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In obese adolescents pancreatic beta-cells may not be able to cope with insulin resistance leading to hyperglycemia and type2 diabetes (T2DM).

To assess oral glucose tolerance, 72-h continuous blood glucose concentrations (CGM) and calculate homeostatic

model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) in 13 adolescents with simple obesity (BMI SDS=4±1.06).

OGTT performed in 13 obese adolescents (13.47±3 years) revealed 3 cases (23%) with impaired fasting glucose (IFG: fasting glucose >5.6 mmol/L), 4 cases (30%) with impaired glucose tolerance (IGT: 2h blood glucose >7.8 <11.1 mmol/L), and none with diabetes. Using the continuous glucose monitoring system (CGMS), IFG was detected in 4 cases, the maximum serum blood glucose (BG : 2h or more after meal) was >7.8 and <11.1 mmol/L (IGT) in 9 children (69%) and >11.1 mmol/L (diabetes) in one case (7.6%). Five cases had a minimum BG recorded of <2.7 mmol/L (hypoglycemia). No glycemic abnormality was detected using HbA1C (5.7±0.3%). 11/13 patients had HOMA values >2.6 and QUICKI values <0.35 denoting insulin resistance. Beta cell mass percent (B %) = 200±94.8% and insulin sensitivity values (IS)=50.4±45.5% denoted insulin resistance with hyper-insulinaemia and preserved beta cell mass.

In obese adolescents, CGMS is superior to OGTT and HbA1C in detecting glycemic abnormalities, which appears to be secondary to insulin resistance.

Keywords: Obesity, Adolescents, Children, Continuous glucose monitoring (CGM), Oral glucose tolerance (OGTT).

РЕЗЮМЕ

НЕПРЕРЫВНЫЙ МОНИТОРИНГ ГЛЮКОЗЫ, ТОЛЕРАНТНОСТЬ К ПЕРОРАЛЬНО ПРИНИМАЕМОЙ ГЛЮКОЗЕ И ПАРАМЕТРЫ ИНСУЛИНА И ГЛЮКОЗЫ У ПОДРОСТКОВ С ПРОСТЫМ ОЖИРЕНИЕМ

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У детей с ожирением панкреатические бета-клетки не справляются с резистентностью к инсулину, что ведет к гипогликемии и развитию диабета 2 типа.

Целью работы явилось определение толерантности к перорально принимаемой глюкозе, концентрации глюкозы в крови в течение беспрерывного 72-часового мониторинга, гомеостатической модели и индекса качественной оценки чувствительности к инсулину у подростков с простым ожирением (BMI SDS=4±1,06).

Пероральная нагрузка глюкозой у 13 подростков (13,47±3 лет) выявила нарушение показателя глюкозы натощак (>5,6 mmol/L) в 3 случаях, в 4 случаях - нарушение толерантности к глюкозе (показатель глюкозы через 2 часа после приема пищи ->7.8 and <11.1 mmol/L), ни у одного подростка не отмечены сдвиги, характерные для сахарного диабета. При проведении 72-часового мониторинга гипогликемия натощак наблюдалась в 4 случаях, у 9 подростков содержание глюкозы было в пределах >7,8 <11,1 mmol/L, в одном случае уровень глюкозы соответствовал диабету (>11,1 mmol/L). В 5 случаях была определена гипогликемия (<2,7 mmol/L). При использовании HbA1C (5,7±0,3%) гликемические нарушения не выявлены. У 11 из 13 пациентов показатель гомеостатической модели превышал 2.6, индекс чувствительности к инсулину был менее 0.35, что указывает на резистентность к инсулину. Процент массы бета-клеток (200±94,8%) и показатели чувствительности к инсулину (50,4±45,5%) указывали на резистентность к инсулину при сохранении массы бета-клеток.

У подростков с ожирением применение непрерывного мониторинга глюкозы в крови имеет преимущество перед пероральной нагрузкой глюкозой и HbA1C для выявления гликемических нарушений, которые, по-видимому, являются следствием резистентности к инсулину.

რეზიუმე

გლუკოზის უწყვეტი მონიტორინგი,ტოლერანტობა პერორალურად მიღებული გლუკოზის მიმართ და ინსულინ-გლუკოზის პარამეტრები მარტივი სიმსუქნის მქონე მოზარდებში

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მსუქან ბავშვებში პანკრეასის ბეტა-უჯრედებს არ შეუძლიათ გადალახონ ინსულინისადმი რეზისტენტობა, რაც იწვევს ჰიპერგლიკემიის და ტიპი 2 დიაბეტის (ტ2დ) განვითარებას.

მიზანი: ორალური გზით მიღებული გლუკოზისადმი ტოლერანტობის განსაზღვრა, 72 სთ-ის განმავლობაში სისხლში გლუკოზის კონცენტრაციის (სგკ) უწყვეტი მონიტორინგი, ჰომეოსტაზური მოდელის (ჰმ) გამოიანგარიშება და ინსულინისადმი თვისობრივი მგრძნობელობის

განსაზღვრა მოზარდებში მარტივი სიმსუქნით (სხეულის მასის ინდექსის SDS=4±1.06).

შედეგები: 13 მსუქან (13,47±3 წლის) მოზარდში ორალური გზით მიღებული გლუკოზისადმი ტოლერანტობის განსაზღვრისას 3 შემთხვევაში (23%) დადგინდა უზმოზე გლუკოზის მაჩვენებლის გაუარესება (>5.6 mmol/L), 4 შემთხვევაში (30%) გლუკოზისადმი ტოლერანტობის დარღვევა (საკვების მიღებიდან 2 სთ-ში გლუკოზის შემცველობა სისხლში >7.8 <11.1 mmol/L), დიაბეტი არც ერთ შემთხვევაში არ გამოვლინდა. გლუკოზის უწყვეტი მონიტორინგის პირობებში უზმოზე გლუკოზის მაჩვენებლის მომატებას ადგილი ჰქონდა 4 შემთხვევაში, საკვების მიღებიდან 2 სთ-ში 9 მოზარდში გლუკოზის შემცველობა შეადგენდა >7.8 <11.1 mmol/L, ხოლო ერთ შემთხვევაში იგი აღემატებოდა 11.1 mmol/L (შეესაბამებოდა შაქრიანი დიაბეტს). 5 შემთხვევაში აღინიშნა ჰიპოგლიკემია (<2.7 mmol/L). გლუკოზის პროფილის დარღვევები HbA1C (5.7±0.3%)-ის გამოყენებისას არ დადგენილა. 11/13 პაციენტს ჰმ>2.6, ხოლო ინსულინისადმი თვისობრივი რეზისტენტობის ტესტი <0,35, რაც ინსულინისადმი რეზისტენტობაზე მიუთითებდა. ბეტა-უჯრედების მასის პროცენტი (200±94.8%) და ინსულისადმი მგრძნობელობის მაჩვენებლები (50.4±45.5%) მიუთითებდა ინსულინისადმი რეზისტენტობაზე და ბეტა-უჯრედების შენარჩუნებულ მასაზე.

მსუქან მოზარდებში გლიკემიური პროფილის დარღვევების დასადგენად, რაც სავარაუდოა, რომ ინსულინის რეზისტენტობას მოსდევს, უპირატესობა ენიჭება სისხლში გლუკოზის უწყვეტ მონიტორინგს, ორალური გზით გლუკოზის დატვირთვის ტესტისა და HbA1C განსაზღვრასთან შედარებით.

CAPILLAROSCOPY AND ECG PARAMETERS IN CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS TYPE I

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All subjects in modern pediatric cardiology, which is about diagnosis, treatment and preventions are of great importance [1-4]. 2-5% of population has diabetes type I and in recent years the disease rate is increasing, especially in children, 6-12 years old, all over the world. Disease rate of diabetes type I increases by 3.5% annually. In 2003 we had 63 new cases, in 2006 – 72. By 2020 diseased population is expected to be significantly increased. At the same times chronic or acute complications of diabetes remain one of the main reasons of lethality or disablement. Prevention of those complications are professional as well as social issue [5,7,10,11]. Diabetes is associated with high risk of cardiovascular diseases. The disease increases the chance of developing cardiovascular pathologies by 2-4 times, compared to healthy population. Development of cardiovascular diseases in children during diabetes is not well studiedproblem [8,9,16]. The disease causes endocrine dysfunction that leads to metabolic changes in myocardium, which effects electric conduction. Arterial hypertension, dyslipidemia and hyperglycemia increases the speed of developing diabetic cardiomyopathy [6,15].

Aim of the research - evaluate EKG parameters during diabetic cardiomyopathies; detecting changes in Capillaroscopic parameters.

Materials and methods. Cases of 32 children (6-15 years old, 17 boys,15 girls) diseased with diabetes type I were studied, who were hospitalized In TSMU pediatric clinic's endocrine department. 13 of them were diagnosed and their cases were studied at once, 10 of them had been diagnosed 2-5 years before, 9 of them – 5-10 years before.

We did capillarosopic examinations. we determined carpillarospopic background (pink, pale, cyanosis), transparency (transparent, dimmed), number of capillaries (6-7 in sight, more or less), diameter of capillaries (dilated, contracted), shape of capillaries (hair like, anastomosis, loop like), Order/Disposition of capillaries (shows some order, does not show any order), blood flow type (homogenous, fast, slow), capillaries(homogenous, non-homogenous). 8 types of ST and T wave changes were determined [1-4].

I group – 12 patients with no complications of Diabetes type I. II group – 20 patients with diagnosed complications of Diabetes type I (Diabetic cardiomyopathy, angiopathy). 6 of them with diabetic encephalopathy , 4 of them with diabetic encephalopathy and peripherial diastolic neuropathy, 3 of them encephalopathy, 4 of them nephropathy and retinal angiopathy. Studies and examinations were held after decompensation of diabetes type I (without keto-acidosis) . Level of glycolised hemoglobin was 8-11%, level of glucose 4 to 15 mmole/L, level of glucose in Urine from 0 to 4%. Control group included 20 healthy children of the same age. EKGs were recorded in 12 standard leads and additional heart leads.

Differences between groups were determined based on coefficient (t>1,96; P<0,05). SPSS 11-5 was used to provide mathematic service.

Results and their discussion. 50% of patients had various subjective complaints – 13 patients complained about tiring easily, 8 – shortness of breath after physical load, 4 – dizziness, 3 – syncope. Majority of these complaints were from patients who had Diabetes type I with complications. Only 4 children who did not have complications complained about tiring easily. Changes in EKG were shown in 29 patients (90,6%) and these changes were quite diverse (Table 1).1/2 of patients had hypertrophied left ventricle, in rare cases right ventricle or both ventricles were hypertrophied. Most patients with hypertrophy of both ventricles were part of Group II, however, Hypertrophy of left ventricle was at the same rate in both groups. Atrial hypertrophies occurred only in group II. As seen from the table, in 1/3 cases we had left atrial hypertrophy, 50% of them were combined with right atrial hypertrophy. Only 1 patient had right atrial hypertrophy alone.

Table 1. ECG changes in children and adolescents with DMT1

Detected Changes	Group II n=20		Group I n=12	
	abs.	%	abs.	%
Left Atrial Hypertrophy	3	15	1	5
Right Atrial Hypertrophy	1	5	-	-
Both Atrial Hypertrophy	3	15	-	-
Left Ventricular Hypertrophy	11	55	4	41.6
Right Ventricular Hypertrophy	4	20	-	-
Both Ventricular Hypertrophy	3	15	-	-
Deep Q wave	10	50	2	16.6
Damaged Ventricular Repolarization	13	65	11	91.6
Low T wave	2	10	5	41.6
Two-phased or Inverted T wave	9	45	3	25
High, Sharpened T wave	2	10	2	16.6
Prolonged Ventricular Electric Systole	4	20	4	33.3

Typical EKG parameter was pathologic Q wave, which was mostly met in group II and in some patients it's depth reached 10-17mm. Electric systole of ventricles also were prolonged.

Parameters of diabetic cardiomyopathy were damaged repolarization, which was shown by ST deviation from the isoline, decreased amplitude, two-phased or inversion of T wave in I, aVL and V4-6 leads. In 13,5% of group II patients in V4-6 leads tall, narrow-based, sharpened T wave was registered; Changes in QRS complex were also more frequent than group I. EKG recorded damages of rhythm and conduction in 64% of patients (Table 2). Sinus tachycardia was in 45%, sinus bradycardia – 40%, slowed heart rhythm was significant in group II patients and in 1/3 of them heart rate was 47-53.

Table 2. Damage types of rhythm and conduction in children and adolescents with DMT1

		Group II n=20		Group I n=12	
		abs.	%	abs.	%
1	Sinus Tachycardia	9	45	5	41
2	Sinus Bradycardia	8	40	4	33.3
3	Ectopic Rhythm	4	20	2	16.6
4	Supraventricular Extrasystole	9	45	3	25
5	Ventricular Extrasystole	3	15	2	16.6
6	Supraventricular Paroxysmal Tachycardia	2	10	-	-
7	Ventricular Paroxysmal Tachycardia	-	-	-	-
8	Disorder of Atrioventricular Conduction	2	10	-	-
9	Disorder of Interventricular Conduction	4	20	1	12.5

Sinus, atrial and ventricular extrasystoles were found rarely and equally in both groups. However, only in group II we had interatrial, atrioventricular and interventricular damages of conduction.

Supraventricular paroxysmal tachycardia was found only in 2 patients who had pulse rate of 133-155. We had not met paroxysmal ventricular tachycardia, what consents with literature data [7,12].

In both groups we studied changes of ST and T wave. The changes were more often in group II. However, alterations in group I were also significant. Thus consideration of ST and T wave changes in children and adolescents with DMT1 seems to be quite important. Capillaroscopy data in groups I and II are represented in tables 3 and 4.

Table 3. Capillaroscopy data in patients with DMT1 without complications (group I)

Index	Changes	%
Capillary background	Pink	100
Transparency	Slightly Dimmed Transparent	66.6 33.3
Capillary Diameter	Normal Slightly Dilated	58.3 41.6
Capillary Shape	Hair Clip like Slightly Bended in venous part	66.6 33.3
Capillary Order	In order	100
Blood Flow	Slow Homogenous	8.3 91.6
Capillary Quantity	Increased Normal	83.3 16.6
General Capillaroscopy Results	Homogenous	100

In patients from the I group capillaries were pink in all cases, transparency was a little dimmed, number of capillaries was increased in 83.3% of cases, shape was mainly hair clip like with curved venous part, diameter normal, disposition in order, blood flow homogenous, capillaries also homogenous.

Table 4. Capillaroscopy data in patients with DMT1 with complications (group II)

Index	Changes	%
Capillary background	Pink Pale Cyanosis	40 35 25
Transparency	Dimmed Transparent	70 30
Capillary Diameter	Normal Pathological changes	30 70
Capillary Shape	Changed	75
Capillary Order	In order	60
Blood Flow	Slow	80
Capillary Quantity	Decreased Normal	70 30
General Capillaroscopy Results	Homogenous	40

In patients from the II group number of capillaries was vastly decreased [9,11], cyanosis was detected in the background, transparency was decreased, capillaries tended to contraction and dilation of venous part. Shape changes were also significant (loop like and bended). Disposition was also out of order, blood flow was slow.

Thus, both EKG and capillaroskopy changes are statistically more significant in the group II patients.

One has to emphasize also that capillaroscopy is cheap, non-invasive method and gives important additional information not only for diagnosis but for the prognosis of complications development as well.

Conclusions: In children and adolescents with Diabetes mellitus type 1 ECG and capillaroscopy should be performed on the regular basis in order to reveal early changes and start the appropriate treatment in time.

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SUMMARY

CAPILLAROSCOPY AND ECG PARAMETERS IN CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS TYPE I

[1,2]Chakhunashvili G., [1]Jobava N., [1]Chakhunashvili K., [1]Shvangiradze M., [1]Chakhunashvili D., [3]Pagava K.

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Aim of the research: Evaluate ECG parameters and detect changes in capillaroscopy parameters in children and adolescents with Diabetes mellitus type 1 (DMT1).

ECG and capillaroscopy were performed in 32 children and adolescents (6-15 years old, 17 boys,15 girls) with DMT1. Disease duration – less than 2 years -13, 2-4 years – 10, 5-10 years – 9 cases. The patients were divided into two groups: I group – 12 patients with no complications of DMT1 (in all them duration of disease was less than 2 years), II group – 20 patients with diagnosed cardiac complications of DMT1 (diabetic cardiomyopathy, angiopathy). Additionally 6 of them had diabetic encephalopathy , 4 - diabetic encephalopathy and peripheral neuropathy, 4 - nephropathy and retinal antipathy. Level of glycosides hemoglobin was 8-11%, level of glucose 4 to 15 mmole/L. Control group included 20 healthy children of the same age.

In group I ECG is less informative. Hypertrophies of left ventricle and atrium and disorders of repolarization were mainly found in group II. In 62.5% of cases rhythm and conduction disorders were revealed, which were more often in group II. Capillaroscopy changes (pale and cyanotic background, decreasing of the number of capillaries in sight, dilated and contracted diameter, pathological shape and order of capillaries, slow blood flow) were seen both in I and II groups with more prevalence and intensity in the latter one.

In children and adolescents with Diabetes mellitus type 1 ECG and capillaroscopy should be performed on the regular basis in order to reveal early changes and start the appropriate treatment in time.

Keywords: Diabetes mellitus type 1, children, adolescents, ECG, capillaroscopy.

РЕЗЮМЕ

КАПИЛЛЯРОСКОПИЧЕСКИЕ И ЭКГ ПАРАМЕТРЫ У ДЕТЕЙ С САХАРНЫМ ДИАБЕТОМ I ТИПА

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Цель исследования - оценка ЭКГ и капилляроскопических параметров у детей и подростков с сахарным диабетом I типа (СДТ-1).

ЭКГ и капилляроскопия проведена у 32 детей и подростков (6-15 лет, 17 мальчиков, 15 девочек) с СДТ-1. Длительность болезни: менее 2 лет – 13, 2-4 года – 10, 5-10 лет – 9 случаев.

Пациенты были разделены на две группы: первая группа – 12 больных без осложнений (у всех длительность болезни не превышала 2 лет), II группа – 20 больных с диагностированными осложнениями СДТ-1 со стороны сердечно-сосудистой системы (диабетическая кардиомиопатия, ангиопатия).

Дополнительно имели место следующие осложнения: диабетическая энцефалопатия - 6, диабетическая энцефалопатия и периферическая невропатия – 4, нефропатия и ретинальная ангиопатия - 4 случая. Уровень гликолизированного гемоглобина - в пределах 8-11%, уровень глюкозы – 4-15 ммоль/л. Контрольную группу составили 20 здоровых детей того же возраста.

В I группе ЭКГ была менее информативна. Гипертрофия левого желудочка и предсердия в основном наблюдались у пациентов II группы. В 62,5% были выявлены нарушения ритма и проводимости, также в основном во второй группе. Капилляроскопические изменения (бледный и цианотический фон, снижение числа капилляров в поле зрения, расширение и сужение капилляров, изменения их формы и упорядоченности, замедление тока крови) наблюдались в обеих группах, однако с большей частотой и выраженностью во второй.

ЭКГ и капилляроскопию следует проводить у детей и подростков с СДТ-1 регулярно с целью выявления ранних изменений и своевременного начала соответствующего лечения.

რეზიუმე

კაპილაროსკოპიული და ეკგ-პარამეტრები ტიპი 1 შაქრიანი დიაბეტის მქონე ბავშვებსა და მოზარდებში

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კვლევის მიზანი: ელექტროკარდიოგრაფიული და კაპილაროსკოპიული ცვლილებების დადგენა ტიპი 1 შაქრიანი დიაბეტის (ტ1შდ) მქონე ბავშვებსა და მოზარდებში.

ეკგ და კაპილაროსკოპია ჩაუტარდა ტ1შდ მქონე 32 ბავშვსა და მოზარდს (ასაკი – 6-15 წელი, 17 ვაჟი, 15 გოგონა). დაავადების ხანგრძლივობა: 2 წელზე ნაკლები – 13, 2-4 წელი – 10, 5-10 წელი – 9 შემთხვევა. პაციენტები გაყოფილი იყო ორ ჯგუფად: I ჯგუფი – 12 პაციენტი გართულებების გარეშე (ყველა მათგანში დაავადების ხანგრძლივობა არ აღემატებოდა 2 წელს), II ჯგუფი – ტ1შდ გულ-სისხლძარღვთა სისტემის გართულებებით (დიაბეტური კარდიომიოპათია, ანგიოპათია), ამასთანავე მათ აღენიშნებოდა სხვა გართულებებიც: დიაბეტური ენცეფალოპათია – 6, დიაბეტური ენცეფალოპათია და პერიფერული ნეიროპათია – 4, ნეფროპათია და რეტინული ანგიოპათია – 4 შემთხვევა. გლიკოლიზირებული ჰემოგლობინი მერყეობდა 8-11% შორის, გლუკოზის დონე – 4-15 mmole/l. საკონტროლო ჯგუფი შედგებოდა 20 ჯანმრთელი ბავშვისაგან. I ჯგუფში ეკგ ნაკლებად ინფორმაციული იყო. მარცხენა პარკუჭის და წინაგულის ჰიპერტროფია და რეპოლარიზაციის დარღვევები აღინიშნა მხოლოდ II ჯგუფში. რითმის და გამტარებლობის დარღვევები დადგენილ იქნა 62,5%-ში, უფრო ხშირად - II ჯგუფში. კაპილაროსკოპული ცვლილებები (ფონის სიფერმკრთალე, ბუნდოვანება, მხედველობის ველში კაპილარების რაოდენობის შემცირება, მათი დიამეტრისა და ფორმის პათოლოგიური ცვლილებები, სისხლის დინების შენელება) აღინიშნებოდა ორივე ჯგუფში, მათი გამოხატულობა და სიხშირე მეტი იყო II ჯგუფში.

კვლევის შედეგები მიგვითითებს, რომ ტ1შდ მქონე ბავშვებსა და მოზარდებში ეკგ და კაპილაროსკოპია რეგულარულად უნდა კეთდებოდეს, რათა გამოვლინდეს ადრეული ცვლილებები და სათანადო მკურნალობა დროულად იქნას დაწყებული.

CLINICAL, BIOCHEMICAL AND RADIOLOGICAL MANIFESTATIONS OF SEVERE VITAMIN D DEFICIENCY IN ADOLESCENTS VERSUS CHILDREN: RESPONSE TO THERAPY

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Low levels of vitamin D are considered a major public health problem especially during the winter [20]. Vitamin D deficiency (VDD) causes rickets in children and osteomalacia in adolescents. Rickets cases are still being reported in the Arab gulf area and worldwide. Osteomalacia also still occurs, but its symptoms are much less specific and are easily missed [1,2,9,11,18,23,25]. Vitamin D deficiency leads to hypocalcaemia, secondary hyperparathyroidism and increased bone turnover. This may be associated with osteoporosis and fractures. In prolonged and severe cases, osteomalacia and rickets (failure in mineralisation of new bone) may occur, resulting in progressive bone pains, myopathy and a waddling gait [16,27]. The clinical spectrum of VDD ranges from subclinical to frank deficiency, with serum 25- hydroxyvitamin D (25OHD) levels less than 20 ng/dl [1,2,9,11,18,20,23,25].

The usual method of supplementation with oral ergocalciferol tablets (1000 IU) is often inadequate, especially in severe deficiency states [21]. To maintain a healthy blood level of 25OHD (80 to 100 nmol/L), most healthy persons require at least 1000 IU of vitamin D each day if they do not get exposure to the sun. Topping up to adequate levels quickly is the goal.

Recommended repletion therapy consists of 50 000 IU of vitamin D2 weekly for 8 weeks or 2000 IU of vitamin D3 daily for 8 weeks. Doses of 4000 IU of vitamin D3 have been used safely for several months, and there is evidence that doses up to 2000 IU/d can be considered safely [6,8,20,26]. However, compliance with oral vitamin D preparation is always not good [20]. A mega dose of intramuscular vitamin D is suggested as an alternative to oral dose to avoid poor compliance [3].

The aim of this study was to monitor the effects of treating hypovitaminosis D in children and adolescents with a mega dose of IM cholecalciferol.

Material and methods. In this prospective study all children and adolescents with VDD attending to the General Pediatric and Endocrine Clinics of Hamad Medical Centre, Doha, Qatar, between October 2008 to October 2011 were studied.

Inclusion criteria included all adolescents and children with history, symptoms and/or signs of VDD and low serum 25OHD <10 ng/ml.

Exclusion criteria included: 1.Vitamin D deficiency associated with underlying disease, such as fat malabsorption, liver disease and renal insufficiency. 2.Patients receiving total parenteral nutrition. 3.Vitamin D deficiency secondary to heritable disorders of vitamin D metabolism, including 1 alpha hydroxylase deficiency (pseudo-vitamin D deficiency rickets), vitamin D receptor defects (hypocalcemic vitamin D resistant rickets. 4.Phosphopenic rickets of any etiology (where hypophosphatemia is the primary cause of the rickets, and not due to calcipenic rickets with secondary hyperparathyroidism).

All patients were subjected to the following:
1. Detailed history taking including nutritional intake and exposure to sun
2. Anthropometric measurements including weight, height, and head circumference.
3. Physical examination ,including clinical manifestations of vitamin D deficiency.
4. Biochemical investigations, including: measurement of serum creatinine, Ca, PO4, albumin, ALP, parathormone (intact PTH molecule) and 25 OHD concentrations. Serum Ca was corrected for individual variations in serum albumin using the formula: corrected serum calcium (mmol/L) = measured serum calcium (mmol/L) + 0.02 x [40 – measured albumin (g/L)].

Patients with plasma 25-OHD levels less than 20 ng/ml were considered to have vitamin D deficiency. The presence or absence of radiological evidence of VDD was determined from routine radiological films of the wrist and/or knee. All participants with VVD were treated with a therapeutic intramuscular injection of cholecalciferol (10,000 U/kg , maximum dose 600.000 IU (15 mg).

During each clinic visit, every 2-3 months, the anthropometric and radiological parameters were reassessed and recorded and the laboratory tests repeated.

PTH, 25 OH D and IGF-I were measured by radioimmunometric assay using kits purchased from Mediagnost; Reutlingen, Germany. Intraassay coefficient of variation (CVs) were 6.9%, 5.8% and 7.9% respectively, and interassay CVs were 7.9%, 5.9% and 8.2% respectively.

Ethical approval
Research Ethics Board, Hamad Medical Centre, Doha Qatar approved the protocol of the study and informed

consents were obtained from all the parents of the subjects enrolled in this study.

Results are expressed as the mean±SD and analyzed by paired student t-test to compare growth parameters and analyte concentrations before versus after treatment. A non-paired Student t test was used to compare age and sex-matched groups. Correlations between variables of interest were examined by linear regression analyses.

Results and their discussion. Infants and young children (age 1.9±0.5 years) with severe VDD had enlarged 3 wrist joints (42/45), cranial bossing (39/45), wide anterior fontanel (27/45), Harrison's sulcus (11/45), chest rosaries (27/45), bow legs (29/45), delayed teething (40/45), delayed motor milestones (sitting, standing , walking appropriate for age (36/45), short stature (length SDS< -2) (12/45); craniotabes (3/45) and hypocalcemic tetany (11/45). The most frequent biochemical abnormality was high alkaline phosphatase (ALP) (45/45), followed by low phosphate (PO4) (36/45) and low calcium (Ca) (8/45).

Variable radiological manifestations due to VDD were detected in all children (45/45) These changes included irregular (interrupted) or absent line of ossification at the metaphyseal front, excessive osteoid deposition (wide wrist space) with cupping, decalcification of the metaphysis, and shafts of long bones (thin cortex) with subperiosteal erosion of the shafts.

At presentation adolescents with severe VDD presented with pain in weight bearing joints, back, thighs, knees, and calves (30/36) difficulty walking and/or climbing stairs and/or running (8/36), muscle cramps and/or facial twitches and/or carpo-pedal spasms (12/36) and genu valgum (2/36). Biochemical serum abnormalities included high ALP (31/36), low phosphate (10/36) and low Ca (4/36).

19 out of 35 of adolescents with VDD had radiological changes. Two different radiological patterns have been recognized in adolescents. In pattern 1 (n=7) the lesions appear as metaphyseal multi-locular cystic lesion with sclerotic margins, exocentric subcortical location without significant cortical erosions, periosteal reaction, osteoporosis, or other metaphyseal manifestations. This pattern occurred in adolescents with normal or increased BMI and good intake of milk/milk products (Fig. 1). Whereas pattern 2 (n=12) appeared as generalized diminished bone density with prominent primary and secondary bone trabeculations, widening of the metaphyseal zone with relatively more lucency (zone of poor ossification) with rather loss of all bone trabeculations. No cupping or fraying of the metaphyses was identified (Fig. 2). This pattern occurred in adolescents with relatively lower BMI (<18- underweight) with no or poor intake of milk/milk products and lower IGF-I levels compared to those with pattern 1 (142±56 ng/ml versus 199±78 ng/ml, p=0.002), p = 0.002).

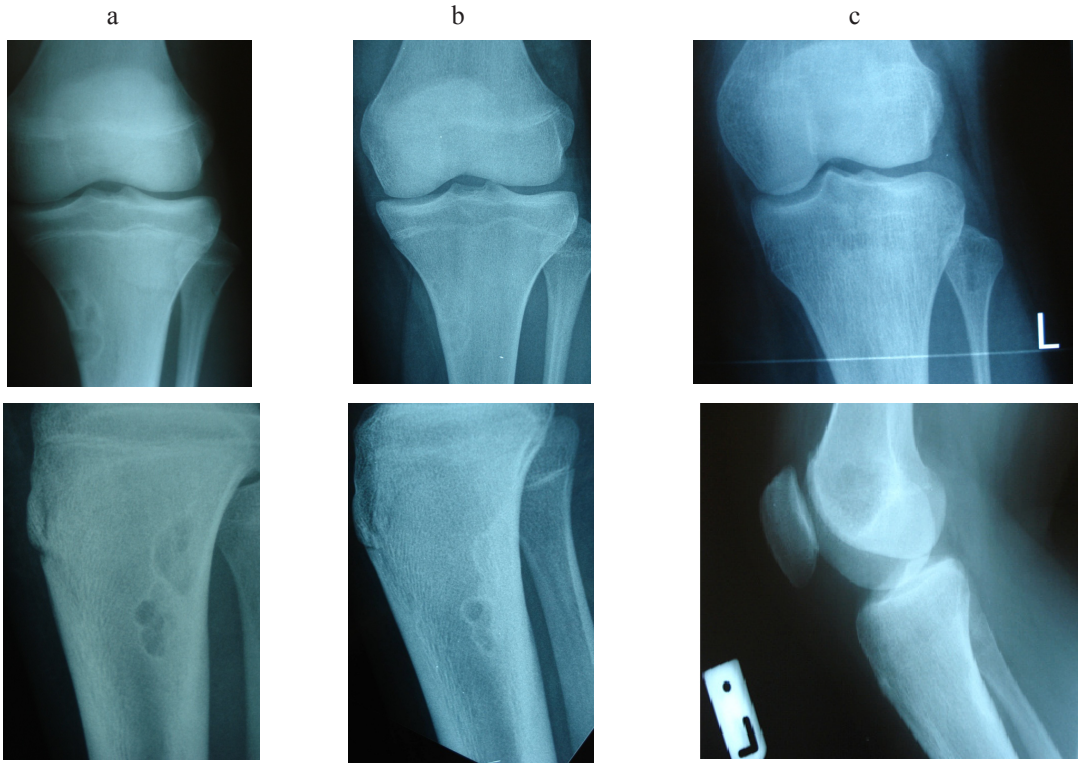

Fig. 1. Plain radiography of the knee joint for an adolescent with VDD and pattern 1: a - the lesions appear as metaphyseal multi-locular cystic lesion with sclerotic margins, exocentric subcortical location; b - after 6 months of treatment; c - after a year of treatment

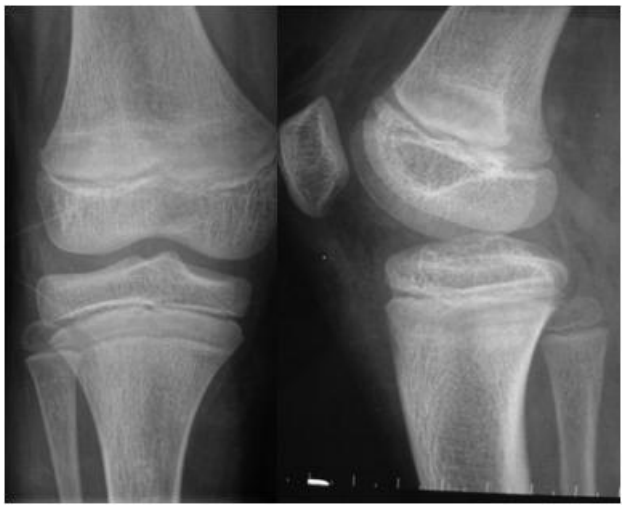

Fig. 2. Plain radiography of the knee joint for an adolescent with VDD and pattern 2: absent line of ossification at metaphyseal front, decalcification of the metaphysic and shafts of long bones (very thin cortex) with subperiosteal erosion of the shafts

Three months after the injection of a mega dose of cholecalciferol all biochemical abnormalities were corrected with significant improvement of symptoms related to vitamin D deficiency in all children (45/45) and in the majority (33/36) of adolescents. Six months after the vitamin D injection, complete healing of the radiological evidence of VDD was achieved in all rachitic children and the majority of adolescents (16/19). Three adolescents with pattern I required treatment for 18 months to achieve a complete disappearance of their radiological signs (cysts) (Fig. 1).

The majority of patients had 25 OH D level equal or > 20 ng/ml.

Table presents a comparison between the 2 study groups: children with VDD (n=45) versus adolescents with VDD (n=36) before and 3 months after injection of a mega dose of vitamin D. Before treatment 25 OH D and Ca concentrations did not differ among the 2 groups. Serum PO4 concentration was significantly lower and PTH and ALP concentration was higher in children compared to adolescents with VDD.

Table. Comparison of laboratory data in children and adolescents with vitamin D deficiency before and 3 months after vitamin D i.m. injection

	Infants (n=45)		**Adolescents (n=36)**	
	before	**after**	**before**	**after**
Ca mmol/L	2.05±0.25	2.2±0.12*	2.1±0.29	2.3±0.12*
PO4 mmol/L	0.98±0.23	1.5±0.29*	1.33±0.55 #	1.6±0.32*
ALP U/L	897±217 #	381±59 *#	495±195	211±59*
25 OH D ng/ml	6.7±2.9	25.5±7 *	7.9±2.2	27.8± 5.2*
PTH pg/ml	212±72 #	32±13 *	141±42	42±18*
IGF-I ng/ml	25±18 #	42±22*#	144±36#	211±65*

** - p<0.01 after versus before treatment*
 # - p<0.05 infants versus adolescents

The injection was successful to keep serum 25OHD levels at normal level (>20 ng/ml) in the majority of children (41/45) and adolescents (31/36) for 3 months but not for 6 months.

Serum creatinine levels remained normal in all participants throughout the study and the 2-hours urine calcium/creatinine excretion index remained in the normal range in all subject.

In this study, adolescents with severe VDD had different clinical and radiological presentations compared to children with VDD. Some of them were asymptomatic and some did not have significant radiological manifestations. Biochemically both adolescents and children with VDD had high PTH and ALP and low phosphate. However, adolescents with VDD have relatively lower PTH and higher phosphate compared to children with VDD.

In a VDD state, only 10-15% of dietary calcium and 50-60% of dietary phosphorus are absorbed. The poor absorption of calcium causes a decrease in serum-ionized calcium levels. This is immediately recognized by the calcium sensor in the parathyroid glands, resulting in an increase in the secretion of parathyroid hormone (PTH). PTH conserves calcium by increasing tubular reabsorption of calcium in both the proximal and distal convoluted tubules. However, PTH enhances the expression of Receptor Activator for Nuclear Factor k B Ligand (RANKL) on osteoblasts to increase the production of mature osteoclasts to mobilize calcium stores from the skeleton. PTH also decreases phosphorus reabsorption in the kidney, causing loss of phosphorus into the urine and hypophosphatemia [19,24]. The significantly higher PTH concentrations in infants with VDD compared to adolescents with VDD can explain their lower serum phosphate level (phosphaturia). Although serum calcium level is usually normal in the majority of patients with

VDD with rickets, it is the low serum phosphorus that leads to an inadequate calcium x phosphorus product, which is necessary to mineralize the osteoid laid down by osteoblasts [10,13,19,24]. This may explain the florid appearance of radiological rachitic manifestations in our infants with VDD patients (with significantly lower PO4 level) compared to adolescents (higher phosphate level). The secondary hyperparathyroidism stimulates the kidneys to produce 1,25(OH)2D.

In addition, a considerable number adolescents with severe VDD (19/36) presented with radiological changes of two different patterns. Analysis of the history and biochemical data of these adolescents revealed that patients with pattern 1 had significantly higher BMI, IGF-I concentrations and were consuming adequate milk/milk products (i.e. better calcium and phosphate intake) [22]. In support to our data serum IGF-I level is significantly higher in simple obese versus non-obese adolescents matched for pubertal stage [24]. In children and adolescents IGF-I functions in an endocrine and autocrine/paracrine manner as a bone trophic hormone that positively affects bone growth and bone turnover by stimulating osteoblasts, collagen synthesis, and longitudinal bone growth and acquisition of bone mass. In adults IGF-I is important in the maintenance of bone mass [10,13,19,24]. The significantly higher IGF-I in adolescents with type 1 pattern can explain the maintenance of their bone mass compared to those with pattern 2 and infants with significantly lower IGF-I level [22]. The two latter groups had significantly osteoporotic changes of the cortices of long bone.

In support of our findings, calcium intake has been shown to correlate with bone density in healthy children and adolescents. In a group of 151 healthy girls and boys, 7-15 yr old, Rizzoli et al. [17] reported that dietary calcium intake was the most significant determinant of spinal bone density and that the majority of children with low spinal and femoral neck bone density had low dietary calcium intake. Dietary calcium supplementation has been shown to improve bone density. Dairy products consumption is reported to positively influence bone mineral density at the spine, hip and forearm in adolescents, leading thereby to a higher peak bone mass [14,15,17,29].

Adolescents appear to have better adaptation to VDD compared to children as evidenced clinically by fewer clinical manifestations, higher phosphates, lower PTH lower incidence of hypocalcemia and fewer radiological changes. This may be explained partially by their higher bone mass, slower rate of growth (lower calcium-phosphate demands) and higher concentrations of IGF-I (promoting bone mineral accretion) compared to children with VDD.

In addition, adolescents with pattern 1 appear to have better adaptation to VDD because of maintaining near-normal bone architecture of the cortex of long bones (better bone mass) and having higher serum PO4 concentrations and absence of hypocalcemic episodes (two patients with pattern II had symptomatic hypocalcemia).

This can be explained by their higher fat mass (BMI >25), IGF-I concentrations and consumption of milk (better calcium and phosphate intake). All these factors have been shown to maintain bone density in children and adolescents [10,13,19,22,24].

Treatment of our adolescents and children with VDD, using a megadose of vitamin D every 3 months, has been shown to have a positive effect on bone, resulting in mineralisation of osteoid, disappearance of osteopenia and correction of epiphyseal, metaphyseal and diaphyseal changes.

A report of bone histomorphometric changes in 28 patients with osteomalacia treated with various vitamin D preparations and calcium showed a significant reduction in osteoid volume and an increase in mineralised bone volume in cortical and trabecular bone after therapy [7].

A meta-analysis reported significant increases in lumbar spine bone mineral density (BMD) after 12 months of therapy, and a slower increase in femoral neck BMD in postmenopausal women [14]. The usual method of supplementation with oral ergocalciferol tablets (1000 IU) is often inadequate, especially in severe deficiency states [20,21]. There are some data to suggest that an annual intramuscular injection of 150,000–300,000 IU of ergocalciferol (vitamin D2), as a form of depot for supplying vitamin D daily requirements, has been associated with a reduction in fractures of the upper limbs in the elderly [2].

People in the Arab Gulf area are at high risk of VDD because of their dark skin (particularly if veiled) and lack of exposure to the sun to avoid the very hot weather especially those with rapid rate of bone growth (infants and adolescents) [5,12]. Exposure of hands, face and arms to one-third of a minimal erythemal dose (MED) of sunlight (the amount that produces a faint redness of skin) most days is recommended for adequate endogenous vitamin D synthesis. If this sun exposure is not possible, then a vitamin D supplement of at least 400 IU (10 μg) per day is recommended.

In VDD, supplementation with 3000-5000 IU ergocalciferol per day for 6-12 weeks is recommended. Larger-dose preparations of cholecalciferol are available and would be useful to treat moderate to severe vitamin D deficiency states. One or two annual intramuscular doses of 300, 000 IU of cholecalciferol have been shown to reverse vitamin D deficiency states [4,5,7]. Our simple dosing regimen (a mega dose every 3 months) proved to be convenient and safe and improved patient compliance as suggested by others [3,28].

In conclusion,decreased circulating IGF-I in patients with VDD appears to be an adaptive process to inhibit linear growth (growth plate) and bone mineral accretion (diaphysis) during vitamin D deficiency to maintain normocalcemia through the osteolytic action of increased PTH. The variability of this adaptation in adolescents with VDD versus (relatively slower rate of growth, higher bone mass, higher serum IGF-I and phosphate concentrations and lower PTH levels) versus children with VDD can explain the differences of clinical and radiological manifestations among the two age groups. An IM megadose of cholecalciferol is an effective therapy for treatment of VDD in adolescents for 3 months but not for 6 months.

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SUMMARY

CLINICAL, BIOCHEMICAL AND RADIOLOGICAL MANIFESTATIONS OF SEVERE VITAMIN D DEFICIENCY IN ADOLESCENTS VERSUS CHILDREN: RESPONSE TO THERAPY

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Objectives: to compare clinical, biochemical and radiological manifestations of severe vitamin D deficiency (VDD - serum 25 OH – vitamin D level <10 ng/ml) in adolescents and children and to investigate the effects of an intramuscular injection (IM) of vitamin D3 megadose.

Design: in this prospective study 36 adolescents and 45 children with severe VDD were studied. An IM dose (10,000 IU/kg, max 600,000 IU) of cholecalciferol was injected and parameters of calcium homeostasis were measured at intervals of 3 months.

Results: at presentation, infants and young children (age 1.9±0.5 years) with severe VDD had enlarged wrist joints (42/45), cranial bossing (39/45), wide anterior fontanel (27/45), Harrison's sulcus (11/45) , chest rosaries (27/45), bow legs (29/45), delayed teething (40/45), delayed motor milestones (36/45), short stature (length/height SDS <-2)(12/45), craniotabes (4/45) and hypocalcemic tetany (11/45). The most frequent biochemical abnormality was high alkaline phosphatase (ALP) (45/45), followed by low phosphate (PO4) (36/45) and low calcium (Ca) (8/45). Adolescents with severe VDD presented with pain in weight bearing joints, back, thighs, knees, and calves (30/36) difficulty walking and/or climbing stairs and/or running (8/36), muscle cramps and/or facial twitches and/or carpopedal spasms (2/36) and genu valgum (2/36). Biochemical serum abnormalities included high ALP (31/36), low phosphate (10/36) and low Ca (4/36). Variable radiological manifestations due to VDD were detected in all children (45/45) and in some of adolescents (19/35). Two different radiological patterns have been recognized in adolescents. Three months after injecting a mega dose of cholecalciferol all biochemical abnormalities were corrected with significant improvement of symptoms related to VDD had been reported in all children (45/45) and in the majority (33/36) of adolescents with VDD. 3-6 months after the injection, complete healing of the radiological evidence of VDD was achieved in all rachitic children and the majority of adolescents (16/19).

Conclusion: it appears that adolescents adapt better to severe VDD compared to infants, with less severe clinical, biochemical and radiological manifestations. An IM mega dose of cholecalciferol is effective therapy for treatment of VDD in children and adolescents for 3 months but not for 6 months.

Keywords: vitamin D deficiency, adolescents, children, radiology, treatment.

РЕЗЮМЕ

КЛИНИЧЕСКИЕ, БИОХИМИЧЕСКИЕ И РЕНТГЕНОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ ТЯЖЕЛОЙ НЕДОСТАТОЧНОСТИ ВИТАМИНА D У ПОДРОСТКОВ И ДЕТЕЙ: ОТВЕТ НА ЛЕЧЕНИЕ

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Целью исследования явилось определение клинических, биохимических и рентгенологических проявлений тяжелой недостаточности витамина D (уровень 25 OH витамина D в сыворотке крови <10 ng/ml) у подростков и детей и определение эффектов внутримышечной инъекции мегадозы витамина D3.

Дизайн: В проспективное исследование были включены 36 подростков и 45 детей с тяжелой недостаточностью витамина D. Внутримышечно вводили холекальциферол (10,000 IU/kg, max 600,000 IU), параметры кальциевого гомеостаза изучались с 3-месячным интервалом.

При поступлении у детей раннего возраста (1,9±0,5 лет) с тяжелой недостаточностью витамина D отмечались утолщение запястьевых суставов (42/45), бугорчатость черепа (39/45), увеличение переднего родничка (27/45), Гаррисонова борозда (11/45), рахитические четки (27/45), искривление ног (29/45), запоздалое прорезывание зубов (40/45), запоздалое развитие моторики (36/45), гипостатура (длина/высота SDS<-2), краниотабес (4/45) и гипокальциемическая тетания (11/45). Наиболее частыми биохимическими сдвигами были повышение щелочной фосфатазы (45/45), снижение фосфатов (36/45) и гипокальциемия (8/45). У подростков же отмечались боль в суставах, подвергающихся весовой нагрузке, спине, бедрах, коленях и голенях (30/36); затрудненные ходьба и/или подъем по лестнице и/или бег (8/36); мышечные спазмы и/или подергивания лица и/или карпопедальный спазм (2/36) и genu valgum (2/36). Отмечались биохимические сдвиги:

повышение щелочной фосфатазы (31/36), снижение фосфатов (10/36) и гипокальциемия (4/36). Различные рентгенологические изменения, обусловленные тяжелой недостаточностью витамина D, имели место у всех детей (45/45) и части подростков (19/35). У подростков отмечались два паттерна рентгенологических изменений. Три месяца спустя после внутримышечной инъекции мегадозы холекальциферола все биохимические параметры нормализовались, отмечалось также существенное улучшение симптомов, обусловленных тяжелой недостаточностью витамина D у всех детей (45/45) и большинства подростков (33/36). 3-6 месяцев спустя после инъекции была достигнута полная нормализация рентгенологических изменений у всех рахитичных детей и большинства подростков (16/19).

Выводы: подростки по сравнению с детьми раннего возраста более легко адаптируются к тяжелой недостаточности витамина D - у них менее выражены клинические, биохимические и рентгенологические проявления. Внутримышечная инъекция мегадозы холекальциферола является эффективной терапией тяжелой недостаточности витамина D у детей и подростков в течение трех месяцев.

რეზიუმე

D ვიტამინის მძიმე დეფიციტის კლინიკური,ბიოქიმიური და რენტგენოლოგიური გამოვლინებები მოზარდებსა და ბავშვებში: პასუხი მკურნალობაზე

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[1]ჰამადის სამედიცინო ცენტრი, პედიატრიისა და რადიოლოგიის დეპარტამენტი, დოჰა, კატარი; [2]კვისისანას ჰოსპიტალი, ბავშვთა და მოზარდთა ამბულატორული კლინიკა, ფერარა, იტალია

მიზნები: D ვიტამინის მძიმე დეფიციტის (შრატში 25 OH – ვიტამინ D-ს დონე <10 ng/ml) კლინიკური, ბიოქიმიური და რენტგენოლოგიური გამოვლინებების შედარება მოზარდებსა და ბავშვებში და D3 ვიტამინის მეგადოზის ინტრამუსკულური ინიექციის ეფექტების შესწავლა.

დიზაინი: პროსპექტულ კვლევაში ჩართული იყო D ვიტამინის მძიმე დეფიციტის მქონე 36 მოზარდი და 45 ბავშვი. ქოლეკალციფეროლი (10 000 სე/კგ, მაქსიმუმი – 600 000 IU) შეჰყავდათ ინტრამუსკულურად; კალციუმის ჰომეოსტაზის პარამეტრები განისაზღვრებოდა 3-თვიანი ინტერვალებით.

შედეგები: მომართვისას D ვიტამინის მძიმე დეფიციტის მქონე ადრეული ასაკის (1,9±0,5 წლის) ბავშვებს აღენიშნებოდა მაჯის სახსრების გამსხვილება (42/45), თავის ქალას ბორცვების გამოხატულება (39/45), წინა ყიფლიბანდის გადიდება (27/45), ჰარისონის ღარი (11/45), გულმკერდის კრიალოსანი (27/45), ქვემო კიდურების დეფორმაცია (29/45), კბილების დაგვიანებული ამოჭრა (40/45), მოტორიკის ჩამორჩენა (36/45), ჰიპოსტატურა (სიმაღლე/სიგრძე SDS<-2) (12/45), კრანიოტაბესი (4/45) და ჰიპოკალციემიური ტეტანია (11/45). უხშირეს ბიოქიმიურ დარღვევებს მიეკუთვნებოდა ტუტე ფოსფატაზის მომატება (45/45), რასაც მოჰყვებოდა ფოსფატების (36/45) და კალციუმის დაქვეითება (18/45). D ვიტამინის მძიმე დეფიციტის მქონე მოზარდებს აღენიშნებოდათ სიმძიმით დატვირთვის მქონე სახსრების, ზურგის, ბარძაყების, მუხლების და წვივების ტკივილი (30/36), გაძნელებული სიარული ან/და კიბეზე ასვლა ან/და სირბილი (8/36), კუნთების სპაზმი ან/და კარპოპედალური სპაზმი (2/36) და genu valgum (2/36). სისხლის შრატში ბიოქიმიური დარღვევები გამოიხატებოდა ტუტე ფოსფატაზის მომატებით (31/36), ფოსფატების (10/36) და კალციუმის დაქვეითებით (4/36). D ვიტამინის მძიმე დეფიციტით განპირობებული სხვადასხვა რენტგენოლოგიურ გამოვლინებას ადგილი ჰქონდა ყველა ბავშვსა (45/45) და მოზარდების ნაწილში (19/36). მოზარდებში გამოვლინდა რენტგენოლოგიური ცვლილებების ორი პატერნი. ქოლეკალციფეროლის მეგადოზის ინიექციიდან 3 თვეში ყველა ბიოქიმიური გადახრა გამოსწორდა, აღინიშნა D ვიტამინის დეფიციტთან დაკავშირებული სიმპტომების მნიშვნელოვანი გაუმჯობესება ყველა ბავშვსა (45/45) და მოზარდების უმრავლესობაში (33/36), ხოლო ინიექციიდან 3-6 თვეში D ვიტამინის დეფიციტის რენტგენოლოგიური გამოვლინებები გამოსწორდა რაქიტის მქონე ყველა ბავშვსა და მოზარდების უმრავლესობაში (16/19).

დასკვნა: მოზარდები, ადრეული ასაკის ბავშვებთან შედარებით, უკეთ ეგუებიან D ვიტამინის მძიმე დეფიციტს; კლინიკური, ბიოქიმიური და რენტგენოლოგიური გამოვლინებებიც ნაკლებადაა გამოხატული. ქოლეკალციფეროლის მეგადოზით D ვიტამინის მძიმე დეფიციტის მკურნალობის ეფექტურობა თვალსაჩინოა ინიექციიდან 3 თვეში.

VITAMIN D STATUS IN HEALTHY EGYPTIAN ADOLESCENT GIRLS

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Over the last decade there had been growing evidence of high prevalence of vitamin D deficiency especially among adolescents [7,12,16]. Contributing factors include dark skin colour [4], dietary calcium deficiency [7], and inadequate sun exposure [6,16]. Females who remain fully covered for religious or social reasons seem to be at greatest risk [9,12]. It is estimated that as many as 1 billion people worldwide suffer from vitamin D deficiency or insufficiency (commonly defined as levels below 20 ng/ml and 30 ng/ml respectively), and this was shown to be prevalent across all age groups, genders, and geographic regions [18].

Optimizing vitamin D levels in vitamin D deficient children and adolescents is one of the strategies of maximizing peak bone mass. Peak bone mass directly affects bone mineral density, and both are risk factors for osteoporosis in later life [21]. The aim of this study was to investigate the vitamin D status in adolescent females in Egypt. The primary outcome was to assess the vitamin D status among a cohort of healthy adolescent girls and its relation to sun exposure. Secondary outcomes included the relation between vitamin D status and dietary intake of calcium and vitamin D, socioeconomic status, and body mass index.

Material and methods. Seventy five healthy adolescent girls aged 14-17 years attending Ain-Shams University Nursing School in Cairo participated in the study. They were all recruited during the summer months in the period between May 2008 and August 2009. The study was approved by the ethics committee of the faculty of medicine, Ain Shams University, Cairo, Egypt. All girls and their families gave informed consent. Girls were excluded if they had history of liver, kidney, or bone disease, or used any medication known to affect bone metabolism including calcium and vitamin D supplements.

Height was measured without shoes, to the nearest 0.1 cm using Harpenden stadiometer (Holtain ltd, Croswell, Crymych, UK). Weight was measured using a digital scale, to the nearest 0·1 kg, wearing light clothing and without shoes. Body mass index (BMI) was calculated using the formula Kg/m^2. All participants completed a food frequency questionnaire for three consecutive days to determine the daily intake of calcium and vitamin D. Daily vitamin D and calcium intake were estimated using national dietary references on the vitamin D and calcium content of food [17]. Calcium insufficiency was defined as less than 50% of the recommended daily intake (RDI). RDI for ages 9-18 years is 1300 mg [2]. Sun exposure questionnaire was completed by all participants including the daily hours of sun exposure, use of topical sunscreens, and type of most commonly worn clothes in order to determine the body surface area exposed to the sun. Sun exposure index was calculated using the method described by Barger-Lux and Heaney [4]. Briefly, each girl provided information on daily daytime exposure to sunlight, identifying the parts of body surface area [BSA] exposed to sunlight (each part was given a percentage value including arms (0.18), legs (0.36), face (0.01), head (0.09) and anterior (0.18) and posterior (0.18) trunk as part of the adapted "rule of nines" values totaling 1.0). The sun exposure index was calculated from the formula = hours of sun exposure per week × fraction of BSA exposed to sunlight [4]. Socioeconomic standard was estimated based on paternal profession, educational level, family income, income score and type of housing. A score of 25-30 is considered high social standards (I), score of 20-25 is considered middle social standard (II), score of 15-20 is low social standard (III), and score of <15 is very low social standard (IV) [8].

Serum concentrations of calcium adjusted for albumin [3.5- patient's albumin (g/dl) + patient's measured calcium (mg/dl)], inorganic phosphate, and alkaline phosphatase were measured using Hitachi 917 autoanalyzer and Roche reagents (Hitachi, Tokyo, Japan). Serum parathyroid hormone was measured using the BioSource hPTH-EASIA which is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiter plates. Calibrators and samples react with the capture polyclonal antibodies (PAb, goat anti 1-34 PTH fragment) coated on microtiter well (Biosource Europe S, A, Rue de l'industrie, 8-B-1400 Nivelles-Belgium). Serum 25 hydroxycholecalceferol (25-OHD) was measured by reagents supplied by Immundiagnostik (Immundiagnostik AG Stubenwald-Allee 8a, D 64625 Bensheim). The test kit is a competitive protein binding assay based on competition of 25 OHD present in the sample with 25-OHD tracer, for the binding pocket of vitamin D binding protein (VDBP, Gc-globulin). Since all circulating 25-OHD is bound to VDBP in vivo, samples have to be precipitated with precipitation reagent to extract the analyte (Immundiagnostik AG, Germany). 25-OHD level above 30 ng/ml was considered sufficient, between 21-30 ng/ml was considered insufficient, and less than 20 ng/ml is vitamin D deficiency [5,21].

The data were analyzed by SPSS statistical software (version 17.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean and standard deviations. Chi square (X^2) test was performed for categorical variables. Comparison of multiple subgroups was done by using ANOVA test. Pearson's correlations were

used to assess the association between variables. For all tests a probability (p) less than 0.05 was considered significant.

Results and their discussion. Seventy five healthy adolescent girls were included in this study. All were pubertal, with a mean age (SD) of 15.8 (0.5) years, and a mean BMI SDS of 0.02 (1.01). More than half (54.7%) had vitamin D deficiency (Table 2). Thirty nine girls (52%) achieved the recommended daily calcium intake. The mean serum calcium, phosphorus, alkaline phosphatase (ALP), albumin, and parathyroid hormone (PTH) were within the normal limits for age and sex (Table 3). BMI was significantly higher among girls with adequate vitamin D levels compared to those who are deficient and those who have vitamin D insufficiency (Table 4). Both sun exposure index and daily sun exposure time were significantly higher in girls with adequate vitamin D levels compared to those with insufficient and deficient vitamin D. Those with vitamin D insufficiency had also higher sun exposure time and sun exposure index compared to girls with vitamin D deficiency. The use of topical sun screen creams did not affect vitamin D levels. Calcium intake was highest in girls with adequate 25-OHD, while there was no difference in vitamin D intake between the three groups (Table 4). The only laboratory parameter that was significantly correlated to 25-OHD level was PTH (Table 5). It was also significantly higher in girls with vitamin D insufficiency compared to girls with adequate serum levels (Table 4). Serum 25-OHD correlated positively with BMI, BMI standard deviation score (SDS), sun exposure index, sun exposure time, and daily calcium intake, and negatively with PTH level (Table 6).

Table 1. Background characteristics of the studied girls

	Mean (SD)	**Range**
Age (years)	15.8 (0.5)	14.1 -17.3
BMI (Kg/m^2)	22.3 (4.1)	16.22 - 36.7
BMI SDS	0.02 (1.01)	-1.48 - 3.56
Socioeconomic status (SES)	I (high) II (middle) III (low) IV (very low)	No (%) 1 (1.3) 11 (14.7) 28 (37.3) 35 (46.7)
BSA exposed to sun (%)	17.1 (7.4)	9.5 - 43.0
Daily sun exposure (minutes)	22.1 (12.7)	5.0 - 60.0
Sun exposure index	45.3 (34.3)	5.5 - 144.7
Use of sun screen creams	Positive: No (%) 28 (37.3)	Negative: No (%) 47 (62.7)
Dietary calcium (mg/day)	647.9 (167.7)	281.2 - 996.3
Achievement of RDI	Achieved: No (%) 39 (52.0)	Not achieved: No (%) 36 (48.0)
Dietary vitamin D (ug/day)	12.5 (5.4)	0.3 - 24.9

Table 2. 25-OHD levels in the studied girls

25-OHD level (ng/ml)	**No (total=75)**	**Percentage**
Adequate (> 30)	16	21.3 %
Insufficient (>20 - <30)	18	24 %
Deficient (< 20)	41	54.7 %

Table 3. Laboratory parameters of the studied girls

	Mean (SD)	**Range**
Calcium (mg/dl)	9.7 (0.4)	7.5 - 10.5
Corrected Calcium (mg/dl)	9.6 (0.4)	7.4 - 10.2
Phosphorus (mg/dl)	5.2 (0.4)	4.2 - 6.8
Albumin (g/dl)	4.6 (0.2)	4.0 - 5.2
Alkaline phosphatase (U/l)	100.8 (48.8)	14.0 - 356.0
Vitamin D (ng/ml)	20.7 (11.0)	4.0 - 48.0
PTH (pg/ml)	38.7 (26.2)	20.0 - 200.0

Table 4. Relation between background characteristics and 25-OHD levels

	Adequate (no=16)	**Insufficient (no=18)**	**Deficient (no=41)**	**Test**	*P*
Age (years) Mean (SD)	 15.7 (0.6)	 15.8 (0.5)	 15.8 (0.5)	F 0.37	 0.69
BMI (kg/m^2) Mean (SD)	 24.7 (4.3)	 22.0 (3.3)	 21.4 (4.1)	F 3.8	 **0.026**
SES I II III IV	No (%) 0 2 (12.5) 9 (56.3) 5 (31.2)	No (%) 0 2 (11.2) 8 (44.4) 8 (44.4)	No (%) 1 (2.4) 7 (17.1) 11 (26.8) 22 (53.7)	X^2 5.5	 0.49
Sun exposure index Mean (SD)	 79.04 (32.6)	 48.8 (39.6)	 30.5 (20.7)	F 16.5	 **0.0001**
Sun exposure (minutes) Mean (SD)	 37.8 (9.1)	 23.1 (12.6)	 15.6 (7.4)	F 33.3	 **0.0001**
Sun screen Positive Negative	No (%) 2 (12.5) 14 (87.5)	No (%) 4 (22.2) 14 (77.8)	No (%) 15 (36.6) 26 (63.4)	X^2 3.7	 0.16
Dietary calcium (mg/day) Mean (SD)	 765.9 (145.4)	 657.4 (158.9)	 597.6 (158.5)	F 6.7	 **0.002**
Dietary vitamin D (ug/day) Mean (SD)	 13.6 (4.8)	 11.9 (5.9)	 12.3 (5.4)	F 0.47	 0.63

F= ANOVA *X^2= Chi square*

Table 5. Relation between laboratory parameters and 25-OHD levels

	Adequate (no=16) Mean (SD)	**Insufficient (no=18) Mean (SD)**	**Deficient (no=41) Mean (SD)**	**F**	***P***
Calcium (mg/dl)	9.5 (0.3)	9.6 (0.2)	9.6 (0.5)	0.48	0.62
Phosphorus (mg/dl)	5.4 (0.5)	5.1 (0.3)	5.2 (0.4)	1.6	0.21
Albumin (g/dl)	4.5 (0.2)	4.6 (0.2)	4.6 (0.3)	1.9	0.15
Alkaline phosphatase (U/l)	86.1 (16.6)	103.0 (31)	105.5 (61.6)	0.93	0.4
PTH (pg/ml)	19.4 (1.7)	36.1 (5.6)	50.6 (31.6)	10.4	**0.0001**

Table 6. Correlations between 25-OHD and different variables

	r	*P*
Age (years)	-0.08	0.51
BMI (kg/m^2)	0.29	**0.013**
BMI SDS	0.33	**0.011**
Sun exposure index	0.52	**0.0001**
Sun exposure time (minutes)	0.63	**0.0001**
Dietary calcium	0.28	**0.014**
Dietary vitamin D	0.002	0.98
Corrected calcium (mg/dl)	-0.12	0.3
Phosphorus (mg/dl)	0.15	0.2
Albumin (gm/dl)	0.18	0.13
Alkaline phosphatase (U/l)	0.11	0.36
PTH (pg/ml)	-0.34	**0.003**

While rickets is the clinical manifestation of vitamin D deficiency in children, adolescents with vitamin D deficiency may present with muscle weakness, difficult walking, limb pains, and carpopedal spasm [6]. Subclinical vitamin D

deficiency even poses a greater challenge because of the lack of clinical symptoms and signs [10,21]. The end result is the negative effect on bone mineralization [21]. Adolescents are at particular risk because almost 50% of peak bone mass accrual occurs during puberty [3,11-13]. 25 Hydroxyvitamin D is the precursor of the active metabolite, calcitriol [12], and its serum concentration is an indicator of the vitamin D status because it reflects both dietary intake and cutaneous synthesis [6]. Cutaneous synthesis is the main source of vitamin D in the body [14], and therefore factors that interfere with appropriate sun exposure are very likely to cause vitamin D deficiency [12]. Cutaneous synthesis of vitamin D occurs through absorption of ultra violet rays (290-315 nm) by 7-dehydrocholesterol. Any factor that influences the number, or the absorption of ultraviolet rays, or the amount of 7-dehydrocholesterol in the skin would influence the cutaneous synthesis of vitamin D3. This includes percentage of body surface area exposed to sun, duration of exposure, and dose of ultraviolet rays, skin colour, and time of the day, season, and latitude [14]. Reports from the Middle East showed higher prevalence of vitamin D deficiency [12]. Although those are mostly sunny parts of the world, vitamin D deficiency had been attributed to inadequate sun exposure because of the effect of cultural and religious factors on the way of dress and the life style [1,9,12,16].

In our cohort of adolescent girls, vitamin D levels correlated positively with the sun exposure index and the sun exposure time. The mean (SD) daily sun exposure was 22.1(12.7) minutes but the range was 5-60 minutes, quite a wide range, and the mean (SD) BSA was 17.1% (7.4), thereby emphasizing the importance of both factors comprising the sun exposure index. i.e. percentage of body surface area exposed to sun and duration of sun exposure. Holick reported that exposure to sunlight for 5-15 minutes daily in summer, autumn, and spring produces enough vitamin D, and that exposure of about 20% of BSA was effective in increasing 25-OHD concentrations [14]. This emphasizes the importance of BSA exposed to sun, because although the mean exposure time was within normal limits in our cohort, the sun exposure index (product of exposed BSA x exposure duration) was significantly higher among girls with adequate vitamin D. Exposure of at least 18% of BSA for at least 37 minutes/day is enough to achieve adequate vitamin D levels in a sunny climate as Egypt. Serum 25-OHD was found to be related to % BSA and sun exposure in other studies from both east and west [6,7,9,12,16,18]. Hatun et al reported that half of their studied population of girls who wore concealing clothes had vitamin D deficiency in winter and their vitamin D level only slightly improved in summer [12]. El-Hajj Fuleihan et al found that girls who covered their head, arms and legs had a mean 25-OHD of 12 ng/ml compared to 18 ng/ml in girls who followed the usual dress code ($p<0.001$) [9]. Concealing clothing is therefore likely to affect vitamin D concentrations, and therefore supplementing those girls with vitamin D is important.

Adolescent girls with adequate vitamin D had significantly higher calcium intake compared to those with deficient and insufficient vitamin D levels. This effect did not exist for vitamin D intake, possibly minimizing the role of dietary vitamin D in vitamin D deficiency or insufficiency. Weng et al, however, in their multivariable logisitic regression, did find that daily vitamin D intake of less than 200 IU was associated with low vitamin D concentrations [20]. The effect of dietary calcium intake was previously explored; an average daily intake of 280 mg was associated with 50% higher risk of vitamin D deficiency [7]. Low calcium levels lead to secondary hyperparathyroidism which in turn results in increased synthesis of 1, 25 dihydroxyvitamin D that degrades 25-OHD to 24, 25 dihydroxyvitamin D, the end result being depletion of vitamin D stores [15].

The relation between SES and vitamin D levels is conflicting. While children and adolescents of lower SES are expected to have poorer dietary calcium and vitamin D intake, they might be expected to spend more time in the sun. Vitamin D deficiency was found more prevalent among adolescents of lower SES in some studies [9,22], while Puri et al in Delhi found no difference between girls from lower and upper socioeconomic strata [19]. We did not find any relation between both variables. Most of the recruited girls were of a low/very low SES which might have affected the results.

This study has a number of limitations. First, the sun frequency questionnaire used to calculate the subject's exposed body surface area and hours of sun exposure was subjective, as it was dependant on the subject's judgement. It would have been more useful to have a more objective tool free from any subjective bias. Second, the studied group might not be representative of Egyptian adolescents because of unidentified sources of bias. Third, other factors such as genetics might play a role, and therefore, reassessing vitamin D status after correction of the deficiency could help confirm/refute the hypothesis.

In conclusion, this study demonstrates that vitamin D deficiency is a common problem among a group of Egyptian adolescent girls. Inadequate sun exposure, possibly related to cultural/social factors influence the mode of dress and therefore sun exposure. Insufficient intake of calcium in diet is another contributing factor. Raising the awareness of the community on the implications of this health problem is of utmost importance. Special emphasis should also be placed on the importance of balanced diet and adequate sun exposure. If not possible, then vitamin D supplementation in the recommended dosages to those girls is important.

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SUMMARY

VITAMIN D STATUS IN HEALTHY EGYPTIAN ADOLESCENT GIRLS

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Over the last decade there had been growing evidence of high prevalence of vitamin D deficiency especially among adolescents. Inadequate sun exposure is considered a precipitating factor. Females who remain fully covered seem to be at greatest risk. The aim of this study was to investigate the vitamin D status in adolescent females in Egypt.

Seventy five healthy adolescent girls aged 14-17 years were recruited during the summer months. Anthropometric measures, calcium and vitamin D intake, sun exposure index, use of topical sun screen, and socioeconomic standard were all determined. Serum calcium, inorganic phosphate, alkaline phosphatase, and 25 hydroxycholecalceferol (25-OHD) were measured.

Sixteen girls (21.3 %) had vitamin D deficiency, 18 were vitamin D insufficient (24 %), and 41 had adequate vitamin D levels (54.7 %). Both sun exposure index and daily sun exposure time were significantly higher in girls with adequate vitamin D levels compared to those with insufficient and deficient vitamin D. Exposure of at least 18% of BSA for at least 37 minutes/day is enough to achieve adequate vitamin D levels in a sunny climate as Egypt. Calcium intake was highest in girls with adequate 25-OHD, while there was no difference in vitamin D intake. Serum 25-OHD correlated positively with BMI, BMI standard deviation score (SDS), sun exposure index, sun exposure time, and daily calcium intake, and negatively with PTH level.

Vitamin D deficiency is a common problem among Egyptian adolescent girls. Inadequate sun exposure, possibly related to cultural/social factors influence vitamin D levels. Insufficient dietary calcium is another contributing factor.

Keywords: vitamin D, adolescents, sun exposure.

РЕЗЮМЕ

СТАТУС ВИТАМИНА D У ЗДОРОВЫХ ДЕВОЧЕК ПОДРОСТКОВ В ЕГИПТЕ

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Согласно литературным данным, у девочек-подростков за последнее время часто отмечается дефицит витамина D. Недостаточная солнечная экспозиция рассматривается как способствующий фактор. Женщины, тела которых полностью покрыты одеждой, находятся под наибольшим риском.

Целью исследования явилось изучение статуса витамина D у девочек-подростков, проживающих в Египте.

75 здоровых девочек-подростков в возрасте 14-17 лет находились под наблюдением в течение июнь - августа. Определялись антропометрические показатели, состояние потребления витамина D и кальция, индекс солнечной экспозиции, частота применения защитных местных кремов в сравнении с социоэкономическим стандартом. В сыворотке крови определяли кальций, неорганический фосфор, щелочную фосфатазу и 25-гидрохолекальциферол (25-OHD).

У 16 (21,3%) девочек выявлен дефицит витамина D, у 18 (24%) - недостаточный, а у 41 (54,7%) – адекватный уровень витамина D. Индекс солнечной экспозиции и время дневной экспозиции были существенно выше у девочек с адекватным уровнем витамина D, чем с недостаточным уровнем витамина D или его дефицитом. Экспозиция по крайней мере 18% поверхности тела в течение хотя бы 37 минут в день оказалась достаточной для достижения адекватного уровня содержания витамина D в условиях солнечного климата Египта. Прием кальция был наивысшим у девочек с адекватным уровнем 25-OHD, что не отмечалось в отношении приема витамина D. Содержание сывороточного 25-OHD коррелировало положительно с индексом массы тела, его стандартным отклонением, индексом и временем солнечной экспозиции; отрицательно – с уровнем паратгормона.

Дефицит витамина D является частым состоянием у девочек-подростков, проживающих в Египте. Недостаточная солнечная экспозиция, возможно связанная с культурно-социологическими факторами, влияет на уровень содержания витамина D, а недостаточное потребление кальция с пищей способствующим этому фактором.

რეზიუმე

D ვიტამინის სტატუსი ჯანმრთელ ეგვიპტელ მოზარდ გოგონებში

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ბოლო წლების ლიტერატურის მონაცემების თანახმად, მოზარდებში აღინიშნება ვიტამინი D-ს მზარდი პრევალენტურობა. მზის არასაკმარისი დასხივება განიხილება, როგორც ხელშემწყობი ფაქტორი. აქედან გამომდინარე, გოგონები, რომელთა სხეული ტანსაცმლით სრულადაა დაფარულნი, მეტი რისკის ქვეშ იმყოფებიან.

კვლევის მიზანს წარმოადგენს ვიტამინი D-ს სტატუსის კვლევა ეგვიპტეში მცხოვრებ მოზარდ გოგონებში.

ზაფხულის თვეებში დაკვირვების ქვეშ იმყოფებოდა 75 14-17 წლის ჯანმრთელი მოზარდი გოგონა. განისაზღვრა ანთროპომეტრიული პარამეტრები, კალციუმისა და D ვიტამინის მიღების დონე, მზის დასხივების ინდექსი, ადგილობრივი დამცველი კრემების გამოყენების მდგომარეობა და მიღებული მაჩვენებლები შედარებულ იქნა სოციალურ-ეკონომიურ სტანდარტთან. სისხლის შრატში შესწავლილ იქნა კალციუმის, არაორგანული ფოსფატების, ტუტე ფოსფატაზის და 25-ჰიდროკალციფეროლის (25-OHD) შემადგენლობა.

16 (21,3%) გოგონას აღმოაჩნდა ვიტამინ D-ს დეფიციტი, 18 (24%) - D ვიტამინის არასაკმარისი დონე, ხოლო 41 (54.7%) - D ვიტამინის ადეკვატური დონე. მზის დასხივების ინდექსი და ექსპოზიციის დღიური დრო არსებითად უფრო მაღალი იყო D ვიტამინის ადეკვატური დონის მქონე გოგონებში იმ გოგონებთან შედარებით,რომლებსაც ჰქონდათ D ვიტამინის დეფიციტი ან უკმარისობა. სხეულის ზედაპირის მინიმუმ 18%-ის დასხივება დღეში 37 წუთის განმავლობაში საკმარისი აღმოჩნდა D ვიტამინის ადეკვატური დონის მისაღწევად ეგვიპტის მზიანი ჰავის პირობებში. კალციუმის მიღება იყო ყველაზე მაღალი გოგონებში 25-OHD

ადექვატური დონით, ასეთი სხვაობა ვერ იქნა მიღებული D ვიტამინის მიმართ. დადგენილი იქნა შრატის 25-OHD დადებითი კორელაცია BMI ინდექსთან, BMI სტანდარტული გადახრის მაჩვენებელთან (SDS),მზის დასხივების ინდექსსა და დროსთან და კალციუმის დღიურ მიღებასთან, ხოლო უარყოფითი – პარათირეოიდული ჰორმონის დონესთან.

D ვიტამინის დეფიციტი ხშირი პრობლემაა ეგვიპტელ მოზარდ გოგონებში. სავარაუდოა,რომ მზის არასაკმარისი დასხივება, დაკავშირებლი კულტურულ-სოციალურ ფაქტორებთან,გავლენას ახდენს D ვიტამინის დონეზე. არასაკმარისი კალციუმი საკვებში კი დამატებითი ხელშემწყობი ფაქტორია.

PAPILLARY THYROID MICROCARCINOMA IN THALASSAEMIA: AN EMERGING CONCERN FOR PHYSICIANS?

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Thyroid cancer is a relatively rare pathology, but it is becoming more frequent in different parts of the world. For example, in Italy in 1983-1987, the standardized incidence rates per 100,000 inhabitants were 2.0 for males and 5.5 for females, while in 1988-1992, they were 2.5 for males and 7.0 for females [30].

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, making up to 70-80 % of all thyroid cancer cases. PTC typically occurs in the middle aged with a peak incidence in the 3rd and 4th decades. It is more common in women with a F:M ratio of 1.6:1 to 3:1. Both genetic and environmental factors may increase the risk of developing PTC. About 3% of cases of PTC are familial [10]. Patients with PTC are usually asymptomatic and present with a solitary thyroid nodule or with a gland that contains multiple thyroid nodules. These nodules are usually palpated on routine physical examination or discovered during an imaging study done for another reasons.

The occurrence of malignancies in thalassaemic patients is an emerging concern for physicians. In a review of the literature through the Medline database we found seven cases of PTC in TM and TI subjects [11,24]. Four were females and three males. Their mean age was 41 years (range 32-57 years). Associated factors were iron overload resulting in iron-induced oxidative damage, high levels of oxygen free radical and high cellular turnover, and infections transmitted via transfusions, such as hepatitis [8].

The pathogenic role of iron in cancer development and/or progression is not fully understood. Several carcinogenic pathways have been described schematically:
a) iron can promote the growth of some cancer cells probably through its role in the activation of ribonucleotide reductase; b) iron may promote the formation of mutagenic hydroxyl radicals; c) iron excess diminishes host defences through inhibition of the activity of CD4 lymphocytes and through the suppression of the tumoricidal action of macrophages; (d) iron can enhance host cell production of viral nucleic acids which may be involved in the development of some human tumors [3,25,28].

In this paper we report three thalassaemic patients with incidental papillary thyroid microcarcinoma (PTMC) and address the controversies in the clinical management.

Patient presentations
Patient 1. A 24 -year-old female came to our out patient clinic for clinical and laboratory evaluation of her thalassaemia intermedia (TI) status.

In the past, she had occasional red cell blood transfusions when her haemoglobin level dropped to 7 g/dl. The past medical history was negative for significant clinical events. There was no history of cancer in the family.

On examination, she was pale with scleral icterus, splenomegaly (two fingers below the costal margin), and

vital signs were normal. There was no perceptible thyroid enlargement. Bilaterally, no adenopathy was palpable.

Her haemoglobin level was low (8.5 g/dl), serum ferritin was high and FT4 and TSH were in the normal range (Table). The antithyroglobulin antibodies (TgAb) measured using a chemiluminescent immunoassay (ICMA) were positive (120 UI/ml; normal < 40 UI/ml), and serum thyroglobulin (Tg, IRMA), determined according to manufacturer recommendations, was in the normal range.

Table 1. Summary of relevant clinical, laboratory and thyroid ultrasound data in 3 thalassaemic patients with papillary thyroid microcarcinoma

Patient (no.)	Age (years) Sex	TM/TI	HCV antibodies	Serum ferritin level (ng/ml)^	Thyroid Function (FT4 and TSH) and TG	Thyroid antibodies (TG Ab and TPO Ab)	Thyroid ultrasound data
1	24/F	TI	Negative	472	Normal	Positive	Round, hypoechogenic nodule in the thyroid isthmus, 8x6.5 mm
2	39/F	TM	Positive	938	Normal	Negative	Irregular, hypoechogenic nodules in the left lobe, 9x7 mm and 4x4 mm
3	42/F	TM	Positive	3540	Normal FT4, marginal increase of basal TSH	Negative	Oval, hypoechogenic nodule with microcalcification in the left lobe, 6 x 4.6 mm

Abbreviations: TM = thalassaemia major; TI = thalassaemia intermedia
^ normal values in females 25 – 160 ng/ml

The thyroid ultrasonography (US) showed a small hypoechoic nodule (8x6.5 mm in diameter) located in the isthmus. Cervical lymph nodes were not observed.

The patient consented to fine needle biopsy (FNAC) and the biopsy revealed histology consistent with papillary carcinoma. The B-RAF mutation was negative.

The patient was referred to a surgeon who, after discussion with the patient, elected to perform a total or near-total thyroidectomy. The surgery went well and the final pathology report confirmed the diagnosis of PTMC. Chronic lymphocytic thyroiditis was also present. The thyroid capsule was not infiltrated by the tumor. Cervical lymphadenopathy was not found. The patient did not undergo radioablation as per low-risk cancer staging. She has been followed closely in the last 12 months with no signs of recurrence. Follow-up visits included measurements of FT4, FT3 and TSH, 2-3 months after suppressive therapy with L-thyroxine, and physical examination, neck ultrasound and rhTSH stimulated serum Tg measurement at 6-12 months.

Patient 2. A 39 year-old female patient followed in the same hospital with the diagnosis of thalassaemia major (TM) was found on routine thyroid US to have two irregular, hypoechogenic thyroid nodules in the left lobe, measuring 9x7 mm and 4x4 mm. The neck examination was normal.

The FNAC was performed on the largest nodule and showed a tumor with a papillary pattern. The B-RAF mutation was not checked.

The patient was HCV-antibody positive. Thyroid function tests showed normal hormone levels. The last serum ferritin level, during subcutaneous iron chelation therapy with desferrioxamine mesylate, was 938 ng/ml and serum ferritin peak at the age of 19 years was 7040 ng/ml (normal values in females 25 – 160 ng/ml). No other endocrine complications were present.

No lymphadenopathy was found on intraoperative assessment. A suppressive dose of L-thyroxine was prescribed and periodic postoperative follow-up was recommended.

Patient 3. A 42-year old female TM patient with severe iron overload and associated laboratory, clinical (cardiac arrhythmias, osteoporosis, chronic HCV hepatitis) and endocrine complications (impaired glucose tolerance test, secondary amenorrhea) underwent thyroid ultrasound for

a marginal increase in the TSH level (5.8 mUI/ml; normal values: 0.5 - <4.5 mUI/ml) with normal FT4 (Table). There was no family history of thyroid pathology or cancer in the family.

An oval, hypoechogenic nodule with microcalcification, measuring 6x4.6 mm, was detected in the left thyroid lobe. The patient consented to FNAC and the biopsy showed histology consistent with PTMC. The B-RAF mutation was negative.

The patient was referred to a surgeon and a near-total thyroidectomy (leaving no more than 3 g of thyroid tissue) was performed. Pathologic specimens confirmed the FNA cytology diagnosis. Postoperative follow-up recommendations were similar to those for Patient no.1.

Results and their discussion. The occurrence of malignancies in thalassaemic patients is an emerging concern for physicians [3,17].

In the last five years, in a single Thalassaemia Unit following 195 thalassaemic patients, eleven cases of carcinoma were diagnosed: 4 cases of liver, 1 of lung, 1 of adrenal gland and 5 cases of PTC (mean age 42.6 years) [11].Therefore, we decided to perform a thyroid ultrasonography in addition to the periodic (every 6-12 months) assessment of FT4 and TSH in all adult TM and TI patients followed at the Thalassaemia Unit of Siracusa and Outpatient Clinic of Quisisana Hospital of Ferrara.

Five TM and TI patients (8.6 % of 56 examined patients) presented with thyroid nodules (maximum diameter, 6 to 26 mm).

To exclude thyroid malignancy, FNAC under US guidance was done. A diagnosis of PTMC was made in 3 female patients. All underwent total or subtotal thyroidectomy with histological confirmation of FNAC cytology diagnosis.

PTMC, as a specific subgroup of PTC, merits attention because of its increased frequency in recent years. PTMC accounts for about 30% of all PTCs [4]. According to the World Health Organization, PTMC is defined as a papillary thyroid carcinoma measuring <or=10 mm in the greatest dimension [7].

PTMCs are mostly detected incidentally, with a high prevalence in autopsy studies and in histopathological examinations of surgical specimens. Also, they are being diagnosed more often with the increased practice of ultrasonography and fine needle aspiration biopsies in recent years.

There are several prognostic risk factors in PTCs. It has been reported that incidental microcarcinomas have a lower risk for recurrence than the patients with nonincidental disease [13].

Although most patients with thyroid cancer are euthyroid, higher TSH concentrations, even within the normal range, may be associated with an increased risk of cancer in a thyroid nodule. Besides age, other important risk factors are tumor size, extension beyond the thyroid capsule and distant metastases [14]. Therefore, PTCMs are considered to have a better outcome. Neverthless, some PTMCs may be more aggressive. In fact, local recurrences in the neck and distant metastases have been reported in several studies [1,29].

Some controversy and concerns still persist regarding the diagnostic approach and the optimal management of these patients. The American Thyroid Association (ATA) suggests that FNAC aspiration should be considered for all thyroid nodules 10 mm or larger [7]. If worrisome aspects present, even solitary nodules <10 mm in size, on an individual basis, should also be considered for FNAC, based on the clinical context, US aspect, patient wishes, and personal experience [21].

The AACE guidelines suggest that if a nodule has at least two sonographic criteria for malignancy, the sensitivity of FNAC is between 87 and 93% [9]. Features suspicious for malignancy include microcalcifications, hypoechoic nodules, increased nodular vascularity, infiltrative margins and masses taller than wide on transverse view. In patients with multiple nodules, the cancer rate per nodule decreases, but the rate of cancer per patient remains equal to that of patients with solitary nodules [5,20].

Most of the guidelines recommend total or near-total thyroidectomy for tumors larger than 1 cm in size [7,20]. However, there is a wide spectrum of treatment modalities in several centers for tumors smaller than 1 cm and the ideal surgical procedure for PTMC has been a debate for decades.

In autopsy studies, PTMC has been found in 1-36% of patients [6]. Therefore, most PTCs are latent. Ito et al. [16] followed 162 patients with biopsy-proven papillary thyroid cancers that were equal to or smaller than 10 mm. Seventy percent of these tumors either got smaller or did not change size over an 8 year period, 10.2% of them enlarged by more than 10 mm and node metastases occurred in 1.2%.

As a result, the authors suggested that microcarcinomas that do not have unfavorable features can be followed without immediate surgical treatment.

However, other Researchers [2,12,18,23,26] have stressed that:
1. PTCs are often found to be multifocal, which is also true for PTMCs. It has been reported that multifocal tumors have a higher relapse rate than unifocal tumors
2. The recurrence rate, after 10 years, was 4.6% in tumors <1 cm, 7.1% in 1.0-1.9 cm, 8.6% in 2.0-2.9 cm, 11.6%

in 3.0-3.9 cm, 17.2% in 4.0-7.9 cm, and 24.8% in tumors >8.0 cm

3. The 10-year recurrence rate was 7.7% for patients treated with total thyroidectomy compared to 9.8% for those who underwent lobectomy ($p<0.05$). Lobectomy alone was associated with a 2.5-fold risk of recurrence and 2.2-fold risk of death compared to those who underwent near-total or total thyroidectomy.

Although large studies are required to determine proper management protocols for PTMCs and despite continuing controversies, in our clinical practice and according to other clinical reports [23,26] we consider total or near-total thyroidectomy as the procedure of choice for the management of nodular thyroid disease, including patients with PTMC. Furthermore, total thyroidectomy reduced the risk of persistent or recurrent disease, facilitated postoperative I-131 ablation and whole body scanning, and allows for more sensitive postoperative thyroglobulin monitoring [22,27].

Opponents to this approach suggest that total thyroidectomy may have complications. However, in expert hands surgical complications such as laryngeal nerve palsy and hypoparathyroidism are extremely rare (<1-2%) [19]. The benefit of prophylactic central node dissection in absence of evidence of nodal disease is controversial and should be performed in cases of preoperatively suspected and/or intraoperatively proven lymph node metastases [19].

Radioiodine therapy is indicated at least in selected patients with PTMC, based on the presence of adverse prognostic factors, such as tumor multicentricity, positive lymph nodes, or capsular or vascular invasion [15].

Routine use of L-thyroxine to suppress TSH secretion is recommended in the management of PTMC. Patients in remission may be shifted from suppressive to replacement LT4 therapy, with the goal of maintaining a serum TSH level within the normal range.

The subsequent follow-up of these patients should be based on yearly physical examination, serum Tg measurement on replacement LT4 and neck ultrasound. Patients with evidence of persistent disease, or with detectable levels of serum Tg increasing with time, require imaging techniques for the localization of disease and appropriate treatment, including therapeutic doses of I-131 [19].

In conclusion, it seems that patients with thalassaemia have a substantial risk for malignancies. Further studies are needed in these patients to clarify the possible link between cellular iron content, hepatitis C virus infection and cancer development. A thyroid ultrasonography is recommended for all adult thalassaemic patients in addition to the annual FT4 and TSH assessment.

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SUMMARY

PAPILLARY THYROID MICROCARCINOMA IN THALASSAEMIA: AN EMERGING CONCERN FOR PHYSICIANS?

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The occurrence of malignancies in thalassaemic patients is an emerging concern for physicians. In the last five years, in a single Thalassaemia Unit following 195 thalassaemic patients, eleven cases of carcinoma were diagnosed: 4 cases of liver, 1 of lung, 1 of adrenal gland and 5 cases of papillary thyroid carcinoma (patient mean age 42.6 years).Therefore, we decided to perform a thyroid ultrasonography (US) in addition to the periodic (6-12 months) assessment of FT4 and TSH in all adult patients with thalassaemia followed at the Thalassaemia Unit of Siracusa and at the Outpatient Clinic of Quisisana Hospital of Ferrara. Thyroid nodules were found in 8.6% of 58 examined thalassaemia major or intermedia patients.

To exclude thyroid malignancy, fine needle biopsy (FNAC) under US guidance was performed. A diagnosis of incidental papillary thyroid microcarcinoma (PTMC) was made in 3 female patients with iron overload. According to the World Health Organization, PTMC is defined as papillary thyroid carcinoma measuring < or = 10 mm in the greatest dimension. Two patients were HCV positive. All underwent a total or subtotal thyroidectomy with histological confirmation of the FNAC cytology diagnosis.

In conclusion, it seems that patients with thalassaemia have a substantial risk for malignancies. Further studies are needed in these patients to clarify the possible link between cellular iron content, hepatitis C virus infection and cancer development. A thyroid ultrasonography is recommended for all adult thalassaemic patients in addition to the annual FT4 and TSH assessment

Key words: thalassaemia, cancer, thyroid, iron overload, hepatitis C virus.

РЕЗЮМЕ

ПАПИЛЛЯРНАЯ ТИРЕОИДНАЯ МИКРОКАРЦИНОМА ПРИ ТАЛАССЕМИИ: НОВАЯ ПРОБЛЕМА ДЛЯ ВРАЧЕЙ

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Развитие злокачественных опухолей у больных с талассемией является новой проблемой для врачей. За последние 5 лет лишь в одном центре по талассемии, в котором проводится наблюдение над 195 пациентами с указанным диагнозом, было выявлено 11 случаев карциномы: 4 – печени, 1 – легких, 1 – надпочечников и 5 – папиллярной тироидной карциномы (средний возраст больных - 42,6 года). Поэтому мы решили в дополнение периодическому (раз в 6-12 месяцев) определению FT4 и TSH у всех взрослых больных, находящихся под наблюдением в центре по талассемии в Сиракузах и амбулаторной клинике госпиталя Квисисана в Ферраре, проводить эхоскопию щитовидной железы. Тиреоидные узелки были обнаружены у 8.6% из 58 обследованных пациентов с большой и средней талассемией. С целью исключения злокачественного новообразования всем больным была проведена биопсия тонкой иглой под контролем эхоскопии. Диагноз сопутствующей папиллярной тиреоидной микрокарциномы был поставлен у 3 женщин с перегрузкой железом. Согласно определению ВОЗ при папиллярной тиреоидной микрокарциноме размер опухоли меньше или равен 10 мм в наибольшем измерении. У двух пациенток имела место гепатит С вирусная инфекция. Всем больным была проведена тотальная или субтотальная тиреоидэктомия. Цитологический диагноз пунктата был подтвержден гистологически. В заключение можно отметить, что пациенты с талассемией имеют существенный риск развития злокачественных опухолей. Необходимы дальнейшие исследования этих больных с целью выяснения возможной связи между содержанием железа в клетках, инфекцией вируса гепатита С и развитием рака. Рекомендуется проведение эхоскопии щитовидной железы в дополнение к ежегодному определению FT4 и TSH у всех взрослых больных с талассемией.

რეზიუმე

პაპილარული მიკროკარცინომა თალასემიის დროს: ახალი პრობლემა ექიმებისთვის

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ავთვისებიანი სიმსივნეების განვითარება თალასემიის მქონე პაციენტებში ახალი პრობლემაა ექიმებისთის. უკანასკნელი 5 წლის განმავლობაში თალასემიის ერთ-ერთ ცენტრში, რომელშიც თალასემიით დაავადებულ 195 პირზე მიმდინარეობდა მეთვალყურეობა, კარცინომის დიაგნოზი დაისვა 11 შემთხვევაში: ღვიძლის სიმსივნის 4 შემთხვევა, ფილტვის – 1, თირკმელზედა ჯირკვლის - 1 და პაპილარული თირეოიდული მიკროკარცინომის (პთმკ) 5 შემთხვევა (პაციენტების საშუალო ასაკი - 42,6 წ.). ამიტომ, ჩვენ გადავწყვიტეთ პერიოდულად (6-12 თვეში ერთხელ) ყველა მოზრდილ პაციენტში, რომლებიც მეთალყურეობის ქვეშ იმყოფებიან სირაკუზას თალასემიის ცენტრში და ფერარას კვისისანას ჰოსპიტლის ამბულატორიულ კლინიკაში, FT4 და TSH დადგენასთან ერთად, ფარისებრი ჯირკვლის ექოსკოპიის (ფჯე) ჩატარება. თირეოიდული კვანძები აღმოაჩნდა დიდი და საშუალო თალასემიის მქონე 58 გამოკვლეული ავადმყოფიდან 8,6%-ს. ფარისებრი ჯირკვლის სიმსივნის გამოსარიცხად ფჯე-ის კონტროლით გაკეთდა ფარისებრი ჯირკვლის ბიოფსია წვრილი ნემსით. 3 ქალში დაისვა თანმხლები პთმკ დიაგნოზი. სამივეს აღენიშნებოდა რკინით გადატვირთვა. ჯანმრთელობის მსოფლიო ორგანიზაციის მონაცემების თანახმად, პთმკ დროს სიმსივნის ზომა ≤10 მმ-ს ყველაზე დიდ განზომილებაში. ორი პაციენტი იყო C ჰეპატიტის ვირუსზე დადებითი. ყველას გაუკეთდა ტოტალური ან სუბტოტალური თირეოიდექტომია. წვრილი ნემსით ჩატარებული პუნქტატის ციტოლოგიური დიაგნოზი დადასტურდა ჰისტოლოგიურადაც. საფიქრებელია, რომ თალასემიის მქონე პაციენტებს აქვთ ავთვისებიანი სიმსივნის განვითარების დიდი რისკი. ასეთ პაციენტებში მიზანშეწონილია ჩატარდეს შემდგომი კვლევა, რათა გარკვეულ იქნას შესაძლო კავშირი უჯრედებში რკინის შემცველობას, C ჰეპატიტის ვირუსის ინფექციასა და კიბოს განვითარებას შორის. რეკომენდებულია თალასემიით დაავადებულ ყველა მოზრდილ პაციენტს, FT4 და TSH ყოველწლიურ განსაზღვრასთან ერთად, გაუკეთდეს ფჯე.

ASN540SER MUTATION IS ASSOCIATED WITH A MILD FORM OF HYPOCHONDROPLASIA: A 7 YEARS FOLLOW-UP IN AN ITALIAN BOY

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The term skeletal dysplasias (SKD) encompasses a wide range of skeletal disorder [9,12,19]. The degree of short stature associated with skeletal abnormalities is highly variable [3,9,12,13]. Some of these conditions do respond to growth hormone (GH) therapy [1,5]. Further height can be gained through leg lengthening procedures [6].

Hypochrondroplasia (HCH) is a genetic disorder characterized by short stature and disproportionately short arms, legs, hands, and feet (short-limbed dwarfism). Short stature often is not recognized until early to mid childhood or, in some cases, as late as adulthood [9,12]. Because HCH has such a wide range of variability, many people mildly affected with HCH may never be diagnosed. Thus, the true incidence of HCH is unknown. No studies have been done to determine the incidence of HCH but it is assumed to be a relatively common disorder with an incidence equal to achondroplasia - one in 15,000 to one in 40,000 live births [7].

HCH is caused by mutations in the Fibroblast Growth Factor Receptor 3 (FGFR3) gene mapped to chromosome 4p 16.3. FGFR3 is a member of the tyrosine kinase receptor family. The four known members (FGFR 1-4) of this family play an important role in the regulation,proliferation differentiation and angiogenesis, as well as other processes involved in growth and development. FGFR3 is expressed during skeletal growth and endochondral ossification. It seems to have a specific role as negative regulator of bone growth, and the known FGFR3 mutatioins result in a lingand independent activation of the receptor [11].

Different FGFR3 mutations can cause very different diseases such as achondroplasia but also Crouzon and Muenke craniostenosis syndromes, CATSHL (Camptodactyly, Tall Stature, and Hearing Loss Syndrome), LADD Syndrome (Lacrimo Auriculo Dento Digital) and Thanatophoric I and II dysplasias [3,7,19].

In about 70 % of HCH patients, mutations of the FGFR3 gene can be identified [4,10].

We report the clinical and radiographic features of an Italian family with HCH with an unusual N540S mutation, inside the common mutation hot spot of this condition.The proband was followed for 7 years.

Patient and family. The proband was a boy from North of Italy, who was referred to the pediatric endocrinologist at 8.9 years of age because of "unexplained" short stature.

He was born at term from non-consanguineous parents. Pregnancy was uncomplicated and the delivery was normal. Birth weight was 3850 g (75^{th}-90^{th} percentile).

His growth was parallel to the 3^{rd} centile up to the age of 7 years, when he started to have a reduction of growth velocity/year (4.5 cm/year). His anthropometric measurements at the first examination are reported in Table 1.

Table 1. Auxological parameters in the proband and father

Auxological parameters	Patient's age (years/months)							Father
	8.9	11.3	12.6	13.7	14.9	15.6	16.7	31
Height (cm)	119.7	129.3	134.1	139	148.1	153.2	157.6	165.7
Height (SDS)	- 2.2	- 2.2	- 2.3	- 2.5	- 2.4	- 2.3	- 2.4	- 1.6
Sitting height (cm)	65.7	69.3	-	78.8	81.9	85.7	89	90.8
Sitting height(SDS)	- 1.5	- 1.8	-	- 1	- 1.2	- 0.86	- 0.6	1.3
Subischial Leg Length (cm)	54	60	-	61.9	66.2	67.5	68.6	74.9
Subischial Leg Length (SDS)	- 2.6	- 2.4	-	- 3.3	- 3.3	3.3	- 3.3	- 4.1

Standing and sitting height measurements were performed using a Harpenden stadiometer and sitting height table. Subischial leg length was obtained by subtracting sitting height from standing height. Standard deviation scores for sitting height and subischial leg length were calculated for chronological age using published tables [20].

His clinical phenotype was unremarkable excepting for a slight bowlegs and stocky hands.

The weight was 27.5 kg (50th centile), head circumferences 54 cm (75th centile) and arm span 121 cm. Acanthosis nigricans was not present, hearing and vision were normal.

The X-ray showed moderate narrowing of interpedicular distances between lumbar vertebrae L1 and L5 , anteroposterior shortening of pedicles and increased dorsal concavity of the vertebral bodies in the lumbar spine, short and broad femoral neck,elongated distal end of the fibula with respect to tibia and mild shortening of 4th and 5th metacarpal bones. Although radiological features were subtle, the study of the skeleton was concordant with the diagnosis of HCH [16,22].

Biochemical and hormonal studies were whitin the normal limits.

The growth hormone (GH) stimulation test showed a GH peak of 13,2 ng/ml, insulin growth factor (IGF-1) was 160 ng/ml (normal values: 70-350 ng/ml), and IGF-binding protein-3 (IGFBP-3) was 3,6 mcg/ml (normal values: 1.8-7.1 mcg/ml).Thyroid function (FT4 and TSH), basal glucose and insulin, gonadotrophins (LH and FSH), bsal serum testosterone were in the normal ranges for the age.

His 31 year-old father also presented a short stature and bowlegs. The anthropometric data are reported in table 1. Therefore, a familiar condition was suspected.

Genetic analysis
On the clinical and radiologic basis suggesting HCH sequence analysis of the tyrosin kinase I domain of the FGFR3 gene was performed. Blood samples were collected after obtaining informed consent from the family.DNA was extracted from leukocytes by standard procedures and exon 13 FGFR3 gene was amplified utilizing oligonucleotide primers and PCR, cloned and sequenced.

The analysis showed in both subjects heterozygosity for an A to G transversion at nucleotide 1619, resulting in substitution of serine to asparagine at position 540 in the tyrosine kinase domain. The unaffected mother did not carry the nucleotide change.

Patient's follow-up
During a 7-years-follow-up, the boy started the puberty at the age of 11.3 years and the growth spurt was observed between 13.7 and 14.9 years (9.1 cm, Table).

During pubertal development the sitting height (SDS) improved from - 1.5 to - 0.6 and the subischial leg length (SDS) progressed from - 2.6 to - 3.3. His school progress was considered from the family " satisfactory".

At the age of 16.7 year the standing height was 157.6 cm (- 2.4 SDS), testicular volume was 15 ml and bone age 16.5 year (Tanner-Whitehouse 20 bones) [21].

Results and their discussion. There are multiple causes of short stature. The most common causes are familial short stature and constitutional growth delay . A variety of endocrine and genetic disorders, including chromosomal disorders, metabolic disorders and single gene disorders can also result in short stature [2,8].

SKDs are genetic disorders that result in abnormal development of part or all of the skeleton and are commonly associated with short stature [22]. Traditionally,the diagnosis is based on the clinical appearance during development and conventional X-ray findings. More recently,the classificationb of SKD has been based upon the expanding understanding of the pathophysiology of bone development and the discovery of the underlying molecular genetic defects [24].

The most common presenting feature of children with HCH is short stature with disproportionate limbs. Birth weight and length are often within the normal range and the disproportion in limb-to-trunk length is often mild and easily overlooked during infancy.

Typically, these children present as toddlers or school-age children to pediatricians or pediatric endocrinologists with failure to grow. With age, limb disproportion usually becomes more prominent in the legs than the arms. Both rhizomelic and mesomelic, shortening have been reported, although others have reported the predominance of neither [9,12,13].

Overall height is usually two to three standard deviations below the mean during childhood, and adult heights range from 138 to 165 cm for men and 128 to 151 cm for women [1,12]. Some investigators have reported the absence of a pubertal growth spurt [1,5].

HCH is a clinically and molecular heterogeneous condition. The diagnosis of HCH can be extremely difficult to make for a number of reasons. There is no one physical feature or X ray finding specific to HCH and there is a great deal of overlap between individuals with HCH and individuals in the general population [12,13].

Several mutations in the *FGFR3* gene have been identified in subjects with HCH. Many cases are caused by one of two specific *FGFR3* mutations, both of which lead to the same change in amino acids in the fibroblast growth factor receptor 3 protein. Specifically, the amino acid asparagine is replaced with the amino acid lysine at protein position 540 (Asn540Lys or N540K). Other *FGFR3* mutations probably cause a small number of cases of HCH. Although the effects of these mutations have not been explained, they probably cause the receptor to be mildly overactivated, which leads to the disturbances in bone growth seen with this disorder .To date, only 70% of clinically diagnosed patients have a known mutation and there are reported familial cases not linked to chromosome 4 that supports a clinically and genetically heterogeneous condition [10,15,16].

Subjects with HCH heterozygous for the Asn540Lys substitution are significantly more disproportionate than individuals without this mutation [3,10,16]. In these patients rGH treatment improves growth and reduces body disproportion [18].

On the contrary, ASN540Ser mutation is associated with a mild form of HCH [14,23].

Mortier et al [14] reported a father and daughter with clinical and radiographic features of HCH who were heterozygous for an A-to-G transition resulting in the replacement of an asparagine residue at position 540 by a serine residue (N540S).Both individual were mildly affected.The father height was on the 10th centile. He had short limbs and relative macrocephaly. X-rays showed definite features of HCH.

The daughters's anthropometric measurements showed a height of 120.1 cm (3rd centile=123cm), weight 23.8 kg (3rd centile), head circumference 52.5cm (50th-75th centile), span 120 cm, lower segment 58 cm(upper to lower segment ratio 1.07), hand length 13.2 cm (3rd centile), and foot length 18 cm (3rd centile=18.7 cm).In addition, a prominent forehead, low nasal bridge,anteroposteriorly flattened thorax, and lumbar hyperlordosis were found on physical examination.

Thauvin-Robinet et al. [23] described a family in which the N540S mutation was present in two brothers and their father. The proband was 2-month-old boy referred for assessment of short limbs and macrocephaly. Height and occipital-frontal circumference were within normal limits (-1 SD and + 1SD, respectively). No facial abnormalities were noted except a slight large head.T here were no visceral malformations.

His brother, age 2.5 years, with macrocephaly, frontal bossing and mild micromelia showed a height within the normal limits.

Family history indicated macrocephaly and micromelia in the grand father, with a height of 163 cm (3rd centile) and the father's sister.

Our case report the present study and the other two cases described in the literature further confirms the clinical and molecular heterogeneity of HCH. In our patient the degree of short stature was mild. For these reason,t he diagnosis is frequently not made until later childhood ,when growth delay is first noted.

Although Asn and Ser are both polar and neutral aminoacids, several evidences imply pathogenicity for this substitution: other substitutions of this critical amminoacid are associated with the disease; other two cases associated with HCH are reported in literature; the mutation segregates in the present family; and finally there is a strong evolutive conservation among species of this aminoacid.

Our study stressess also the important role of the asn 540 site in the tyrosine kinase I domain in the pathogenesis of HCH and underlines the importance that, in patients with HCH who do not have the common N540K mutation, sequence analysis of the tyrosine kinase I domain of FGFR3 should be performed to exclude other changes in that region.

Diagnosis requires a high degree of clinical suspicion, collaboration between an experienced clinician, an informed radiologist and molecular and clinical geneticists.

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SUMMARY

ASN540SER MUTATION IS ASSOCIATED WITH A MILD FORM OF HYPOCHONDROPLASIA: A 7 YEARS FOLLOW-UP IN AN ITALIAN BOY

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Skeletal dysplasias (SKD) are genetic disorders that result in the abnormal development of part or all of the skeleton and are commonly associated with short stature. The most common SKDs that typically result in short stature include achondroplasia/hypochondroplasia (HCH) both caused by different mutations in the same gene. HCH diagnosis is based on the clinical appearance during development and conventional X-ray findings. In about 70% of patients, missense mutations in the gene coding for the fibroblast Growth Factor Receptor 3 (FGFR3) affects the amino acid at position 540, mostly resulting in the amino acid exchange N540K.Subjects with HCH, heterozygous for the N540K substitution are significantly more disproportionate than individuals without this mutation. We report the clinical and radiographic features of an Italian family with HCH with an unusual N540S mutation, inside the common mutation hot spot of this condition. This is the first case reported in Italy and the third in the literature. During a 7-years-follow-up, the boy started the puberty at the age of 11.3 years and the growth spurt was observed between 13.7 and 14.9 years (+ 9.1 cm.).During pubertal development the sitting height (SDS) improved from - 1.5 to - 0.6 and the subischial leg length (SDS) progressed from - 2.6 to - 3.3.At the age of 16.7 year the standing height was 157.6 cm (- 2.4 SDS), testicular volume was 15 ml and bone age 16.5 year. The present study and the other two cases reported in the literature stress the important role of the asn 540 site in

the tyrosine kinase I domain in the pathogenesis of HCH and underline the importance that, in patients with HCH who do not have the common N540K mutation, sequence analysis of the tyrosine kinase I domain of FGFR3 should be performed to exclude other changes in that region.

Keywords: hypochondroplasia, short stature, ASN540Ser mutation, follow-up.

РЕЗЮМЕ

ASN540S МУТАЦИЯ, АССОЦИИРОВАННАЯ С ЛЕГКОЙ ФОРМОЙ ГИПОХОНДРОПЛАЗИИ: 7-ЛЕТНЕЕ НАБЛЮДЕНИЕ НАД ИТАЛЬЯНСКИМ МАЛЬЧИКОМ

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К дисплазиям скелета (ДС) относятся генетические нарушения, ведущие к неправильному развитию всего скелета или его части, которые обычно ассоциируются с гипоплазией. Наиболее частые ДС, протекающие с гипостатурой, включают в себя ахондроплазию/гипохондроплазию (ГХП), обусловленные различными мутациями одного и того же гена. Диагноз ГХП основывается на клинических проявлениях и общепринятых рентгенологических изменениях. Примерно у 70% больных бессмысленная мутация гена, кодирующего третий рецептор фактора роста фибропластов (FGFR3), повреждает аминокислоту в позиции 540 (N540K). Лица с ГХП, гетерозиготные в отношении N540K, более диспропорциональны, чем лица без этой мутации. В работе представлены клинические и рентгенологические показатели у мальчика из итальянской семьи с ГХП с необычной N540S мутацией внутри участка обычных мутаций при этом состоянии. Описываемый нами случай единственный, описанный в Италии, и третий в мировой литературе. Мальчик наблюдался в течение 7 лет. Пубертат начался в возрасте 11,3 лет, ростовой спурт имел место в периоде от 13,7 до 14,9 лет (+9,1 см). В течение пубертатного развития показатель роста сидя (SDS) изменился с -1,5 до -0,6, показатель длины ноги (SDS) - с -2,6 до -3,3. К возрасту 16,7 лет рост составил 157,6 см (-2,4 SDS), объем тестикул 15 мл, костный возраст – 16,5 лет. В настоящем исследовании и в двух случаях, описанных в литературе, акцентируется значение ASN540S в I домейне тирозинкиназы в патогенезе ГХП и подчеркивается необходимость секвенциального анализа I домейна тирозинкиназы FGFR3 у больных, не имеющих обычной N540K мутации, с целью исключения других сдвигов в этом участке.

რეზიუმე

ASN540S მუტაცია, ასოცირებული ჰიპოქონდროპლაზიის მსუბუქ ფორმასთან: 7 წლის დაკვირვება იტალიელ ვაჟზე

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ჩონჩხის დისპლაზიები (ჩდ) წარმოადგენს გენეტიკური დარღვევებს, რაც მთელი ჩონჩხის ან მისი ნაწილის არანორმულ განვითარებას განაპირობებს და, ჩვეულებრივ, ჰიპოსტატურასთან არის ასოცირებული. ჰიპოსტატურის გამომწვევ ყველაზე ხშირ ჩდ-ს მიეკუთვნება აქონდროპლაზია/ჰიპოქონდროპლაზია (ჰქჰ). ორივე ერთსა და იმავე გენში სხვადასხვა მუტაციითაა გამოწვეული. ჰქჰ დიაგნოზი ემყარება კლინიკურ გამოვლინებებს და რენტგენოლოგიური გამოკვლევის საყოველთაოდ მიღებულ შედეგებს. ავადმყოფების დაახლოებით 70% ფიბროპლასტების ზრდის ფაქტორის მესამე რეცეპტორის (FGFR3) მაკოდირებელი გენის უაზრო მუტაცია აზიანებს 540-ე პოზიციაში მყოფ ამინომჟავას (N540K). ჰქჰ მქონე ჰეტეროზიგოტური პირები არიან უფრო დისპროპორციული, ვიდრე ჯანსაღები. ნაშრომში წარმოდგენილია კლინიკური და რენტგენოლოგიური ცვლილებები ჰქჰ-ის მქონე ერთ იტალიელ ვაჟში N540S უჩვეულო მუტაციით ამ მდგომარეობისათვის დამახასიათებელ უბანში. ეს იტალიაში აღწერილი ერთადერთი შემთხვევაა, ხოლო მსოფლიოში - მესამე. ვაჟი 7 წლის განმავლობაში იმყოფებოდა დაკვირვების ქვეშ. პუბერტატი დაიწყო 11,3 წლის ასაკიდან, ზრდის სპურტს ადგილი ჰქონდა 13,7 და 14,9 წელს შორის (+9.1 cm). პუბერტული განვითარების პერიოდში სიმაღლის მაჩვენებელმა (SDS)

მჯდომარე პოზიციაში იმატა -1,5-დან -0.6-მდე, ფეხის სიგრძის მაჩვენებელი (SDS) შემცირდა -2,6-დან -3,3-მდე. 16,7 წლის ასაკისთვის სიმაღლე შეადგენდა 157,6 სმ (-2.4 SDS), სათესლეების მოცულობა – 15 მლ, ძვლოვანი ასაკი - 16,5. ჩვენს შემთხვევაში და ლიტერატურაში აღწერილ 2 შემთხვევაში ხაზგასმულია თიროზინკინაზას I დომეინში ASN540 საიტის მნიშვნელოვანი როლი ჰქპ-ის პათოგენეზში. მიზანშეწონილია, რომ ჰქპ მქონე პაციენტებს, რომლებსაც არა აქვთ ჩვეულებრივი N540K მუტაცია, ჩაუტარდეთ FGFR3-ს თიროზინკინაზას I დომეინის სექვენტური ანალიზი, რათა გამოირიცხოს სხვა ცვლილებები ამ უბანში.

A RARE CASE OF ORGASMIC DISORDER: PSYCHOGENIC ANEJACULATION IN AN ADOLESCENT

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The age of first male masturbation occurs between 12 and 14 years of age and the vast majority of young males experience masturbation and nocturnal emissions before 18 years of age [6,15]**.**

The events that lead up to normal climax of male sexual activity are distinct in 4 stages: erection, emission, ejaculation and orgasm. This process is mediated by an intricate system of humoral, neurological and circulatory events controlled by the parasympathetic nervous system. Orgasm and associated ejaculation are mostly controlled by the sympathetic nervous system [2,4,7].

The process of ejaculation begins with genital stimulation in combination with erotic impulses from brain [2,4,7]. Ejaculatory latency time (ELT) is probably a biological variable, which is genetically determined and may differ between populations and cultures, ranging from extremely rapid through average to slow or retarded ejaculation [2,4,7].

Ejaculation disorders are uncommon but important causes of infertility. Several heterogeneous dysfunctions belong to this group and may be of either psychogenic or organic origin [2,7]. The most common form of sexual dysfunction in young men is premature ejaculation. Other forms of orgasm and ejaculatory disorders are uncommon during the adolescent years [4,5].

This first case of anejaculation in an adolescent with emotional discomfort. We did not find other report in the PubMed biomedical literature citations.

Case report.
A sixteen year-old Caucasian male presented to the Adolescent Outpatient Clinic complaining of an inability to consciously ejaculate after 40-45 minutes of masturbation. His sexual potency was normal but no nocturnal emission was reported. Past medical history was not significant. He denied alcohol and marijuana use.

On examination: weight = 67 kg, stature = 172 cm, and blood pressure =115/75 mmHg. Physical examination showed normal head and neck, chest and abdomen. No rash, pallor or dyspigmentation. Neurologic examination revealed normal sensory and motor systems and intact reflexes. Pubic hair was at Tanner's stage 5, and testicular volume = 20 ml (Prader's orchidometer). The sensitivity of his glans penis was normal. Digital rectal examination and transrectal ultrasound to define prostate and seminal vesicles were normal.

Laboratory evaluations showed normal hemogram, renal and hepatic functions, serum electrolytes and urinalysis. The serum levels of LH, FSH, testosterone and prolactin were within the normal range (LH = 1.8 mUI/l; FSH = 3.1 mUI/l; testosterone = 541 ng/dl; prolactin = 6.6 ng/ml).

Vibratory stimulation was unsuccessful to obtain semen. The success rate of this procedure usually is 85%, depending on the reason for the ejaculatory failure. The absence of retrograde ejaculation was confirmed by urine examination after vibratory stimulation and masturbation. Pshychosocial evaluation was consistent with feeling of anxiety related to

the inability to ejaculate, reduced erotic sensation of genital stimulation and low self-esteem.

A diagnosis of psychogenic or idiopathic etiology of anejaculation or inhibited ejaculation was made. Consequently, he was counselled to reduce anxiety and to increase self-confidence discussing openly the sexual functions with a psychotherapist. During the follow-up he gradually improved in sexual function and after 3 months he started to have spontaneous normal ejaculations with a referred ELT, during masturbation of 15 minutes. The mean ELT value is 18 minutes during intercourse and 15 during masturbation [13].

Results and theur discussion. Male sexual dysfunctions can be divided into two main categories: endocrine-related sexual dysfunctions and ejaculatory disorders [14].

Male hypogonadism can result from primary (testes) or secondary (pituitary and/or hypothalamus) dysfunction. Testosterone deficiency can have multiple presentations depending on the age of onset. Hypogonadism in men may decrease sexual interest, quality of erections and quality of life [3].

Ejaculatory disorders can be subdivided into premature ejaculation (PE), delayed ejaculation (DE), retrograde ejaculation (RE) and anejaculation (AE)/anorgasmia [14].

DE is defined by the American Psychiatric Association (APA) as: 'the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation, which causes personal distress [1].

A review by Simons and Carey over 10 years suggests that DE or orgasmic disorders occur in 8% of community [12]. Laumann and Cow reported the same results in a large epidemiological analysis of 1246 American men aged 18 and 59 years [8].

DE may be lifelong or acquired, global (when it occurs in all sexual situations) or situational (when it occurs just in certain situations). Etiologically it may be: 1. psychological such as those associated with cultural or religious beliefs, fear of inducing pregnancy, emotional distress or 2. Organic, such as those associated with surgical interventions, medical illness (diabetes, spinal cord injury, multiple sclerosis, retroperitoneal llymph node dissection, trauma or retroperitoneal surgery) or 3. Pharmacological use of antidepressants, antihypertensive, antipsychotics drugs [2,4,6,7,15].

RE or dry ejaculation is the absence of anterograde ejaculation because semen passes backwards through the bladder neck into the bladder. Patients experience a normal or decreased orgasmic sensation and contraction of the ischeo- and bulbo-cavernosus muscles at the basis of the penis [2,4,7]. RE may be secondary to bladder neck incompetence, urethral obstruction, neurogenic illnesses or drugs assumption.

AE is the complete absence of anterograde or retrograde ejaculation. It is caused by failure of emission of semen from prostate and seminal ducts into the urethra. Anejaculation is usually associated with a normal orgasmic sensation and is always connected with central or peripheral nervous system dysfunction or influence of drugs. However, if there is no organic cause, then it is considered idiopatic or psychogenic [2,4,7,14].

Men with sexual dysfunction should be evaluated with detailed medical and sexual history, physical examination and appropriate investigations.

In our patient a diagnosis of psychogenic or idiopathic etiology of anejaculation or inhibited ejaculation was made. The following criteria were used for the diagnosis: inability to consciously ejaculate after masturbation, the absence of retrograde ejaculation, absence of infections /inflammation of the prostate, no personal history of drug consumption or surgical procedures and absence of identifiable endocrine or organic diseases.

A high level of anxiety was present in our patient and probably was caused by excessive control of sexual performance. Counselling was successful in reducing anxiety and to increasing self-confidence and was followed by gradual improvement of sexual function and normal ejaculations was attained during masturbation within 3 months and maintained during one year follow-up.Therefore, an early diagnosis and intervention in adolescent age seems to have a better prognosis compared to secondary lack of ejaculation, which is acquired in later years of life [10].

In conclusion, clinicians following adolescents should be able to handle a variety of tasks. Teenagers generally ask only for limited counseling (e.g. sexually transmitted diseases, contraception).To counsel adolescents about sex, the physician must be knowledgeable about the developmental psychodynamics of adolescent sexuality, with its biologic, psychosocial, and moral implications. Sexual education and information are also important to overcome any inhibition due to a lack of knowledge or misinformation [9,11]. Causes of sexual dysfunction may be due to a variety of medical and non-medical disorders such as: diseases, medications, surgical procedures, cultural and religious beliefs, concurrent psychopathology [2,4,6,7,15]. Although ejaculation disorders are uncommon, more research is needed in the adolescent population for a better understanding of male orgasmic disorders.

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SUMMARY

A RARE CASE OF ORGASMIC DISORDER: PSYCHOGENIC ANEJACULATION IN AN ADOLESCENT

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A sixteen year-old Caucasian male presented with inability to ejaculate after 40-45 minutes of masturbation. Physical and neurologic examinations were normal. Genital and rectal examination and transrectal ultrasound showed normal testicles, penis, prostate and seminal vescicles. Gonadotropins, testosterone and prolactin levels were normal. Vibratory stimulation was unsuccessful to obtain semen. The absence of retrograde ejaculation was confirmed by urine examination after vibratory stimulation and masturbation. Pshychosocial evaluation was consistent with feeling of severe anxiety related to inability to ejaculate. A diagnosis of psychogenic of anejaculation was given and consequently he was counselled to reduce anxiety. During the follow-up gradual improvement of sexual function and spontaneous normal ejaculations were achieved.

Keywords: adolescence,anejaculation,sexual dysfunction.

РЕЗЮМЕ

РЕДКИЙ СЛУЧАЙ ОРГАЗМИЧЕСКОГО НАРУШЕНИЯ: ПСИХОГЕННАЯ АНЭЯКУЛЯЦИЯ У ПОДРОСТКА (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Описан случай 16-летнего юноши кавказского происхождения с неспособностью эякулировать после 40-45 минут мастурбации. Физическое и неврологическое исследование патологических изменений не выявило. Генитальным, ректальным и трансректальным УЗ исследованиями семенники, член, простата и семенные пузырьки оказались в норме, также как уровни гонадотропина, тестостерона и пролактине.

Вибрационная стимуляция оказалась безуспешной для получения семени. Отсутствие ретроградной эякуляции установлено посредством анализа мочи после вибрационной стимуляции и мастурбации. Психосоциальная оценка выявила высокий уровень тревожности в связи с невозможностью эякулировать. Поставлен диагноз психогенной анэякуляции, назначено психотерапевтическое лечение для снижения уровня тревожности. Последующее наблюдение выявило постепенное улучшение сексуальной функции; достигнута спонтанная нормальная эякуляция.

რეზიუმე

ორგაზმის დარღვევის იშვიათი შემთხვევა: ფსიქოგენური ანეაკულაცია მოზარდში

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აღწერილია 16 წლის კავკასიური წარმოშობის ვაჟის შემთხვევა ეაკულაციის უუნარობით 40-45 წუთიანი მასტურბაციის შემდეგ. ფიზიკური და ნევროლოგიური გამოკვლევის მაჩვენებლები - ნორმის ფარგლებში, ასევე სასქესო ორგანოების რექტალური და ტრანსრექტალური ულტრაბგერითი გამოკვლევის შედეგად სათესლეები, ასო, წინამდებარე ჯირკვალი და სათესლე ბუშტუკები - ანომალიის გარეშე. გონადოტროპინის, ტესტოსტერონისა და პროლაქტინის დონე - ნორმული. ვიბრაციული სტიმულაციისას თესლი არ გამოიყო. რეტროგრადული ეაკულაცია გამოირიცხა შარდის ანალიზით ვიბრაციული სტიმულაციისა და მასტურბაციის შემდეგ. ფსიქოსოციალურმა შეფასებამ დაადგინა შფოთვის მაღალი დონე, რაც დაკავშირებული იყო ეაკულაციის უუნარობასთან. დაისვა ფსიქოგენური ანეაკულაციის დიაგნოზი, ჩაუტარდა ფსიქოთერაპია შფოთვის შესამცირებლად. თანდათანობით სექსუალური ფუნქცია გაუმჯობესდა და მიღწეული იქნა სპონტანური ნორმული ეაკულაცია.

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