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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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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 Child and Adolescent Medicine and Physiology
Guest Editors – Zurab Vadachkoria, Karaman Pagava

Номер журнала посвящается вопросам детской и подростковой медицины и физиологии
Приглашенные редакторы – Зураб Вадачкориа, Караман Пагава

ნომერი ეძღვნება ბავშვთა და მოზარდთა მედიცინის და ფიზიოლოგიის საკითხებს
მოწვეული რედაქტორები - ზურაბ ვადაჭკორია 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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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

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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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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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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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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.

ბაკურიანი
BAKURIANI

Bakuriani spring water is recommended
for use in baby food under the certificate
issued by G. Natadze Scientific
& Research Institute
of Sanitation and Hygiene.

ბალანსირებული
ბავშვთა კვება

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НАУКА

ВЛИЯНИЕ ФАКТОРОВ РИСКА У ДЕТЕЙ РАННЕГО ВОЗРАСТА НА ОСОБЕННОСТИ ПОЗНАВАТЕЛЬНОГО РАЗВИТИЯ

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Увеличение числа детей с когнитивными нарушениями – расстройствами речи, внимания, восприятия, памяти и других познавательных функций, влияет на формирование комплекса школьных трудностей, связано с проблемами формирования сложных когнитивных навыков (письмо, чтение и счет) и приводит к нарушениям эмоционально-личностного развития и «срыву» школьной адаптации.

Многие авторы указывают на различные нарушения в раннем возрасте, которые в дальнейшем сказываются на становлении познавательных функций [28]. Доказано, что нарушения в пре- и постнатальном развитии часто приводят к трудностям формирования познавательной деятельности. Педиатры отмечают, что в нарушениях когнитивного развития на первом году жизни велика роль наследственной отягощенности по речевой патологии (70%), стигм дизэмбриогенеза (60%), наличие синдрома возбуждения ЦНС (60%), нарушений сна (50%), повышенного внутричерепного давления (61%), мышечной дистонии (88%), задержки моторного развития (50%) [16,17]. После рождения в качестве причинных и провоцирующих факторов чаще фигурируют последствия черепно-мозговых травм различной тяжести и перенесенных вирусных или бактериальных инфекций, с поражением центральной нервной системы [18,19,6]. Дети с нарушениями здоровья также как группа риска возникновения комплексных нарушений речи, отставания в познавательном развитии и школьной дезадаптации выделяются в отдельную группу. В развитии детей дошкольного и младшего школьного возраста проблема когнитивных нарушений выходит за рамки медицинских, психологических и педагогических вопросов, и приобретает социальное значение) [23,24,30,31,1,3].

По данным диспансеризации 2007 года, проведенной среди всех организованных дошкольников г. Москвы (280 тыс.), в анамнезе 85% детей с когнитивными нарушениями имеются документально подтвержденные указания на неблагоприятное течение беременности и осложненные роды [14].

Факторы риска натального и постнатального развития выявлены у 67-87% детей с недоразвитием речи [32]. При этом отмечается тенденция преобладания речевого недоразвития у мальчиков.

У детей с тяжелыми гипоксически-травматическими поражениями ЦНС, получившими на первом, втором и третьем годах жизни комплексную медицинскую реабилитацию, темпы психо-моторного и речевого развития выравнивались и достоверно не отличались от таковых у здоровых детей [14]. В случаях, когда реабилитационные мероприятия не были проведены развитие детей значительно отставало, а частота нарушений речевого развития от задержки до комбинированных форм дизартрии, с трудом поддающихся логопедической коррекции возрастала более, чем в 7 раз [8,13,16].

Современная модернизированная реанимация новорожденных значительно увеличила выживаемость глубоконедоношенных детей во всем мире и в России в частности. Глубоконедоношенные дети выживают, но индекс заболеваемости и риск нарушений развития, в том числе и когнитивного, у них увеличивается, что в дополнение к экстренной и интенсивной медицинской помощи в момент и после рождения, диктует необходимость длительной комплексной реабилитации с участием врачей разных специализаций – педиатров, неврологов, психиатров, реабилитологов, нутрициологов, специалистов по лечебной физкультуре и т.д., и, в обязательном порядке – педагогов и психологов-дефектологов, поскольку проблема перерастает чисто медицинские рамки [7,11,12,15,27].

Практика показывает, чем раньше и всесторонне проводится реабилитация, тем быстрее и лучше ее результаты [2,5,21,24].

Цель исследования - выявление наиболее распространенных факторов риска, патогенетически значимых в развитии когнитивных нарушений и обоснование комплексного подхода к их коррекции и реабилитации.

Материал и методы. Углубленное обследование дошкольников и младших школьников с когнитивными нарушениями, получавших консультативную и реабилитационную помощь в Центре диагностики развития

ИВФ РАО, включало: анамнез, комплекс патопсихологических психологических и нейрофизиологических обследований.

Анамнез обследуемых изучался методами анкетирования и углубленного интервьюирования родителей с учетом особенностей течения беременности, подробностей родов и развития ребенка в первые годы жизни (моторного, речевого, психологического), а также особенностей социальной адаптации в детских коллективах [26]. При обращении и в динамике наблюдения за ребенком проводилось исследование ЭЭГ [21], особенностей брахиоцефального и церебрального кровотока в режиме реального времени с анализом артериального и венозного звеньев гемоциркуляции [29]. Изучение Эхо-ЭГ проводилось по материалам обследования детей на первом году жизни (нейросонография - НСГ и поликлиническое М-эхо). В комплексе обследования использовались данные нейропсихологического, логопедического и патопсихологического обследований.

Оценка речевого профиля осуществлялась по методике «Диагностика речевых нарушений школьников с использованием нейропсихологических методов»[32].

Для оценки уровня интеллектуального развития использовался тест Д. Векслера в модификации А.Ю. Панасюка (1973).

Сопоставление данных анамнеза, результатов ЭЭГ, Эхо-ЭГ, УЗДГ, транскраниальной допплерографии (ТКДГ) с заключением нейропсихолога, данными патопсихологического и логопедического обследований позволило верифицировать диагноз и составить программу комплексного коррекционного лечения ребенка.

Результаты и их обсуждение. Результаты исследования показали**,** что в структуре интранатальной патологии в анамнезе детей с трудностями дошкольного и школьного обучения в 71% случаев применялись различные способы родовспоможения (стимуляция родовой деятельности, стремительные или затяжные роды, пособие по Кристеллеру, оперативные роды или наложение выходных щипцов или их сочетание). Тугое обвитие пуповиной шеи встречалось в 18,0% случаев, зафиксированное травматическое повреждение ЦНС – у 54,9%, реанимационные мероприятия указаны в документах 57,6% наблюдаемых (рис. 1).

Факторы риска нарушения предречевого и последующего речевого развития диагностировались у детей уже на первом и втором годах жизни (рис. 2).

Среди детей с признаками когнитивной недостаточности позднее начало (после 6-8 месяцев жизни) или полное отсутствие гуления отмечалось в анамнезе 72% детей с когнитивными нарушениями, а позднее начало или отсутствие лепета (после 1 года) – у 80% этих детей. Отсутствие или резкая задержка предречевого развития редко вызывали тревогу. Ранняя диагностика, проведение своевременного обследования позволяли разработать программу комплексной реабилитации, однако, несмотря на констатацию этих фактов и даже вынесение их в лист уточненных диагнозов, коррекционные мероприятия у 96% детей начинались только в возрасте 5 лет и более старшем возрасте.

Полное отсутствие гуления и лепета может быть признаком последующего позднего развития речи или ее задержки.

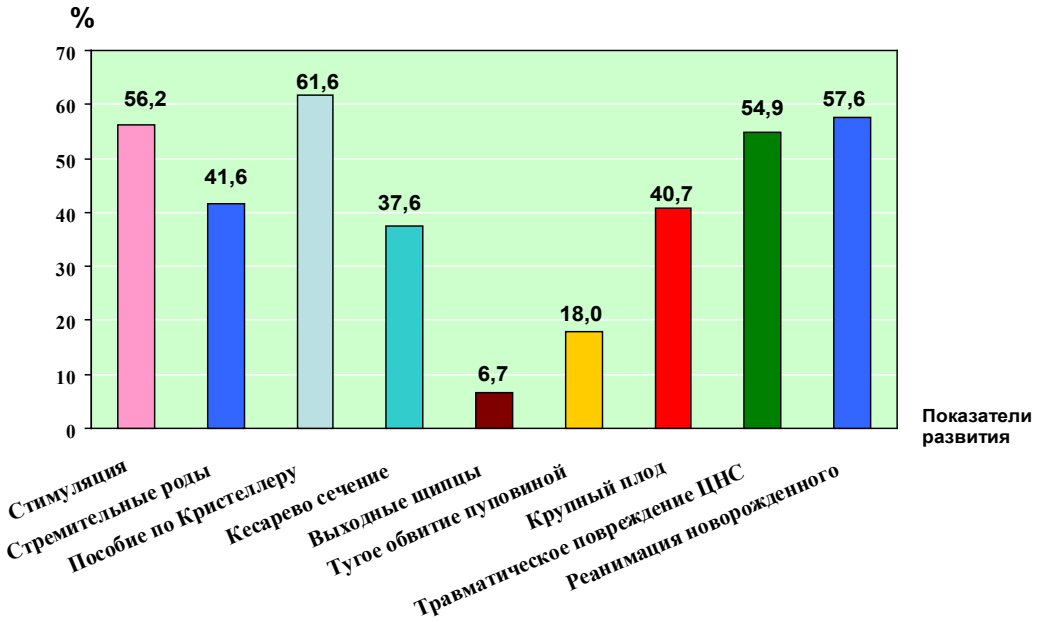

Рис. 1. Структура интранатальной патологии у детей с трудностями дошкольного обучения

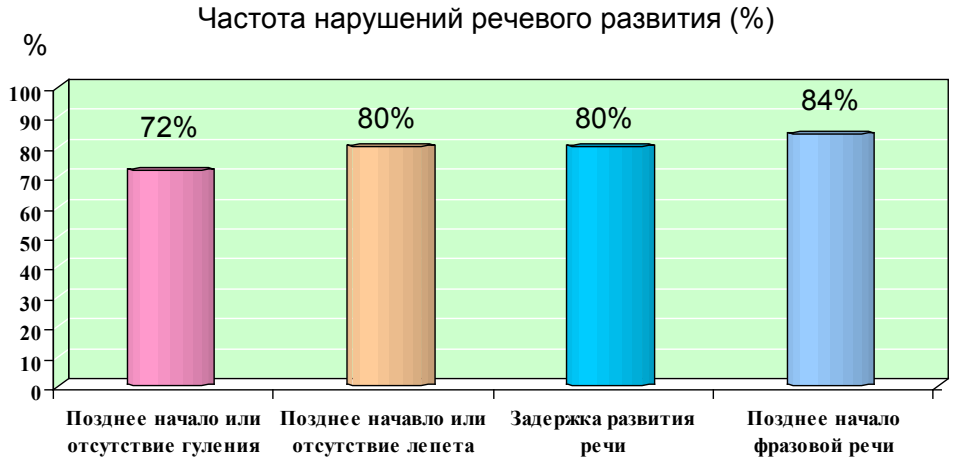

Рис. 2. На первом и втором годах жизни у детей с когнитивными проблемами диагностируется нарушение предречевого и речевого развития

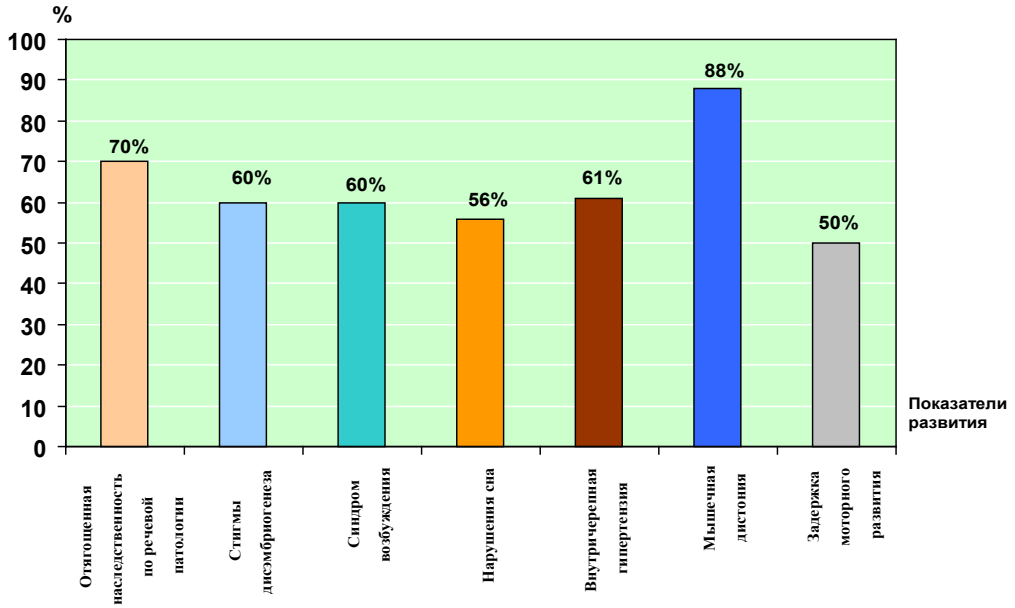

Рис. 3. Факторы риска нарушения когнитивных функций у детей на первом году жизни (%)

На первом году жизни у обследованных детей фиксировались симптомы неврологического развития, стигмы дисэмбриогенеза, нарушение сна, мышечная дистония и задержка моторного развития, что также могло стать обоснованием для своевременной коррекционной работы (рис. 3).

По нашим данным, индивидуальный темп моторного и эмоционального развития тоже свидетельствовал о нарушениях развития когнитивных функций у детей на первом году жизни. Отсутствие эмоциональных реакций на появление родителей и близких – также тревожный синдром, а отсутствие этих признаков после 6-месячного возраста является прямым показанием для серьезного разговора с неврологом (рис. 3).

Суммируя изложенное, можно утверждать, что в анамнезе обследованных и наблюдаемых нами детей с когнитивными проблемами в старшем дошкольном и младшем школьном возрасте в 93% случаев выявлены особенности развития, связанные с перинатальной патологией. Среди них наиболее часто встречаются задержка и нарушение речевого развития, синдром дефицита внимания с гиперактивностью или без нее, протестные реакции и даже агрессивность в поведении. На этом фоне зачастую и формировались нарушения коммуникативных навыков, препятствующих освоению школьной программы и социализации детей. Поверхностный подход нередко приводил к гипердиагностике нарушений и переводу учащихся в разряд «необучаемых» или в коррекционные школы.

Рассмотрим конкретные случаи.
Случай 1. Феликс М. 5 лет, 10 мес. Родители обратились по поводу повышенной возбудимости, неусидчивости, ярких протестных реакций на любые замечания, агрессивности, назойливости поведения в общении со старшими, провокации конфликтов с драками, плохого развития речи, множества аграмматизмов, тиков.

Предварительное тестирование на медико – психолого - педагогической комиссии, анамнез: синдром дефицита внимания с гиперактивностью, рекомендовано обучение в коррекционной школе 8 типа (с задержкой психического и речевого развития).

Родился в семье педагогов, матери 35 лет, отцу – 44 года. На данный момент семья в разводе. Проживают с родителями матери.

Анамнез. Ребенок от 5 беременности, вторых родов. Беременность протекала с токсикозом 1 половины на фоне сниженного артериального давления; в 17 недель отмечена частичная отслойка плаценты. Роды на 39 неделе, самопроизвольные, стремительные – за 3 часа. Применялось пособие по Кристеллеру. Вес при рождении 3700 г, длина 52 см., Апгар – 8/9 баллов. Закричал сразу, громко, к груди приложили в родовом зале. Эксклюзивное грудное вскармливание до 6 месяцев. Смешанное - до 1 года 1 мес.

Моторное развитие: голову держал с 1 мес. (!), переворачивался с 4,5 мес., сидел с 6 мес., ползал с 7 мес., вставал с 8 мес., пошел в 10 мес. Гуление редкое, не активное, тихое, лепет – с 8 мес., в 1 год – 2-3 слова, затем перестал говорить. Расширение словаря – после 2 лет, простая фраза – с 2,5 лет. Фразовая речь – с 3,5 лет.

Детский сад посещает с 3 лет, адаптировался легко. В 4 года, на фоне бурного конфликта в семье (развод родителей) начались проблемы поведения, остановилось развитие речи.

При первом обращении проведено комплексное обследование, показавшее, что степень зрелости электрической активности (ЭА) коры по ЭЭГ соответствует возрасту. Определяются билатерально-синхронные изменения ЭА глубинного генеза, генерализованные функциональные изменения ЭА стволового генеза, нарастающие на фоне ритмической фотостимуляции (РФС) и гипервентиляции (ГВ) и по окончанию ГВ. Эхо-ЭГ: смещения срединных структур не выявлено. Отмечена вентрикуломегалия боковых желудочков – до 7 мм. Значительное количество дополнительных эхосигналов с обеих сторон Эхо-пульсация усилена до 40-46%. Ультразвуковая допплерография (УЗДГ) Признаки ангиодистонии в брахиоцефальных артериях с ускоренным кровотоком в левой внутренней сонной и позвоночных артериях. Признаки венозной дисгемии в левом полушарии головного мозга (нарушена венозная гемоциркуляция). Транскраниальная допплерография (ТКДГ): Церебральная ангиодистония с ускоренным кровотоком в артериях левого каротидного бассейна, правой передней мозговой, обеих позвоночных и основной артериях. Вазомоторная лабильность. Признаки нарушения церебральной венозной гемоциркуляции с ускоренным кровотоком в прямом синусе. Магнитно-резонансная томография (МРТ) - сканирование выявило множественные участки уплотнений в периваскулярных и перивентрикулярных пространствах.

Объективно, по результатам наблюдения в процессе обследования:
Контактность: мальчик контактный, активный, доброжелательный, поведение адекватное, «границы» не нарушает, мотивация к обследованию формируется. Ребенок улыбчивый, но контакт «глаза в глаза» кратковременный.

Латеральный профиль: рисует, ест и все навыки самообслуживания осуществляет правой рукой.

Память: стихи учит без выраженных затруднений или особенностей, но быстро забывает (вспомнить стихотворение не смог).

Запоминание и воспроизведение зрительных стимулов (10 картинок) происходит только после многократного повторения и вербализации. Отсроченное воспроизведение спустя 15-20 минут

Внимание и организация деятельности: внимание неустойчивое и требуется постоянный внешний контроль взрослого и обратная связь (повтори, что надо сделать). Вербальную инструкцию в полном объеме не удерживает и может повторить со 2-го – 3-го раза. Импульсивность – присутствует (не дослушивает до конца, «встревает», перебивает говорящего).

Артикуляционная моторика: несколько повышенный уровень саливации. Выраженная судорога языка по направлению от корня к кончику. Тремор и девиация языка – отсутствуют. Уздечка без особенностей. Язык подвижный, хорошо переключается с позы на позу. Плавное переключение со звука на звук при пропевании звуковых рядов из гласных звуков не затруднено (А-У-О, У-А-Э и т.д.).

Речевое развитие:
Звукопроизношение: нарушено, боковое (правостороннее) произнесение свистящих, шипящих и аффрикат.

Особенности произнесения свистящих звуков: звук «С» - употребляется не чисто, слышится присвист; звук «З» - изолированно в словах произносится правильно, в

речи - оглушается. Шипящие звуки («Ш-Ж») и аффрикаты («Ч-Щ») заменяются и не используются в речи.

Сонорные звук («Л-ЛЬ и Р-РЬ) заменяются и не употребляются в произвольной речи.

Фонематический слух: не сформирован как на базовых (опорных) звуках, так и на нарушенной группе звуков. При внесении внешнего контроля и после многократного повторения опорных звуков, возможно добиться правильного переключения со звука на звук.

Повторение ритмического рисунка (конфликтная проба) при адекватной возрасту скорости подачи ритма и наличии времени для анализа слышимой информации – верное воспроизведение и удержание инструкции, не затруднено.

Словарный запас и фразовая речь: словарный запас достаточный, хотя в речи встречаются семантические замены (олень → козел, осел; дракон → динозавр, Горыныч). Фраза без выраженных аграмматизмов, развернутая, но не полная. Присутствуют пропуски глаголов и служебных частей речи.

Словообразование возможно, но не автоматизировано, допускаются ошибки в употреблении суффиксов уменьшительно-ласкательной формы имен существительных. Словарь антонимов практически освоен. Образование названий детенышей животных от родителей не сформировано (кот – котявы, коза – козленки, овца – овчишка).

В эмоционально окрашенной ситуации в речи появляются запинки.

Интеллектуальное развитие: по Векслеру соответствует возрасту. Без особенностей. Построение простого умозаключения возможно по наводящим вопросам.

Эмоционально-волевая сфера: эмоционально лабилен. Ярко проявляет неудовольствие и гнев, огорчение и переживания.

Работоспособность и утомление: соответствуют возрасту. Признаки выраженного утомления наступили спустя 40 мин, при этом мальчик мог еще выполнять задания.

Пространственные и моторно-графические навыки: соответствуют возрасту. Пространственные задачи решает. Требуется время для анализа деталей изображения. Сложнокоординированные (графические) функции без особенностей (в рисунках линии четкие, тремор и наличие дополнительных штрихов отсутствуют).

Комплексное заключение специалистов: Последствия перинатального поражения ЦНС в форме дисциркуляторной энцефалопатии, гемоликворная гипертензия, дистония языка (дизартрия), общее недоразвитие речи (ОНР) III уровня, нарушение формирования школьных навыков (дислексия, дисграфия, дискалькулия) запинки в речи дыхательного характера, тики, невротические реакции.

На основании сопоставления анамнеза, клинического обследования, данных ЭЭГ, МРТ и УЗДГ определены составляющие комплексной работы с ребенком: медикаментозная терапия включала сосудистую коррекцию, антиоксидантные, метаболические, ноотропные, легкие седативные и витаминные препараты в сочетании с массажем на воротниковую зону. Терапия проводилась курсами параллельно с логопедической работой и психологической коррекцией.

Занятия с дефектологом были направлены на исправление звукопроизношения и развитие связной речи, понятийного мышления, произвольного внимания.

Эффективность комплексной коррекционной работы: значительно улучшились нейрофизиологические показатели, нормализовалась гемоликворная ситуация и сняты явления хронической гипоксии мозга, пропали конфликтность, агрессивность и значительно улучшилось состояние когнитивных функций.

За время работы с дефектологом удалось достичь определенных положительных результатов, как в компенсации нарушений речи, так и управляющих функций.

В настоящее время на фоне продолжающейся медикаментозной терапии по сей день сохраняется недостаточный уровень сформированности ряда процессов: управляющих функций (произвольная организация деятельности и внимания), структурных компонентов речи (звукопроизношение, фонематическое восприятие и связанная речь – ОНР III уровень, стертая дизартрия) и эмоционально-волевой сферы. По окончании комплексной реабилитации планируется обучение в общеобразовательной школе.

Рекомендации:
1. Продолжить наблюдение и терапию невролога.
2. Продолжить обязательные занятия с дефектологом, направленные на умение правильно произносить звуки речи, развитие связной речи и расширение словарного запаса, понятийного мышления, произвольной организации деятельности, произвольного внимания и комплексную подготовку к школе.
3. Обязательные занятия с психологом, направленные на развитие эмоционально-волевой сферы и обогащение сенсорного опыта.
4. Занятия спортом или танцами.

Случай 2. Илья Ц. 7 лет 6 мес. находится под наблюдением в течение 2 лет 5 мес. (с 5 лет 4 мес.).

При первом обращении: жалобы на отсутствие вербального общения, задержку психического развития, невозможность общаться с ребенком, непонимание обращенной речи, инструкций родителей, страхи, тревожности, «все нюхает», очень медленное привыкание к новой обстановке, новым людям.

Предварительное экспресс-обследование в медико – психолого - педагогической комиссии, диагноз: ранний детский аутизм, при отсутствии возможности вербального общения. Рекомендовано оформление инвалидности (синдром раннего детского аутизма - РДА).

Анамнез: Ребенок молодых здоровых родителей от второй беременности, двух родов. Беременность протекала без токсикоза 1 половины беременности. Во 2 половине беременности поздний гестоз: отеки, повышение А/Д до 150/100, многоводие, стареющая плацента, прибавка веса у матери за беременность – 16 кг.

Роды на 39 неделе самопроизвольные, за 11 часов. Применялось пособие по Кристеллеру. Родился весом 3240, длиной 49 см, Апгар 6/8 баллов. Не кричал. После отсасывания слизи крик писклявый, очень тихий. К груди приложили спустя 2 часа, сосал неактивно. Ранее развитие с задержкой: голову держал с 3 мес., переворачивался – с 4 мес., сидел с 7 мес., ползал мало к 8 мес., вставал с 9-10 мес., пошел в 1 год 2 мес. Гуление вялое, лепет – очень редко тихо к 1 году. К 2 годам множественный кариес передних зубов. В 1 год 4 мес. – грыжесечение, в 2 года 10 мес. - аденэктомия. Обе операции под общим наркозом. До момента осмотра – без признаков вербального общения.

С 1,5 лет обращались к неврологу по поводу задержки речевого и психического развития. Проведено несколько курсов ноотропной терапии без предварительного обследования. Коррекция эффекта не дала.

При первом обращении проведено дополнительное обследование: ЭЭГ: уровень развития ЭА коры соответствует возрастной норме. Данные ЭЭГ указывают на выраженные изменения ЭА по общемозговому типу. Выраженные изменения ЭА в глубинных отделах лобно-височных областей обоих полушарий, выраженные функциональные генерализованные изменения ЭА стволового генеза. Эхо-ЭГ: смещения срединных структур не выявлено. Признаки расширения боковых и 3 желудочка (8 мм), большое количество дополнительных эхо-сигналов. Пульсация – до 49%. Признаки внутричерепной гипертензии. УЗДГ: признаки ангиодистонии в брахиоцефальных артериях с ускоренным кровотоком в левой внутренней сонной и позвоночных артериях, признаки венозной дисгемии в области позвоночных венозных сплетений, сброс венозного объема посредством затылочных эмиссариев (нарушена венозная гемоциркуляция). ТКДГ: признаки церебральной ангиодистонии с ускоренным кровотоком в правой средней, позвоночных, передней мозговой и основной артериях

Латеральный профиль: ест и рисует правой рукой, а при выполнении «ненаученных» действий (разложение картинок, нанизывание бус, составление картинок из кубиков) активнее работает левой рукой.

Обследование дефектолога выявило ОНР 1 уровня (полное отсутствие речи, «писк», крик и плач - средства взаимодействия с миром). Очень высокий тембр голоса. Стереотипии. Не рисует, карандаш держит в кулаке.

Психологический статус: средний ребенок в семье. Есть старший брат (учится в первом классе) и младшая сестра (около года). Развитие их соответствует норме. Инфантильный, с аутистическими проявлениями, погруженный в себя, контакт глаза в глаза устанавливает на несколько секунд, взгляд направлен в пол. Интереса к играм и игрушкам на первых порах не проявлял. По аналогии работал после многократных повторений. Навыки автоматизировал очень долго.

Интеллектуальное развитие при первом обращении трудно было оценить ввиду трудностей контакта.

Физическое и моторное развитие: Маленького роста Отставание биологического от паспортного возраста на 2-2,5 года. Моторное развитие на 2 года. Мяч не ловит и не бросает, прыгает на двух ногах, но неловко. На одной ноге прыгать не мог. Катание на велосипеде и самокате не освоены.

Социальные компетенции: самостоятельно одевается с трудом, путает правую и левую стороны в обуви, молнию и пуговицы застегнуть не может. Ест плохо и маме приходится постоянно его докармливать. Посещал д/с компенсирующего вида.

Комплексное заключение специалистов: последствия постгипоксического перинатального поражения ЦНС в форме афазии развития (сенсорная и моторная алалия), ОНР 1 уровня (отсутствие вербальных средств общения), гемоликворная гипертензия, дисциркуляторная энцефалопатия, вторичная задержка психического развития.

Коррекционная работа:
В комплексе ведения ребенка проводится медикаментозная терапия по купированию гемоликворной дистензии, коррекции брахиоцефального и церебрального кровотока, метаболическая коррекция, витаминотерапия, антиоксидантная и седативная терапия, массаж на

воротниковую область – все курсами под контролем ЭЭГ, Эхо-ЭГ, УЗДГ и ТКДГ в динамике лечения.

Работа с родителями: родители нуждались в реабилитации и поддержке психолога, т.к. не верили в то, что мальчика удастся реабилитировать. (Многолетние обращения к специалистам не давали желаемых результатов).

Включение родителей в совместную работу со специалистами (дефектолог и психолог).

Коррекционная работа с ребенком вначале была направлена на разрушение стереотипий, побуждение к элементарным познавательным действиям на основе наглядно-образного действенного мышления и включало:
- формирование мотивации и потребности говорения у мальчика;
- формирование у ребенка опорных гласных и согласных звуков, простых слов и простой фразы из 1-2-х слов;
- развитие мелкой моторики и элементарных творческих навыков (пластилин, аппликация, пальчиковые краски), песочная терапия;
- двигательная и сенсомоторная коррекция (иппотерапия, дельфины).

Результаты коррекционной работы и рекомендации: по мере развития речи и накоплении словарного запаса, расширяются познавательные возможности мальчика. Ребенок выучил алфавит и начал читать, используя технику глобального чтения, начал считать и знакомится с составом числа, расширились представления ребенка о событиях и явлениях окружающего мира. Посещает занятия по арттерапии.
Сильной стороной в психофизиологическом профиле ребенка является хорошая зрительная память.

Эффективность 1 этапа нейрореабилитационной терапии. На фоне комплексной коррекционной работы и спустя 2,5 года с момента начала (в настоящее время) мальчик проявляет хорошую речевую активность, общается с окружающими, адекватно реагирует на обращенную речь, отвечает по существу, освоил чтение отдельных слов и простых предложений, счет в пределах первого десятка и способы уравнивания в пределах 5, нахождение фигур в шуме и по эталону, штриховка и рисование по образцу.

Полностью освоены навыки самообслуживания. Мальчик хорошо катается на самокате и учится плавать.
Сохраняются трудности звукопроизношения отдельных звуков и построения развернутого высказывания, понимания сложных логико-грамматических конструкций, решения сложных пространственных задач, моторного развития и социальной адаптации.

Рекомендации:
1. Продолжить медикаментозной терапии, наблюдение и лечение неврологом.
2. Продолжить занятия с дефектологом, психологом и нейропсихологом, развивать сложноорганизованные двигательные навыки ребенка. Совершенствовать социально-личностную компетентность.
3. С сентября - начало систематического обучения по программе массовой школы по индивидуальному плану освоения основных базовых функций (письмо, счет и чтение).

Случай 3. Лиза А. находится под наблюдением невролога и сопровождается психологом-дефектологом в течение 4 лет 6 мес. (с 7 лет 6 мес.). В настоящее время, девочке 11 лет и 2 мес.

При первом обращении: жалобы на отставание в развитии от сестры-близнеца, медленно осваивает навыки, требующиеся для учебы (чтение, письмо, счет), проблемы со зрением (астигматизм, косоглазие), быструю утомляемость, истощаемость, проблемы удержания внимания в течение продолжительного времени, логорея. В школе рекомендуют индивидуальное обучение. При этом у девочки хорошая слухо-речевая память, старательность, стремление преодоления трудностей.

Анамнез: беременность посредством ЭКО (4 попытка). Протекала на фоне токсикоза 1 половины беременности, пиелонефрита матери, почечной колики, гормональной терапии (дексаметазон – в течение всей беременности), отмечено повышение билирубина – болезнь Жильбера. В третьем триместре повышался оксипрогестерон, наблюдались аллергические реакции на полиглюкин и баралгин – бронхоспазм. Выраженный отечный синдром, асцит. При пункции удалено около 3 литров жидкости. Во время беременности у матери отмечены обострения herpes labialis.

Роды после отмены гормональной терапии на 36 неделе, кесарево сечение. Девочка вторая из двойни. Вес при рождении 2250 г., длина 48 см. Апгар 7/8 баллов. Плацента – оболочки окрашены зеленым. 3-кратное обвитие пуповиной. Легкая асфиксия при рождении, умеренно выраженный синдром угнетения. Морфофункциональная незрелость, мышечная дистония (гипотонус в проксимальных, гипертонус – в дистальных отделах).

На первом году жизни: голову держала к 3-4 мес., переворачивалась после 6 мес., сидела с 8 мес., не ползала, вставала после 9 мес., пошла в 1 год 3 мес. Гуление и лепет в соответствии с возрастом. К 1 году - до 5 слов. Расширение словаря к 1,5 годам. Первые фразы к 2 годам, фразовая речь к 2,5 – 3 годам.

Первое обращение к неврологу – в 3 года. Отмечены повышение тонуса мышц, нарушение глоточных рефлексов, повышенное в/ч давление. Терапия только гомеопатическая. В листе уточненных диагнозов: перинатальная энцефалопатия (ПЭП), задержка психического и речевого развития, правосторонний гемисиндром. Терапии не получала. К 4 годам выявлены минимальные мозговые дисфункции (ММД), синдром гипервозбудимости с дефицитом внимания. Наблюдается у офтальмолога: косоглазие сходящееся, альтернирующее, непостоянное, ангиопатия сетчатки.

Результаты углубленного обследования при первом обращении: ЭЭГ - уровень развития ЭА коры не соответствует возрастной норме. Данные ЭЭГ указывают на функциональные генерализованные изменения ЭА стволового генеза, выраженные функциональные изменения ЭА верхнестволового (фронто-таламического) генеза. На Эхо-ЭГ признаков нарушения ликворной дистензии не выявлено. Позиционное влияние на характер кровотока в позвоночных артериях. Признаки венозной дисгемии в левом полушарии головного мозга (нарушена венозная гемоциркуляция). ТКДГ: признаки церебральной ангиодистонии с ускоренным кровотоком в позвоночных, основной артериях, вазомоторная лабильность. Признаки нарушения церебральной венозной гемоциркуляции с ускоренным кровотоком в глубоких венах мозга, прямом синусе, с выраженной дисциркуляцией.

Латеральный профиль: компенсаторная левша.
Психофизиологическая диагностика показала комплексную несформированность ряда высших психических функций и социально-коммуникативных навыков:
- произвольная организация деятельности и произвольное внимание, импульсивность; логорея;
- простейших счетных операций и представлений о составе числа;
- пространственного восприятия (ориентировка «право»-«лево») и зрительно-моторных координаций (трудности штриховки, проведения прямой и волнистой линии, копирование);
- мелкой моторики;
- зрительной памяти;

У ребенка низкий уровень мотивации и высокая утомляемость, низкая неустойчивая работоспособность. Девочка не читала и не писала.

Наиболее сформированной функцией была речь, но она не являлась регулятором поведения и деятельности. Отсутствовало нарушение звукопроизношения и фонематического слуха. Фраза развернутая, без аграмматизмов, словарь – достаточный, но с отдельными периодическими трудностями актуализации понятий.

Комплексное заключение: Последствия перинатального гипоксически- травматического поражения ЦНС в форме нейроциркуляторной энцефалопатии, задержки психо-моторного развития, синдром мышечной дистонии, правосторонний гемисиндром (остаточные явления), компенсаторное левшество, нарушение формирования школьных навыков – дисграфия, дислексия, дискалькулия.

Коррекционная работа:
В комплексе с медикаментозной терапией: сосудистая коррекция мозгового кровотока, особенно в части венозной дисгемии, антиоксиданты, метаболиты мозга и церебропротекторы, ноотропные препараты. Следует отметить, что попытка интенсифицировать ноотропную терапию осложнилась появлением на ЭЭГ пароксизмальных изменений ЭА в глубинных отделах центрально-нижнелобной области левого полушария и негрубых вторичных локальных изменений в теменной области правого полушария, при сохранении признаков незрелости коры, что еще раз подчеркивает необходимость тщательного контроля при ноотропной терапии, широко используемой в настоящее время при коррекции школьных трудностей.

Терапию в дальнейшем проводили, в основном, по типу коррекции метаболических нарушений. Лишь спустя 6 месяцев вернулись к мягкому ноотропному воздействию,

Незрелость электрогенеза коры головного мозга была сглажена лишь к 10 годам. Именно в эти сроки была отмечена прогрессивная положительная динамика в формировании школьных навыков.

Коррекционная программа на первом этапе включала согласованную работу психолога-дефектолога и учителя по формированию элементарных графических умений, звукобуквенного анализа, мелкой моторики (штриховка, шнуровка, бусы, природные материалы), простейших пространственных представлений на основе предметно-манипуляторных действий.

Одновременно с использованием разнообразных приемов и наглядных пособий формировались представления о числе, составе числа и способах образования чисел.

В течение трех лет обучения счет в уме в пределах первого десятка усваивался очень плохо, но считала на калькуляторе. На третьем году обучения была предпринята попытка заучивания арифметических действий. Именно это и послужило толчком к преодолению трудностей и переносу счета во внутренний план. На сегодняшний день девочка считает в уме в пределах двух десятков и учит таблицу умножения.

К концу первого года обучения программа первого класса по основным предметам письму и чтению была освоена.

Важно отметить, что на протяжении всех лет обучения индивидуально подбирались методические пособия и сохранялась сложившаяся традиция обсуждения результатов и коррекция методик и приемов обучения со специалистами, родителями, педагогом.

Особое место занимала двигательная коррекция. Девочка освоила горные лыжи, что дало качественный скачок.

Этапная эффективность: комплексная коррекционная работа позволила значительно улучшить нейрофизиологические показатели, нормализовать гемоликворную ситуацию и снять явления хронической гипоксии мозга, достичь нормативной степени зрелости коры головного мозга и значительно улучшить состояние когнитивных функций.

После второго года обучения был сделан тест Векслера. Результаты выявили, что показатели вербального, невербального и общего интеллекта составляют 100-102 усл. ед. В настоящее время Лиза А. дублирует обучение в III классе частной школы по программе массовой школы в индивидуальном темпе.

Рекомендации:
1. Продолжение медикаментозного лечения и наблюдения неврологом.
2. Сохранение принципа индивидуализации обучения и прохождение программы по индивидуальному плану.
3. Занятия с психологом – дефектологом, Арт-терапия, двигательная – коррекция.

Заключение.
Рассмотренные примеры позволяют утверждать, что при определении диагноза, а зачастую и определении судьбы, детей с нарушением познавательного развития и трудностями обучения необходим системный подход, учитывающий все особенности темпа индивидуального развития (медицинский, психологический, нейропсихологический, психофизиологический и социальный). Такой подход позволяет выявить причинно-значимые факторы, негативно влияющие на развитие, поведение и обучение, разработать эффективные индивидуальные программы медицинской реабилитации и педагогической коррекции. В процессе комплексной помощи необходимо сопровождение специалистов, внимательное наблюдение за изменением состояния и поведением, промежуточная диагностика и внесение необходимых изменений в рекомендации по коррекции.

Отсутствие комплексного подхода и учета индивидуальности и уникальности каждого ребенка, стандартные подходы в диагностике и коррекции не позволяют преодолеть отставания в развитии, минимизировать риски дезадаптации и обучаться в массовой школе, что в подобных случаях неизбежно приводит к умственной отсталости и инвалидности.

Приведенные случаи еще раз подтверждают высокий компенсаторный потенциал своевременных, систематических научно-обоснованных, комплексных воздействий, снижающих влияние факторов риска раннего развития, свидетельствующих о пластичности развития мозга детей на разных этапах онтогенеза.

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SUMMARY

INFLUENCE OF RISK-FACTORS IN INFANTS ON THE PECULIARITIES OF COGNITIVE DEVELOPMENT

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The importance of risk-factors during the early development of children on development of cognitive difficulties in preschoolers and school children are reviewed. The effectiveness of comprehensive diagnostic of main reasons of disorders of cognitive development is shown. The importance of complex medical, pedagogical, psycho-physiological and neuropsychological treatment of cognitive disabilities in children is demonstrated as well.

Keywords: children, cognitive development, risk factors, medical and psychological treatment

РЕЗЮМЕ

ВЛИЯНИЕ ФАКТОРОВ РИСКА У ДЕТЕЙ РАННЕГО ВОЗРАСТА НА ОСОБЕННОСТИ ПОЗНАВАТЕЛЬНОГО РАЗВИТИЯ

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Рассмотрено влияние факторов риска раннего развития на возникновение когнитивных нарушений в

старшем дошкольном и младшем школьном возрасте. Показана эффективность комплексной диагностики ключевых причин нарушений когнитивного развития и необходимость системной медицинской, педагогической, психофизиологической и нейропсихологической коррекции.

რეზიუმე

ადრეული ასაკის ბავშვებში რისკ-ფაქტორების ზეგავლენა შემეცნებით განვითარებაზე

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განხილულია ადრეული განვითარების რისკ-ფაქტორების ზეგავლენა კოგნიტიური დარღვევების გამოვლენაზე უმცროს და უფროს სასკოლო ასაკის ბავშვებში. ნაჩვენებია კოგნიტიური დარღვევების ძირითადი მიზეზების კომპლექსური დიაგნოსტიკის ეფექტურობა და სისტემური სამედიცინო, პედაგოგიური, ფსიქოფიზიოლოგიური, ნეიროფსიქოლოგიური კორექციის მნიშვნელობა.

НЕКОТОРЫЕ ОСОБЕННОСТИ РАЗВИТИЯ И ТЕЧЕНИЯ БРОНХИАЛЬНОЙ АСТМЫ У ДЕТЕЙ В АЗЕРБАЙДЖАНЕ

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В последние десятилетия ВОЗ предприняла целый ряд инициатив в разработке глобальной стратегии по борьбе с бронхиальной астмой у детей. Такая активная позиция ВОЗ исходит из того факта, что бронхиальная астма является нарастающей проблемой современности [5,6].

За исторически короткий отрезок времени эта болезнь вошла в число наиболее часто регистрируемых хронических заболеваний. Распространенность БА возрастает повсеместно, особенно среди детей. Согласно результатам исследований, проведенных во многих странах, показатели распространенности симптомов астмы у детей значительно отличаются. Несмотря на множество исследований по заболеваемости БА в различных странах и популяциях, отсутствие единых стандартов обследования существенно затрудняет сравнение данных о распространенности болезни и факторах, влияющих на рост числа детей с бронхиальной астмой в различных регионах мира [6,7,10,11].

Известно, что генетическая восприимчивость играет значимую роль в развитии атопических заболеваний. Однако трудно предположить, что за столь короткий промежуток времени произошли какие-либо серьезные генетические мутации, которыми можно было бы объяснить такие высокие темпы роста аллергопатологии.

Исходя из вышеизложенного, за последние годы большое количество научных работ посвящено изучению сложных взаимодействий между генетическими факторами и факторами внешней среды, которые в той или иной степени причастны к росту заболеваемости БА [4,9].

Учитывая глобальность проблемы, группой известных ученых в 1989 году предложена программа исследования астмы и аллергии у детей («ISAAC») [8], которая одобрена ВОЗ и в настоящее время широко применяется во всем мире. Программа создана с целью повышения эффективности эпидемиологических исследований по астме и аллергическим заболеваниям, определения эволюции патологии в одном и том же регионе, сравнения показателей в разных регионах, в том числе распространенности, форм и тяжести, независящих от квалификации исследователя, уровня медицинской помощи путем установления стандартизованной методологии и содействия международному сотрудничеству.

Научные данные свидетельствуют, что непосредственное влияние на распространенность бронхиальной астмы оказывают внешнесредовые условия. Среди которых выделяют экологическую ситуацию в регионе, урбанизированность населения, проживание в условиях повышенной влажности, горной и лесистой местности или, наоборот, в районах с сухим континентальным климатом.

Азербайджан довольно подходящая страна для исследования влияния различных климатогеографических факторов на здоровье детей одной популяции, так как на довольно компактной территории республики из 11 существующих на земном шаре типов климата представлены 9. Амплитуда высот суши колеблется от 28 м ниже уровня океана (Ленкорань) до 4466 м абсолютной высоты (вершина Базар-Дюзи). В республике, наряду с крупными промышленными городами Баку и Сумгаит, расположены экологически чистые регионы, где в последние годы создается инфраструктура курортов международного значения.

Учитывая вышеперечисленное и актуальность обсуждаемой проблемы, целью исследования явилось изучить распространенность, особенности развития бронхиальной астмы и роль средовых факторов, способствующих манифестации этой болезни у предрасположенных к ней детей, проживающих в различных климатогеографических регионах Азербайджана.

Материал и методы. Исследование проводилось при содействии Министерства образования (письмо №46-03-2443/16 от 17.06.2003), Министерства здравоохранения (письмо №05/19-2552 от 08.07.2003), Министерства экологии и природных ресурсов Азербайджана (письмо №4/1409-01 от 23.06.2005) и с разрешения Азербайджанского Национального комитета по биоэтике (письмо №01-04/958 от 25.09.2003).

Для осуществления поставленной цели были выбраны четыре различных в климатогеографическом плане региона страны:
I – Апшеронский полуостров расположенный в зоне полупустынь и сухих степей (промышленный Баку и Сумгаит), далее – город-п/п;
II – Кура-Араксинская низменность (исследование проводилось в Али-Байрамлах, Сальянах, Сабирабаде). В климатическом отношении Кура-Араксинская низменность относится к полупустыне и сухим степям, далее – село-п/п;
III – Субтропический регион (Ленкорань, Масаллы, Астара), далее - субтропики;
IV – Районы, расположенные вдоль южных склон Большого Кавказского хребта (Исмаиллы, Гах, Закаталы, Белоканы), далее - горный регион.

Результаты и их обсуждение. В течение 1998-2009 гг. по международной программе «ISAAC» (International Study of Asthma and Allergy in Childhood) проанкетированы 14693 учеников первых и восьмых классов из 350 общеобразовательных школ страны. Распределение по регионам и объем обследуемого контингента представлены в таблице 1.

Первый этап исследования (анализ анкет) показал, что распространенность симптомов бронхиальной астмы (положительные ответы на пятый вопрос анкеты «ISAAC» о наличии «затрудненного хрипящего, свистящего дыхания и свистов в грудной клетке») в I регионе составляет 5,9% (n=4765); во II регионе – 4,8% (n=3010); в III регионе 5,7% (n=3133); в IV – регионе – 2,7% (n=3571). Результаты представлены в таблице 2.

Таблица 1. Количество проанкетированных в четырех регионах детей

Регионы	**Проанкетировано детей**
I. Город (п/п)	4979
II. Село (п/п)	3010
III. Субтропики	3133
IV. Горный	3571
Всего	14693

Таблица 2. Кол-во положительно ответивших на пятый вопрос анкеты «ISAAC»

Регионы	**Кол-во положительно ответивших на 5 вопрос анкеты, (%)**
I. Город (п/п), (n=4979)	5,9
II. Село (п/п), (n=3010)	4,6
III. Субтропики (n=3133)	5,7
IV. Горный (n=3571)	2,7

Таблица 3. Распространенность бронхиальной астмы в регионах Азербайджана

Регионы	Кол-во детей с бронхиальной астмой, (%)
I. Город (п/п),	4,6
II. Село (п/п),	2,5
III. Субтропики	2,8
IV. Горный	1,8

Данные таблицы 2 указывают на неравномерную распространенность симптомов бронхиальной астмы в обследуемых регионах. Причем в I (город) и в III регионах (субтропики) частота симптомов встречалась достоверно чаще, чем в промышленно менее развитом и экологически чистом горном регионе (IV). Выявлена почти одинаковая частота симптомов бронхиальной астмы в I и III регионах. Симптомы бронхиальной астмы во II регионе (село-п/п) были несколько меньше, чем в I и III регионах и почти в 1,5 раз превышают показатели у детей, проживающих в горном регионе (таблица 2).

Для верификации диагноза бронхиальной астмы (второй этап исследования, в рамках международной программы ISAAC) применены аллергологические, клинико-функциональные и лабораторные методы исследования среди детей с симптомами бронхиальной астмы.

Проведенные исследования показали зависимость распространенности бронхиальной астмы у детей от региона проживания (таблица 3).

Бронхиальная астма чаще обнаруживается в условиях промышленного города, реже - у детей, проживающих в субтропиках (2,8%). У школьников, проживающих в регионе Кура-Араксинской низменности, бронхиальная астма была верифицирована в 2,5% случаях. Согласно полученным данным, самый низкий показатель распространенности бронхиальной астмы у детей выявлен в горном регионе Азербайджана (1,8%).

В Азербайджане подобное исследование осуществлено в 1971-1975 гг., проведены массовые обследования распространенности аллергических болезней среди детей, проживающих в различных климатогеографических регионах республики, включающих Баку, Мингечаур, Казах, Губа, Геокчай, Шуша, Ленкорань, Северо-Восточный банк [1-3]. Обследовано 100994 детей. Сравнение результатов данного исследования с позиций оценки динамики распространенности аллергических заболеваний, в том числе бронхиальной астмы в Азербайджане, с результатами исследования 1998-2009 гг. выявило, что исследование проведено по единой методике в два этапа: первый этап включал опрос родителей по специальной анкете, второй – детальное обследование выявленных больных. Распространенность бронхиальной астмы в Баку по данным 1975 г. составила 2,1%, в Мингечауре - 0,22%, в Ленкоране - 0,8%, в Геокчайском районе - 0,3%, в Кубинском, Казахском, Шушинском районах и Северо-восточном банке астмой болели соответственно 0,17%, 0,7%, 0,09% и 0,28% процентов обследованных детей. Анализ данных указанных двух периодов выявил рост числа детей, страдающих БА, в 2 и более раз.

В соответствии с результатами экологического мониторинга указанных регионов республики, загрязнение окружающей среды некоторыми химическими компонентами зарегистрировано только в промышленном Сумгаите. Согласно информационному письму министра Экологии и природных ресурсов Азербайджана от 23.06.2005 №4/1409-01, концентрация оксида азота в воздухе Сумгаита в 1.5-1,6 превышает допустимую санитарную норму. Вместе с тем, зафиксировано загрязнение почвы на территориях промышленных предприятий города ионами тяжелых металлов: показатели содержания никеля, кобальта и хрома превышали санитарную норму соответственно в 5, 3,5 и в 2 раза.

В других трех регионах республики (Кура-Араксинский, субтропики, юг Большого Кавказа) основные показатели, характеризующие состояние экологии были в пределах санитарной нормы.

Результаты исследования позволяют констатировать, что относительно высокие показатели распространенности бронхиальной астмы у детей отмечаются в регионах с загрязнением окружающей среды химическими соединениями промышленных предприятий и автотранспорта.

Загрязнение внешней среды выхлопными газами автомобилей в последние годы в Баку и Сумгаите превратилось в злободневную проблему, требующую проведения безотлагательных мероприятий, направленных на ужесточение требований к эксплуатации автотранспорта, на который приходится основная доля вредных выбросов в атмосферу. По данным различных авторов, доля выхлопных газов составляет 70% от всех загрязняющих воздух выбросов в современных мегаполисах.

Наряду с экологическим неблагополучием, значимое влияние на формирование бронхиальной астмы оказывают бытовые, пыльцевые, грибковые и пищевые аллергены. Спектр этих аллергенов разнится в зависимости от климата и географического расположения региона.

Одной из наиболее частых причин формирования атопической БА, является сенсибилизация к бытовым аллергенам. Основной бытовой аллерген – домашняя пыль. Аллерген домашней пыли многокомпонентный. В его состав входят клещи домашней пыли, бактерии, эпидермис человека, эпителий и шерсть животных, микрогрибы, библиотечная пыль. Наиболее выраженными аллергенными свойствами обладают клещи домашней пыли, относящиеся к роду Dermatophagoides – Dermatophagoides pteronyssinus и Dermatophagoides farinae. Они составляют около 90% акарофауны в жилых помещениях. Имеются данные о том, что домашние клещи являются наиболее распространенным бытовым аллергеном, ассоциированным с бронхиальной астмой. Клещевая сенсибилизация во многих странах занимает ведущее место: среди больных бронхиальной астмой она встречается от 45 до 86%.

Проведенные исследования среди учащихся восьмых классов общеобразовательных школ в различных регионах Азербайджана выявили частую сенсибилизацию к аллергенам домашней пыли и к клещам вида Dermatophagoides. Так, у школьников, проживающих в условиях города, сенсибилизация к аллергенам домашней пыли выявлена в 62,6% случаях, а сенсибилизация к клещам Dermatophagoides - у 56,1% детей с БА. Несколько меньше сенсибилизация обнаруживалась в районах расположенных в Кура-Араксинской низменности: 51,6% - к аллергенам домашней пыли и 42,2% - к аллергенам клещей Dermatophagoides. В субтропиках эти показатели выявлены, соответственно, в 48,6% и 44,3% случаев. В районах, расположенных вдоль южных склон Большого Кавказского хребта чувствительность к этим аллергенам обнаружена у 51,9% и 46,2% детей с БА. Отметим, что наибольшее значение средней степени сенсибилизации к аллергенам обеих групп была у детей, проживающих в условиях города, (2,64±0,06 к Dermatophagoides pteronyssinus и 2,42±0,08 к Dermatophagoides farinae).

Другой значимой составляющей домашней пыли являются эпидермальные аллергены. По данным зарубежных авторов [4], частота сенсибилизации к эпидермальным аллергенам у детей, страдающих бронхиальной астмой, колеблется в пределах от 3 до 55%.

Проведенные исследования по выявлению сенсибилизации к эпидермальным аллергенам (использованы микст-аллергены животных, включающие эпителий хомяка, собаки, кролика, кошки, морской свинки) в различных регионах республики показали, что в городских условиях она является минимальной (27,3%) в сравнении с детьми жителями сельских регионов (Кура-Аракс – 40,6%, субтропики 34,3%, горный регион – 36,5%). Вместе с тем, степень (уровень) сенсибилизации к эпидермальным аллергенам у детей, проживающих в городе, была самой высокой в сравнении с данными сельских регионов республики.

Одной из частых причин клинической манифестации БА является наличие сенсибилизации к пыльцевым аллергенам. Среди детей с атопической конституцией, аллергия к пыльце растений отличается тем, что её проявления в большей степени, чем других аллергических реакций, зависят от таких факторов внешней среды, как климатогеографические условия, экология, флора. Поэтому особое значение в изучении этой патологии отводится эпидемиологическим исследованиям, которые позволяют установить особенности распространенности заболевания на конкретных территориях, оценить значение различных факторов, способствующих его возникновению.

Согласно собственным наблюдениям, проведенным в регионах страны, около 50% обследуемых детей с бронхиальной астмой в той или иной степени имеют сенсибилизацию к пыльце дикорастущих и культурных злаков. Чаще обнаруживается сенсибилизация к пыльце сорных трав (полынь, лебеда, амброзия) – около 50% детей с бронхиальной астмой. К злаковым (райграс, ежа, овсяница, тимофеевка, пырей) сенсибилизация выявлена реже, в зависимости от региона проживания - в пределах от 16% до 44%. Наименьшая сенсибилизация у детей, проживающих в городских условиях, выявлена к растительным аллергенам – 19,6-24,5% (бук, дуб, граб, лещина); у детей, проживающих в субтропиках и в районах, расположенных вдоль южных склон Большого Кавказа, сенсибилизация к пыльце указанных деревьев встречается довольно часто и достигает 45%.

У детей пищевая сенсибилизация является стартовой, оказывая огромное влияние на формирование и последующее развитие аллергических заболеваний.

Посредством прик-тестов исследовано наличие сенсибилизации к ряду пищевых аллергенов растительного и животного происхождения у школьников общеобразовательных школ с БА. Согласно результатам обследования дети, проживающие в городских условиях, чаще сенсибилизированы к аллергенам куриных яиц – 32%, коровьего молока – 30,9%, рыбы – 27,6%. В районах Кура-Араксинской низменности выявлен высокий показатель аллергии к рыбе (29,7%), меду (26,6%) и помидорам (28,1%); в субтропиках преимущественно обнаруживалась сенсибилизация к цитрусовым

(35,2%), рыбе (31%) и меду (26,8%). В горном регионе превалирует сенсибилизация к мёду (35,2%), орехам (33,3%) и коровьему молоку (22,2%).

Результаты исследования показали, что сенсибилизация к пищевым продуктам зависит от региона проживания.

Наряду с бытовыми, пыльцевыми и пищевыми аллергенами, значимую роль в развитии, прогрессировании и усугублении течения бронхиальной астмы у детей играют аллергены плесневых грибов (грибы родов Alternaria, Cladosporium, Aspergillus, Mucor, Candida, Penicillum, Epicoccum).

Частой грибковой сенсибилизации способствует неприхотливость грибов к среде обитания, наличие выраженной аллергенной активности и повсеместная распространенность их в окружающей среде. В марте 2005 г., по данным подкомитета по номенклатуре аллергенов Международного союза иммунологических обществ, зарегистрировано 86 грибковых аллергенов, список которых размещен на сайте www.allergen.org.

В ходе исследования изучен спектр сенсибилизации к аллергенам грибов Epicoccum purpurascens, Cladosporium herbarum, Candida albicans, Penicillium notatum, Alternaria tenuis, Phoma betae и Aspergillus fumigatus в регионах республики Азербайджан с различными климатическими характеристиками. Проведенные исследования показали, что сенсибилизация к грибам чаще выявляется в районах, расположенных в субтропическом климатическом поясе. Причем в этом регионе среди детей с БА преобладает чувствительность к аллергенам Alternaria tenuis (у 41,5%), Epicoccum purpurascens (43,4%) и Phoma betae (39,6%). К этим же аллергенам отмечен самый высокий уровень сенсибилизации. Незначительная сенсибилизация к плесневым грибам обнаружена у детей, проживающих в горном регионе с длительной холодной зимой и небольшим количеством осадков. У этих детей чаще определялась сенсибилизация к Alternaria tenuis (28,2%) и Cladosporium herbarum (23,1%). В условиях промышленного города сенсибилизация выявлена к Cladosporium herbarum (36,5%) и Alternaria tenuis (33,8%). Школьники Кура-Араксинского региона, расположенного в зоне полупустынь наиболее сенсибилизированы к аллергенам Epicoccum purpurascens (35,8%) и Alternaria tenuis (28,3%).

Одним из наиболее распространенных социальных факторов окружающей нас среды, способствующим проявлению и обострению бронхиальной астмы, является курение и воздействие табачного дыма.

Актуальность проблемы табакокурения и необходимость пропаганды борьбы с этим широко распространенным негативным явлением подтверждается результатами проведенного нами анкетирования среди учащихся восьмых классов общеобразовательных школ в различных регионах республики. Оказалось, что от 52,5% до 70,8%(!) детей, страдающих бронхиальной астмой, систематически подвергаются воздействию табачного дыма. Причем, дети с БА и её тяжелыми формами достоверно чаще и дольше подвергались неблагоприятному влиянию табачного дыма по сравнению с детьми, не страдающими этой болезнью.

Оценка клинического течения и функции внешнего дыхания у детей с бронхиальной астмой позволила установить тяжесть течения болезни. Распределение детей по тяжести течения бронхиальной астмы, представлено в таблице 4.

Таблица 4. Распределение детей по тяжести течения бронхиальной астмы

Регион	Тяжесть течения бронхиальной астмы					
	легкое		среднетяжелое		Тяжелое	
	абс	%	абс	%	абс	%
I. полупустыня (Сумгаит) (n=221)	179	81,1	31	14,0	11	5,0
II. субтропики (n=88)	72	81,8	12	13,6	4	4,5
III. полупустыня (село) (n=76)	64	84,2	10	13,2	2	2,6
IV. горный (n=65)	57	87,7	7	10,8	1	1,5
всего (n=450)	372	82,66	60	13,33	18	4
достоверность различий	-	н.д.	-	н.д.	-	p_1 <0,005 p_2 <0,05

примечание: p_1 – достоверность различия между I и IV регионом;
p_2 – достоверность различия между II и IV регионом

До проведенного нами обследования, диагноз БА был поставлен, в основном, только детям с тяжелым и среднетяжелым течением заболевания, у которых достаточно часто проявлялись дневные и ночные симптомы болезни.

Данные таблицы 4 указывают, что бронхиальная астма легкого течения распространена у подавляющего большинства больных во всех регионах, независимо от их месторасположения и климатических условий и составляет свыше 80% детей страдающих этим недугом.

Бронхиальная астма среднетяжелого течения во всех регионах выявлена приблизительно с одинаковой частотой с незначительным превалированием в регионе полупустыни. Что касается тяжелого течения астмы, по регионам наблюдаются значительные отличия в зависимости от региона проживания: в городе (п/п) показатель составляет 5,0%, в субтропиках - 4,5%, в горном регионе - 1,5%.

Анализ обращаемости за медицинской помощью в Республиканский аллергологический центр, функционирующий на базе Детской клинической больницы №6 г. Баку, выявил, что в клинику поступают 61% детей со средней, 27% - с тяжелой формой БА. 6% детей поступают в лечебное учреждение састматическим статусом.

В заключение следует отметить высокую эффективность программы «ISAAC» по своевременному выявлению бронхиальной астмы, т.е. в период легкого течения. Именно на этой стадии болезни родители, а нередко и врачи не проявляют адекватного внимания к этой серьёзной болезни и лечат её под диагнозом банальных ОРЗ, ОРВИ, ринита, что и является причиной, утяжеления процесса.

Результаты проведенных в Азербайджане клинико-эпидемиологических исследований в рамках международной программы «ISAAC» позволяют сделать нижеследующие выводы:

1. Распространенность бронхиальной астмы у детей в Азербайджане обнаруживает зависимость от климато-географических условий и минимальна в экологически чистом горном регионе (1,8%). В условиях одного и того климата (полупустыни), распространенность бронхиальной астмы почти в 2 раза выше в экологически неблагополучном городе (4,6%), чем в селе (2,5%). Среди детей из трех сельских регионов республики бронхиальная астма чаще встречается в субтропиках (2,8%).
2. Оценка клинического течения и функции внешнего дыхания показала, что в структуре тяжести бронхиальной астмы среди детей преобладают легкие формы (82,6%). Среднетяжелое течение болезни встречается у 13,3%, тяжелое - у 4% детей. Тяжелые формы БА у детей достоверно чаще обнаруживаются в условиях промышленного города (5%) и в субтропиках (4,5%) по сравнению с проживающими в горном регионе (1,5%).
3.Число детей, страдающих бронхиальной астмой, в Азербайджане в период 1998-2009 гг. по сравнению с 1975 г. возросло, в среднем, более чем в 2 раза.
4. У детей с бронхиальной астмой наиболее частая сенсибилизация обнаружена к бытовым аллергенам. В городских условиях превалирует сенсибилизация к домашней пыли (до 62,6%), в сельских регионах – к эпидермальным аллергенам (40,6% против 27,3%). Наибольшая сенсибилизация к грибам выявлена в районах, расположенных в субтропическом климатическом поясе. Причём в этом регионе среди детей с БА преобладает чувствительность к аллергенам Alternaria tenuis (41,5%), Epicoccum purpurascens (43,4%) и Phoma betae (39,6%). К этим же аллергенам отмечен самый высокий уровень сенсибилизации. Наименьшая сенсибилизация к плесневым грибам обнаруживается у детей, проживающих в горном регионе.

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SUMMARY

SOME FEATURES OF DEVELOPMENT AND COURSE OF BRONCHIAL ASTHMA IN CHILDREN IN AZERBAIJAN

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According to the international «ISAAC» program, we studied the peculiarities of bronchial asthma in children at the age of 13-14 years, in various climatic and geographic regions of Azerbaijan. At the first stage of investigation, 14693 eighth class pupils of high school from the four various regions were surveyed: the I region (n=4979) – an industrial city, placed in a semi-desert area; the II region (n=3010) – rural areas, located in a semi-desert climatic zone; the III region (n=3133) – areas, located in a subtropical climatic zone; the IV region (n=3571) – an ecologically clean mountainous region, located along southern slopes of the Greater Caucasian ridge. At the second stage of the investigation allergological, clinical-functional examinations were carried out in children with symptoms of allergic diseases. It was established that prevalence of BA was reliably more frequent in the industrial city (4,6%) than in other three, especially rural areas. In subtropical climatic area 2,8%, in rural semi-desert area – 2,5%, in mountainous region – 1,8% of examined children were suffering from BA.

Study of the clinical course of diseases in children with allergic diseases and their allergic status revealed that structure and expressiveness of sensitization to domestic, pollen, fungous and food allergens depends on residing area.

Keywords:bronchial asthma, Azerbaijan, ISAAC.

РЕЗЮМЕ

НЕКОТОРЫЕ ОСОБЕННОСТИ РАЗВИТИЯ И ТЕЧЕНИЯ БРОНХИАЛЬНОЙ АСТМЫ У ДЕТЕЙ В АЗЕРБАЙДЖАНЕ

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По протоколу международной программы изучения астмы и аллергии у детей («ISAAC»), в различных регионах Азербайджана изучены особенности бронхиальной астмы (БА) у детей в возрасте 13-14 лет. На первом этапе исследования проанкетировано 14693 учащихся восьмых классов школ в четырёх регионах: I регион (n=4979) – крупный промышленный город, расположенный в зоне полупустынь и сухих песков; II регион (n= 3010) – районы преимущественно с сельским укладом жизни, расположенные в зоне полупустынь и сухих песков; III регион (n= 3133) – районы, относящиеся к субтропической климатической зоне; IV регион (n=3571) – районы, расположенные на южных склонах Большого Кавказского хребта. На втором этапе детям с симптомами аллергических заболеваний проведены аллергологические, клинико-функциональные исследования. Установлено, что заболеваемость БА достоверно чаще встречается в городе (4,6%), чем в трёх других сельских регионах. В субтропиках БА выявлена у 2,8% детей, в сельской полупустыне - у 2,5%, в горном регионе - у 1,8% детей. Изучение клинического течения и аллергологического статуса детей с аллергическими заболеваниями выявило, что структура и выраженность сенсибилизации к часто встречающимся в окружающей среде бытовым, пыльцевым, грибковым и пищевым аллергенам зависят от региона проживания.

რეზიუმე

ბავშვებში ბრონქული ასთმის განვითარებისა და მიმდინარეობის თავისებურებანი აზერბაიჯანში

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საერთაშორისო ISAAC პროგრამის ფარგლებში შესწავლილ იქნა აზერბაიჯანის სხვადასხვა კლიმატურ რეგიონში მცხოვრები 13-14 წლის ბავშვთა ბრონქული ასთმის (ბა) მახასიათებლები. კვლევის პირველ ეტაპზე გამოკითხულ იქნა 4 სხვადასხვა რეგიონის საშუალო სკოლის 14693 მერვეკლასელი: I რეგიონი (n=4765) – ინდუსტრიული ქალაქი, ნახევრადუდაბნოს ტიპის დასახლება,II რეგიონი (n=3010) – სოფლის ტიპის დასახლება ნახევრადუდაბნოს ტიპის კლიმატურ ზონაში განთავსებული, III რეგიონი (n=3133) – სუბტროპიკულ კლიმატურ ზონაში მდებარე ტერიტორია, IV რეგიონი (n=3571) ეკოლოგიურად სუფთა მთიანი რეგიონი,მდებარე დიდი კავკასიონის ქედის სამხრეთ ფერდობზე. კვლევის მეორე ეტაპზე ალერგიული დაავადების სიმპტომების მქონე ბავშვებს ჩაუტარდა ალერგოლოგიური და კლინიკურ-ფუნქციური გამოკვლევები. დადგინდა, რომ ბა-ის პრევალენსი გაცილებით მაღალი იყო ინდუსტრიულ ქალაქში (4,6%), სუბტროპიკული კლიმატის არეში პრევალენსი იყო 2,8%, სოფლის ნახევრადუდაბნოს რეგიონში – 2,5%, მთიან რეგიონში კი ბა გამოკვლეულთა მხოლოდ 1,8%-ს დაუდგინდა.

ალერგიული დაავადების მქონე ბავშვების დაავადების კლინიკური სურათის შესწავლამ,

ალერგიულმა სტატუსმა და სენსიტიურობის ექსპრესიამ სხვადასხვა ალერგენის მიმართ, როგორიცაა ოთახის მტვერი,მცენარეული,სოკოს თუ საკვებისმიერი ალერგენი, ცხადყო, რომ საცხოვრებელ ადგილს მნიშვნელოვანი როლი ენიჭება დაავადების განვითარებაში.

CANNABIS: A CONTROVERSIAL 21ST-CENTURY DRUG OF ANTIQUITY

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Cannabis (marijuana, Indian hemp, pot) has been known for many millennia and remains very popular in the 21st century because of the delta-9-tetrahydrocannabinol (THC)-induced euphoric state THC produces in pot smokers [21,22]. Research has broadened the knowledge of cannabis to the endocannabinoid system (cannabinoid receptors [CB1 and CB2] and key endogenous cannabinoids [2-arachidonoyl glycerol and anandamide]) that were identified in the 1980s (Table 1) [21,22]. Research is also looking at the use of phytocannabinoids to treat various medical disorders. The potential use of "medicinal" pot along with a general perception that it is a safe, natural, plant drug has lead to a global campaign to legalize its use. This review considers the question of whether or not cannabis is a safe drug or one that actually represents an oubliette that imprisons many of those who are unable to stop their cannabis smoking.

Table 1. Types of Cannabinoids [21,22]

Endogenous cannabinoid agonists
Anandamide (arachidonoyl ethanolamide)
2-AG (2-arachidonoyl glycerol)
Cannabigerol (CBG) (alpha-2-adrenergic receptor agonist)
Cannabinol (**CBN**) (THC metabolite)
Cannabidiol (CBD) (THC isomer)
Tetrahydrocannabinolic acid (THC biosynthetic precursor)
Synthetic cannabinoid agonists
HU-210
CP-55940
JWH-133
WIN 55,212-2

Table 2. DSM-5 Cannabis-Related Disorders [5]

Cannabis Use Disorders
Cannabis Intoxication
Cannabis Withdrawal
Other Cannabis-Induced Disorders
Unspecified Cannabis-Related Disorders

Prevalence
Cannabis represents one of the most popular illicit drugs in many parts of the world [21,22]. Lifetime use in European adolescents, based on the 2007 ESPAD (European School Survey Project on Alcohol and other Drugs) noted an average of 19% among 35 surveyed countries with a range of 3% in Armenia to 45% in the Czech Republic [27]. The Centers for Disease Control (CDC)'s YRBS (Youth Risk Behavioral Surveillance) identified an increased prevalence for high school youth (13 to 18 years of age) in the United States that was 31.3% in 1991 and 39.9% in 2011 [7]. Research concludes that there were over 13 million persons who were dependent on cannabis in the world in 2010 [14]. Cannabis use and abuse is part of a global burden of disease caused by illicit drug use and abuse in the world that includes increased consumption by adults as cannabis continues to gain acceptance at all ages as a safe drug [15]. Part of the reason for cannabis popularity can be found in a historical look at pot usage.

History of the Plant, Canabis sativa
Cannabis sativa or the cannabis plant has been known by humans for thousands of years and perhaps the first worn fabric may have been made from the hemp plant 8000 BCE and hemp seeds used as food have been dated to China in 6000 BCE [22]. Cannabis has been regarded by humans as a wonder plant for countless millennia. The Chinese emperor Shen-Nung (2737 BCE), called the Red Emperor, is identified by history as the first classifier of medicinal herbs. Cannabis is listed in his famous Pen Ts'ao book as a medicinal plant product. The Hindu sacred text, Arthava-Veda, calls cannabis "sacred grass" and lists it as one of 5 sacred plants that was consumed in India as medication as early as 1200 BCE [19]. Confucius (551-479 BCE) wrote his Chinese classics that included comments about growing and consuming the cannabis plant [22].

Dioscorides (40-90 AD) was a famous Greek physician to the Romans; he was also a pharmacologist and botanist who wrote his medical treatise, De Materia Medica, and discussed uses of cannabis for making strong rope as well as treating ear aches [22]. Galen (130-200 AD), the most famous Greek physician of ancient Rome, wrote about the custom of Romans using a cannabis-seed desert but did warn of symptoms from an overdose of this so-called treat. Cannabis was a popular product in the Middle East in the 12th century and it spread from there to other parts of the world. Li Shi Chen (1517-1593 AD) wrote a classic text of medicine which included cannabis as medicine. Thus, there is a very long history of cannabis use by human beings for millennia who considered it as a safe, helpful, and even sacred plant. It is in a long list of botanical products used in as food, medicine, and religious rites by Homos sapiens for countless millennia.

Additional Drug Use/Abuse
For those wishing to evaluate the safety or harm of cannabis use it is important to understand that pot use/abuse does not occur alone in many cases, but in conjunction with other drugs [21,22]. For example, pot smokers may increase the THC sedative effects by adding diazepam or alcohol. The euphoria experienced by cannabis smokers can be enhanced by the addition of such drugs as lysergic acid diethylamide (LSD), opioids, cocaine, or nicotine. PCP (phencyclidine) may be added to the pot cigarette (joint) along with an added organic solvent, such as formaldehyde.

Cannabis smokers are often tobacco smokers and research notes that in those smoking both drugs, nearly 50% started with tobacco first, one-third started with cannabis first, and most cannabis smokers who stopped tobacco did so after becoming regular pot smokers [41]. Research has reported that cannabis consumption can be a trigger for other drug use, such as tobacco and cocaine [33]. Thus, the role of marijuana as a gateway drug for adolescents should never be under-estimated [23]. The link of cannabis to other illict drug consumption should be a warning to youth and adults alike. This is one of the reasons why it has been difficult to identify specific some harmful effects of cannabis since it is often taken with other illict drugs.

Designer THC: Cannabimimetics
Another toxic issue for those studying the effects of pot consumption on the world's youth is the problem of synthetic cannabinoids (cannabinoid designer drugs, cannabimimetics). It is not just a matter of smoking pot in the 21st century with a low concentration of THC but increasingly higher THC concentrations in both natural and designer THC products. Synthetic cannabinoids resemble C. sativa plant THC and produce THC-like euthoria but can be considerably heighted since the psychoactive effects can be 10-times higher than seen with plant (C. sativa) THC (10). The danger of these potent drugs, though advertised by some as harmless with exotic names (i.e., Spice Gold, Yucatan Fire, Aroma), should be understood [42].

Adverse Effects: Psychiatric
Neurodevelopment effects
Research with both animal and humans demonstrates that the high neuronal plasticity of the developing brain in the prenatal and young adolescent periods of life can be negatively affected by exposure to cannabis. Multiple studies have concluded that young adolescents who use cannabis are at increased risk for abnormalities of thinking, cannabis dependence, neuropsychiatric diseases (including schizophrenia), and addition of other illicit drugs [16,21,22,42]. This is a clear warning that adolescents who smoke pot are at risk for drug dependence and interference with normal developmental parameters that can lead to dysfunction in the home, school, or at work. Cannabis affects on the dopamine and opioid neurotransmitter systems can lead to increased risk for ADHD, anxiety, mental slowness, lowered motivation, and problematic decision making [5,21,22,]. Perhaps one-third or more of heavy cannabis consumers also have attention deficit hyperactivity disorder (ADHD)

[39]. Certainly these problems can be compounded by the use of additional drugs in adolescence.

Cannabis Use Disorders

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), that was published in 2013 lists a number disorders related to cannabis smoking, as noted in Table 1 [20]. Youth who are cannabis dependent can spend many hours a day obsessed with finding and smoking cannabis. It is of little wonder that those who are dependent on cannabis consumptions are active champions of advocating for cannabis legalization. Cannabis intoxication can last longer with oral cannabis as opposed to smoking pot. Risk factors for cannabis use disorders include conduct disorder and differentiation of cannabis-induced mental health disorders from primary psychiatric disorders can be difficult. Some researchers speak of cannabis dependence and suggest that 7 to 10% of pot smokers develop cannabis dependence while a susceptibility gene (NRG1) has been linked with pot dependence in African-Americans [1,2].

Cannabis Withdrawal Syndrome

Research has demonstrated a withdrawal syndrome in heavy or chronic pot users that can begin within 48 hours of stopping pot consumption, can cease in 2 to 12 weeks after complete abstinence, and should be included in the differential diagnosis of youth who present with disordered eating patterns [21,22,25]. Symptoms of this withdrawal can include irritability, anxiety, restlessness, sleep problems, and even aggressive behavior. These symptoms can be relieved by smoking pot, oral intake of THC, or even use of other illicit drugs.

Cannabis and Psychosis

Chronic cannabis consumption has been linked with increased rates of psychosis and this is especially seen in those consuming the high potency designer THC products [9,18,28,29,34]. Those with a psychotic disorder appear to be highly susceptible to acute marijuana effects [34]. Clinicians have also observed that patients with schizophrenia often smoke pot and paranoia can develop in some pot smokers [21,22]. Though most who smoke pot do not develop psychosis, this link of pot consumption to some with psychosis is a complex yet sobering prospect for chronic pot consumers.

Medical Adverse Effects

General

Pot smokers are certainly aware that cannabis smoke can lead to injected conjunctiva and pharyngitis. Pot users may not be aware that they are also at increased risk for oral infections, dental caries, and periodontal disease [13,21,22]. Chronic use has been reported to lead to weight gain from overeating and less exercise. There can also be rapid eye movement suppression and diffuse slowing of background electroencephalographic (EEG) activity [21,22]. As noted by Claudius Galen 2 centuries ago, overdose is harmful and altered consciousness has been reported in infants anecdotally exposed to cannabis smoke or oral ingestion. A modern form of overdose is found in smugglers who pile up cannabis in their gastrointestinal tracts and then develop abdominal pain if there is colonic perforation and peritonitis. The modern movement of designer drugs produces potent synthetics agonists of cannabinoid receptors called Spice/K2 drugs with potentially severe consequences including seizures, acute renal injury, hallucinations, psychosis, and adverse cardiovascular effects [42].

Pulmonary

Exposure to cannabis smoke can lead to bronchitis (acute and chronic) though research does not demonstrate deterioration in pulmonary function because of smoking cannabis [37]. Marijuana, however, contains a toxic mixture of noxious gases and other injurious chemicals known to be harmful to the pulmonary system - as noted with tobacco. Some pot smokers inhale more cannabis particulate matter into their lungs than even noted with cigarette smoking that can result in increased levels of carbon monoxide and nitric oxide. This is indeed worrisome and pot smokers typically continue their consumption despite chronic cough, bronchitis, or psychiatric effects of pot. Chronic or heavy pot use can lead to bullous emphysema and pneumothorax [37]. Combining pot with tobacco leads to well-known negative tobacco effects. Cannabis users can develop pulmonary infections and sharing of water pipes can lead to pulmonary tuberculosis [21,22]. Cannabis that contains fungal spores can cause pulmonary aspergillosis in immunocompromised individuals.

Cardiac

Pot smoking can lead to an increase in heart rate and typically mild increase in blood pressure. Some can also develop orthostatic hypotension due to decreased vascular resistance [35]. Most young smokers can withstand these changes but there are anecdotal reports of congestive heart failure, myocardial infarction, arrhythmias, and acute coronary syndrome usually in adults. Increased cardiac risk with the designer cannabis products are reported [6]. Thus, one with known cardiac disorder should avoid cannabis consumption. A patient with a cardiac death and positive urine for cannaboinoid should have a plasma THC level done before implicating cannabis.

Cannabis Hyperemesis

First described in 2004 in Australia, cannabis hyperemesis is seen in cannabis smokers who develop sudden emesis that is severe, can be cyclic, and resolves with intravenous hydration, antiemetic medication, as well as halting of their pot consumption [32]. Though pot has been used to manage chronic nausea and emesis, the cannabis hyperemesis syndrome represents a paradoxical gastrointestinal effect and may last for 2 days. Patients may report some temporary relief with hot baths or showers and it may be confused with the cyclic vomiting syndrome.

Sports Doping
Though some athletes have tried to use cannabis to improve their sports performance, the opposite typically occurs [40]. Reasons for reduction in sports capacity include a reduced exercise testing during maximal exercise, increased heart rate at less than maximal exercise levels, increase in blood pressure, and decreased psychomotor activity [21,22]. Cannabis is one of the many drugs banned by the World Anti-Doping Agency and the International Olympic Committee since 1989.

Cannabis and Motor Vehicle Accidents (MVAs)
Smoking cannabis and driving motor vehicles has been shown to be very dangerous and adolescents as well as young adults who drive under the influence of marijuana have a two-time increase risk in MVAs that can lead to injury and death [38]. These drivers can experience deadly distortion of oncoming car or truck lights and the driving impairment worsens with increased amounts of pot consumed as well as the addition of other illicit drugs.

Management Options for Cannabis Use Disorders
Prevention
Treatment of a chronic cannabis user has proven to be very difficult and the success rate of cannabis cessation is poor [21,22,30]. Those with cannabis dependence do not wish to stop their drug habit partly because of the cannabis-induced cognitive impairment seen in these youth. Thus, prevention is the key to help our youth avoid a life time of cannabis dependence and co-morbid illicit drug use. This successful strategy involves comprehensive drug prevention education given in the school milieu starting in the elementary years of childhood education. Clinicians should seek to offset the pernicious message given to youth by the media, media stars, and society that cannabis is a benign plant that is safe to use and part of a happy, thrill-seeking, fulfilled life.

Behavioral Therapy
Management options include therapy designed to help the drug user stop co-morbid drugs that may be found in the chronic cannabis user - as for example alcohol, tobacco, methamphetamine, and heroin. Those with psychosis and cannabis consumption should receive behavioral therapy to treat both problems and not just one. Cannabinoids have anti-psychotic effects and their use for psychosis treatment is under research to evaluate the success of utilizing products that do not contain psychoactive THC. Chronic pot users should receive suicide screening.

Therapy should seek out specific risk factors in the pot smoker, such as social anxious youth who smoke cannabis to help them deal with these anxieties [10]. If the social avoidant behavior can be corrected, the person who wishes to stop smoking cannabis can be more successful in this goal. Therapy should help the drug user deal with cannabis craving and factors that trigger relapse (i.e., cigarette smoking, certain friends or environments, others). Cognitive behavioral therapy may be helpful to some cannabis users (i.e., older teenagers with no co-morbid psychiatric disorder) while multidimensional family therapy may be more helpful for others (i.e., younger teens with co-morbid conduct disorder or oppositional defiant disorder) [4].

Pharmacologic Therapy
Unfortunately there is no pharmacologic agent which corrects or cures problematic cannabis consumption [21,22]. Co-morbid psychiatric illnesses should be appropriately treated, such as use of antipsychotic agents for co-morbid or pot-induced psychosis. Pharmacology for co-morbid nicotine addiction should be provided to help the patient allow successful tobacco cessation. Trazodone may help with cannabis-induced chronic insomnia.

Management of cannabis dependence may be helped with nabilone, a synthetic THC analogue that has improved bioavailability when compared to dranabinol, another synthetic cannabinoid [26]. Research has noted some benefit with the use of rimonabant, olanzapine (a thienobenzodiazepine), and the anxiolytic agent, buspirone [21,22]. Rimonabant is a CB1-selective cannabinoid receptor antagonist/inverse agonist that has been pulled from the American and European markets because of concerns with adverse effects of depression and suicide. Research is also evaluating the potential benefit from use of oxytocin (neurohypophysial hormone) to improve mood and social dysfunction in some cannabis users and N-acetylcysteine (NAC) for cannabis dependence [21,22].

Cannabis intoxication may be improved with use of propranolol (sympatholytic non-selective beta-blocker) and rimonabant while research is looking at potential beneficial use with flumazenil (benzodiazepine receptor antagonist) and cannabidiol; no specific agent is recommended [11,12]. Oral THC (dronabinol) may improve cannabis withdrawal symptoms while benefit may also occur with use of lofexidine (alpha-adrenergic receptor agonist) and the anti-depressant, mirtazapine [21,22].

Conclusion.
The consumption of cannabis (marijuana, pot, Indian hemp) has been a popular activity for Homo sapiens for over 10,000 years. The euphoria produced by delta-9-tetrahydro-cannabinol (THC) has made it the most illicit drug in the world and global movements toward cannabis legalization are gaining momentum [17]. Cannabis has been utilized down through the ages as a safe and even sacred plant while it is also being promoted as a medicinal plant despite limited evidence in this regard. The exact role of cannabis for management of various medical or psychiatric problems remains to be elucidated with research as the 21st century continues [36].

Youth who smoke this drug should understand that it, like other illicit drugs, has negative adverse effects which are

both psychiatric and medical in nature. Potential psychiatric complications to cannabis consumption include cannabis use disorders, cannabis intoxication, cannabis withdrawal, and induction of psychosis. It is very difficult for the chronic or heavy cannabis smoker to stop using this drug and management options are limited at this time. Young adolescent smokers are at particular risk for central nervous system damage from cannabis exposure that includes increased risk for major depressive disorders, schizophrenia, and drug addiction [31]. The dangers of operating a motor vehicle under the influence of cannabis must be understood by all drivers including adolescents [8].

Medical side effects may include cannabis hyperemesis, chronic conjunctivitis, cough, bronchitis, bullous emphysema, and pneumothorax. Others include increase in heart rate, blood pressure, dental caries, and periodontal disease. Additional potential negative effects are mentioned in this article. Management is essentially behavioral therapy though research is currently and actively looking for pharmacologic agents that will help with cannabis use disorders, withdrawal, and intoxication.

The best way to deal with cannabis problems in adolescents is prevention through comprehensive drug education started early in the school years and continued into adulthood. We must not allow uneducated, pococurante legislators nor cannabis-dependent, adult myrmidons to foudroyantly lure our youth into a lifetime oubliette of epinosic cannabis abuse that may also include co-morbid illicit drug addiction. These humans are clearly the pied pipers of the 21st century luring our unsuspecting youth into the perilous seas of destruction (4). We must teach our children to avoid the false, lubricious, minacious, promises of apolaustic plant euphoria. We should teach our children the lambent joys of Beethoven, Brahms, Bach, Balanchivadze, Bardanashvili, and Basilaia.

"*Pied Piper: I attract attention/ Chiefly with a secret charm/.....Who doesn't know of the Pied Piper?*
Alas, alas for Hamelin!.....

They wrote the story on a column,
And on the great church-window painted
The same, to make the world acquainted
How their children were stolen away....."
The Pied Piper of Hamelin (Robert Browning: 1812-1889)

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SUMMARY

CANNABIS: A CONTROVERSIAL 21ST-CENTURY DRUG OF ANTIQUITY

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Cannabis consumption has been popular for thousands of years and its historical use is noted in many parts of the world including ancient China, India, the Middle East. It is currently the most popular illicit drug in the world, is being utilized as a medicinal plant, and many parts of the world are legalizing this drug. This discussion considers various aspects of cannabis use including its prevalence, history, co-morbid drug abuse, designer cannabinoids, psychiatric adverse effects, medical adverse effects, and management options. The youth of the world should be comprehensively taught that cannabis is neither a safe nor a benign drug. Prevention with comprehensive drug education is the best plan for our youth since management of a chronic or heavy cannabis consummer remains difficult and fraught with failure if cessation is the goal. Caveat emptor!

Keywords: cannabis consumption, history, prevalence, management.

РЕЗЮМЕ

МАРИХУАНА: СПОРНЫЙ НАРКОТИК XXI ВЕКА, ИЗВЕСТНЫЙ ЕЩЕ В АНТИЧНОСТИ

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Употребление марихуаны (гашиша) было популярным в течение тысячелетий; ее используют во многих странах света, включая древний Китай, Индию и Ближний Восток. В настоящее время марихуана - наиболее популярный наркотик в мире, используется также как медицинское растение и во многих странах легализована. Обсуждаются различные аспекты ее использования: частота, история, сопутствующая наркотическая зависимость, каннабиноиды с измененной химической формулой, психиатрические и медицинские (соматические) побочные эффекты, возможные варианты решения проблемы. Молодежь во всем мире должна быть полностью информирована, что марихуана является небезопасным и недоброкачественным препаратом. Превенция посредством всесторонней информированности молодежи является наилучшим выходом, так как справиться с хронической или тяжелой марихуанновой зависимостью и прекратить ее применение весьма сложно. Caveat emptor! Покупателю следует быть настороже!

რეზიუმე

მარიხუანა: ანტიკურობიდან ცნობილი XXI-ე საუკუნის სადისკუსიო ნარკოტიკი

დ. გრეიდანუსი, მ. ჰოლტი

დასავლეთ მიჩიგანის უნივერსიტეტი, პედიატრიული და მოზარდთა მედიცინის დეპარტამენტი, სამედიცინო სკოლა, კალამაზუ, მიჩიგანი, აშშ

მარიხუანას (ჰაშიშის) გამოყენება ათასწლეულებს ითვლის, მას ფართოდ ხმარობდნენ მსოფლიოს მრავალ ქვეყანაში, ჩინეთში, ინდოეთში და ახლო აღმოსავლეთში. ამჟამად იგი ყველაზე პოპულარულ ნარკოტიკად ითვლება, გამოიყენება როგორც სამკურნალო მცენარე; მრავალ ქვეყანაში მიმდინარეობს მისი ლეგალიზაცია. ნაშრომში მისი გამოყენების მრავალი ასპექტია განხილული: სიხშირე, ისტორია, თანდართული ნარკოტიკული დამოკიდებულება, კანაბინოიდები შეცვლილი ქიმიური ფორმულით, ფსიქიური და სომატური გვერდითი მოქმედება, პრობლემის გადაწყვეტის შესაძლებლობები. ახალგაზრდობა მთელ მსოფლიოში უნდა იყოს ინფორმირებული, რომ ჰაშიში არც უსაფრთხოა და არც საკეთილდღეო. ახალგაზრდობის სრულყოფილი განათლება პრევენციის საუკეთესო საშუალებაა, მით უფრო, რომ ჰაშიშის ქრონიკული და ინტენსიური ხმარებისას პრობლემის თავის გართმევა - მარიხუანის ხმარების შეწყვეტა, ფრიად ძნელია. Caveat emptor! მყიდველი უნდა ფრთხილობდეს!

FINAL HEIGHT, TARGET HEIGHT AND THE COMMUNITY

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Height varies with age, and it varies with historic time. Figure 1 illustrates the average increase in height of Czech children since 1951. Modern children are taller at all ages. It is known that poverty and malnutrition lead to growth impairment, and it is general belief that overcoming these factors plays a major role in the recent positive secular trend in height. A closer view into historic growth charts however reveals that much of the impairment in height was impairment in developmental tempo. European children of the 19th century were short, but they were also delayed in maturation. Puberty occurred later than today. This is true for most children of historic samples, and for children who grow up under unfavourable conditions. Figure 2 exemplifies the acceleration in tempo and the forward displacement of the pubertal growth spurt in height velocity curve since 1951 of Czech children [17,18]. When adjusting the X-axis of such plots for tempo differences, it becomes obvious that the shortness of historic children mainly resulted from a significantly blunted adolescent growth spurt (Fig. 3). Blunted adolescent growth has been observed in many historic European populations.

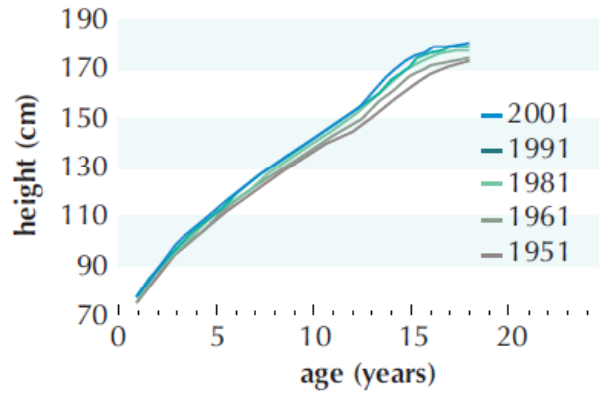

Fig. 1. Average body height of Czech children since 1951 (Figure adopted from Hermanussen 2013)

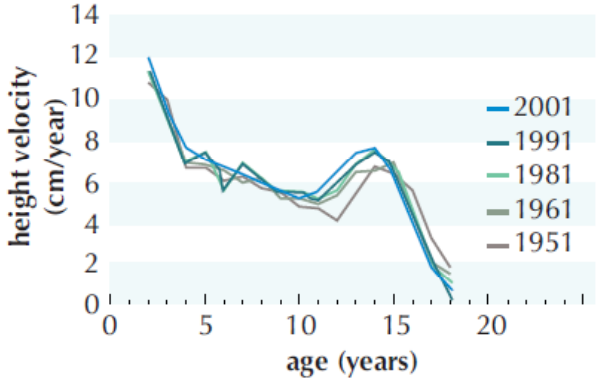

Fig. 2. Average height velocity of Czech children since 1951 (Figure adopted from Hermanussen 2013)

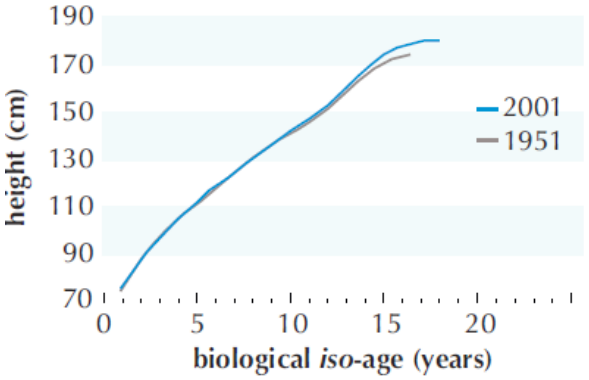

Fig. 3. Average height of two Czech cohorts corrected for tempo (the age scale is depicted as iso-age: the cohorts are synchronized for peak height velocity). The adolescent growth spurt is smaller in the 1951 cohort (Figure adopted from Hermanussen 2013)

The differential effects of living conditions on developmental tempo and on adolescent growth and final height have been documented in school children from Oslo. During World War II, Oslo school girls were shorter at all ages than before and after the war [3]. But growth impairment of the war cohorts was not permanent. These girls caught up after the war and achieved normal adult height at an age of 18 years. The girls illustrated a remarkable insensitivity of final height to temporarily unfavourable conditions. Final height does not simply reflect growth condition during childhood and adolescence. The "Oslo experiment" suggests an independent regulation of adolescent growth and final height.

It is known that height clusters within a population. People who live together are usually similar in height. This is common knowledge and was true also in history. In the mid-19th century, average body height of Dutch military conscripts was close to 165 cm [16]. Some were taller, some were shorter, but less than one percent reached the modern average of 183.8 (SD 7.1) cm [7]. On the other hand, few modern conscripts are shorter than the 19th century average, and today nobody remains shorter than 157 cm which was the 30th height centile of mid-19th century Dutch conscripts. This does not surprise at first view since living conditions have improved since that time. But also in the mid-19th century some people lived under very affluent conditions, and still were short. Not even the sons of the wealthiest citizens surpassed the modern 90th height centile. Figure 4 provides an illustrative example of a 19th century, and a modern conscript height distribution from the Swiss district of Schaffhausen [12]. Both distributions are narrow, with little overlap. None of the 19th century conscripts reached 190 cm.

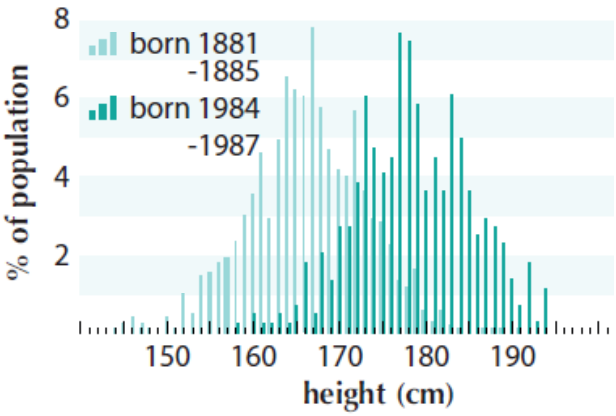

Fig. 4. Height distribution of a historic and a modern cohort of Swiss conscripts mustered in the district of Schaffhausen (Figure adopted from Hermanussen 2013)

Several factors apart from genes, hormones and the socioeconomic background are known to influence final height. Final height depends on bone age, on BMI, and in girls also on menarcheal age. Late maturing girls become taller than early maturing girls [9]. Final height is low in poor and chronically malnourished populations and populations who suffer from high loads of infectious diseases or iodine deficiency [10]. And there are environmental factors that both affect final height and mortality, life expectancy and

fertility – final height is inversely related to the number of children per woman. But none of these factors provide a convincing explanation why short stature was so prevalent even in the affluent social strata some 130 years ago, and for the narrowness of the two height distributions.

Individual body height clusters around average height of the community. Recent evidence suggests that the social network is involved in the regulation of adolescent growth and final height (community effect on growth [1]). Social networks affect human biology in various ways. E.g. Christakis and Fowler discussed the spread of obesity [5], and the dynamics of smoking [4], Rosenquist et al. [11] investigated the spread of alcohol in social networks. We chose military data to study the spread of height in the geographic network of Switzerland. Switzerland is small and separated by mountain chains rising to more than 4500 meters with great river valleys in between. Politically Switzerland is divided into 26 independent cantons and each canton, into districts. Two thirds of the population speak German, about 20% French, about 7% Italian and less than 1% Romansh in the canton of Graubünden (Grisons). The distinct internal geographic and language barriers in combination with long term political stability make Switzerland an ideal region for studying the effect of physical connectedness and disconnectedness on body height. Annual documents of military conscriptions are available since the end-19th century.

We investigated mean height of Swiss conscripts (N=86,202) conscripted in 2004-2009 [13,14]. The data were obtained from 169 districts, with 21 to 2,897 conscripts per district. Additional information was available on standard deviation for height, body mass index, and average per capita household income [https://www.credit-suisse.com/upload/news-live/000000021556.pdf]. Information on population, geographic coordinates of the district capitals, altitude above sea level, and major road connections, was obtained from the Swiss Federal Statistical Office [http://www.bfs.admin.ch/bfs/portal/de/index/news/02/03/01/01.html] and publicly accessible internet sources [e.g. https://maps.google.de/maps].

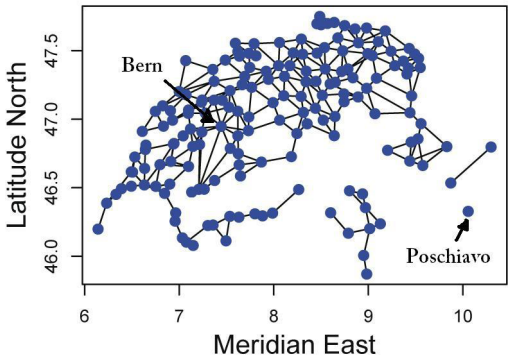

Fig. 5. The geographic network of Switzerland consists of 169 district capitals (nodes) and 335 connecting roads (edges). Each node is linked with 0 (e.g. Poschiavo) to 11 (Bern) neighbouring nodes

We formed a geographic network consisting of 169 nodes (district capitals) and 345 connecting edges (inter-district roads). First order neighbours in this network were defined as districts capitals connected by direct roads. In order to better mirror physical connectedness, we omitted 10 high altitude, scarcely used inter-district connections leaving a network with 335 edges connecting 169 nodes. Each node was linked with zero (Poschiavo) to 11 (Bern) neighbouring nodes (Fig. 5).

Average height of Swiss conscripts is 178.2 cm (SD 6.5 cm), but the distribution of height is significantly overdispersed, i.e. districts differ more in height than to be expected by random. Conscripts of Acquarossa (mean height 174.1, SD 6.4 cm) are the shortest and 6.2 cm shorter than conscripts of Münster, Goms (mean height 180.36, SD 5.8 cm). District height clusters. Short stature districts have short, tall stature districts have tall neighbours. We found significant height correlations between 1st (r=0.58), 2nd (r=0.64), 3rd (r=0.45) and even 4th order neighbours (r=0.42). It appears that adolescents regulate body height according to those who live close confirming earlier findings that individual height tends to cluster around average height of the community [1]. Similar phenomena are evident in migrant populations who tend to grow towards the new height target of their host population [2], and in populations that merge due to political events. E.g. East Germans caught up in height after the German re-unification in 1989 when the two German countries merged and the former socialist society fused with its economically advanced Western neighbours (Fig. 6).

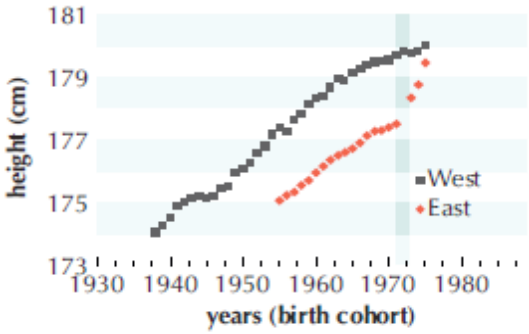

Fig. 6. Average body height of West and East German conscripts before and after the German re-unification in 1989 (affecting birth cohorts 1971, 1972, 1973) Figure adopted from Hermanussen 2013)

Final height matters in children who are considered too short, or too tall for age. There are many occasions when parents want to get a height prediction for their child. Several methods have been applied to predict height. They refer to parental height, to actual height, to bone age, and of course to particular individual circumstances such as growth in chronic disease or syndromes [9]. Parental height

is usually considered "the target" that will be reached by the child. Tanner [15] suggested defining target height as the sex-corrected mean-parental height plus/minus 6.5 cm for males/females. Cole proposed target height as the mean parental height SDS [2000]. Both proposals ignore the fact that tall parents have too few tall children, and short parents have too few short children. Offspring height tends to regress to the population mean.

We therefore proposed calculating conditional target height as follows [8]:

cTHSDS = (father SDS + mother SDS)/2 *0.72

The conditional target height SDS equals mean parental height SDS, multiplied by the factor 0.72 with a 95% confidence interval of

$+/-2\ \sqrt{(1-0.57^2)} = +/- 1.64$SDS

The formula does not condition on sex.

In conclusion, final height is determined by endocrine parameters and genetics, by nutrition and health, by environmental factors, by birth weight, early growth, BMI, and developmental tempo. Yet, none of these factors explain the apparent regression to the population mean, and the narrowness of the height distribution both in historic and in modern populations. New modelling of longitudinal data rather suggests that the target for growth and final height may also be set by the community. Tall stature communities generate tall people, short stature communities generate short people, and migrants orientate towards the new height target of their host population.

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SUMMARY

FINAL HEIGHT, TARGET HEIGHT AND THE COMMUNITY

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Height varies with age, and it varies with historic time. Final height is determined by endocrine parameters and

genetics, by nutrition and health, by environmental factors, by birth weight, early growth, BMI, and developmental tempo. European populations of the 19th century were short, but their shortness did not result from growth impairment at all ages. In those days, shortness was mainly due to a significantly blunted adolescent growth spurt. New modelling approaches suggest an independent regulation of adolescent growth and final height: the target for growth and final height appears to be set by the community. In order to test this hypothesis, we formed a geographic network of Switzerland consisting of 169 nodes (district capitals) and 335 connecting edges (roads), and investigated military conscript data obtained between 2004 and 2009. Average height of Swiss military conscripts was 178.2 cm (SD 6.5 cm). But conscripts from first order neighbouring districts were more similar in height than expected. Short stature districts have short, tall stature districts have tall neighbours. We found significant height correlations between 1st (r=0.58), 2nd (r=0.64), 3rd (r=0.45) and even 4th order neighbours (r=0.42). It appears that tall stature communities generate tall people, short stature communities generate short people, and migrants orientate towards the new height target of their host population (community effect on growth).

Keywords: Height, influencing factors, conscripts.

РЕЗЮМЕ

КОНЕЧНЫЙ РОСТ, ЦЕЛЕВОЙ РОСТ И ОБЩЕСТВО

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Рост меняется вместе с возрастом и в историческом аспекте. Конечный рост детерминирован эндокринными параметрами и генетикой, факторами среды, весом при рождении, ранним развитием, индексом массы тела и темпом роста. В XIX веке население в Европе было низкорослым, однако низкорослость не была обусловлена нарушением роста в возрастных периодах - основной причиной низкорослости был недостаточно выраженный спурт роста у подростков. Согласно новым подходам моделирования, регуляция роста подростков и конечный рост не зависят друг от друга. Создается впечатление, что целевой рост и конечная высота определяются общиной. Для проверки данной гипотезы авторами статьи создана георграфическая сеть Швейцарии, состоящая из 169 узлов (районные центры) и 335 краев (дороги). Проанализированы данные физического развития призывников 2005-2009 гг. Их средний рост составил 178.2 см (SD 6.5 см). Существенная корреляция по росту имела место в соседних общинах I порядка (r=0.58), II порядка (r=0.64), III порядка (r=0.45) и, даже, IV порядка (r=0.42). Таким образом, остается впечатление, что в общинах с высокой статурой имеют высокий рост, а с низкой – более низкий. У мигрантов, целевой рост ориентируется на показатели, характерые для тех общин, куда они переселились (влияние общины на рост).

რეზიუმე

საბოლოო სიმაღლე, სამიზნე სიმაღლე და საზოგადოება

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სიმაღლე იცვლება ასაკთან ერთად და ისტორიულ გარემოში. საბოლოო სიმაღლე დეტერმინირებულია ენდოკრინული და გენეტიკური ფაქტორებით, კვებით, ჯანმრთელობით, გარემოს ფაქტორებით, დაბადების წონით, ადრეული განვითარებით, სხეულის მასის ინდექსით და განვითარების ტემპით. XIX საუკუნეში ევროპის მოსახლეობა იყო ტანდაბალი, მაგრამ ტანდაბლობა არ იყო განპირობებული ზრდის დარღვევით ყველა ასაკობრივ პერიოდებში. იმ პერიოდში ტანდაბლობა განპირობებული იყო მოზარდობაში ზრდის სპურტის ნაკლები გამოხატულობით. მოდელირების ახალი მიდგომების თანახმად, მოზარდთა ზრდისა და საბოლოო სიმაღლის რეგულაცია დამოუკიდებლად მიმდინარეობს. რჩება შთაბეჭდილება, რომ სამიზნე სიმაღლე და საბოლოო სიმაღლე საზოგადოების მიერ დგინდება. ამ ჰიპოთეზის შესამოწმებლად ავტორების მიერ შედგენილია შვეიცარიის გეოგრაფიული ბადე, რომელიც შედგებოდა 169 კვანძისაგან (რაიონების ცენტრები) და 335 მხარისგან (გზები). გაანალიზებულია 2005-2009 წლებში სამხედრო სამსახურში გაწვეული პირების მონაცემები. მათი საშუალო სიმაღლე იყო 178.2 სმ (SD 6.5 სმ). სიმაღლეში სარწმუნო კორელაცია აღინიშნებოდა I რიგის (r=0.58), II რიგის (r=0.64), III რიგის (r=0.45) და თვით IV რიგის სამეზობლოებშიც (r=0.42). ამრიგად, რჩება შთაბეჭდილება, რომ მაღალი სტატურის თემებში ახალგაზრდებს აქვთ მაღალი სტატურა, ხოლო დაბალი სტატურის თემებში – უფრო დაბალი. მიგრანტებში სამიზნე სიმაღლე ორიენტირებულია იმ მაჩვენებლებზე, რომელიც დამახასიათებელია თემისთვის, სადაც ისინი დასახლდნენ (თემის ზეგავლენა სიმაღლეზე).

CLINICAL ANALYSIS OF 102 CASES OF EPSTEIN-BARR VIRUS INFECTIONS IN CHINESE CHILDREN

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Infectious mononucleosis (IM; also known as mono, glandular fever, Pfeiffer's disease, Filatov's disease, and sometimes colloquially as the kissing disease from its oral transmission) is an infectious, widespread viral disease caused by the Epstein-Barr virus (EBV), one type of herpes virus, against which over 90% of adults are likely to have acquired immunity by the age of 40. In some cases, primary infection can result in infectious mononucleosis [9]. Epstein-Barr virus (EBV) establishes lifelong latent infection. Almost every adult (about 90%) acquires EBV and will be seropositive to this virus [3].Occasionally, the symptoms can recur at a later period. Most people are exposed to the virus as children, when the disease produces no noticeable or only flu-like symptoms. In developing countries, people are exposed to the virus in early childhood more often than in developed countries. As a result, the disease in its observable form is more common in developed countries. It is most common among adolescents and young adults [8].

Especially in adolescents and young adults, the disease is characterized by fever, sore throat and fatigue, along with several other possible signs and symptoms. It is primarily diagnosed by observation of symptoms, but suspicion can be confirmed by several diagnostic tests. It is generally a self-limiting disease, and little treatment is normally required [13]. It is well known that EBV is common opportunistic infection agents in the immunocompromised, including human immunodeficiency virus-infected individuals, and are a major source of serious viral complications in organ transplant recipients [4]. Children are also a susceptible population at high risk of EBV infection. During growth and development, EBV infection can depress the host immune response: this is a major cause of recurrent childhood microbial infection [10]. Cytomegalovirus and EBV have so much in common,coinfection with these two viruses occurs occasionally in children [1].

A drug allergy, viral or bacterial infection and other causes of infectious mononucleosis in children is called infectious mononucleosis syndrome. The clinical analysis of 102 cases children of EB virus in April 2012 to October 2013 in Pediatric Dept of Shaanxi Provincial People's Hospital are summarized as follows.

Material and methods.

1.1 General data

In the 102 cases, 67 male cases (65.69%), 35 female cases (34.31%), and the ratio of men to women age is 1.9:1; 12 cases (11.76%) of children under 1 year old, 12 cases (11.76%) 1-3 years old, 56 cases (54.90%) of 3-7 years old, 12 cases (11.76%) of 7-14 years old, and mostly are in preschool children. 60 children cases were diagnosed with infectious mononucleos, accounting for 58.82%, they are in line with the diagnostic criteria of IM; 16 cases of atypical EB virus infection , 26 cases of EB infection, accounting for 25.49%. The cause of the difference in gender distribution is unclear.

1.2 Clinical manifestations

85 cases of fever (83.33%), 42 cases cervical lymph node enlargement (41.18%), 13 cases where in the heating with neck lymph nodes (12.74%), cough 35 cases (34.31%), including 25 cases fever with cough (24.51%), hepatomegaly 19 cases (18.63%), changes, revealed by abdominal B-mode ultrasound -22 cases (21.57%). The fever was the main clinical manifestation.

1.3 Laboratory examination

67 cases of the white blood cell increase (65.69%), 58 cases of blood VCA-IgM, EA-IgG was positive (56.86%), 29 cases of specific lymphocyte more than 10 percent (28.43%), 56 cases of the specific lymphocyte quantitative +EB positive (54.9%), 38 cases of abnormal liver function (37.25%).

1.4 The treatment and prognosis

In addition to general symptomatic treatment after diagnosis, 92 cases were treated with ganciclovir antiviral therapy, everyday 5-10mg/kg, intravenous drip, 1 times/d, period of treatment is 7-10d. In 10 cases of intravenous injection of gamma globulin in 400 mg/ (kg · d), 1 times a day, for 4-5 days, can make the improvement of clinical symptoms. If is the merger of bacterial infections, use antibiotics, the clinical signs and symptoms gradually improved, all the laboratory indexes back to normal, all clinical improved or cured, there are no death or ineffective treatment in children.

Results and their discussion. The clinical manifestation of children with EB virus infection is varied. There are 60 (58.8%) cases Children with infectious mononucleosis, 26 (25.49%) cases Epstein-barr virus infection ,16 cases atypical EB virus infection,accounting for 15.67%. 78% children were under 7 years of age, 12% were 7 to 14 years of age. There are differences in the symptoms and signs among the different age groups.

This study showed that EBV-associated IM in Chinese children still occurs mostly in young children less than 7 years of age, with a peak incidence at 3 to 7 years. The

incidence of fever and headache, fever duration, the proportion of females to males, and liver enzyme elevation all showed positive association with advancing age in children with EBV-associated IM. When compared to previous Chinese studies about 15 years ago, the age distribution was similar and the incidence of hepatosplenomegaly was lower in our Study.

We studied the clinical and laboratory presentation of 102 patients with EBV VCA IgM positive IM patients aged from 13 months to 14 years. The pathogenesis of EBV remains unknown [5]. Although EBV-infected T cells and NK cells have been found to play a central role [6,7,12]. The virus has secretions mainly in oral cavity, so oral transmission is an important route of transmission. According to the data display, it is most common in preschool children, accounting for 41.94%. Thus, the IIF method to detect antibodies may merely indicate that a child has been infected with a respiratory pathogen between one week and three months before the sample was obtained [11]. The majority of patients with primary infections are usually asymptomatic, except for the acute infectious mononucleosis that is most common in China in children in the 3-6 years age group.In most Chinese studies, the proportion of IM in the disease spectrum is only about 20%, and the most common effect is respiratory tract infection (about 40% compared with 30% in our study) [2].

In the 102 cases, 67 male cases (65.69%), 35 female cases (34.31%), and the ratio of men to women age is 1.9:1; 12 cases (11.76%) of children under 1 year old, 12 cases (11.76%)1-3 years old, 56 cases (54.90%) of 3 - 7 years old, 12 cases (11.76%) of 7-14 years old, and mostly are in preschool children.

Characterized by irregular fever, angina, systemic lymph node enlargement and the typical change of hemogram, peripheral blood mononuclear cells and atypical lymphocytes increased significantly. The disease usually has fever, ranging from 38.5-40, no fixed heat type, fever process mostly 1-2 weeks, a few up to several months. Some patients have no obvious fever, but has other symptoms. The majority of patients with superficial lymph node enlargement, can appear in the first week of illness. In the peak of the disease, systemic lymph node involvement, the neck is the most common, elbow block lymph node enlargement often prompted the possibility of this disease, lymph node without adhesion, tenderness is not apparent, fade often in several weeks of the heat back. Mesenteric lymph nodes, can be accompanied by abdominal pain, axillary and inguinal lymph nodes were only found in the long disease duration. Liver in about 20-62%, most in the rib within 2 cm, can appear abnormal liver function, some part has mild jaundice. About half of patients have mild splenomegaly, with pain and tenderness. The characteristic is: the early onset of peripheral blood leukocyte count can be normal or low, then gradually increased, high up to 30×109-50×109/L. White blood cell classify at early stage, neutrophilia, after lymphocyte number can reach more than 60%, and the emergence of a large number of heterotypic lymphocytes, atypical lymphocytes more than 10% or its absolute value is more than 1*109/L, with diagnostic significance. EBV primary infection can occur in infants 2-3 months after the disappearance of maternal antibody, EBV specific antibody detection and quantitative detection of EBV-DNA has important value in the diagnosis of the diagnosis of the disease.

The clinical manifestations of the disease are very diverse, can affect multiple systems in the nervous system, mainly for the viral encephalitis or multiple neuritis, renal involvement mainly for hemorrhagic nephritis, mainly involving the lung respiratory interstitial, interstitial pneumonia, but generally not associated with severe and persistent complication. The blood system and more complications, but generally does not appear the bone marrow suppression.

In this paper of 102 cases of EB infection in children, has the most favorable prognosis, the data also confirmed this point, because about this disease there is no effective preventive measures, clinical manifestations are diverse and complex, patient of mild disease only fever, angina, head and neck lymph node enlargement, but a severity patient merge the vital organ damage, this explained that EB virus enter into the human body can cause different degree of system damage, some malignant diseases including nasopharyngeal cancer, Hodgkin's disease was also associated with EB virus infection. Therefore, clinicians should raise the awareness of the disease, reduce misdiagnosis, diagnose earlier, treat earlier, prevent the appearence of serious complications.

In **conclusion**, this study showed that EBV-associated IM in Chinese children still occurs mostly in young children less than 7 years of age, with a peak incidence at 3 to 7 years. The incidence of fever and headache, fever duration, the proportion of females to males, and liver enzyme elevation all showed positive association with advancing age in children with EBV-associated IM. When compared to previous Chinese studies about 15 years ago, the age distribution was similar and the incidence of hepatosplenomegaly was lower in our Study.

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SUMMARY

CLINICAL ANALYSIS OF 102 CASES OF EPSTEIN-BARR VIRUS INFECTIONS IN CHINESE CHILDREN

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The purpose of this study is to investigate the clinical manifestations and disease severity, to evaluate the recent trend of clinical manifestations and differences in the clinical and laboratory findings of EBV-associated IM (infectious mononucleosis) according to the age of children.

We retrospectively collected cases on hospitalized patients a majority of 7 years old with characteristic symptoms of IM and serologically diagnosed EBV-associated IM at Shaanxi Provincial Peoples University Hospital in Xi'an from Apr, 2012 to Oct, 2013. All their medical records were reviewed and analyzed. For each patient, clinical, laboratory data and outcome were collected retrospectively and compared to previous studies to evaluate the differences between the clinical and laboratory findings of patients of different ages.

The clinical manifestations in children with EB virus infection varied. There were 60 (58.8%) cases of children with infectious mononucleosis, 26 (25.49%) cases of Epstein-barr virus infection,16 cases of the atypical EB virus infection, accounting for 15.67%. 78% children were under 7 years of age, 12% were 7 to 14 years of age. There are differences in the symptoms and signs among the different age groups.

The clinical manifestations in children with EB virus infection involved multiple systems and produced harm is heavier and should be paid attention to during the treatment. The disease continues to occur mostly in children under 10 years of age. When compared to previous Chinese studies about 15 years ago, the age distribution was similar and the incidence of hepatosplenomegaly was lower in our study.

Keywords: Epstein-Barr virus, infectious mononucleosis, children.

РЕЗЮМЕ

АНАЛИЗ 102 СЛУЧАЕВ ИНФЕКЦИИ ЭПШТЕЙН-БАРРА У КИТАЙСКИХ ДЕТЕЙ

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Цель исследования - определение современных трендов клинических проявлений и показателей тяжести у детей различного возраста при инфекционном мононуклеозе, ассоциированном с инфекцией вируса Эбштейн-Барра.

Ретроспективно проанализированы клинико-лабораторные данные 102 детей, 67 мальчиков и 35

девочек с клинической картиной инфекционного мононуклеоза; 78% детей были младше 7 лет. Серологические исследования на вирус Эбштейн-Барра проведены у всех детей. Дети были госпитализированы в университетский госпиталь провинции Шаанкси в период с апреля 2012 года до октября 2013 года. Данные сравнивались с результатами предшествующих исследований. В 60 (58.8%) случаях поставлен диагноз инфекционного мононуклеоза, в 26 (25.49%) – инфекция Эпштейн-Барра, в 16 (15.67%.) – атипичная инфекция Эпштейн-Барра. С увеличением возраста отмечается отягощение клинических проявлений. Сравнение с результатами аналогичного исследования, проведенного 15 лет назад, показало, что возрастное распределение осталось тем же, частота гепатоспленомегалии уменьшилась.

რეზიუმე

ებშტეინ-ბარის ვირუსის ინფექციის 102 შემთხვევის ანალიზი ჩინელ ბავშვებში

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სამედიცინო დეპარტამენტების ასპირანტების 2011 წლის გამოშვება, ჩსრ

კვლევის მიზანი - ებშტეინ-ბარის ვირუსის ინფექციასთან ასოცირებული ინფექციური მონონუკლეოზის კლინიკური გამოვლინებებისა და სიმძიმის მაჩვენებლების თანამედროვე ტრენდების დადგენა სხვადასხვა ასაკის ბავშვებში.

რეტროსპექტულად გაანალიზებულია ინფექციური მონონუკლეოზით დაავადებული 102 ბავშვის (67 ვაჟი,35 გოგონა) კლინიკურ-ლაბორატორიული მონაცემები; 78% პაციენტების ასაკი იყო 7 წელზე ნაკლები. სეროლოგიური კვლევა ჩატარდა ყველა შემთხვევაში. ბავშვები ჰოსპიტალიზირებული იყვნენ შაანქსის პროვინციის უნივერსიტეტის ჰოსპიტალში 2012 წლის აპრილიდან 2013 წლის ოქტომბრამდე. შედეგები შედარებული იქნა წინა კვლევების მონაცემებთან.

60 შემთხვევაში დაისვა ინფექციური მონონუკლეოზის დიაგნოზი,26-ში ეპშტეინ-ბარის ვირუსული ინფექცია, 16-ში - ატიპიური ეპშტეინ-ბარის ვირუსული ინფექცია. ასაკის მატებასთან ერთად აღინიშნებოდა კლინიკური გამოვლინებების დამძიმება. 15 წლის წინ ჩატარებული კვლევის შედეგებთან შედარებისას დადგინდა,რომ ასაკობრივი განაწილება იგივეა, ჰეპატოსპლენომეგალიის სიხშირე იკლო.

FUZZY APPROACHES IN PEDIATRICS

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Since fuzzy set theory was developed by L. Zadeh in 1965 [39] usage of this methodology in medicine were proposed many times. Some of them are considered only from theoretical point of view, another are real practical applications.

Fuzzy logic pure and in cooperation with other branches of computational intelligence such as neural networks and evolutionary algorithms offers a sound theoretical basis for applications, in particular, in medicine. Not mentioned numerous of scientific articles, magazines, conferences, workshops, papers, (only query "Fuzzy logic + medicine" in Google or in MEDLINE® database shows 620.000 and 34.900 sites respectively), it is worth to point out at least the recent fundamental books devoted to fuzzy logic and medicine [4,23,33,35].

The main explanation why fuzzy logic is so popular in applications to medical problems is simple: uncertainty and vagueness inherent to the whole medical environment can be modeled with this theory for computing. It is interesting to mention, that the seminal paper of Lotfi Zadeh [39] that is a point of departure of the fuzzy logic development, was motivated by the discrepancies between the strict

mathematical techniques and real situations in biology and medicine, and, in general, humanistic systems:
". . .mainstream mathematical techniques - aimed as they were, and still are - at the analysis of mechanical systems, did not provide effective tools for the analysis of biological, or, more generally, humanistic systems in which human judgment, perceptions and emotions play an important role". Since that time fuzzy logic attachedly serves for medicine (see, for example, [1]).

From the first system, so called "grandfather" of medical expert systems MYCIN [30], the history of medical expert system development has done a long way. Through the CADIAG [2], MILORD [10], CASNET , INTERNIST [20] and many other medical expert systems based on fuzzy logic and successfully working in many medical directions (see, e.g., [7,14,35]), a fuzzy logic community in medicine has reached a certain level, however, with particular important conclusions: the prophesied golden role of FL has still not come to full fruition in medicine. Probably the reason is the same as under construction of each intelligent system which tries to take over some human functions to facilitate this "terrestrial life" [28]. To achieve the great degree of protagonism for FL in medicine the following steps have to be done [4]: a) new theoretical contributions as well as new methodologies which are adequate for the specifics of the domain are needed; b) there is a need for design and computational implementation tools; c) the design of intelligent systems in medicine should be approached from the heterogeneous perspectives. These general directions formulated - due to L. Zadeh ([4], a foreword) - by "two prominent informaticians" and active researchers in the field S. Barro and R. Marín, can position our contribution among others that try to systematically describe the application of fuzzy logic in different medical directions. For our review we use so called the general scheme that allow to consider the different applications in pediatrics and adolescence medicine from the unique point of view. The idea of this general scheme simply comes from everyday observations: a physician, making conclusions about a patient's state, takes into account manifestations, symptoms, signs, tests, other information about a patient and based on the professional experience, knowledge and intuition, makes a diagnosis. A formal representation of this process allows to consider the different existing approaches not as separate parts valid only for particular applications, but as a part of a unique approach. From one side this view allows easy understanding of the described processes and from another, imparts a nice flexibility and variety of representations under the unique theoretical background. The introduced scheme facilitates the conversation and negotiations with a medical expert when the knowledge for an expert system is collected. Without detailed mathematical explanations the proposed scheme allows clearly to represent the modeled processes to physicians, who as usually have no special technical education. This general scheme allows to describe the interesting applications of fuzzy logic in pediatrics in a unique framework.

Due to the traditional terminology of Artificial Intelligence [11], knowledge representation, knowledge acquisition, knowledge processing are components of each knowledge-based system (Fig. 1).

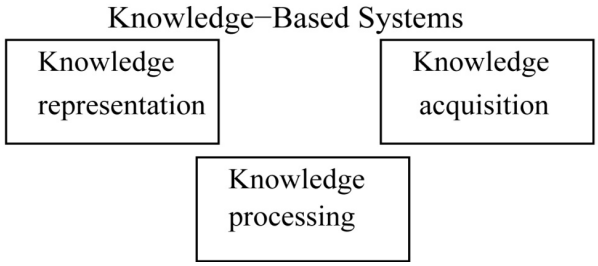


Fig. 1. The components of a knowledge-based system

Medical expert systems are a kind of knowledge-based systems. It is known that an expert system is a program that embodies the knowledge of experts in a particular field and allows non-expert users to access it. They have an idealized structure as is shown in Figure 2 [32]. Also in the ideal case, the inference engine (program) should draw conclusions independently of the domain described in the knowledge base (data). But a very general-purpose program proves to be much less efficient than one which is specialized to the task in hand [32]. Therefore a compromise should be found.

Medical consultation systems and decision support systems generalize medical expert systems by emphasizing their broader range of used methods, instead of focusing on the expert knowledge (Fig. 3). The expert knowledge is often regarded as equal to production (if-then) rules in their various forms. In fuzzy expert systems, the knowledge is usually represented by a set of fuzzy production rules, which connect antecedents with consequences, premises with conclusions, or conditions with actions. They most commonly have the form "If F then G" where F and G are fuzzy sets [19].

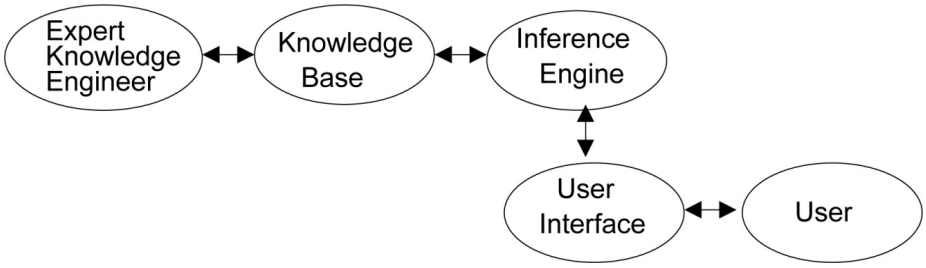


Fig. 2. An expert system

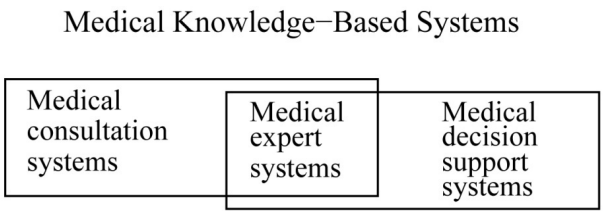


Fig. 3. One classification of medical knowledge-based systems

2 Fuzzy sets and fuzzy logic

Formal description of fuzzy sets and fuzzy logic will be done in the next sections. The term "fuzzy logic" has the meaning of the theory of approximate reasoning, in particular, reasoning based on fuzzy production rules.

2.1 Uncertainty and vagueness in medicine

The information used in medicine is imperfect in the sense described above. It is uncertain, incomplete, inaccurate, inconsistent, vague, unsharp, imprecise. This list can be continued.

Examples can be found everywhere in medicine. Patients cannot describe exactly what has happened to them or how they feel, their information is subjective, exaggerated, underestimated, or incomplete.

Doctors and nurses cannot tell exactly what they observe, mistakes can be made in the physical examination, and symptoms may be overlooked. Laboratories report results only with some degree of error, and exact borderline between normal and pathological is often unclear. X-rays and other similar procedures require correct interpretation of the results. Physiologists do not understand precisely how the human body works, medical researchers cannot precisely characterize how disease alter the normal functioning of the body, pharmacologists do not fully understand the mechanisms accounting for the effectiveness of drugs, and no one can precisely determine one's prognosis. In the face of the uncertainty concerning the observed symptoms of the patients as well as the uncertainty concerning the relation of the symptoms to a disease entity, it is nevertheless crucial that the physician determines the diagnostic label that will entail the appropriate therapeutic regimen [18,34].

2.2 Fuzzy logic basic notions

"Fuzzy logic has been and to some extent still is an object of controversy. Some are turned-off by its name. But, more importantly, fuzzy logic is tolerant of imprecision and partial truth. It is this tolerance that is in conflict with the deep-seated Cartesian tradition of aiming at truth which is bivalent, with no shades of grey allowed.

There are many misconceptions about fuzzy logic. In large measure, the misconceptions reflect the fact that the term "fuzzy logic" has two distinct interpretations. More specifically, in a narrow sense, fuzzy logic is the logic of approximate reasoning: But in a wider sense which is in dominant use today fuzzy logic, denoted as FL, is coextensive with the theory of fuzzy sets, and contains fuzzy logic in a narrow sense as one of its branches. In fact, most applications of FL involve modes of analysis which are computational rather than logical in nature [38].

In this section the uniform notation of fuzzy sets and their properties has been formulated. This is based on the definition of a fuzzy set as a function which maps from the set U to the unit interval.

Definition 3. Assume U is a universe. A fuzzy set F (or a fuzzy subset F of U) is defined as a mapping:

$$\mu_F : U \rightarrow [0, 1]$$

In the framework of fuzzy set theory μF is called also the membership function. This terminology stresses the idea that for each x ∈ U, μF (x) indicates the corresponding membership value.

Let F,G, F' and G' be fuzzy sets; $F, F' : U \rightarrow [0, 1]$; $G,G' : V \rightarrow [0, 1]$. The inference scheme for fuzzy logic is as follows: given a fuzzy rule $F \Rightarrow G$ ("IF F THEN G") and the fact F' we can infer G' (provided that from F we can infer G). And can be interpreted as follows

$$G'(y) = \sup\{\min(F'(x), \min(F(x),G(y))) \mid x \in U\} \quad (1)$$

This interpretation is often used in the practical applications.

Let fuzzy sets $F, F_1, \ldots, F_n, G, G_1, \ldots, G_n$ be defined on a universe U and a rule-base be given. In applications, a fuzzy rule base is usually composed of finitely many rules of the form

$$\text{IF } L_1 = T_1 \text{ and } \ldots \text{ and } L_n = T_n \text{ THEN } L_{n+1} = T_{n+1} \quad (2)$$

where $L_1, \ldots, L_n, L_{n+1}$ are linguistic variables and $T_1, \ldots, T_n, T_{n+1}$ are linguistic terms assigned to the linguistic variables. An interpretation assigns to every linguistic variable L_i a non-empty set U_i and to every term T_i a fuzzy set F_i on U_i. After using the appropriate mapping from $[0, 1]^n$ to [0, 1] interpreting "and", the fuzzy set F can replace the expression $L_1 = T_1$ *and* $\ldots$ *and* $L_n = T_n$ and the fuzzy set G can replace $L_{n+1} = T_{n+1}$. If there are more than one rule in the rule-base, the following inference mechanisms can be used.

The fuzzy relations $S_i(x, y)$ ($\forall x, y \in U$ and i ∈ {1, . . . , n}) are defined as:

$$S_i(x, y) = min(F_i(x),G_i(y)) \qquad S(x, y) = max(S_1(x, y), \ldots, S_n(x, y))$$

For a fuzzy set $F : U \rightarrow [0, 1]$ operators *FATI(F)* and *FITA(F)* are defined by

$$FATI(F) = F \circ S \quad (3)$$
$$FITA(F) = F \circ S_1 \cup \cdots \cup F \circ S_n. \quad (4)$$

For a fuzzy set $F : U \rightarrow [0, 1]$ and a fuzzy relation $S : U \times U \rightarrow [0, 1]$ the standard product $F \circ S$ is defined as:

$$(F \circ S)(y) = \sup \min(F(x), S(x, y))x \in U.$$

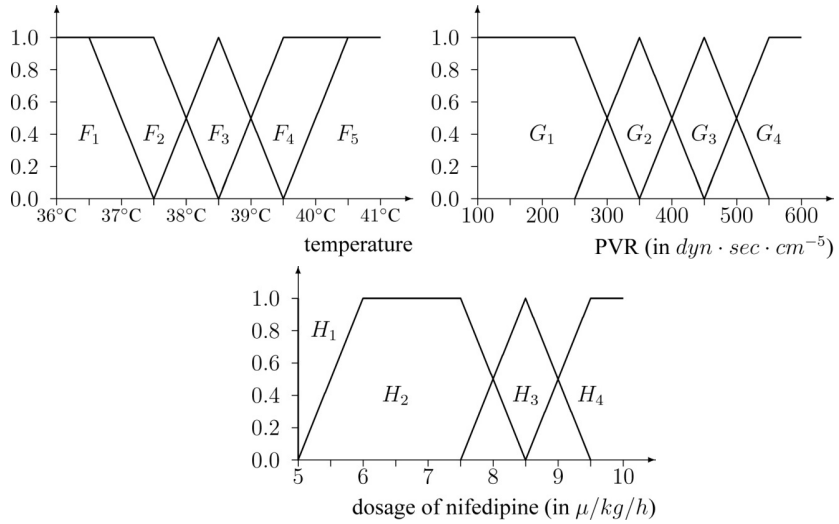
To make above mentioned formula more clear for physicians, let us consider an example, that illustrates the theoretical definitions.

Approximate reasoning is a main part of *fuzzy expert systems* [5,8,9,12,15,16,25,31,36,37]. In the following the inference mechanism of a "toy-example" of a medical expert system is demonstrated. The parameters are taken from the intensive care units (ICUs) [13].

The rule-base is given:

IF *F1* : temperature is very low	THEN *G1* : pulmonary vascular resistance is small
IF *F2* : temperature is low	THEN *G1* : pulmonary vascular resistance is small
IF *F3* : temperature is middle	THEN *G2* : pulmonary vascular resistance is little
IF *F4* : temperature is high	THEN *G3* : pulmonary vascular resistance is middle
IF *F5* : temperature is very high	THEN *G4* : pulmonary vascular resistance is high
IF *G1* : pulmonary vascular resistance is small	THEN *H1* : no dosage of nifedipine
IF *G2* : pulmonary vascular resistance is little	THEN *H2* : dosage of nifedipine is low
IF *G3* : pulmonary vascular resistance is middle	THEN *H3* : dosage of nifedipine is middle
IF *G4* : pulmonary vascular resistance is high	THEN *H4* : dosage of nifedipine is high

In other words, there are two groups of rules (it is so called two level inference process [22, 6]), the first is from temperature to pulmonary vascular resistance and the second is from pulmonary vascular resistance to dosage of nifedipine : Fuzzy sets are defined as shown on the following diagrams. A universe $U =_{def} [36^0C, 41^0C]$ is for temperature, a universe $V =_{def} [100dyn \cdot sec \cdot cm^{-5}, 600\ dyn \cdot sec \cdot cm^{-5}]$ is for degrees of the pulmonary vascular resistance (PVR) and a universe $W =_{def} [5\mu/kg/h, 10\ \mu/kg/h]$ is for nifedipine.



Here the fuzzy set F_1 is temperature is very low, the fuzzy set G_1 is pulmonary vascular resistance small and so on[1]. The fuzzy set H_1 no dosage of nifedipine is defined as:

$$H_1(z) =_{def} \begin{cases} 1, & if\ z = \frac{5\mu}{\frac{kg}{h}} \\ 0, & if\ z \neq \frac{5\mu}{\frac{kg}{h}} \end{cases}$$

$\forall$ z $\in$ W.

[1]*Here modifier "very" is choosed empirically.*

Our task is to define the nifedipine dosage for the patient with the temperature 39^{0}C. We use FITA method for inference and COM for defuzzification.

The input value $F(x) = F_{39^\circ C}(x)$ in our case is a singleton, i.e., a fuzzy set $F_{x0} : U \to [0, 1]$:

$$F_{x_0}(x) =_{def} \begin{cases} 1, & if\ x = x_0 \\ 0, & if\ x \neq x_0 \end{cases}$$

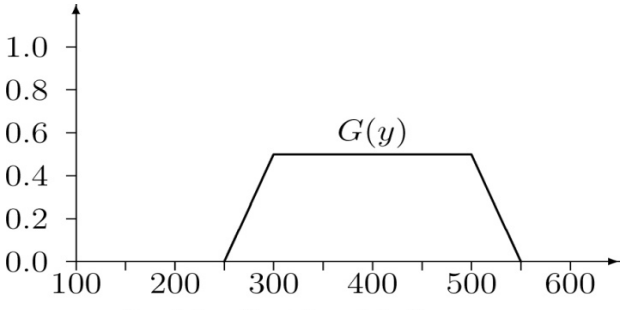
For the first level inference process FITA is as follows: $\forall y \in V$

$$G(y) = \max \begin{cases} F_{39^\circ C}(x) \circ S_1(x,y) \\ F_{39^\circ C}(x) \circ S_2(x,y) \\ F_{39^\circ C}(x) \circ S_3(x,y) \\ F_{39^\circ C}(x) \circ S_4(x,y) \\ F_{39^\circ C}(x) \circ S_5(x,y) \end{cases} \Rightarrow \quad (5)$$

$$\Rightarrow \max \begin{cases} \sup\{\min(F_{39^\circ C}(x), \min(F_1(x), G_1(y)))|x \in U\} \\ \sup\{\min(F_{39^\circ C}(x), \min(F_2(x), G_1(y)))|x \in U\} \\ \sup\{\min(F_{39^\circ C}(x), \min(F_3(x), G_2(y)))|x \in U\} \\ \sup\{\min(F_{39^\circ C}(x), \min(F_4(x), G_3(y)))|x \in U\} \\ \sup\{\min(F_{39^\circ C}(x), \min(F_5(x), G_4(y)))|x \in U\} \end{cases} \Rightarrow \quad (6)$$

$$\Rightarrow \max \begin{cases} \min(F_1(39°\mathrm{C}), G_1(y)) \\ \min(F_2(39°\mathrm{C}), G_1(y)) \\ \min(F_3(39°\mathrm{C}), G_2(y)) \\ \min(F_4(39°\mathrm{C}), G_3(y)) \\ \min(F_5(39°\mathrm{C}), G_4(y)) \end{cases} \Rightarrow \quad (7)$$

$$\Rightarrow \max \begin{cases} \min(0.5, G_2(y)) \\ \min(0,5, G_3(y)) \end{cases} \quad (8)$$



result of the first level inference process

Applying COM defuzzification method we get:

$$y^{\cdot} = \frac{300 + 500}{2} = 400 \quad (9)$$

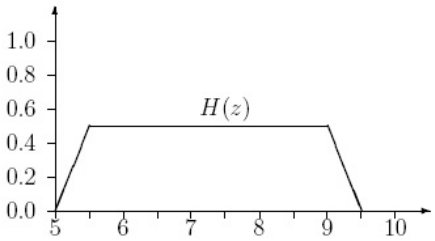
It means that pulmonary vascular resistance of the patient with 39^{0}C is equal *400 dyn·sec· cm^{-5}*.

Analogously, we get the result of the second level inference process: $\forall z \in W$

$$H(z) = \max \begin{cases} G_{400}(y) \circ S_1(y,z) \\ G_{400}(y) \circ S_2(y,z) \\ G_{400}(y) \circ S_3(y,z) \\ G_{400}(y) \circ S_4(y,z) \end{cases} \Rightarrow \quad (10)$$

$$\Rightarrow \max \begin{cases} \sup\{\min(G_{400}(y), \min(G_1(y), H_1(z)))|y \in V\} \\ \sup\{\min(G_{400}(y), \min(G_2(y), H_2(z)))|y \in V\} \\ \sup\{\min(G_{400}(y), \min(G_3(y), H_3(z)))|y \in V\} \\ \sup\{\min(G_{400}(y), \min(G_4(y), H_4(z)))|y \in V\} \end{cases} \Rightarrow \quad (11)$$

$$\Rightarrow \max \begin{cases} \min(G_2(400), H_2(z)) \\ \min(G_3(400), H_3(z)) \end{cases} \quad (12)$$



result of the second level inference process

After defuzzification we get

$$z^{\cdot} = \frac{5.5 + 9}{2} = 7.25\ z^{\cdot} = \frac{5.5 + 9}{2} = 7.25 \quad (13)$$

The dosage of nifedipine for the patient with the temperature 39^{0}C is equal *7.25 μ/kg/h*.

If defuzzification is not used between two levels of the inference process, *H(z)* is calculated as follows:

$$H(z) = max \begin{cases} G(y)^\circ S_1(y,z) \\ G(y)^\circ S_2(y,z) \\ G(y)^\circ S_3(y,z) \\ G(y)^\circ S_4(y,z) \end{cases} \quad (14)$$

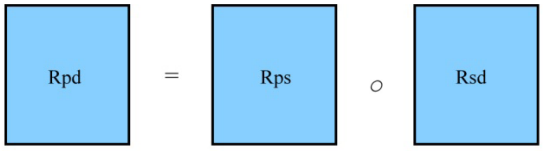
Description of this approach can be found in [22, 21,6].

As the complexity of a system increases, our ability to make precise and yet significant statements about its behavior diminishes until a threshold is reached beyond which precision and significance (or relevance) become almost mutually exclusive characteristics.

As was already mentioned in the Introduction, the idea to introduce a general scheme for medical diagnosis is based on the daily observation: a physician takes into account information about a patient and based on his/her professional experience, knowledge and intuition, makes a diagnosis. This can be presented as a following scheme in Figure 4(a), where block “diagnosis” denotes a decision of a physician about a patient, block “symptoms” denotes the information about a considered patient and block “medical knowledge”

represents a physician. In the case of a computer-assisted system a physician is "substituted" by a knowledge-based system. The arithmetic sign "=" can be read in this case as "as a result of" and "+" denotes the "combination". Of course, it is a very simplified version of the medical diagnosis process, but serves as a point of departure for the following formalizations.

(a) Medical diagnosis from daily observations



(b) Medical diagnosis from daily observation in symbolic form

Fig. 4. Diagnosis scheme with common-sense characterization and in symbolic form

Let rewrite Figure 4(a) as shown in Figure 4(b) with one-to-one correspondence between their elements: R_{PD} represents diagnosis, R_{PS} - symptoms, R_{SD} - medical knowledge and ∘ denotes the interaction between patient's symptoms and medical knowledge. R_{PD}, R_{PS}, R_{SD} belong to the sets of all diagnoses, all symptoms, all medical knowledge.

We believe, that the formal representation of the diagnostic process, i. e.,:

$$(R_{SD},\ R_{SP},\ \circ\ ,\ R_{PD}) \qquad (15)$$

can serve as **a general scheme** in the sense, that different interpretations of its components, i.e., R_{SD},R_{PS}, ∘, R_{PD}, correspond to the different types of knowledge representation and inference of different medical systems considered later.

We believe, that (15), interpreted in the fuzzy relation-based framework, is flexible enough to consider several systems from the general point of view, under the same umbrella, although their "facades" often differ at the first glance.

On the base of this scheme it is possible to explain the relationships between components in medical diagnosis. This scheme allows a physician to easily interact with each medical diagnosis system to accomplish the task.

4 Applications

4.1 How to predict the need for advanced neonatal resuscitation efforts in the delivery room

In [26] the authors propose the use of a fuzzy expert system to predict the need for advanced neonatal resuscitation efforts in the delivery room. This system relates the maternal medical, obstetric and neonatal characteristics to the clinical conditions of the newborn, providing a risk measurement of need of advanced neonatal resuscitation measures. It is structured as a fuzzy composition developed on the basis of the subjective perception of danger of nine neonatologists facing 61 antenatal and intrapartum clinical situations which provide a degree of association with the risk of occurrence of perinatal asphyxia. The resulting relational matrix describes the association between clinical factors and risk of perinatal asphyxia. Analyzing the inputs of the presence or absence of all 61 clinical factors, the system returns the rate of risk of perinatal asphyxia as output. If we consider this system from the general scheme perspectives, R_{PS}, R_{PD}, R_{SD} will be the clinical conditions of the newborn, 61 clinical factors, relational matrix describes the association between clinical factors and risk of perinatal asphyxia correspondingly.

4.2 Information about muscular coordination

In [29] an important tool for analysing the gait of children with cerebral palsy (CP), the surface EMG detected simultaneously at different muscles has considered , as it offers essential information about muscular coordination. However, the interpretation of surface EMG is a difficult task that assumes extensive knowledge and experience. As such, this noninvasive procedure is not frequently used in the general clinical routine. An Artificial Intelligence (AI) system for interpreting surface EMG, that is RPS in our denotations, signals and the resulting muscular coordination patterns could overcome these limitations. To support such interpretation, an expert system based on fuzzy inference methodology was developed. The knowledge-base of the system implemented 15 rules, it can be considered as R_{SD} from which the fuzzy inference methodology performs a prediction of the effectiveness of the muscular coordination during gait. i.e. R_{PD}.

4.3 Estimation of neonatal mortality

In [24] a fuzzy model to estimate the possibility of neonatal mortality was developed. A computing model was built, based on the fuzziness of the following variables: newborn birth weight, gestational age at delivery, Apgar score, and previous report of stillbirth. These parameters correspond to S in the denotation of the general scheme. The inference used was Mamdani method (1) and the output was the risk of neonatal death given as a percentage. R_{PD}. 24 rules were created according to the inputs that is RSDin the denotation of the proposed general scheme. The validation model used a real data file with records from a Brazilian city.

4.4 Risky decision making

In [27] a fuzzy-trace theory explains risky decision making in children, adolescents, and adults, incorporating social and cultural factors as well as differences in

impulsivity. Here, the authors provide an overview of the theory, including support for counterintuitive predictions (e.g., when adolescents "rationally" weigh costs and benefits, risk taking increases, but it decreases when the core gist of a decision is processed). This information can be considered as *S* presentation from the general scheme. Then, the authors delineate how emotion shapes adolescent risk taking - from encoding of representations of options, to retrieval of values/principles, to application of those values/principles to representations of options. The author's review indicates that: Gist representations often incorporate emotion including valence, arousal, feeling states, and discrete emotions; and Emotion determines whether gist or verbatim representations are processed. The authors recommend interventions (R_{PD})) to reduce unhealthy risk- taking that inculcate stable gist representations, enabling adolescents to identify quickly and automatically danger even when experiencing emotion, which differs sharply from traditional approaches emphasizing deliberation and precise analysis.

5 Conclusions

As can be seen from the above presented examples, the methodology of fuzzy sets can be easily applied for many medical problems, in particular, in pediatrics[17]. The proper definition of the membership functions and corresponding formulation of the rules using fuzzy methodology, lead to the natural representation of the medical problem for formalisation and computations. [3]

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SUMMARY

FUZZY APPROACHES IN PEDIATRICS

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In this paper we present a review of applications of fuzzy methods in children and adolescence health care. Based on the several examples, available from journal papers, conference proceedings and book chapters we have concentrate ourselves on problems in the pediatrics that have been or can be solved with the help of fuzzy methodology.

The paper is organised as follows. In section I we consider the general considerations about fuzzy logic and medicine. Section II considers the basics of fuzzy sets and fuzzy logic, the main methodological approaches for medical practical applications. Section III describes problems and the way of their solving using fuzzy approaches in pediatrics. Conclusions summarise the review in Section IV.

Keywords: fuzzy methods, application, pediatrics

РЕЗЮМЕ

НЕЧЕТКИЕ ПОДХОДЫ В ПЕДИАТРИИ

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В статье представлен обзор работ по применению методов нечеткой логики в здравоохранении детей и подростков. Основываясь на результаты текущей и ретроспективной научной литературы, авторы сконцентрировались на тех педиатрических проблемах, которые решены или могут быть решены посредством нечетких методик.

В статье рассмотрены основы нечеткой логики и теории размытых множеств, основные методические подходы для практического применения в медицине; дан перечень проблем в педиатрии и пути их решения посредством нечетких подходов.

რეზიუმე

არამკაფიო მიდგომები პედიატრიაში

[1]ტ. კისელიოვა, [2]ყ. ფაღავა

[1]ი. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, კომპიუტერული მეცნიერებების დეპარტამენტი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ბავშვთა და მოზარდთა მედიცინის მიმართულება, საქართველო

სტატიაში წარმოდგენილია ნაშრომების მიმოხილვა არამკაფიო ლოგიკის მეთოდების გამოყენების შესახებ ბავშვთა და მოზარდთა ჯანდაცვაში. რჩეულ სტატიებზე, კონფერენციის მასალებში შეტყობინებებისა და წიგნებში თავებზე დაყრდნობით ჩვენ დავკონცენტრირდით იმ პედიატრიულ პრობლემებზე, რომელიც გადაწყვეტილია ან შეიძლება გადაწყვეტილ იქნას არამკაფიო მეთოდიკების გამოყენებით. სტატიაში განხილულია ზოგადი მოსაზრებები არამკაფიო ლოგიკასა და პედიატრიაზე; არამკაფიო ლოგიკისა და არამკაფიო სიმრავლეების თეორიის საფუძვლები, ძირითადი მეთოდური მიდგომები მათი მედიცინაში პრაქტიკული გამოყენებისთვის; პედიტრიული პრობლემების ნუსხა და მათი გადაწყვეტის გზები არამკაფიო მიდგომების მეშვეობით; გამოტანილია დასკვნა.

CONGENITAL DISEASES OF THE GASTROINTESTINAL TRACT

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With the rapid increase in knowledge on the genetic origin of diseases within the gastrointestinal tract the number of congenital diseases, which already manifest during childhood have drastically increased [7]. Do to the large application of molecular genetics the number is steadily increasing. To make the access to these rare diseases fast and efficient the data base of the National Library of Medicine (Online Mendelian Inheritance of Man – OMIN) is a very helpful online tool, with which all these disease entities can be found easily (http://www.ncbi.nlm.nih.gov/omim) [11]. The following tables give an overview on the today's known congenital diseases of the GI-tract. Table 1 shows the diseases, in which the mutation is known, table 2 shows disease, in which the responsible chromosome has been indentified, but the mutation is still unknown and table 3 lists diseases, in which the genetic origin is still unknown.

All diseases have their OMIN number, which can be searched for in the NIH data base for further information.

Table 1. Gastrointestinal diseases with known genetic mutations

The first numbers of the OMIM code are related to the mode of inheritance: 1 = autosomal dominant, 2 = autosomal recessive, 3 = x-chromosomal recessive, 5 = mitochondrial.

Digestion, Hydrolysis, Absorption and Secretion

Carbohydrates
- Sucrase-Isomaltase-Deficiency(222900)
- Glucose-Galactose-Malabsorption (182380)
- Congenitale Lactase-Deficiency (223000)
- Adult Hypolactasia (223100)
- CDG (Carbohydrate deficient glycoprotein)-Syndrome Typ Ia (212065)

Amino acids
- Cystinuria, Typ 1 (220100)
- Hartnup Disease (234500)

Fat
- Abetalipoproteinemia (200100)
- Hypoalphalipoproteinemia (107680)
- Hypobetalipoproteinämie (107730)
- Morbus Anderson (246700)

Vitamins, Minerals, others and Combinations
- Congenital Chloride Diarrhea (214700)
- Congenital Sodium Diarrhea (270420)
- Congenitale Transcobalamine II-Deficiency (275350)
- Hereditary Hypophosphatemia Type II (307810)
- Primary Bile acid Malabsorption (601295)

Selective Vitamin E-Deficiency (277460)
Cystic Fibrosis (219700)
Menke's Disease (309400)
Hereditary Hemochromatosis (235200)
Acrodermatitis enteropathica (201100)
Enterokinase-Deficiency (226200)
Primary Hypomagnesemia (248250)
Triple-A Syndrome (231550)
Shwachman-Diamond-Syndrome (260400)
Johanson-Blizzard-Syndrome (243800)

Motility Disorders of Gastrointestinal Tract
Coffin-Lowry-Syndrome (303600)
Muscular Dystrophy Duchene (310200)
Morbus Hirschsprung Type I/II (142623/600155)
Myoneurogastrointestinal Encephalopathy (550900)
Myotonic Dystrophy Steinert-Batten (160900)
Morbus Wardenburg-Hirschsprung (277580)
IPEX-Syndrome (304790)

Gastrointestinal Polyposis, Polyps and Neoplasiás
Basal Cell Nevus Syndrome (109400)
Morbus Cowden (158350)
Leiomyomatosis of Esophagus
with Alport-Syndrome (308940)
Familial Adenomatous Polyposis coli
(Gardner Syndrom) (175100)
Familial infiltrative Fibromatosis (135290)
Hereditary Colon Carcinoma without Polyposis,
Type I/II (114500/114400)
Multiple endocrine Neoplasias, Typ I/IIb
(131100/162300)

Bleeding within the Gastrointestinal Tract
Venous Malformations, multiple cutaneous and mucosal (600195)
Haemophilia A/B (306700/306900)
Morbus Osler-Weber-Rendu, Typ I/II
(187300/600376)
Wiskott-Aldrich syndrome (301000)
CDG-Syndrome Ib Mannosephosphate-
isomerase-deficiency) (602579)

Structural Disorders of the Gastrointestinal Tract
Congenital Microvilluos Inclusion Disease (251850)
Tufting Enteropathy

Table 2. Gastrointestinal Diseases with known Localisations on one or several Chromosomes

Digestion, Hydrolysis, Absorption and Secretion
Carbohydrates
Alpha-Amylase Deficiency (104650)
Amino acids
Lysinuric Protein Intolerance (222700)
Lysin Malabsorption Syndrome (247950)
Fat
Pancreatic Lipase-Deficiency (246600)
Combined Lipase-Deficiency(246650)
Vitamins, minerals and others
Congenital Intrinsic-Factor Deficiency
(261000)
Congenital Vitamin-B12-Malabsorption
(261100)
Congenital Sodium-Hydrogen-Exchanger-
Deficiency (182307)
Congenital Folate Malabsorption (229050)
Congenital Iron Malabsorption (206200)

Motility disorders of the gastrointestinal tract
Oculopharyngeal Muscular Dystrophy (164300)
Riley-Day Syndrome (223900)
x-chromosomal Intestinal Neuronal Dysplasia
(300048)
Morbus Hirschsprung Typ III (600156)
Morbus Ondine-Hirschsprung (209880)
Ichthyosis Follicularis-Atrichia-Photophobia-
Syndrome (308205)
Myoneurogastrointestinal Encephalopathy-
Syndrome (603041)
Partial Agenesis of Corpus callosum(304100)

Diseases of the intestinal mucosa
Celiac disease (212550)
Morbus Crohn (266600)
Ulcerative colitis (191390)
Dihydropyrimidase deficiency (222748)

Gastrointestinal Polyposis, Polyps and Neoplasias
Juvenile Polyposis Coli (174900)
Heredit ary mixed Polyposis Syndrome (601228)
Peutz-Jeghers Syndrome (175200)
Tylosis with Esophagus Carcinoma (148500)
Muir-Torre Syndrome (158320)
Turcot Syndrome (276300)
Generalised juvenile Polyposis with Pulmonary
arterio-venous Malformations (175050)

Gastrointestinal Bleeding
Familial cutaneous Amyloidosis (301220)
Noonan-Syndrome (163950)
Thromboxane A Synthetase Deficiency (274180)
Hermansky-Pudlak Syndrome(203300)
Pseudoxanthoma elasticum (264800)
Thromcytopenia with Aplasia of Radius (274000)

Table 3. Gastrointestinal Diseases with unknown Origin

Digestion, Hydrolysis, Absorption and Secretion
Carbohydrates
Maltase-Glucoamylase Deficiency
(154360)
Satoyoshi Syndrome (600705)

Trehalase Deficiency (275360)

Amino acids

Blue Diaper Syndrome (211000)
Dibasic Aminoaciduria I (222700)
Methionine Malabsorption Syndrome (250900)
Intestinal Protein losing Syndrome (226300)
Congenital intestinal Lymphangiectasia (152800)
Villous edema and Enteropathy (600351)
Cow's milk Allergy (147050)

Motility disorders of the gastrointestinal tract

ABCD-Syndrome (600501)
Familial progressive Scleroderma (181750)
Familial visceral Myopathy Type I, II, III (155310)
Familial visceral Myopathy with external Oph thalmoplegia (277320)
Groll Hirschowitz Syndrome (221400)
Anal Sphincter Myopathy (105565)
Colon irritabile
Megacystis Microcolon Hypoperistalsis Syndrome (249210)
Neuronal Intestinal Dysplasia Type A/B (243180/601223)
Prune-Belly-Syndrome (100100)

Gastrointestinal Polyposis, Polyps and Neoplasias

Barrett's esophagus (109350)
Neurofibromatosis-Pheochromocytoma-Duodenal-Carcinoid-Syndrome (162240)
Polyposis of gastric Fundus without Polyposis coli (175505)

Gastrointestinal Bleeding

Blue-Rubber-Bleb Naevus (112200)
Hereditary Neurocutaneous Angioma (106070)
Vascular Hyalinosis (277175)

Other Diseases of the gastrointestinal Tract

Familial Giant Gastritis (Morbus Ménétrier) (137280)
Pachydermoperiostosis (167100)
Pearson-Syndrome (557000)
Deficiency of Secretory-Piece of IgA (269650)

Disturbances of Digestion, Hydrolysis, Absorption and Secretion

Lactose Intolerance

The congenital lactose deficiency is very rare and occurs almost only in Finland. It is an autosomal recessive disease with the occurrence of watery diarrhea after the introduction of breast milk. The enzyme activity of lactase-phlorizin-hydrolase in the intestinal mucosa is absent while the structure of the mucosa remains normal. The reason for the enzyme deficiency was found in coding gene of lactase-phlorizin-hydrolase on chromosome 2q21 [6]. 5 distinct mutations in 21 Finish families were indentified. Therefore a genetic test for this very rare condition is established.

The hypolactasia of adults is present in 1/3 to ½ of the world's population. In the affected subjects after an uneventful childhood the lactase activity is diminishing after the 3-4th year of life. After the ingestion of milk or other lactose containing milk products, watery diarrhea and abdominal colics occur. In populations, where milking animals were part of their culture, the lactase gene persisted. These lactase persisters are the genetic variant in the world. In Europe there is a North-South gradient with low incidence of hypolactasia in Scandinavia and high incidence in South-Europe. The prevalence in Georgia is unknown. In central Europe the prevalence is about 17% of the population. The genetic defect of hypolactasia is also on chromosome 2q21-22, but is located 13910 base pairs upstream of the lactase gene. It is characterized by a singular mutation C/C13910.

Diagnosis: the diagnosis can be established by the nutrition history and subsequent pathological H-2 breath test after lactose challenge. Enzyme activity in the intestinal mucosa is decreased and the C/C13910-mutation can be identified [13]. Although the enzyme activity is not inducible, affected individuals can support more lactose with age due to the increased fermentation in the large bowel.

Therapy: the decrease of lactose containing food. Yoghurt and hard cheese are better supported than milk. Lactase capsules are available as drug, also lactose free milk and yoghurts.

Sucrose-Intolerance

In sucrose intolerance the intestinal enzyme sucrase-isomaltase is deficient due to an autosomal-recessive mutation on the chromosome 3q25-q26 (15). Maltose is partially hydrolysed and sucrose as well as isomaltose are not hydrolyzed in the intestinal epithelial cells. The unhydrolyzed sucrose is transported into the colon and produces watery osmotic diarrhea and bloating when sucrose containing foodstuff is ingested. In general the affected individuals have no failure to thrive.

Diagnosis: the diagnosis is established by a pathological H-2 breath test after sucrose challenge or direct measurement of decreased sucrase-isomaltase activity in intestinal mucosa.

Therapy: elimination of sucrose containing food from the nutrition. The oral administration of bakers yeast or Saccharomyces cerevisiea (beer yeast) helps to hydrolyse ingested sucrose.

Glucose-Galactose-Malabsorption

The uptake of glucose and galactose is carried out by the sodium dependant glucose transporter 1 (SGLT-1), which

is located within the microvillus membrane of the intestinal absorptive cells. Is this transporter defective by a autosomal recessive mutation on the chromosome 22q13, life threatening watery diarrheas occur after the first feeding with breast milk or formula [8].

Diagnosis: the diagnosis is established be elimination of glucose and/or galactose and starch from the nutrition and by pathological H-2 breath test after glucose challenge. The mutation can be identified by molecular genetic testing. The structure of the intestinal mucosa is normal.

Treatment: After birth affected infants need to be fed with a carbohydrate free formula, to which step by step fructose is added gradually from 1-5%. Carbohydrate free formulas are available on the market. After the introduction of solid food these individuals are more or less pure meat eaters.

Fructose Malabsorption
The uptake of fructose in the intestine is performed by facilitated transport of the glucose transporter 5 (GLUT-5) located in the apical membrane of the intestinal absorptive cell. The abundance of GLUT-5 transporter varies within the population. About 5 % of the population have a lower abundance of this transporter and can therefore support less fructose containing foodstuff, which will lead to bloating and watery diarrhea in affected subjects. Particularly juices from apples, pears, cherries and oranges contain large amounts of fructose. When ingesting larger amounts of these juices, diarrhea and meteorism can occur in children below 6 years of age. The history of ingested fruits or fruit juices will lead to the diagnosis of fructose malabsorption.

Diagnosis: is established by a pathological H-2 breath test after fructose challenge.

Treatment: reduction of ingested fruits or juices or combination with sucrose containing food.

Trehalase Deficiency
The activity of the enzyme trehalase located in the microvillous membrane of the intestinal cells is decreased or is missing. The disaccharide trehalose, which is present in mushrooms, cannot be hydrolysed and leads to diarrhea in affected individuals after the ingestion of mushrooms. The role of trehalase in man is unclear, because it is only present in mushrooms and insects. It is speculated, that trehalase is an "old" enzyme, which might have been important in the development of mankind, where insects were part of the food chain.

Enterokinase (Enteropeptidase) Deficiency
Enterokinase is an enzyme within the brush border membrane of the duodenal mucosa and responsible for the hydrolysis of trypsinogen into trypsin, which also activates the other hydrolyzing enzymes chymotrypsinogen, proelastase and procarboxypeptidase. The enterokinase gene is located on chromosome 21q21. Mutations of the gene are known and domains of the enzyme show homologies with the LDL-receptor, complement C1r, the metalloproteinase meprin and the macrophage scavenger receptor MSR1. The light chain of enterokinase is homologue to the trypsin like serine proteinase 7. Also secondary defects of the enzyme in exocrine pancreatic insufficiency, e.g. cystic fibrosis, are described.

Mutations of the gene lead to profuse life threatening diarrheas after birth with severe failure to thrive, anemia and hypoproteinemia.

Diagnosis: determination of decreased enzyme activity within the intestinal mucosa

Treatment: Elemental diet or extensively hydrolysed formula. Later pancreatic enzyme replacements, when solid food is introduced.

Congenital Chloride Diarrhea
This autosomal recessive disease occurs already during pregnancy with severe fetal watery diarrhea in utero and after birth with failure to thrive. It occurs predominantly in Finland. The cause is a mutation of the DRA-chloride transporters, which is located in the close neighbourhood of the CFTR on the chromosome 7q22q31 [5]. Several mutations have been found in affected Finish patients. The DRA-chloride transporter is responsible for the exchange of Na^+/HCO_3^- in the lumen of the intestine.

The clinical symptoms are severe watery diarrhea with loss of chloride in stools and hypochloraemia. During pregnancy polyhydramnion occurs. Fluid filled loops of intestine of the fetus and the newborn can be seen by sonography. The images can be misinterpreted as mechanical ileus.

Diagnosis: In serum severe hypochloraemia occurs with metabolic alkalosis. In stool high concentrations of chloride are measured. The stools are acid.

Treatment: oral and/or parenteral administration of high doses of NaCl and KCl. A total parenteral nutrition can be necessary for longer periods. The prognosis is good by adequate replacement of chloride losses. The children growth and develop normally.

C*ongenital Sodium Diarrhea*
The congenital sodium diarrhea is due to defect in the sodium absorption in the intestine, because of a mutation in the SPINT2 gene [3]. The disease is characterized by sever secretory diarrhea, double sided channel artesian, common anomalies of fingers and erosions of the cornea.

Diagnosis: similar to congenital chloride diarrhea polyhydramnion is present during pregnancy. Fluid filled intestinal

loops are detected by sonography in the fetus and newborn. The liquid stools, which are often mistaken as urine, contain high concentrations of sodium up to 145 mmol/l. The concentration of chloride in stool is less than that of sodium. The stools are alkaline. Because of the additional anomalies the children are relatively easy to detect.

Treatment: Administration of sodium citrate and glucose-electrolyte solutions guarantee normal growth with persistent secretory diarrhea. The prognosis is worse than that of chloride diarrhea.

Congenital Hypomagnesaemia
This autosomal-recessive disease is characterized by malabsorption of magnesium in the intestine [9]. The absorption is only 15% that or normal absorption. Boys are two times more frequent affected than girls. The cause is a mutation in the claudin-16-gene located on chromosome 3q27 [14].

The first symptoms occur a few day after birth with severe hypomagnesaemia and hypocalcaemia leading to titanic convulsion which not answer to the administration of vitamin D or calcium. Some patients have loose stools, oedemas and protein losing enteropathy prior to the start of magnesium therapy.

Diagnosis: is established by the determination of very low magnesium levels in blood (lower than 1 mmol/l) and calcium lower than 3,5 mEq/l). Serum phosphate is variable, potassium in serum is normal. The structure of the intestine is normal. The absorption of other minerals and nutrients is also normal (glucose, fat, vitamins).

Treatment: Initially magnesium sulphate is administered i.m. (0,4 mmol/kg/day) together with orally given calcium gluconate (13 mmol/kg/day), vitamin D3 (40.000 IU /day) and phenytoin (7,5 mg/kg/day). Thereafter high doses of magnesium are given p.o. (10-20 g magnesium citrate/day) as replacement of losses. Prognosis is bad, some patients die before the age of 20 years.

Primary Bile Acid Malabsorption
This congenital disease is characterized by a lack of bile acid absorption in the intestine due to a mutation in the bile acid transporter SLC10A2 on chromosome 13q33 [17]. Four different mutations have been found in the SLC10A2 gene.
The clinical symptoms start shortly after birth with severe persistent diarrheas and loss of bile acids in stool more than 900 mg/m^2 body surface/day, hepatomegaly, failure to thrive, anasarca and diaper rash.

Diagnosis: Determination of increased bile acid concentrations in stools, decreased LDL-cholesterol in plasma, some times combined with elevated serum antibodies and detection of circulating immune complexes and decreased complement in plasma.

Treatment: Reduction of long chain fatty acids in the nutrition and replacements by MCT's. Supplementation of zinc improves the diarrhea, increases the fat absorption and improves the nutritional status.

Acrodermatitis enteropathica
Autosomal recessive inherited mutations in the solute carrier 39 (SLC39A4) on chromosome 8q24.3 lead to malabsorption of zinc in the intestine. The body stores of zincs are depleted. Girls are slightly more often affected than boys. After stopping breast feeding the infants develop bullous changes on their skins on mouth, hands, feet and ano-genital region (Fig. 1). The skin changes are seen together with loss of hair, paronychia and severe diarrhea. The children are lethargic, anorectic and show recurrent infections of the skin with candida, conjunctivitis, photophobia and glossitis.

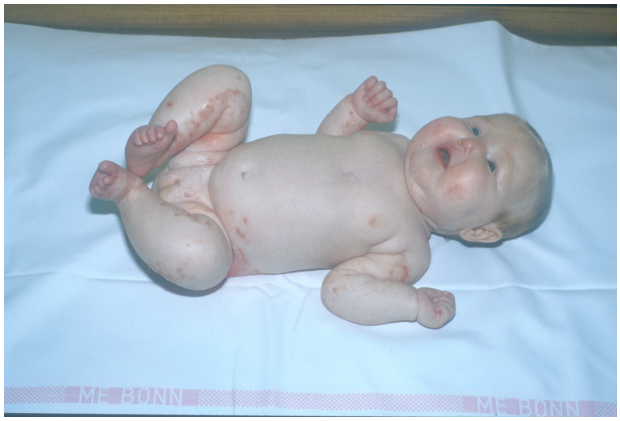

Fig. 1. Acrodermatitis enteropathica in a child with Cystic Fibrosis

Diagnosis: severely decreased zinc levels in plasma (<6 mmol/l). Urine zinc excretion also decreased.

Treatment: Oral administration of high doses of zinc aspartate (2 mg/kg/day), which leads to normalisation of all symptoms except the paronychia. During zinc replacement therapy the concentration of copper in serum needs to be monitored, because they share the same transporter. Pregnant women with this disorder need close monitoring, because low zinc levels in the mother can lead to malformations of the fetus.

Menkes Syndrome
Menkes "kinky hair" syndrome is a x-chromosomal inherited disease with a intracellular transport defect of copper within the intestinal enterocyte, which leads to copper deficiency in the body [18]. The absorbed copper accumulates in the intestinal cells. The lack of copper affects copper depending enzymes like the tyrosinase of the skin, the lysyloxidase in connective tissue and blood vessels, the dopamine-β-hydroxylases, the cytochrome-oxydases and the superoxyde-dismutase in the central nervous system.

Clinical symptoms: Typical is the abnormal kinky hair, hypopigmentations of the skin, progressive cerebral degenerations, bone changes, rupture of arterial vessels, thrombosis and hypothermia. The hair is curled into itself and of grey ivory colour. The face is characterized by affected eyebrows and slight flabby cheeks, which can already be noticed in newborns. Gastrointestinal symptoms are vomiting and diarrhea, some times with protein losing enteropathy. Female gene carriers can show depigmentations of the skin and changes of their hair (pili torti).

Diagnosis: determination of decreased copper and coeruloplasmine concentration in serum. Copper concentration in the liver is strongly decreased, that of the intestine strongly elevated. The genetic identification of a mutation confirms the diagnosis.

Treatment: the oral absorption of copper is decreased. Parenteral administration of copper normalises serum copper concentration, but does not influences the progression of the disease. A useful therapy does not exist for the time being.

Microvillous Inclusion Disease
In this autosomal recessive inherited structural abnormality of the small and large intestine the affected subjects develop profuse watery diarrhea after birth. The stool volumina are 100-800 ml / kg / day. The defect in the mucosa is within the microvilli of the intestinal cell. They are not anchored on the apical part of the cells due to a mutation in the myosin 5B-gene [10]. This leads to structural disturbances within the microskeleton of the cell which affects the absorption of micronutrients and water.

Result is a severe osmotic-secretory diarrhea with metabolic acidosis and dehydration.

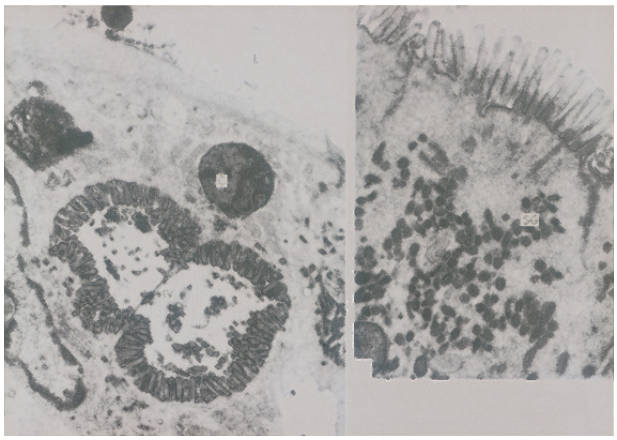

Fig. 2. Microvillous Inclusion Disease by electron microscopy: A. typical brush border membrane vesicles with the intestinal cell and B. Granules towards the apical membrane

Diagnosis: is established by an intestinal biopsy. The histological picture of intracellularly located PAS-positive brush border membranes and severe intestinal atrophy is pathognomonic for the disease [12]. By electron microscopy the intracellularly located globules of brush border membrane can be identified (Fig. 2). The identification of the mutation establishes the diagnosis.

Treatment: the therapy is purely symptomatic by administration of total parenteral nutrition. Only intestinal transplantation has shown to be effective in these patients [4].

C*ongenital Tufting Enteropathy*
1994 Reif and co-workers described a form of chronic diarrhea in the newborn with severe watery stool outputs. The morphology of the intestinal mucosa shows characteristic tufts together with an atrophy of the mucosa. The tufts consist of a multilayer of epithelial cells. The etiology of these pathognomonic changes is due to a mutation within the epithelial cell adhesion molecule epCAM. This disease overlaps with the above described sodium diarrhea.

Diagnosis: determination of the typical changes of the intestinal mucosa as well as the identification of a mutation within the epCAM or SPINT2-genes

Treatment: purely symptomatic with total parenteral nutrition. The prognosis is bad.

X-Linked Immun-Dysregulation, Polyendocrinopathy and Enteropathy (IPEX-Syndrome)
This x-chromosomal recessive disease is characterized by severe symptoms already in infancy: insulin dependant diabetes mellitus, ichtyosiform dermatitis, thyroiditis, hemolytic anemia and intractable diarrhea. The disease is caused by mutations in the FOXP3-gene [2]. The genetic defect leads to unregulated activation of T-lymphocytes with consecutive multiple autoimmune diseases. High antibodies in serum against thyroid, pancreas, kidney and intestine can be found in affected children. The bad prognosis of the disease can only be improved by immunosuppressive therapy using corticosteroids and ciclosporine. The use of bone marrow transplantation is uncertain [1].

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SUMMARY

CONGENITAL DISEASES OF THE GASTROINTESTINAL TRACT

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With the rapid increase in knowledge on the genetic origin of diseases within the gastrointestinal tract the number of congenital diseases, which already manifest during childhood have drastically increased. Due to the large application of molecular genetics the number is steadily increasing. To make the access to these rare diseases fast and efficient the data base of the National Library of Medicine (Online Mendelian Inheritance of Man – OMIN) is a very helpful online tool, with which all these disease entities can be found easily (http://www.ncbi.nlm.nih.gov/omim).

Detailed tables are given to find most of the congenitally inherited disease, which affect the gastrointestinal tract. A variety of congenital diarrheas with disturbances of digestion, hydrolysis, absorption and secretion is described in detail: lactose intolerance, sucrose intolerance, glucose-galactose malabsorption, fructose malabsorption, trehalase and enterokinase deficiency, congenital chloride and sodium diarrhea, congenital hypomagnesaemia, primary bile acid malabsorption, acrodermatitis enteropathica and Menke's syndrome. Also described in detail are diseases with structural anomalies of the intestine like microvillous inclusion disease, congenital tufting enteropathy and IPEX syndrome.

The diagnosis in the disturbances of carbohydrate hydrolysis or absorption can be established by H2-breath tests after appropriate sugar challenge. Treatment consists of elimination of the responsible sugar from the diet. The diagnosis of the congenital secretory diarrheas is established by investigation of electrolytes in blood and stool. Substitution of high doses of the responsible mineral can improve the clinical outcome. In acrodermatitis enteropathica low serum zinc level together with the typical skin lesions guide to the diagnosis. High doses of oral zinc aspartate can cure the symptoms of the disease. The diagnosis of structural congenital lesions of the intestine can be established by histology and/or electron microscopy and molecular identification of the responsible mutations. The treatment of these diseases is difficult and therefore the prognosis remains poor.

Immunosupressive therapy, total parenteral nutrition and even intestinal or bone marrow transplantation are the only choice for treatment.

Keywords: congenital disorders, gaastro-intestinal tract, children.

РЕЗЮМЕ

ВРОЖДЕННЫЕ ЗАБОЛЕВАНИЯ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Быстрый рост числа исследований о генетическом происхождении болезней с поражением желудочно-

кишечного тракта выявил множество болезней, которые манифестируются уже в детском возрасте. Ввиду широкого внедрения молекулярной генетики их число неуклонно увеличивается. Доступ к информации, касающейся редких болезней, возможен посредством базы данных, наличествующей в http://www.ncbi.nlm.nih.gov/omim.

Представлены детальные таблицы, касающиеся большинства врожденных наследственных болезней, протекающих с поражением желудочно-кишечного тракта. Описано многообразие врожденных диареей с нарушением переваривания, гидролиза, абсорбции и секреции – непереносимость лактозы, сукрозы, мальабсорбция глюкозы-галактозы, фруктозы, дефицит трегалазы и энтерокиназы, врожденная хлоридная и натриевая диаррея, врожденная гипомагнемия, первичная мальабсорбция желчных кислот, энтеропатический акродерматит и синдром Менке. Опсаны также болезни с структурными аномалиями кишечника – болезнь с включениями в ворсинки, врожденная дисплазия кишечного эпителия, синдром IPEX.

Нарушения гидролиза и абсорбции углеводов устанавливается дыхательным тестом с водородом, после нагрузки с соответствующим углеводом. Лечение заключается в исключении этиологически значимых углеводов из диеты. Диагноз врожденных секреторных диареей устанавливается определением электролитов в крови и кале. Дача высоких доз этиологически значимых минералов может улучшить клиническое течение. Диагноз энтеропатического акродерматита ставится на основании сочетания низкого уровня цинка в сыворотке крови и типичных изменений кожи.

Диагностика врожденных структурных поражений кожи осуществляется посредством гистологических методов и электронной микроскопии и молекулярной идентификации ответственной мутации. Лечение этих заболеваний является трудной задачей и прогноз остается тяжелым. Иногда иммуносуппрессивная терапия, полное парэнтеральное лечение и даже трансплантация кишечника или костного мозга являются единственным выбором лечения.

რეზუმე

გასტროინტესტინური ტრაქტის თანდაყოლილი დაავადებები

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კუჭ-ნაწლავის ტრაქტის დაავადებების გენეტიკური წარმოშობის შესახებ ცოდნის სწრაფ ზრდასთან ერთად მკვეთრად იმატა იმ დაავადებების ჩამონათვალმა, რომელიც უკვე ბავშვთა ასაკში ვლინდება. მოლეკულური გენეტიკის დანერგვის გამო მათი რიცხვი სტაბილურად იზრდება. ამ იშვიათი დაავადებების შესახებ ინფორმაციის სწრაფი მოძიებისთვის მიზანშეწონილია მივმართოთ მონაცემთა ბაზას - http://www.ncbi.nlm.nih.gov/omim.

ტაბულებში დეტალურადაა წარმოდგენილი კუჭ-ნაწლავის ტრაქტის დაზიანებით მიმდინარე თანდაყოლილი მემკვიდრეობითი დაავადებების უმრავლესობა. დიარეების მრავალსახეობა მონელების, ჰიდროლიზის, აბსორბციისა და სეკრეციის დარღვევებით აღწერილია დეტალურად: ლაქტოზის და სუკროზას აუტანლობა,გლუკოზა-გალაქტოზას მალაბსორბცია, ფრუქტოზას მალაბსორბცია, ტრეჰალაზას და ენტეროკინაზას დეფიციტი, თანდაყოლილი ქლორიდული და ნატრიუმის დიარეა, თანდაყოლილი ჰიპომაგნიემია, ნაღვლის მჟავების პირველადი მალაბსორბცია, ენტეროპათიული აკროდერმატიტი და მენკეს სინდრომი. ასევე დეტალურადაა აღწერილი დაავადებები ნაწლავებში სტრუქტურული ცვლილებებით, როგორიცაა მიკროხაოებში ჩანართების დაავადება,ნაწლავური ეპითელის თანდაყოლილი დისპლაზია და IPEX სინდრომი.

ნახშირწყლების ჰიდროლიზის ან აბსორბციის დარღვევები დადგენა წარმოებდა H2-სუნთქვის ტესტით, შესაბამისი ნახშირწყლით დატვირთვის შემდეგ. მკურნალობა მდგომარეობს დიეტიდან შესაბამისი შაქრის გამორიცხვაში. თანდაყოლილი სეკრეტორული დიარეის დიაგნოზი დადგენა ხდება ელექტროლიტების განსაზღვრით სისხლსა და განავალში. შესაბამისი ელექტროლიტების მაღალი დოზით მიცემამ შეიძლება გააუმჯობესოს კლინიკური გამოსავალი. ენტეროპათიული აკროდერმატიტის დროს შრატში ცინკის დაბალი დონე და კანის ტიპიური ცვილებები მიუთითებენ დიაგნოზზე. ორალურად დანიშნული ცინკის ასპარტატის მაღალი დოზები დაავადების გამოვლინებებს ხსნის. ნაწლავების თანდაყოლილი სტრუქტურული დაზიანებების დადგენა შესაძლებელია ჰისტოლოგიური მეთოდებით ან ელექტრონული მიკროსკოპიით და პაუხისმგებელი მუტაციის მოლეკულური იდენტიფიკაციით. ამ დაავადების მკურნალობა ძნელია და პროგნოზი მძიმე. იმუნოსუპრესიული თერაპია,სრული პარენტერალური და ნაწლავის ან ძვლის ტვინის ტრანსპლანტაცია ზოგჯერ მკურნალობის ძირითადი არჩევანია.

THE HEALTH OF ADOLESCENTS AROUND A WORLD IN TRANSITION

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A global look on adolescent health

The World Health Organization defines "adolescents" as people aged 10-19; "youth" as those aged 15-24; and "young people" as those aged 10-24 [19,26]. This definition is somehow arbitrary, since this period of life varies between individuals and cultures. For instance, there is a 4-5 year variation in the onset of puberty ("pubertal timing") within members of a community or across countries and races.

More and more authors adopt a life-course perspective when it comes to describing adolescent development and health [19] stating that many non-communicable diseases, including mental disorders have their origin in the adoption of specific behaviours during adolescence. Indeed, a cluster of health compromising behaviours and states that largely start in adolescence (tobacco, alcohol, obesity, physical inactivity) are potential causes of future non-communicable diseases in adults [2]. As expressed recently in several publications, in comparison to children, adolescents have seen fewer health gains over the last decades [8,14,15]. While the mortality of children had declined by over 80% in the last 50 years in many countries, mortality among adolescents has improved only slightly. This is mainly due to the fact that over time, causes of death in adolescents have changed with a decrease in deaths from infectious disease in most high and middle-income countries and a rise in violent deaths. This is true for high as well as many low and middle income countries (LMIC). This lack of improvement in adolescents' mortality rates partly explains the recent interest for the health and development of adolescents and a focus on both curative and preventive interventions. The aim to prioritise the focus on adolescent health is to preserve the integrity of a very important portion of the population, which to much extent, is a guarantee for the future and the wealth of any country.

Among the main causes of death and disability during this period of life are the injuries, which include sports and traffic accidents, interpersonal violence, war and suicide. Injuries account for substantial mortality and morbidity during adolescence [27,28]. Causes of deaths among males aged 10 to 24 years include injuries which are responsible for almost half of the cause. Death rates are around 14‰ from road traffic injuries, 9‰ from interpersonal violence, 6‰ from self-inflicted injuries, 5‰ from drowning and 3‰ linked with war; among females, the respective rates are 6‰ from self-inflicted injuries, 5‰ for road traffic injuries and 2,5‰ from drowning. Road traffic accidents have especially increased in some LMIC and constitute approximately 90% of the world's road traffic deaths. This is partly linked with the increase in vehicles, a low level of driving skills among young people, as well as poor roads or other infrastructure, a lack of car safety or of legislation around seat-belts and finally due to the use of alcohol while driving. Another cause of violence is physical fights: during early adolescence, these are often linked with family conflicts or arguments between mates, whereas during later adolescence, they are more often related to drug trade and other forms of illegal activities. Unemployment is probably the single most important risk factor for such behaviour. Among other factors playing a role in the occurrence of violence, is the economical and political situation of the country. For example, countries which have the largest gap between richer and poorer inhabitants (as measured by the Gini index) have higher rates of violence among adolescents overall [24].

A leading cause of morbidity among young people, which also jeopardize their future, is mental disorders and psychological problems, which account for a heavy load of disease burden among young people. Specifically, around 8% of adolescents suffer from some kind of depression, and schizophrenia, bipolar disorder), alcohol use disorders and auto-inflicted violence constitute a leading cause of disease burden in young people. Some authors believe that there has been an overall increase in these pathologies over the last couple of decades [18], but explanations for such trend need to be clarified. This mental health burden has increased the need of adolescents to access mental health care but LMIC display a real lack of provision of professionals who can adequately address these problems [13]. Also, many of these emotional problems could theoretically be dealt with by family doctors and private practitioners, but they often lack a capacity to respond to their young patients' need, such as being able to communicate well with young people, screen for mental health problems and provide treatments which include…?

In this respect, suicide and self-harm represent an area of great concern among adolescents and young adult years in many countries. Around the world, they represent the second leading cause of death among young people, with a higher rate of mortality by suicide among boys than girls. Self-harm is even much more common and is a risk factor for suicide. In high income countries, one out of twenty 20 young people report some self-harm, such as self-laceration or self-poisoning. Figures for LMIC are lacking and one has to take into account the fact that the prevalence of such behaviour is difficult to ascertain through population based survey, as some adolescents may be reluctant to disclose such events and some countries will not report it as such.

The roots of such behaviour lie both in individual and contextual and environmental factors, such as impulsivity or poor social problem solving skills, as well as disconnection from community and family ties, parental conflicts, experience of bullying or a history of sexual or physical abuse.

Substance use disorders including those related to alcohol use become prominent in the later adolescent and young adult years and represent the leading risk factor for disease burden in this population. Tobacco use commonly begins during the adolescent years but is a major contributor to the disease burden later in life. While underestimated by many adults and health professionals, alcohol misuse in this age group accounts for a similar burden of disease as HIV. Thus, misuse of legal and illegal substance is also a major contributor to mortality and disease related disability later in life.

According to the Global Youth Tobacco Survey (GYTS), nearly 2 of every 10 in-school adolescents report currently using a tobacco product and LMIC exhibit a disturbing upward trend in such use. Also, boys are significantly more likely than girls to use any tobacco products even tough, in several high income countries, the percentages of girls who smoke exceeds the one of the boys. The use of alcohol is heavily linked with cultural and religious contexts, which explains why its use varies considerably across countries. Although, contrary to adults, no evidence exists of significant health benefits from moderate alcohol consumption for young adults, it is essential to remind that the hazardous use of alcohol (also named as alcohol abuse or problematic alcohol use) represents a serious problem during adolescence because of its short- and long-term consequences, such as violence, unprotected sex and injuries while driving under the influence of alcohol or developing alcohol dependence once they enter adulthood. In Western countries, especially in Europe, the rate of adolescents reporting hazardous use of alcohol (on a more or less regular basis) has increased over the last two decades.

Besides alcohol, cannabis is the most frequently used illicit drug worldwide by adolescents. The lifetime prevalence of cannabis use, however, differs greatly from one country to another. The available data suggest that lifetime prevalence rates of cannabis use, misuse (problematic use) and abuse are on the increase in many countries. The figures for Georgia are less disturbing than in other countries [12], but the lower figure may be linked with some fear of disclosing their consumption by young people. In most countries, a much lower but still substantial percentage of young people have access to other illicit drugs such as ecstasy, cocaine and heroin, especially in high-income countries.

Young people engage in substance use for a variety of reasons such as curiosity and peer pressure for example. Factors identified among young people who misuse substances include vulnerability related to mental health, family difficulties, school failure and unemployment, but cultural, economic and legal contexts in which adolescent development takes place also influence patterns of initiation and progression of substance use.

Chronic malnutrition in earlier years is responsible for widespread stunting and adverse health and social consequences throughout the life span. This is best prevented in childhood but actions to improve access to food could benefit adolescents as well. Anemia is one of the key nutritional problems in adolescent girls. Adolescence is a timely period to shape healthy eating and exercise habits that can contribute to physical and psychological benefits during the adolescent period and to reducing the likelihood of nutrition-related chronic diseases in adulthood. WHO has recognized that overweight and obesity represent a major public health challenge, reaching pandemic proportions among adults as well as among children and adolescents. While obesity is mostly spread in high-income countries such as the USA and Western Europe, it also occurs in some Eastern Europe countries, as well as in South America, East Asia and around the world. This trend is a result of obesogenic environments, increasing calorie consumption, more sedentary life habits and low physical activity.

Another area of concern in the field of nutrition is the mounting prevalence of eating disorders, mostly in high- and middle-income countries. Anorexia nervosa typically affects adolescents, whereas bulimia nervosa tends to affect young adult females, and more and more girls or even boys also suffer from atypical eating disorders called EDNOS ('eating disorder not otherwise specified'), which are conditions only partially fulfilling the criteria for anorexia or bulimia, but are the source of much suffering, serious consequences on adolescents' health and often responsible for an overuse of health care.

Nutritional problems represent a typical example of chronic conditions, which affects more and more young people: Indeed, as the importance of infections is decreasing around the world, thanks to vaccination, pharmacological treatments and the improvement of hygiene, non-communicable diseases more and more constitute a real challenge. Given the improvement in medical care of many severe conditions, a lot of individuals currently survive into adolescence and adulthood, where formerly they would not have survived past infancy. The increase in survival rate is thus directly associated with an increase in prevalence of chronic conditions. Around 10% of adolescents suffer from some type of chronic condition broadly defined as conditions necessitating some care for at least six months [22], most of them belonging to the so-called "non communicable diseases".

Most chronic conditions affect the adolescent's bio psychosocial development and well-being. The extent of this impact depends on age of onset, duration, whether they

are congenital or acquired. Areas affected include growth and puberty, self-esteem, isolation from peers or over-protection by parents, and lack of school or professional achievement [22].

Sexual and reproductive health : an area of challenge for many young people

Young people who engage in active sexual life are clearly more vulnerable than adults, for many reasons including the fact they have to experience a new field of feelings, sensations and communication. The changes in cultural norm, the universal access to internet create opportunities for healthy sexual development but also risks of unplanned and/or early pregnancy, STIs including HIV, and sexual violence and abuse. An important issue during adolescence is the acquisition of a stable sexual orientation. LGBT youth (Lesbian/Gay/bisexual/transsexual) often endure difficulties in their coming out process, especially in certain societies which condemn homosexuality. LGBT adolescents display more mental health problems and engage in suicidal conducts at a higher rate.

The age at which young people engage in sexual experiences varies, depending on contextual and cultural factors [3]. In many regions of the world, the gap between the first sexual experience and marriage is widening: thus, most early sexual experiences occur among unmarried young women and men. In some places, many adolescent girls have their first sexual intercourse while married; moreover, as these girls often do not use any contraception or protection, they are at high risk of acquiring STIs.

Many young women experience pregnancy and may be confronted with medical complications as well as psychological burden. If they choose to keep the pregnancy, they may face maternal morbidity or even mortality in regions which do not offer proper care. If they choose to have an abortion, especially in countries where they are illegal, they may as well end up with severe infections, fertility problems or even death. Not rarely, such pregnancies are the result of sexual coercion, defined as forcing, an individual to engage in sexual behavior against his/her will using physical/verbal violence. Such coercion has long term consequences, such as post-traumatic stress disorder, psychological breakdown etc. The World Health Organization has recently developed evidence-based guidelines addressing six areas [5]: preventing early marriage; preventing early pregnancy through sexuality education, increasing education opportunities and economic and social support programs; increasing the use of contraception; reducing coerced sex; preventing unsafe abortion; and increasing the use of prenatal care childbirth and postpartum care.

Sexually transmitted infections including HIV are obviously another major area of concern. Their prevalence and incidence seem to increase, due to a lack of availability of protection, provision of sound information and sexual education. It tends to occur at a younger age in females than in males: this could be linked with a different profile of sexual activity. In general, young people are more vulnerable than adults to such STIs, due to their inexperience, lack of access to protective devices (condom) and access to information and care. It is estimated that every year, 4.1 million individuals become newly infected with HIV and that around 10 millions young people are living with HIV/AIDS. A recent publication of WHO [17] provides a comprehensive review of evidence-based strategies to reach this objective. While programs focusing exclusively on abstinence do not seem to be effective, those that involve young people and use multiple approaches to reach them (e.g., through actions in the school setting and media campaigns as well as outreach interventions targeting specific vulnerable groups) appear to have an impact on the transmission of HIV among young people. Also, public health programs should focus on offering HIV testing to young people to identify those who are already HIV-positive and to help them access the services that will keep them healthy and teach them the skills to protect those with whom they have sex. Screening young people for HIV is a great opportunity to deliver sound preventive information, even if the test is negative.

How can the health services and structures respond to adolescent needs?

It is clear from the preceding section that health care service delivery should be tailored to the particular needs of young people. One important concept which has been developed since around ten years is the one of youth or *adolescent friendly services*. In 2002, the WHO called for the development of adolescent friendly health services (AFHS). This is a now a worldwide adopted model [11] which is also largely spread by UN agencies such as UNICEF and UNFPA. The five main areas covered by AFHS are equity, effectiveness, accessibility, acceptability, and appropriateness of care. The model is applicable in LMIC as well as high income countries [25].

Accessibility and acceptability of services represent key barriers to effective service delivery [23]. For instance, adolescents don't use services because of its cost, the lack of convenience (localisation away from where young people live or have inconvenient opening hours), or lack of publicity and visibility. Fear of a lack of confidentiality is a further major reason for young people's reluctance to seek help. When young people do seek help, they are often unhappy with the style of consultation and then don't return for follow up [23]. There is a consensus among the many young people involved in the development of the WHO framework (from various countries) that confidentiality represent a key issue when it comes to the adaptation of health care structures to adolescents' needs, whether in hospitals, outpatient clinic or school health services [1].

The American Medical Association has provided guidelines for Adolescent Preventive Services (GAPS) [6] that have

been largely adopted around the world and which allow for the early detection of health problem that would potentially benefit from early intervention. The importance of screening young people for psychosocial issues and health risk behaviours could not be underestimated. The acronym "HEEADSSS" is a simple mnemonic screening tool, designed to cover the main risk areas among young people [7] and which invites health care professionals to cover (in one or several separate sessions) various areas such as: **H**ome, **E**ducation and school, **A**ctivities, **D**rugs use and abuse, **S**exuality, **S**uicidal behaviour and **S**afety (e.g. health compromising behaviour). Of course, it is usually not enough to identify problems in these different domains, but one has to discuss/provide some clues as how to address the burden and difficulties and overcome them or refer to other specialists according to the needs.

These screening guidelines are based on the assumption that once a problematic behaviour is identified, the delivery of an intervention will contribute to modify the natural course of such behaviour, were it substance misuse, eating disorder or unsafe sex. The idea is to provide some early intervention that will assist the young person in modifying his potentially detrimental behaviour. Such early intervention efforts have focused on ten main area: physical activity, nutrition, tobacco, alcohol and other drugs, family planning, mental health, violent and abusive behaviours, unintentional injuries, sexually transmitted diseases and clinical preventive services. For example, clinical intervention in an emergency room to reduce unintentional injuries showed that adolescents receiving counselling in a single risk area increased the use of seat belts and bicycle helmets compared to the controls [10]. Other example showing effectiveness of early intervention are programmes of tobacco cessation combining a variety of approaches, including taking into account the young person's preparation for quitting, support behavioural change and enhance motivation [9], or intervention for young people hospitalized for alcohol abuse [20].

Prevention & health promotion: does it work?

There are many early onset behavioural problems implicated in non-communicable diseases include unsafe driving, mental health, violence, alcohol, tobacco and drug misuse as well as unsafe sex and teen pregnancy[15]. Many of these health risks are preventable, and there is a good deal of researches suggesting that prevention programs that seek to reduce family management problems or academic failure are likely to prevent multiple problems despite the fact that the programs themselves may be focused on single problems such as conduct problems or academic success. As a matter of fact, it is often more effective to intervene on the level of the young people' environment than focusing exclusively on educational approaches. Longitudinal, prospective studies have identified factors that promote positive social development and reduce behaviour problems, including individual factors such as high intelligence; resilient temperament; social, emotional, and cognitive competence; and environmental factors: opportunities for prosocial involvement; recognition for positive involvement; bonding; and healthy beliefs and standards for behaviour [4]. A growing number of controlled trials have found that environmental interventions are efficacious in preventing adolescent health problems. For instance, the gatehouse project is a primary prevention programme, which includes both institutional and individual focused components to promote the emotional and behavioural wellbeing of young people in secondary schools. The research was conducted in Melbourne, Australia, but has been similarly implemented in other regions of the world (e.g. France). This programme, which aims at improving the ethos of the school, the respect of individuals for each other, youth participation and the acquisition of life skills has shown effectiveness on behaviours such as substance use by young people, with a 3% to 5% risk difference between intervention and control students for any drinking, any and regular smoking, and friends' alcohol and tobacco use across the three waves of follow up [16].

Some programmes focus on the strengthening of educational competencies of parents. For instance, the "Strengthening Families Program for Parents and Youth 10-14" is a seven week universal parent training program offered to parents and adolescents in weekly 2-hour sessions' which targets family, peer, and individual risk and protective factors, including parent communication and child management skills; children's social skills, stress management, and ability to refuse peer drug offers; and parent/child conflict resolution and bonding. The program, run in the United States, has been shown to reduce substance use and delinquency up to five years after the participation of the involved adolescents [21].

The prevention of injuries is also an area in which environmental factors have proven effective: improving the wearing of helmets, compulsory use of seatbelts, and improvement the condition of traffic (e.g. special tracks for bicycles), reducing the speed of motor vehicle all are measures that have impacted on the rate of fatalities and injuries, especially among young people [28].

It has to be recognized that most research focusing on the effectiveness of preventive interventions have been run in high income countries. However, there are no reasons to think that these strategies could not be as effective in other contexts, such as the one of LIMC. Still, one current challenge is how the use of tested, efficacious prevention policies and programs be extended globally while recognizing that communities and nations are different from one another, and need to decide locally what policies and programs they use, because risk and protection factors as well as the cultural and the political context vary by community.

Conclusion.

There is now recognition that adolescence is central to major global health agendas beyond sexual and reproductive health. In the field of injury, mental health and risks for later life, it is difficult to conceive a successful strategy that does not address the onset of these problems in the adolescent years. In addition there are major social and economic challenges that will continue to drive adolescent health and disease in the years to come. These include the ongoing economic difficulties in many countries with resultant high youth unemployment, the rapid urbanisation of many countries and loss of traditional communities, the growth in migration both within and between countries and ongoing civil unrest and military conflict in many parts of the globe.

For countries such as Georgia, there are clearly no simple answers to these challenges. Health professionals as well as professionals from other field should work in a collaborative way to build cross-disciplinary strategies which will improve the adolescent environment and well-being. These include the provision of youth friendly health care, the development of a sound school health service promoting healthy lifestyles and youth participation, and the implementation of legislative and environmental policies that take into account local culture and history.

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SUMMARY

THE HEALTH OF ADOLESCENTS AROUND A WORLD IN TRANSITION

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Since several years, the health of adolescents is on the agenda of ministers, decision makers and health professionals. Around the world, while there has been a steady decrease of the death rates among young children, this is not the case for young people. This is mainly linked with the fact that mortality and morbidity during this period of life is largely linked with non communicable diseases and conditions, including deaths from injuries, suicide, homicides and drug abuse. Unplanned pregnancies, illegal abortions, newly acquired HIV infections are also situations that have short and long term consequences. This paper reviews the epidemiological data pertaining to adolescent health and disease. It proposes evidence-informed avenues as how to address these issues in the field of health care (e.g. adolescent friendly services) and of prevention and health promotion. It also stresses the importance of creating safe environments for the development and well-being of young people and thus, of an interdisciplinary and inter sectorial approach to their complex health problems and challenges.

Keywords: adolescents, health problems, epidemiology data.

РЕЗЮМЕ

ЗДОРОВЬЕ ПОДРОСТКОВ В МЕНЯЮЩЕМСЯ МИРЕ

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Уже несколько лет как здоровье подростков находится в эпицентре внимания лиц, принимающих решения и профессионалов здравоохранения. Во всем мире отмечается резкое снижение смертности детей, однако среди подростков подобной тенденции не наблюдается.

Предполагается, что в этом возрастном периоде смертность и заболеваемость, в основном, обусловлены следующими факторами: неинфекционные болезни, за исключением СПИДа, несчастные случаи, убийство и самоубийство, наркозависимость, незапланированная беременность, нелегальный аборт. В работе представлен обзор материалов, касающихся здоровья подростков, предлагаются основанные на принципах доказательной медицины пути к улучшению здоровья и превенции заболеваний (сервисы, дружественные молодежи).

Подчеркивается значение необходимости создания безопасной среды, а также использования междисциплинарных и интерсекторальных подходов для преодоления трудностей и вызовов подростковой медицины.

რეზიუმე

მოზარდთა ჯანმრთელობა ცვლად მსოფლიოში

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რამდენიმე წელია რაც მოზარდთა მედიცინა გადაწყვეტილების მიმღებთა და ჯანდაცვის პროფესიონალთა ყურადღების ეპიცენტრშია. მსოფლიოს მასშტაბით დაფიქსირებული ბავშვთა ასაკის სიკვდილობის ურყევი კლება არ შეესაბამება იმავე მონაცემებს მოზარდებთან მიმართებაში, რაც ავტორების აზრით, განპირობებულია იმ გარემოებით ამ ასაკობრივ პერიოდში სიკვდილობა და ავადობა უპირატესად გამოწვეულია ისეთი ფაქტორებით, როგორიცაა არაგადამდები დაავადებები, შიდსის გარდა, უბედური შემთხვევები, მკვლელობა და თვითმკვლელობა, წამალდამოკიდებულება, დაუგეგმავი ორსულობა, არალეგალური აბორტი. ნაშრომში წარმოდგენილია მოზარდთა ჯანმრთელობის ამსახველი მასალების მიმოხილვა. ავტორები გვთავაზობენ მტკიცებულებებზე დაფუძნებულ გზებს, თუ როგორ მივმართოთ რესურსები მოზარდთა ავადობის პრევენციისა და ჯანმრთელობის ხელშეწყობისათვის (მოზარდებისადმი მეგობრული სერვისები). ყურადღება გამახვილებულია მოზარდთა განვითარებისა და კეთილდღეობისათვის უსაფრთხო გარემოს შექმნაზე, ასევე, დისციპლინათაშორისო და ინტერსექტორულ მიდგომებზე მოზარდთა მედიცინის სირთულეების და გამოწვევების გადასალახავად.

МЕДИКО-СОЦИАЛЬНЫЕ ОСОБЕННОСТИ СОСТОЯНИЯ ЗДОРОВЬЯ ШКОЛЬНИКОВ В УКРАИНЕ

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Здоровье нации определяется, прежде всего, состоянием здоровья ее детей. Данные многочисленных исследований показывают, что источник возникновения различий в здоровье взрослых следует искать в их детстве [14]. Здоровье детей является интегральным показателем общего благополучия общества, а также чувствительным индикатором всех социальных и экологических проблем [7].

В последнее время ситуация со здоровьем детей в Украине приблизилась к критической: повышается уровень общей заболеваемости и распространенность заболеваний отдельных органов и систем. Этому способствует рост интенсивности воздействия на здоровье детей и подростков факторов экологического и медико-социального риска, ухудшение структуры питания, снижение эффективности проведения традиционных профилактических мероприятий. Особенностью современности является стремительный рост количества и изменение соотношения факторов риска, влияющих на гомеостатические, иммунологические показатели, развитие и состояние здоровья детей. Состояние здоровья детей имеет большое значение, поскольку именно от состояния здоровья подрастающего поколения зависит развитие общества в будущем. Результаты различных исследований свидетельствуют о тенденции ухудшения показателей здоровья детей и подростков в Украине [4,8,11]. В стране наблюдается рост количества функциональных расстройств, острой и хронической соматической заболеваемости, синдрома дезадаптации, врожденных пороков развития, морфофункциональных отклонений. Растет число детей-инвалидов, немалую озабоченность вызывает рост числа детей с расстройствами психики и поведения [2,3,9,10].

На наш взгляд, вышеизложенное связано не только с ухудшением экологической ситуации, снижением уровня социального обеспечения и медицинской культуры населения, но и с недостаточными возможностями действующих методик оценки состояния здоровья детей по выявлению патологических отклонений у них на донозологическом этапе. Наличие выраженных неблагоприятных тенденций в состоянии здоровья подрастающего поколения диктует необходимость принятия качественно новых решений при организации и проведения медико-профилактических мероприятий. Наиболее приоритетной задачей современной педиатрии является разработка новых и усовершенствование существующих методов по сохранению здоровья здорового ребенка [12]. Прежде всего, это связано с поверхностным изучением особенностей состояния здоровья школьников в современных условиях, что практически исключает возможность ранней профилактики его нарушений.

В литературе существует множество определений понятия «здоровье». Первое официальное определение здоровья принадлежит ученому Ричарду Сигеристу (США): «Здоровье - это не просто отсутствие болезней: это нечто положительное, радость жизни, бодрое восприятие личностью всей ответственности, возложенной на человека жизнью».

Р. Сигерист отмечет, что здоровье следует воспринимать не только как физическое или душевное состояние человека, но и как социальное явление. Это вдохновило экспертов Всемирной организации здравоохранения (ВОЗ) на определение понятия «здоровье» в контексте концепции Р. Сигериста, которое в 1946 г. принято как часть преамбулы Устава ВОЗ: «Здоровье – это состояние полного физического, психического и социального благополучия человека, а не только отсутствие болезней» [6].

Итак, здоровье – это естественное состояние организма, которое характеризуется его уравновешенностью с окружающей средой и отсутствием каких-либо болезненных состояний [5], а уравновешенность организма с внешней средой – это степень его приспособленности, адаптированности к условиям биологической и социальной среды, дееспособности.

Такой подход к характеристике здоровья особенно важен касательно детей, поскольку уравновешенность с внешней средой обеспечивает своевременность роста и развития детского организма, что дает возможность посещать дошкольные и школьные учреждения, овладевать знаниями и навыками, соответствующими возрасту, без возникновения признаков дезадаптации.

В государственном докладе о положении детей в Украине за 2010 год сообщается, что в течение последних лет сохраняется устойчивая тенденция к ухудшению состояния здоровья детей [1]. Об этом свидетельствуют и результаты научных исследований. По данным Министерства здравоохранения Украины, наблюдается рост распространенности болезней на 17,92% (с 1 694,62 на тысячу детей соответствующего возраста в 2003 г. до 1 998,3 - в 2010 г.). Аналогично отмечается рост заболеваемости (впервые выявленных болезней) на 23,88% (с

1 174,46 до 1 454,96 на тысячу детей 0-17 лет, соответственно в 2003 и 2010 гг.) На первом и втором местах остаются болезни органов дыхания и органов пищеварения, которые в 2010 г. составили соответственно 51,82% и 7,25% всех зарегистрированных болезней. На третьем месте - болезни глаз и придаточного аппарата (5,28%), далее - эндокринной системы (4,69%), болезни кожи и подкожной клетчатки (4,34%).

В структуре распространенности болезней среди детей в возрасте 7-14 лет в 2010 г. первые пять ранговых мест занимали болезни органов дыхания (48,05%), пищеварения (9,34%), эндокринной системы (6,19%), глаз и придаточного аппарата (6,10%), костно-мышечной системы (5,24%).

К сожалению, даже эти статистические данные о распространенности хронической соматической патологии среди детей не отличаются достаточной точностью: не всегда они выделены среди отдельных классов заболеваний. Не менее расплывчатыми являются данные о количестве здоровых детей в популяции, так как по данным литературы, количество здоровых детей может колебаться в пределах от 2 до 80% [2-6].

Известно, что на формирование здоровья подростков влияют такие факторы, как экологическая ситуация, уровень материально - бытовых условий, распространение среди подростков курения, употребление алкогольных напитков и других токсичных веществ, неадекватность учебных нагрузок, психологический климат в семье, отсутствие установки на здоровый образ жизни. В то же время достаточно значимой является организация медицинской помощи детям школьного возраста. Ввиду определенного ресурсного ограничения медицины в Украине именно дети школьного возраста выпадают из-под контроля врачей. Дети старшего школьного возраста зачастую в течение длительного времени не обращаются в поликлинику, что приводит к значительному риску хронизации заболеваний.

Вышеизложенное диктует необходимость разработки и внедрения новых научно обоснованных программ по профилактике, диагностике и лечению школьников, восстановлению их здоровья, внедрению системы мониторинга здоровья школьников и методов оценки популяционного и индивидуального здоровья.

Целью исследования явилась оценка медико-социальных особенностей состояния здоровья школьников г. Львова и Львовской области и определение их зависимости от возраста и места проживания.

Материал и методы. Кафедра педиатрии Львовского национального медицинского университета имени Данила Галицкого с 2002 года по 2012 год, совместно с Львовским городским советом, городским и областным управлениями образования, благотворительным фондом «Крылья надежды» и другими общественными организациями проводился мониторинг состояния здоровья школьников г. Львова и Львовской области. Созданы и валидизированы специальные анкеты, которые позволяют определить основные медико-социальные особенности школьников, возрастную распространенность основных жалоб и заболеваний, их динамику в течение последних лет, выделить группы риска, которые требуют углубленного обследования и/или консультаций, уточнить возрастные особенности физического развития детей Львовского региона. Все данные хранятся в компьютерной базе данных, защищенной от несанкционированного доступа. Исследования проводились с учетом основных принципов Хельсинкской декларации по биомедицинским исследованиям и положений существующих биоэтических норм.

В 2002 году проанкетированы 20000 школьников Львова, в 2012 году - 32000 детей г. Львова и 16000 детей из 4 районов Львовской области.

Результаты и их обсуждение. Анализ заполненных школьниками и их родителями анкет выявил, чтов 2002 году 96,5% родителей школьников считают своих детей условно здоровыми; по опросу 2012 года здоровыми считают своих детей 81,9% родителей Львова и 73,6% родителей Львовской области. Некоторые родители не смогли четко определиться с ответом на этот вопрос, однако считают, что их ребенок нуждается в дополнительном обследовании или консультации специалистов.

В начале века в условиях неполной семьи воспитывалось 14,4% школьников Львова, на сегодняшний день их количество уменьшилось до 11,8%.

Оценивая материально бытовые условия семей и их доход, выявлена весьма интересная тенденция. В 2002 г. 15,1% детей и их родители оценивали материально-бытовые условия как неудовлетворительные, а в 2012 году в г. Львове их количество сократилось до 2,3%, тогда как в районах Львовской области недостаточный доход отмечала каждая третья семья (32,6%). По данным первого анкетирования 17,3% детей имели дома собаку, 24,6% - кота, 6,2% - птиц. На сегодняшний день распространенность домашних любимцев незначительно возросла и составляет 24,0%, 28,7% и 19,6% соответственно. Эти данные необходимо учитывать при анализе соматической и инфекционной заболеваемости, угрозы глистной инвазии. Выявлена также тенденция распространенности органических заболеваний в семьях школьников. Так, в 2002 году в семьях школьников в 31,2% были зарегистрированы случаи заболеваний желудка у родителей или братьев/сестер. На сегодняшний день их число увеличилось (38,1%), однако, распространенность язвенной болезни желудка

уменьшилась с 16% до 13,7%. В течение 10 лет в семьях уменьшилось число случаев заболеваний сердечно-сосудистой системы – с 33,5% до 27,3%, почек – с 23,9% до 20,1%, хронического бронхита – с 14,1% до 10,6%, туберкулеза – с 1,6% до 0,8%, при постоянных показателях распространенности бронхиальной астмы – 9,3% и 9,7% соответственно.

Известно, что значимым элементом развития ребенка является его питание. По данным первого анкетирования, питание 86,2% детей, по мнению родителей, регулярное, в 83,1% хорошее по качественному составу. На сегодняшний день 91,6% родителей детей, проживающих в г. Львове и 78,6% в Львовской области считают питание школьников регулярным, а хорошим по качественному составу - 84,5% и 71,1%, соответственно. Что касается мытья рук перед едой, по данным опроса 2002 года 6% детей не моют руки, в 2012 году - 5,3%.

Оптимальная частота приема пищи у школьников составила 4-5 раз в день, включая перекусы. По нашим данным в 2002 году регулярно питались 49,6% школьников, на сегодня их количество составляет 63,8% во Львове и 33,2% в районах Львовской области. Остальные школьники принимают пищу от одного до трех раз в сутки. 86,7% родителей дают детям в школу карманные деньги на обед или сладости. Школьные обеды получают 31,8% школьников Львова и 49% школьников в районах Львовской области. Популярной школьной едой оказались булочки, печенье, круасаны, сок, различные продукты фастфуда. Треть школьников не завтракают перед школой, большинство школьников ужинают перед сном. Так, в 2002 году их количество составляло 41,7% не зависимо от возраста ребенка, в 2012 г. во Львове их количество - 39,4% и в районах области - 45,6%.

Согласно рекомендованным нормам, мясные продукты должны входить ежедневный рацион каждого школьника. По данным опроса, 41,2% школьников потребляют мясные продукты ежедневно, 20% только 1 раз в неделю независимо от места проживания. В сельской местности 44,7% школьников вообще не употребляют молока и молочных продуктов.

По мнению родителей, 44,7% школьников потребляют рыбу в недостаточном количестве, 16,4% - мясо, 12,9% - овощи и 10,3% - фрукты.

При первом анкетировании у 39% детей в анамнезе указывается на наличие глистов, треть детей в течение года получала курс антибактериальной терапии, 17,1% получали антибиотики в течение года 3 и более раз. На современном этапе глисты были диагностированы врачами в 29,1% школьников, 16,2% лечились по поводу заболеваний пищеварительной системы, частота использования антибактериальной терапии остается достаточно высокой. При последнем опросе 15,7% школьников находились на диспансерном учете, из них 31,9% у врача аллерголога, 28,6% у гастроэнтеролога, 20,8% у кардиолога и 18,5% у нефролога.

Интересно появление различных жалоб у школьников, которые могут свидетельствовать о процессах школьной дезадаптации, функциональные нарушения или органические заболевания.

По данным М.С. Яцулы [13], уже спустя несколько месяцев обучения первоклассников общеобразовательных и специализированных школ у значительного числа школьников появлялись жалобы, которые можно было объяснить как проявления школьной дезадаптации. Анализ данных анкетирования позволил определить наиболее распространенные жалобы первоклассников, среди жалоб преобладали быстрая утомляемость - 50,7%, головная боль - 43,2%, нарушение сна - 40,7%, периодическая боль в животе - 38,6%. Спустя 2 месяца после начала обучения у 36,4% первоклассников общеобразовательных и специализированных школ наблюдалось снижение аппетита, у 5,4% - чрезмерный аппетит [13]. Снижение аппетита, возникающее у первоклассников в первые месяцы учебы следует считать тревожным сигналом и свидетельствовует о высоком риске синдрома школьной дезадаптации.

По данным анкетирования, наиболее распространенной жалобой школьников была боль в животе. В 2002 70,6% детей жаловались на боли в животе (60,4% - редко, 9,1% – часто, 1,1% – постоянно), без значительных возрастных отклонений этого показателя. В 2012 г на боли в животе жаловались 78,7% школьников (69,4% - редко, 8,2% - часто, 0,3% - постоянно). Изжогу при первом опросе чувствовали 11,9% детей, в результате чего у 3,6% отмечалось нарушение сна. На периодическую изжогу жаловались 23% школьников г. Львова, у 0,9% она имела интенсивный характер. У детей сельской местности изжога наблюдалась реже, в 4,7% случаев. 75,3% школьников имели привычку запивать пищу водой, компотом.

Распространенной жалобой среди школьников была быстрая утомляемость. Так в 2002 г она наблюдалась у 50,4% школьников, этот показатель практически не менялся с возрастом. В 2012 г такие жалобы были зафиксированы у 46,1% школьников г. Львова и 62,1% детей из районов Львовской области.

Довольно часто школьники жаловались на головную боль: в 2002 г - в 70,8% случаев, с четким преобладанием у школьников начальных классов. В анкетах 2012 года на головную боль указывают 45,3% школьников Львова и у 62,8% детей из районов Львовской области.

Периодическая тошнота наблюдалась при первом опросе у 46,4% школьников и практически не зависела от возраста, при повторном опросе такие жалобы встречались у 49,5% городских школьников и у 26,1% школьников из районов области.

Нарушение аппетита наблюдалось в 2002 г. у 40,1% школьников, плохой аппетит – у 4,1%, 44,6% детей неохотно завтракали утром. При последнем опросе нарушение аппетита наблюдалось у 39,9% школьников г. Львова и у 23% детей Львовской области, плохой аппетит у 4,4% и 5,4% соответственно. Чрезмерный аппетит, по мнению родителей, наблюдался у 7,3% городских и сельских школьников.

Симптомы вегетативной лабильности, признаки астенического синдрома в обоих опросах встречались у 30-45% школьников, с четким преобладанием в начальных и выпускных классах, что предположительно может быть связано с уровнем педагогической нагрузки, действием стресогенных факторов, на фоне недостаточной физической активности.

Анализ данных анкетирования 2002 года, по вопросам образа жизни школьников, выявил, что 46,4% школьников находились на свежем воздухе в течение суток менее 2 часов, однако 70,9% более 2 часов проводили за просмотром телевизионных программ. Компьютеры имели 15,7% школьников, за которыми 94% из них проводили более 2 часов в сутки. По данным опроса 2012 года, персональные компьютеры имеют 87,3% городских школьников и 38,4% детей в районах области, за которыми 59,7% детей проводят более 2 часов. В то же время 2 часа и более находятся на свежем воздухе 56,6% школьников Львова и 75,2% детей в районах области.

56% школьников начальных классов и все учащиеся старших классов имеют мобильный телефон; 54,1% школьников пользуется им более 1 часа в сутки, 5,7% - 3 часа и более.

Регулярно занимаются спортом 24,7% школьников Львова и 11,2% Львовской области, 4,7% львовских школьников не посещают уроки физкультуры.

По данным, полученным от родителей, 26,8% школьников г. Львова свободное время проводят на свежем воздухе, 16,9% - работают с компьютером, 15,9% предпочитают смотреть телепрограммы или кинофильмы, заниматься спортом – 11,2%, слушать музыку – 10,0%, читать художественную литературу – 8,1%, любят бездельничать – 4,9%.

Для 20,5% родителей школьников г. Львова было трудно определить средний уровень успешности обучения их детей. Начальный уровень успеваемости (1-3 балла) был определен у 0,3% школьников, средний (4-7 баллов) у 3,4%, достаточный (8-9 баллов) – у 43,6%, а высокий (10-12 баллов) – у 32,3% школьников. 92,2% школьников Львова имели собственный стол для подготовки к занятиям, а 91,5% – собственную кровать.

Несмотря на систематическое медицинское наблюдение школьников в г. Львове 17,6% родителей, отмечали, что их ребенок требует консультации врача педиатра. В течение последнего года 21% школьников г. Львова консультировались у стоматолога, 18,4% – у отоларинголога, 18,3% – у окулиста, 14,5% – у ортопеда, 13,7% – у невропатолога, 17,1% – у логопеда, 6,9% – у психиатра.

Родители современных школьников обеспокоены распространенностью среди подростков потребления наркотиков и алкоголя. Основными причинами чего они считают: влияние социального окружения и друзей (20,8%), доступность наркотических веществ и алкоголя (16,8%), недостаточную борьбу с распространением алкоголя и наркотиков (11,8%), ошибки в семейном воспитании (11,4%), социальные проблемы и связанное с ними психологическое состояние неопределенности, депрессии (10,2%), популяризацию телевидением (7,9%), проблемы проведения свободного времени (7,6%), способ самоутверждения молодежи (6,3%), низкий социальный и образовательный статус (3,4%), нерешенные бытовые проблемы (3%).

Для преодоления этого проблемного явления родители предлагают усилить борьбу органов правопорядка с распространением наркотиков и алкоголя среди подростков (26,7%), внедрять программы досуга для молодежи (22,9%) и образовательные программы для учащихся школ и вузов (21,5%) и родителей (6,5%), усилить антиалкогольную и антинаркотическую пропаганду (16,8%).

Выводы.
Таким образом, в процессе оптимизации комплексного подхода к организации научных исследований в таком важном направлении педиатрии, как сохранение здоровья школьников, значимая роль принадлежит изучению состояния здоровья детей с учетом их индивидуальных возрастных особенностей на всех этапах развития с одновременным определением влияния на детский организм различных факторов микро- и макросоциума. Без учета сложного действия основных факторов риска и факторов защиты невозможно создать эффективную систему профилактических, организационных и других технологий, направленных на улучшение и сохранение здоровья детей.

Анализируя данные анкетирования, следует заключить, что за последние десятилетия состояние здоровья

школьников Львовского региона не имеет тенденции к улучшению. Среди факторов, способствующих снижению уровня здоровья школьников, важнейшая роль принадлежит учебным школьным нагрузкам, стресогенное действие которых ведет к развитию дезадаптационного синдрома с невротическими реакциями различной степени выраженности. Скрининговое анкетирование школьников, которое проведено на значительной выборке, позволяет определить основные медико-социальные особенности жизни школьников, оценить возрастную распространенность основных жалоб и угрожающих симптомов, основные тенденции в их привычках, выделить группы риска для дальнейшего углубленного осмотра и обследования. Комплексный подход к оценке состояния здоровья детей, внедрение новых оздоровительных технологий, объединение усилий медицинских работников, педагогов и родителей позволит предупредить рост показателей функциональных нарушений и органической патологии у школьников, их хронизации, уменьшить риск школьной дезадаптации, повысить уровень здоровья.

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SUMMARY

MEDICAL-SOCIAL PECULIARITIES OF HEALTH STATE OF SCHOOLCHILDREN IN UKRAINE

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In the article there are results of the surveys on school children's health in Lviv region in years 2002 and 2012. The basic risk factors for functional disorders, school disadaptation syndrome, neurotic reactions are presented as well as the age prevalence of basic complaints. Among the factors that contribute to the decline of child's health level an important role belongs to the educational loading. It causes fast development of disadaptation syndrome with the neurotic reactions in different degree of expressiveness. The complex estimation of the children's health state and introduction of new technologies of revitalizing give an opportunity to prevent the increase of functional disorders and organic pathology in schoolchildren.

Keywords: schoolchildren, health, school disadaptation, diseases.

РЕЗЮМЕ

МЕДИКО-СОЦИАЛЬНЫЕ ОСОБЕННОСТИ СОСТОЯНИЯ ЗДОРОВЬЯ ШКОЛЬНИКОВ В УКРАИНЕ

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В статье представлены результаты анализа данных анкетирования за 2002 и 2012 гг. состояния здоровья школьников г Львова и Львовской области, рассмотрены основные факторы риска формирования

функциональных нарушений, синдрома школьной дезадаптации, невротических реакций, возрастная распространенность основных жалоб. Выявлено, что среди факторов, способствующих снижению уровня детского здоровья, значимая роль принадлежит учебной нагрузке, стрессогенное действие которой ведет к быстрому развитию дезадаптационного синдрома с невротическими реакциями различной степени. Комплексный подход к оценке состояния здоровья детей, внедрение новых оздоровительных технологий позволит предупредить рост функциональных нарушений и органической патологии у школьников.

რეზიუმე

უკრაინაში მოწაფეების ჯანმრთელობის მდგომარეობის სამედიცინო-სოციალური თავისებურებები

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სტატიაში წარმოდგენილია ქ. ლვოვსა და ლვოვის ოლქში 2002 და 2012 წლებში მოწაფეების ჯანმრთელობის დასადგენად ჩატარებული ანკეტირების მონაცემების ანალიზის შედეგები. განხილულია ფუნქციური დარღვევების, სკოლისადმი დეზადაპტაციის სინდრომის,ნევროზული რეაქციების ჩამოყალიბების ძირითადი რისკ-ფაქტორები,უმთავრესი ჩივილების ასაკობრივი განაწილება. დადგენილია, რომ იმ ფაქტორებს შორის,რომელიც განაპირობებს ბავშვთა ჯანმრთელობის დონის დაქვეითებას,მნიშვნელოვანი როლი ენიჭება სასწავლო დატვირთვას და მის სტრესოგენულ მოქმედებას დეზადაპტაციური სინდრომის სწრაფ განვითარებაზე სხვადასხვა გამოხატულების ნევროტიული რეაქციებით. მოწაფეებში ფუნქციური დარღვევებისა და ორგანული პათოლოგიის განვითარების სიხშირის შემცირების მიზნით ავტორებს მიზანშეწონილად მიაჩნიათ ბავშვთა ჯანმრთელობის შეფასებისადმი კომპლექსური მიდგომა და გამაჯანსაღებელი ტექნოლოგიების დანერგვა.

CHILDHOOD VASCULITIS HOSPITALIZATIONS IN SPAIN, 1997-2011

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Vasculitis is defined as the presence of inflammation in the blood vessel wall [31]. Clinical and pathological features depend on the site and type of blood vessels that are affected [26]. Primary vasculitis are those processes of vasculitis of unknown cause, whereas secondary vasculitis are associated to an underlying disease, such as lupus erythematosus, juvenile dermatomyositis, infection, malignancy or drug exposure [17,26,31].

Primary vasculitis account for approximately 2-10% of all pediatric conditions evaluated in pediatric rheumatology clinics [19,26]. Annual incidence of primary vasculitis in children and adolescents younger than 17 years is approximately of 23 per 100,000 [10]. Childhood vasculitis include a wide spectrum of diseases, being Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD) the most frequent ones. Other rare conditions affecting children are macroscopic and microscopic polyarteritis, Wegener`s granulomatosis, Takayasu`s disease, cutaneous polyarteritis, hypersensivity angiitis, vasculitis associated with connective tissue disorders such as dermatomyositis, Behçet syndrome and miscellaneuous [17,31].

Vasculitis hospitalizations analysis is useful to show the most severe and costly forms of these diseases. In this sense, national databases of inpatient hospitalizations are suitable tools to assess the impact of vasculitis because they provide a complete record of hospital admissions. National health statistics and information on hospital inpatient contribute both to health decision-making and to identify research

priorities. Most previous studies on childhood vasculitis do not refer to nationwide surveys and are limited to hospital case series [22,27,29]. In Spain, there are regional studies referring childhood vasculitis hospitalizations [3,6,9].

The aim of this study is to describe the national hospital burden of vasculitis in children in Spain (1997-2011), considering type of disease, hospitalization rates and time trends.

Metherial and methods. Data were obtained from the National Discharges Basic Minimum Data Set (National Patient Data Base, CMBD on its Spanish acronym) from 1997 to 2011. As CMBD does not release patient identifiers for confidentially reasons, we used hospital discharge as the unit of measure for the analyses.

CMBD diagnoses are codified according to the Ninth Revision of the International Classification of Diseases (ICD-9CM). Principal diagnosis is the main condition diagnosed at the end of the hospitalization (in-patients) or day treatment (day cases).

Inclusion criteria were hospital admissions for patients younger than 15 years old with vasculitis as principal diagnosis. Vasculitis were identified by ICD9-CM: Takayasu arteritis 446.7, Polyarteritis nodosa 446.0, Kawasaki disease 446.1, Wegener`s granulomatosis (granulomatosis with polyangiitis) 446.4, Churg-Strauss syndrome 446.4, and Henoch-Schönlein Purpura 287.0. Due to ICD9-CM limitations (same code), Wegener`s granulomatosis and Churg-Strauss syndrome were analyzed together.

Other vasculitis were not included in this study because they are not easily identify in ICD9-CM, i.e. isolated cutaneous leucytoclastic vasculitis (classify as other specified hypersensitivity angiitis).

Besides principal diagnosis, clinical and administrative variables were selected for each hospitalization: age, gender, length of stay, cost per inpatient hospital care and patient outcome (survival at hospital discharge or death).

Annual hospitalizations rates were calculated per 100,000 children population. SPSS statistics (version 19) was used to smooth rates (T4253H procedure) and to perform linear time trend test.

Results and their discussion. A total of 14,518 inpatient events, in which principal diagnosis was vasculitis, were identified in children younger than 15 years old in Spain from 1997 to 2011. The most common type of vasculitis was Henoch-Schönlein purpura (HSP), accounting for 72.08% of childhood vasculitis hospitalizations overall. The second most frequent was Kawasaki disease (KD) with a 26.01%. The remaining 1.91% are rare vasculitis hospitalizations in children: Takayasu arteritis, Polyarteritis nodosa, Wegener`s granulomatosis or Churg-Strauss syndrome. Overall vasculitis hospitalizations were not different between sexes. Male excess was found in KD (60.89%) and Takayasu arteritis (64.81%). In contrast, 83.96% of Wegener granulomatosis - Churg Strauss hospitalizations correspond to females.

Table 1. Annual hospitalization rates by type of vasculitis (per 100,000 children)

Year	Takayasu arteritis	Polyarteritis nodosa	Wegener`s granulomatosis and Churg-Strauss	Henoch-Schönlein purpura (HSP)	Kawasaki disease (KD)
1997	0.064	0.064	0.032	14.914	2.590
1998	0.033	0.115	0.049	14.156	3.005
1999	0.033	0.117	0.083	12.886	2.867
2000	0.084	0.084	0.084	12.231	3.125
2001	0.084	0.067	0.067	13.900	3.530
2002	0.083	0.250	0.033	11.475	3.930
2003	0.033	0.180	0.016	11.803	3.754
2004	0.048	0.226	0.048	10.927	4.277
2005	0.016	0.159	0.079	10.586	4.514
2006	0.031	0.156	0.344	11.074	4.833
2007	0.092	0.122	0.337	10.252	4.453
2008	0.075	0.075	0.149	7.960	4.346
2009	0.088	0.147	0.235	8.540	4.490
2010	0.014	0.029	0.043	8.188	4.751
2011	0.072	0.072	0.043	7.653	4.649
TOTAL	0.057	0.123	0.111	10.997	3.969

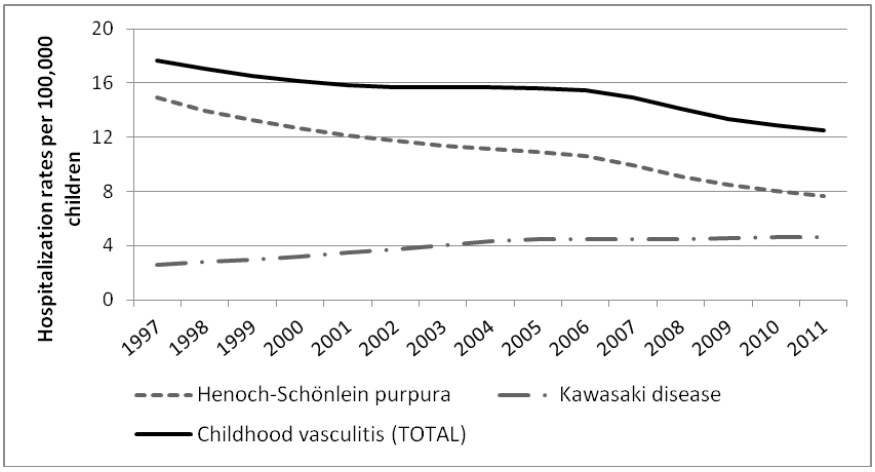

Fig. 1. Smoothed hospitalization rates of those childhood vasculitis with significant time trends

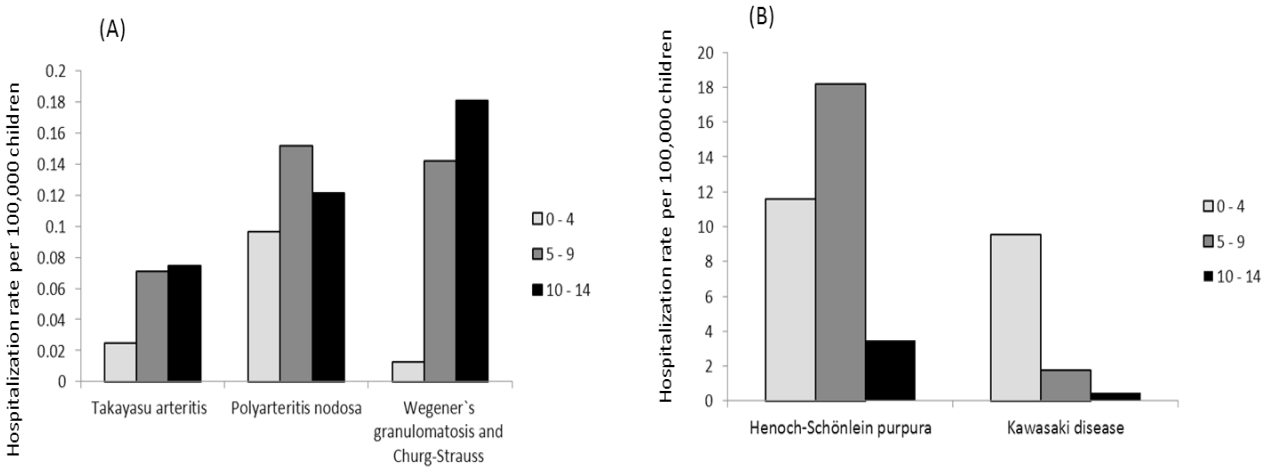

Fig. 2. Hospitalization rates by age groups (A) Rare childhood vasculitis and (B) the most frequent childhood vasculitis

The average rate of childhood vasculitis hospitalizations was 13.33±1.71 per 100,000, decreasing from 17.67 in 1997 to 12.49 in 2011 ($p<0.001$). Vasculitis represent 0.27% overall inpatient events in children younger 15 years. Hospitalization rates by type of vasculitis were: 11.00 for HSP, 3.97 for KD, 0.12 for Polyarteritis nodosa, 0.11 for Wegener`s granulomatosis - Churg Strauss syndrome and 0.06 for Takayasu arteritis, all expressed per 100,000 (Table 1). Only two childhood vasculitis showed significant trends during the period of study: HSP decreased ($p<0.001$) whereas KD increased ($p<0.001$). Smoothed rates and significant time trends are shown in Fig. 1.

Childhood hospitalization rates by both type of vasculitis and age groups are shown in Figure 2. Maximum rates were found in the following age groups: 5 to 9 years for HSP (18.16 per 100,000 children); 0 to 4 years for KD (9.57 per 100,000 children). The remaining vasculitis are less frequent in childhood.

The average length of stay for childhood vasculitis hospitalizations was 6.04 days. The longest stay corresponds to Wegener`s granulomatosis - Churg Strauss syndrome (11.44 days) whereas HSP (5.36 days) has the shortest. Estimated cost per inpatient hospital care was 2,847€ for the 15 years period, ranged from 2,145€ in 1997 to 4,613€ in 2011. Annual length of stay and estimated costs by type of vasculitis are shown in Table 2.

Hospital case fatality rate was 0.05% for overall vasculitis. The highest case fatality rate was reported in children hospitalizations due to Polyarteritis nodosa (0.08%). Children were discharged routinely to home in 98.19% of the cases, and 1.16% of the inpatient events required further care (other hospital or home health care).

This study provides epidemiologic information and time trends on childhood vasculitis hospitalizations in Spain over 15 years (1997-2011). There are few studies regarding vasculitis discharges in children and this is the first nationwide estimation in Spain.

Table 2. Annual length of stay and estimated costs by type of vasculitis in children younger than 15 years

Years	Takayasu arteritis			Polyarteritis nodosa			Wegener`s granulomatosis and Churg-Strauss syndrome			Henoch-Schönlein purpura			Kawasaki disease		
	Inpatient events (N)	Average Length of Stay (days)	Cost per inpatient hospital care (€)	Inpatient events (N)	Average Length of Stay (days)	Cost per inpatient hospital care (€)	Inpa-tient events (N)	Average Length of Stay (days)	Cost per inpatient hospital care (€)	Inpa-tient events (N)	Average Length of Stay (days)	Cost per inpatient hospital care (€)	Inpa-tient events (N)	Average Length of Stay (days)	Cost per inpa-tient hospital care (€)
1997	4	3.5	2177	4	6.5	3385	2	26	2072	927	6.2	2120	161	9.4	2258
1998	2	1.5	2311	7	4.4	2311	3	23.7	4315	862	6.0	2337	183	8.8	2368
1999	2	2	2164	7	4.3	3328	5	3.4	3248	773	6.1	2321	172	8.4	2269
2000	5	2.6	2164	5	11.6	2164	5	5	3175	728	5.8	2313	186	8.8	2264
2001	5	3.4	2168	4	2	2379	4	33.7	4181	827	6.1	2271	210	7.5	2094
2002	5	6	2291	15	6.5	2264	2	6.5	4196	689	5.6	2652	236	7.4	2368
2003	2	4	2347	11	9.2	2932	1	23	7641	720	5.5	2648	229	7.6	2487
2004	3	28.3	4142	14	17.6	3669	3	25.7	5204	677	5.3	2897	265	7.4	2841
2005	1	4	9141	10	18.7	4491	5	1	6964	666	5.1	2625	284	7.3	2798
2006	2	9	2081	10	16.1	3814	22	4.1	5828	708	5.2	2541	309	7.2	2462
2007	6	14.7	2420	8	10.6	2169	22	3.4	6170	670	4.9	2670	291	7.1	2674
2008	5	8.6	4464	5	5.8	2897	10	4.2	4839	533	4.7	2934	291	6.9	2990
2009	6	3.2	5453	10	5.1	3807	16	3.3	6019	582	5.1	3025	306	7.2	3103
2010	1	3	5781	2	6	5033	3	7.7	6318	567	4.5	4377	329	6.2	4574
2011	5	10.8	7421	5	13.2	5378	3	1	9094	535	4.2	4477	325	7.6	4739

HSP is the most common childhood vaculitis, with annual incidence ranging from 10 to 20.4 cases per 100,000 [6,10,25]. It is clinically characterized by purpuric rash, arthritis, nephritis and gastrointestinal symptoms [17]. HSP is a leukocytoclastic vasculitis that predominantly affects the small blood vessels [17,31]. According to our results, HSP is the most frequent disease accounting for 72% of overall childhood vasculitis hospitalization in Spain. HSP hospitalization rate has decreased by half during the period of study in Spain (14.9 to 7.6 per 100,000). However, our study only estimated the number of HSP children who need hospitalizations because of the disease course is usually benign and self-limited, and thus hospitalization is not always indicated. Although HSP is relatively common in children, there are few large-scale epidemiological studies reporting nationwide data [30,33]. Another difficulty when comparing with other countries rates is the difference in methods and time study periods.

Childhood HSP is more frequent from 5 to 15 years of age, being the average age 4 to 7 years [6,10,29,21]. In our study, hospitalizations rates showed a maximum in children from 5 to 9 years of age (18.2 per 100,000 children). Similar age distribution was observed in North West Spain, where average incidence was 10.5 per 100,000 children under 14 years [6]. It was lower than the reported incidence in United Kingdom (20.4 per 100,000 children under 17 years) [27] or Taiwan (12.9 per 100,000 children) [33]. Childhood HSP sex ratio varied among different studies. Our results did not show differences between sexes, whereas other studies proposed HSP in children was more common in males [3,10,27] or females [1,6].

KD is the second most frequent vasculitis in children accounting for 26% of all childhood vasculitis hospitalization in Spain. Hospital discharge data are suitable for surveillance and for providing incidence estimates because most of the young children with KS are hospitalized [7,11,14]. This is a syndrome typically affecting infants and toddlers [17,31]. The most serious complication of KD is coronary artery aneurysm. An increasing trend of KS hospitalization rates was observed in Spain, from 2.59 per 100,000 in 1997 to 4.65 in 2011. This trend was also reported in other countries, for instance in England, KD incidence rates raised from 4.0 in 1991 to 8.1 in 2000 per 100,000 children younger than 5 years [12]. For this age group, average annual incidence gradually increased from 1981 to 1999 and thereafter stabilized in Denmark [8]. In Japan, both incidence rate and inpatient events have dramatically increased since the mid-1990 [20]. India also reported rising number of KD patients from 1993 to 2008 [28]. The reasons why KD is raising are unclear and the etiology remains unknown.

KD hospitalizations occurred more frequently in males, as it was previously described [7,15,31]. The maximum hospitalization rate was observed in Spain for children younger than 5 years (9.57 per 100,000). For this age group, other European estimations are 8.1 per 100,000 in England [20] and 15.2 per 100,000 in Ireland [18]. In the United States, KD incidence estimates ranged from 4 to 19 children [2,7,11,15]. Asian population studies reported much higher incidence rates: Japan has the highest KD incidence in the world (137.7 per 100,000 children <5 years) [32], followed by Korea (105 per 100,000 children < 5 years of age) [23] and Taiwan (69 per 100,000 children < 5 years of age) [16].

The remaining vasculitis are very rare in children. Majority of patients are diagnosed during adolescence and case reporting increase at older ages [4,5,13,17,24,31]. This is why childhood hospital admission rates reported in present study were low: 0.12 per 100,000 in Polyarteritis nodosa, 0.11 per 100,000 in Wegener`s granulomatosis - Churg Strauss syndrome and 0.06 per 100,000 in Takayasu arteritis.

Regarding limitations of our study, the Hospital Discharge Database (CMBD) reliability depends not only on the quality of both discharge report and clinical history, but also on the codification process [24]. This study includes only hospitalizations with principal diagnosis of vasculitis condition. Therefore inpatient events in which vasculitis were incidental or not firmly established, were not considered. In addition, CMBD only showed the number of admissions and some patients may very well have been re-admitted. Thus, prevalence may have been over-estimated. These data derived from CMBD do not provide information on the overall prevalence of vasculitis in the general population. However they are useful to know the hospital burden of these diseases on the Spanish Health System.

In conclusion, these findings provide national estimates of the burden of childhood vasculitis in Spain, which are based on inpatient events. The monitoring of hospitalization rates could be a valuable tool for evaluating the occurrence of childhood vasculitis and its epidemiologic features. This epidemiological information will be useful to assess childhood vasculitis impact on public health, identify possible changes in clinical practice and encourage future research.

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SUMMARY

CHILDHOOD VASCULITIS HOSPITALIZATIONS IN SPAIN, 1997-2011

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The aim of this study is to describe the childhood vasculitis hospital burden in Spain (1997-2011), considering type of disease, hospitalization rates and time trends. Data were obtained from the National Discharges Basic Minimum Data Set (National Patient Data Base). Inpatient events of children younger than 15 years of age were analyzed. Principal diagnosis of vasculitis were selected according Ninth Revision of the International Classification of Diseases: Takayasu arteritis, Polyarteritis nodosa, Kawasaki disease, Wegener`s granulomatosis, Churg-Strauss syndrome, and Henoch-Schönlein purpura. A total of 14518 children hospitalizations related to vasculitis were identified in Spain from 1997 to 2011. The average hospitalization rate for children was 13.33±1.71 per 100,000. Henoch-Schönlein purpura and Kawasaki disease were the most common type of vasculitis, hospitalization rates were 11.00 and 3.97 per 100,000 children, respectively. Other vasculitis hospitalizations are much rare in childhood. Average length of stay was 6.04 days and estimated cost per inpatient hospital care was 2,847€. Hospital case fatality rate was 0.05% for overall vasculitis. In conclusion, epidemiological data of childhood vasculitis are useful both to health decision-making and to identify research priorities.

Keywords: systemic vasculitis, hospitalization, children, Spain.

РЕЗЮМЕ

ГОСПИТАЛИЗАЦИЯ ДЕТЕЙ С ВАСКУЛИТОМ В ИСПАНИИ, 1997-2011 гг.

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Цель исследования - анализ показателей госпитализации детей с васкулитом в Испании за 1997-2011 гг. Проанализированы данные госпитализированных детей младше 15 лет. Данные были получены из National Discharges Basic Minimum Data Set (National Patient Data Base) – Национальной базы данных пациентов. Основной диагноз васкулита был указан согласно IX пересмотру международной классификации болезней: Такаясу артериит, узелковый полиартериит, болезнь Кавасаки, грануломатоз Вегенера, Черджа-Стросса синдром и пурпура Шенлайна-Геноха. Всего в Испании за 1997-2011 гг. госпитализировано 14518 детей с васкулитом. Средний показатель госпитализации составил 13,33±1,71 на 100000. Пурпура Шенлайна-Геноха и болезнь Кавасаки были наиболее частыми типами васкулита. Показатели госпитализации составили 11,00 и 3,97 на 100 000 детей, соответственно. Остальные формы отмечались гораздо реже. Средняя продолжительность пребывания в стационаре составила 6,04 дней, приблизительная стоимость госпитального лечения - 2,847€, показатель госпитальной смертности, в среднем, 0,05%.

В заключение следует отметить, что эпидемиологические данные по васкулиту у детей могут быть полезными как для прннятия решений в здравоохранении, так и для идентификации приоритетов научных исследований.

რეზიუმე

ვასკულიტით დაავადებულ ბავშვთა ჰოსპიტალიზაცია ესპანეთში, 1997-2011 წწ.

ანა ვილავერდე-ჰუესო,ვერონიკა ლონსო,ანტონიო მორალეს-პიგა,მანუელ ჯეი ჰენს-პერეზი,იგნასიო აბაიტუა და მანუელ პოსადა-დე-ლა-პაზი

იშვიათი დაავადებების კვლევითი ცენტრი, კარლოს III-ის სახელობის ჯანმრთელობის დაცვის ინსტიტუტი,მადრიდი,ესპანეთი. იშვიათი დაავადებების ბიოსამედიცინო კვლევის ბადის ცენტრი (CIBERER), ესპანეთის იშვიათი დაავადებების რეგისტრების კვლევითი ბადე (SpainRDR)

კვლევის მიზანია 1997-2011 წწ. ესპანეთში ვასკულიტით დაავადებულ ბავშვთა ჰოსპიტალიზაციის მაჩვენებლების ანალიზი. გაანალიზებულია 15 წლამდე ასაკის ბავშვთა ჰოსპიტალიზაციის მაჩვენებლები. მონაცემები მოპოვებულია პაციენტთა ეროვნული მონაცემთა ბაზიდან (National Discharges Basic Minimum Data Set). ვასკულიტის ძირითადი დიაგნოზები მოცემულია დაავადებათა კლასიფიკაციის მეცხრე გადახედვის მიხედვით: ტაკაიასუს არტერიიტი, კვანძოვანი პოლიარტერიიტი, კავასაკის დაავადება, ვეგენერის გრანულომატოზი, ჩარგ-სტრაუსის სინდრომი და ჰენოხ-შონლაინის პურპურა. მთლიანობაში ესპანეთში 1997-2011 წლებში ვასკულიტით და-

ავადებული 14518 ბავშვი იქნა ჰოსპიტალიზებული. ჰოსპიტალიზაციის საშუალო სიხშირე ყოველ 100000 ბავშვზე შეადგენდა 13.33±1.71. ვასკულიტების ყველაზე გავრცელებულ ფორმას ჰენოხ-შონლაინის პურპურა და კავასაკის დაავადება წარმოადგენდა. მათი ჰოსპიტალიზაციის სიხშირე იყო შესაბამისად 11.00 - 3.97 ყოველ 100000 ბავშვზე. სხვა ვასკულიტებით გამოწვეული ჰოსპიტალიზაცია გაცილებით იშვიათია. საწოლ-დღეების საშუალო რაოდენობა 6.04 დღეს, ჰოსპიტალური მკურნალობის ღირებულება - 2847 ევროს, ჰოსპიტალური სიკვდილობის მაჩვენებელი საშუალოდ 0.05%-ს შეადგენდა.

ავტორებს მიაჩნიათ, რომ ჯანდაცვაში გადაწყვეტილების მიღებისა და კვლევების პრიორიტეტების განსაზღვრის დროს გათვალისწინებული უნდა იყოს ბავშვთა ასაკში ვასკულიტების ეპიდემიოლოგიური კვლევის მონაცემები.

A NEED FOR PHENOTYPING PEDIATRIC ASTHMA IN EPIDEMIOLOGIC STUDIES

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Population-based surveys on childhood asthma reveal a substantial variation in the prevalence of pediatric asthma. The results of the largest project in the field known as International Study of Allergy and Asthma in Children (ISAAC) show a broad range of country-specific estimates, from less than 5% to over 20% [18]. Among possible reasons of the apparent variation the issue of different distribution of risk factors of asthma attracts due scientific attention, particularly to explore so-called East-West gradient in the prevalence of the disease, still seen in Europe [19]. Both ISAAC findings and results of other projects show a relatively low prevalence of pediatric asthma in Eastern Europe [12,28,34]. Regardless of variability in potentially causative exposures an important consideration stems from the fact that in population-based surveys the prevalence of pediatric asthma is usually assessed by questionnaires, according to the parental answer to the question "has a doctor ever diagnosed asthma in your child". Positive answer to this question can reflect the true occurrence of asthma under the condition that all children with the disease have been properly diagnosed and the firm diagnosis has been established.

Epidemiological approach to the estimation of asthma prevalence in children is sensitive to at least two contradicting phenomena: underdiagnosis and overdiagnosis of pediatric asthma. Results of recently performed studies in Poland suggest that the magnitude of underdiagnosis could be as large as 50% and the problem is described by studies in other countries [3,20,27]. On the other hand some reports provide evidence on overdiagnosis of asthma, the phenomenon best described in so-called westernized populations [23]. Both phenomena have serious consequences. A child with undiagnosed asthma does not receive appropriate treatment and the disease is likely to progress over time. A child without asthma but erroneously labeled as asthma case receives unnecessary treatment. However, in terms of the disease burden underdiagnosis and – as a result - undertreatment of pediatric asthma have a serious impact, perceived as an important clinical and public health issue [3,6].

In general, underdiagnosis of pediatric asthma may have non-medical and medical reasons. Among non-medical reasons a number of socio-economic and behavioral factors can affect the recognition of symptoms in a sick child [13]. Other factors include serious family problems and a low economic standing of families probably affecting the access to health care [1,29]. Medical factors include a number of potential obstacles. First of all a conclusive diagnostic process requires time and access to facilities enabling proper assessment of respiratory and allergic status of a child and a careful differential diagnosing [3,10]. Another pertinent issue, perhaps of particular importance in the countries of Eastern Europe, is related to diagnostic patterns and nosologic preferences. In Poland such traditional labels as "spastic or asthmatic bronchitis" are not uncommon. The traditional diagnostic labels could serve as surrogate diagnoses particularly that the prevalence of spastic bronchitis diagnosed by physicians is relatively high in Poland and other countries of Eastern Europe [12,22,28]. A well

know feature of natural history of asthma is its gradual progression and young children with mild symptoms are more likely to be undiagnosed [13]. Finally, existing diagnostic guidelines, even if available in several published national and international consensus documents, are often not applied in general practice [22].

In clinical setting a correct diagnosis of asthma can rarely be based only on clinical symptoms. A working definition of asthma, including pediatric asthma, states that "asthma is a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness. It presents with recurrent episodes of wheeze, cough, shortness of breath, and chest tightness" [27]. The definition includes objective criteria that require testing of lung function. Objective measurements are included in the set of diagnostic methods recommended by recent US guidelines. In addition to detailed medical history and physical examination a diagnostic procedure should include spirometry performed to demonstrate airflow obstruction and assess its reversibility. The latter criterion, reversibility, is determined either by an increase in FEV1 of >12% from baseline or by an increase of >10% of predicted FEV1 after inhalation of a short-acting bronchodilator [5]. A recently published international consensus on pediatric asthma adds to the above recommendations a need to evaluate atopy, bronchial hyperresponsiveness and airway inflammation (sputum eosinphils, FeNO) as well as therapeutic trial [27]. A satisfactory diagnostic procedure cannot be completed without methods undertaken to exclude alternative diagnoses. Differential diagnosis should focus first of all on infectious chest diseases, immunological disorders and specific bronchial pathologies.

Today, after years of experience and international efforts aiming at proper practices in diagnosing, assessing and managing asthma the above mentioned methods appear necessary but not sufficient. The major advance in understanding asthma is the recognition of its heterogeneity – clearly the general term "asthma" embraces a number of specific phenotypes [16,26].

Asthma is not a single disease but it is a complex syndrome, composed of similarly manifested disorders related to specific pathogenetic mechanisms [2,7,33]. Until now the leading interest in phenotyping asthma stems from the expectation that better classification will improve management of the disease and will add to predicting the prognosis [17,24,26]. Emphasis on purely clinical applications of phenotyping should not obscure other efforts related to phenotyping asthma, such as developing methods of early diagnosis, improving investigations into risk factors, adding objective tools to population-based screening, etc. Each and every goal requires that every case of asthma is characterized and classified in the most reliable and precise way. However, two approaches to phenotyping, namely clinical and etiological assessments, do not provide means of complete classification of the disease. This universal problem is under debate in relation to asthma in adults and deserves a due scientific attention in relation to pediatric asthma. A relatively novel and promising research area that takes advantage of the concept of phenotyping involves biomonitoring. The interest in biomonitoring has a reason - clinical classification of asthma comes across a number of obstacles. Two major factors used to describe the clinical manifestation of the disease are severity and persistence. However, there is no universally accepted consensus concerning the exact value of that approach and as such it is recommended only for the initial classification of the disease [32]. A more useful way is a practical approach that takes into account clinical course – pertinent to classification of severity that includes the assessment of a quality of life. The method referred to as asthma control distinguishes between 'complete' 'good', 'partial' and 'none' control, as shown in the table below [27].

Almost all components can be analyzed using questionnaires and standard respiratory health questionnaires include specific questions on occurrence and intensity of symptoms. Nevertheless the answers depend on subjective self-assessment of the study subjects, usually parents in the case of epidemiological projects on pediatric asthma.

Understanding of interplay between immunologic status, allergic inflammation and clinical manifestation of the disease is believed to contribute to more specific definitions of asthmatic phenotypes. However, the lack of knowledge hampers the development of specific algorithms [15].

Table. Assessment of asthma according to the level of its control

Component	Control			
	Complete	Good	Partial	None
Symptoms – daytime	None	=<2/week	>2/week	Continuous
Symptoms – nighttime	None	=<1/month	>1/month	Weekly
Need for resque medication	None	=<2/week	>2/week	Daily
Limitation of activity	None	None	Some	Extreme
FEV1, PEF (% p.v.)	>80%	=>80%	60-80%	<60%
Exacerbations/year	0	1	2	>2

Table 2. Characterization of study population for prospective clinical trials (i.e., baseline information)

Core Outcomes	**Serologic multiallergen screen (IgE) to define atopic status (also for observational studies)**
Suplemental Outcomes	1. FENO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE4
Emerging Outcomes	1. Allergen skin prick testing 2. Sputum neutrophils and analytes 3. Airway imaging 4. Exhaled breath condensate markers 5. Discovery through genetics and genomic

Table 3. Prospective clinical trial efficacy/effectiveness outcomes

Core Outcomes	**None**
Suplemental Outcomes	1. FENO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE4
Emerging Outcomes	1. Allergen skin prick testing 2. Sputum neutrophils and analytes and analytes 3. Airway imaging 4. Exhaled breath condensate markers 5. Discovery through genetics and genomica

Table 4. Observational study outcomes

Core Outcomes	**None**
Suplemental Outcomes	1. FENO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE4
Emerging Outcomes	1. Sputum neutrophils and analytes 2. Airway imaging 3. Discovery through genetics and genomics

Etiologic classification of asthma is an alternative approach to phenotyping of the disease [3]. The classification takes into account circumstances that precede the symptom manifestation in the disease. Trigger-specific phenotypes include 'virus-induced asthma', 'exercise-induced asthma', 'allergen-induced asthma', 'unresolved asthma'. The latter category as well as a possible overlay between the trigger-specific conditions are likely to impair conclusive differentiation. There is a need to explore relationships between trigger-based phenotypes and biomarker profiles, and epidemiological studies could provide necessary observations. The most important challenge is to select noninvasive rather than invasive biomarkers and to apply validated tests. The goal could can be facilitated by taking advantage of existing recommendations, such as current recommendations agreed by the expert panels under the auspices of US National Institutes of Health [24]. Three tables below (modified from the reference: 25) provide a concise summary of the current recommendations.

Evidence behind the consensus on recommended biomarkers comes from numerous studies that infrequently addressed many biomarkers in one study protocol and this is true especially as far as studies in children are taken into account. There is a need to verify the concept of recommended biomarkers in real life circumstances and a number

of markers examined in every subject should help to arrive at specific profiles. Above all the quoted report includes the statements that there is a lack of standardization, a need for studies on real meaning of the recommended biomarkers – both conclusions are used to justify implementation of clinical and epidemiological studies aiming at phenotyping asthma using the recommended biomarkers.

As an example, two specific and important contributions are related to the role of determination of non-invasive biomarkers in asthma studies. Earlier findings provided by clinical observations suggest that the measurement of biomarkers of inflammation in sputum and of nitric oxide (NO) concentration in exhaled air is useful in clinical practice. Other biomarkers examined for clinical usefulness are cellular phenotypes and cytokines in blood [9]. Despite a long experience with the method the exact value of the measurement of NO in exhaled air – perhaps the best know noninvasive biomarker of inflammation in asthma research – remains to be established even in clinical management of the disease and further studies are needed [25]. There is a reason to conclude that the need for further evaluation of the method is obvious in the field of diagnostics and epidemiology of asthma. Another potentially useful method is the measurement of biomarkers in saliva. In children, especially in those with less severe asthma, obtaining sputum is a difficult procedure. However, sputum analyses resulted in identification of four "molecular phenotypes" of asthma [31]. It remains to be established if determination of biomarkers in saliva has similar potential. Published evidence shows that in asthma patients saliva can be tested positive for protein, surfactants protein, 8-isoprostan and IL-8 in 80% of the subjects [8]. Epidemiological studies could take advantage of the findings obtained in clinical setting.

Investigations into biomarkers are subject to specific protocols that include formal requirements, however it is very seldom that one biomarker meets all criteria [30]. For identified biomarkers some criteria are critical and respond to the questions asked below [21]. All questions addressed in clinical setting deserve the answers also in epidemiological context:
a) are biomarkers identifiable and the results of measurements repeatable?
b) what is the level of intra- and inter-individual variability of the levels?
c) do levels depend on host factors and environmental exposures?

In summary, classification of asthma based on the nature of underlying inflammation is a promising method that could aid not only the management of asthma [11]. Application of different methods, including biomarkers, may enhance the characterization and understanding of heterogeneity of asthma. Analyses of cellular inflammation are considered a valuable and necessary tool in identifying specific phenotypes. In general, the areas and issues to be addressed by epidemiological studies can be summarized by current priority research recommendations regarding phenotyping of childhood asthma [27]:
a) asthma phenotypes in childhood should be further characterized in detail and defined, using epidemiological, statistical, and biological criteria;
b) the clinical value of phenotype/endotype classifications, including differential response to treatment and/or natural history, needs to be demonstrated;
c) Phenotype-specific biomarkers will be useful in practice;
d) identify biomarkers for airway inflammation that are both informative for initial and ongoing treatment decisions and also practical for clinical use;
e) diagnostic and prognostic markers for asthma and/or specific phenotypes are clearly needed;
f) indirect, noninvasive measures of airway pathology will help the diagnostic investigation in young children.

The above mentioned recommendations can serve as "signposts" in epidemiological asthma research, both in observational studies (target: occurrence of asthma and its characterization) and in analytical studies (target: risk factors of asthma, effects of interventions). Given the complexity of clinical assessment of pediatric asthma, its natural history and heterogeneity of the disease, the impact of medical practices and preferences, contribution from non-medical factors it is not surprising that epidemiological investigations into occurrence and risk factors of physician-diagnosed pediatric asthma provide differing findings. However, the most important obstacle is related to heterogeneity of pediatric asthma. According to the "good epidemiological practice" health events under study should be measured in the best possible way. The goal is to avoid or limit erroneous classification resulting in bias affecting estimates of the occurrence and causality. A convincing evidence concerning the advantage of correct phenotyping of allergic disease in analytical epidemiology was provided by the study characterizing intermittent and persistent types of allergic rhinitis [14]. Two phenotypes of what is classified as one disease appeared to be distinct not only in terms of some clinical features but also in terms of allergen-specific sensitization (different risk factors for two identified phenotypes of allergic rhinitis).

The requirement of precise measurement of the disorder under study easily translates to so-called case definition and in epidemiological studies on pediatric asthma it should promote the development of precise and valid definitions of phenotypes of the disease. Focus on specific phenotypes and its components could provide a better opportunity to explore asthmatic disorders in children and such a potential benefit should be verified by epidemiological projects involving the measurement of various phenotype-specific markers, including validation studies. Published recommendations and research priorities related to the question of phenotypes of asthma formulate a promising direction of future epidemiological studies on pediatric asthma.

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SUMMARY

A NEED FOR PHENOTYPING PEDIATRIC ASTHMA IN EPIDEMIOLOGIC STUDIES

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Epidemiological studies on pediatric asthma reveal a substantial variation in the prevalence of the disease. Differing population-specific data on the occurrence of the disease, defined as a physician-diagnosed asthma, are attributed to differences in risk factors, nosologic preferences, availability of diagnostic facilities, socio-economic factors, etc. As a result some findings could be affected by so-called underdiagnosis although in some populations overdiagnosis of pediatric asthma cannot be excluded. Diagnosing pediatric asthma can be difficult even in clinical setting. Among factors hampering that process heterogeneity of the disease plays an important role. Evidence show that asthma is not a single disease but it is a complex syndrome composed of similarly manifested disorders. As a result a significant scientific effort is directed to describe phenotypes of pediatric asthma. Two well known approaches to phenotyping include clinical and etiological assessment. The former approach takes into account the clinical presentation. The latter one involves recognition of the circumstances that precede the symptom manifestation in the disease: 'virus-induced asthma', 'exercise-induced asthma', 'allergen-induced asthma', 'unresolved asthma'. The mentioned approaches do not provide means of complete classification of the disease. A relatively novel and promising research area in the field of phenotyping asthma takes advantage of biomonitoring. Biomarkers of allergy and immunological responses are used in clinical setting (for example: assessment of atopy, eosinophils count, FENO), however many tests need more validation. Of particular interest is availability of non-invasive biomarkers, their repeatability, sensitivity and specificity. Several national and international guidelines and recommendations point to the importance of specific studies addressing the role of biomonitoring in phenotyping asthma. Epidemiological perspective investigations into biomarkers in pediatric asthma can contribute to observational and analytical goals. Focus on specific phenotypes and its components could provide a better opportunity to explore asthmatic disorders in children. Epidemiological projects should also address validation issues. Both research directions deserve more attention in epidemiological studies on pediatric asthma.

Keywords: Bronchial asthma, children, epidemiology, phenotyping.

РЕЮЗМЕ

НЕОБХОДИМОСТЬ ФЕНОТИПИРОВАНИЯ ПЕДИАТРИЧЕСКОЙ АСТМЫ В ЭПИДЕМИОЛОГИЧЕСКИХ ИССЛЕДОВАНИЯХ

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Эпидемиологические исследования по педиатрической астме выявили существенный разброс данных по частоте болезни. Отличающиеся популяционно-специфические данные о выявляемости заболевания, определяемые как диагносцированная врачом астма, характеризуются различиями по риск-факторам, нозологическим предпочтениям, доступности диагностических возможностей, социально-экономическим факторам и т.д. В результате некоторым выводам может быть нанесен ущерб ввиду т.н. гиподиагностики, хотя в некоторых популяциях не исключена и гипердиагностика. Диагностика бронхиальной астмы весьма затруднительна даже в клинических учреждениях. Среди факторов, препятствующих этому процессу, значительную роль играет сама гетерогеничность заболевания. Имеются доказательства, указывающие что астма не отдельная нозологическая единица, а сложный синдром, состоящий из клинически похожих проявлений. Соответственно, существенные научные усилия направлены на описание фенотипов педиатрической астмы. Два хорошо известных подхода к фенотипированию включают клиническое и этиологическое определения. Первый подразумевает клинические проявления, другой включает определение обстоятельств, предшествующих проявлению симптомов заболевания – "вирус-индуцированная астма", "упражнениями индуцированная астма", "аллерген-индуцированная астма", "астма неизвестной этиологии". Указанные подходы не обеспечивают полной классификации болезни. Биомаркеры аллергии и иммунологического ответа используются в клинических учреждениях (например, определение атопии. количество эозинофилов, FENO), тем не менее, некоторым тестам необходима большая валидация. Предметом особого интереса являются доступность неинвазивных биомаркеров, их повторяе-

мость, чувствительность и специфичность. Во многих национальных и международных гайдлайнах указывается на значение специфических исследований, направленных на определение роли биомониторинга в фенотипировании астмы. Эпидемиологические перспективные исследования биомаркеров при педиатрической астме способствуют достижению обсервационных и аналитических целей. Фокусирование на специфических фенотипах и их компонентах предоставляет лучшие возможности для изучения астматических проявлений у детей. При проведении эпидемиологических проектов необходимо также учитывать вопросы валидации. Оба направления исследований заслуживают большего внимания к эпидемиологическим исследованиям в области педиатрической астмы.

რეზიუმე

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სილეზიის სამედიცინო უნივერსიტეტი,კატოვიცეს სამედიცინო სკოლა, ეპიდემიოლოგიის დეპარტამენტი, პოლონეთი

პედიატრიული ასთმის ეპიდემიოლოგიური გამოკვლევები სიხშირის შესახებ მონაცემთა გარკვეულ დაშორებას ავლენს. დაავადების, რომელიც განისაზღვრება როგორც ექიმის მიერ დიაგნოსცირებული ასთმა, პოპულაცია-სპეციფიკური მაჩვენებლების განსხვავებულობა განპირობებულია სხვადასხვა რისკ-ფაქტორის არსებობით, ნოზოლოგიური სასურველობით,დიაგნოსტიკური გამოკვლევების მისაწვდომობით და სოციალურ-ეკონომიური ფაქტორებითა. აქედან გამომდინარე, ზოგიერთი შედეგის სანდოობა ირღვევა ე.წ. ჰიპოდიაგნოსტიკის გამო, თუმცა ზოგიერთ პოპულაციაში ჰიპერდიაგნოსტიკაც არ არის გამორიცხული. ბრონქული ასთმის დიაგნოსტიკა შეიძლება კლინიკურ დაწესებულებებშიც იყოს გაძნელებული. სადიაგნოსტიკო პროცესს აფერხებს თვით დაავადების ჰეტეროგენობა. არის მტკიცებულებები, რომელთა თანახმად ასთმა არ არის ცალკე ნოზოლოგიური დაავადება, არამედ რთული სინდრომია, რომელიც მოიცავს კლინიკურად მსგავს გამოვლინებებს. შესაბამისად, არსებითი სამეცნიერო მცდელობა მიმართულია პედიატრიული ასთმის ფენოტიპების აღსაწერად. ფენოტიპირებისადმი მიდგომა მოიცავს კლინიკურ და ეტიოლოგიურ განსაზღვრას. პირველი მათგანი ყურადღებას აქცევს კლინიკურ გამოვლინებებს. მეორე კი მოიცავს იმ გარემოებების განსაზღვრას, რომელიც წინ უსწრებდა დაავადების სიმპტომების გამოვლინებას – “ვირუს ინდუცირებული ასთმა”, “ფიზიკური ვარჯიშით გამოწვეული ასთმა”, “ალერგოგენით ინდუცირებული ასთმა”, “გაურკვეველი ასთმა”. ეს მიდგომები არაა საკმარისი დაავადების სრულყოფილი კლასიფიკაციის განსახორციელებლად. შედარებით ახალი და იმედისმომცემი კვლევის არეა ფენოტიპირების დადგენა ბიომონიტორინგის უპირატესობების გამოყენებით. ალერგიისა და იმუნური პასუხის მარკერები გამოიყენება კლინიკურ დაწესებულებებში (მაგალითად, ატოპიის დადგენა, ეოზინოფილების რაოდენობის დადგენა, FENO), მაგრამ ზოგიერთ ტესტს მეტი ვალიდაცია ესაჭიროება. განსაკუთრებული ინტერესის საგანია არაინვაზიური მარკერების დადგენის შესაძლებლობა, მათი განმეორადობა, მგრძნობელობა და სპეციფიურობა. მრავალ ნაციონალურ და საერთაშორისო გაიდლაინში მითითებულია სპეციფიური კვლევების მნიშვნელობაზე, რომელიც მოიცავს ბიომონიტორინგს. შესაბამისი ეპიდემიოლოგიური პერსპექტიული კვლევები ბიომარკერების როლის დასადგენად პედიატრიული ასთმის დროს ხელს შეუწყობს ობსერვაციული და ანალიტიკური მიზნების უკეთეს მიღწევას; სპეციფიურ ფენოტიპებზე და მათ კომპონენტებზე ფოკუსირება კი ასთმის გამოვლინებების უკეთეს შესწავლას ბავშვებში. ეპიდემიოლოგიური პროექტები მიმართული უნდა იყოს აგრეთვე ვალიდაციის საკითხებზე. ორივე მიმართულება მეტ ყურადღებას თხოულობს პედიატრიული ასთმის ეპიდემიოლოგიური კვლევების ჩატარებისას.

FAMILIAL MEDITERRANEAN FEVER IN GEORGIA

[1]Pagava K., [2]Rauscher B., [1]Korinteli I.A., [1]Shonvadze[1] D., [2,3]Kriegshauser G., [2]Oberkanins Ch.

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Familial Mediterranean Fever (FMF) is a hereditary auto-inflammatory disorder caused by mutations in the MEFV gene. The disease is mainly present in Sephardic Jewish, Armenian, Arab and Turkish populations, but occurs in lower frequencies also in other Mediterranean countries. Correspondingly, carrier rates for MEFV gene mutations are known to be particularly high among these nationalities [1-7,9,11,12,14,16-19]. The situation regarding FMF in Georgia, a direct neighbour to Armenia and Turkey, is largely unknown to date. Despite of numerous Armenian diaspora and a high frequency of mixed marriages in the country, only very few and preliminary reports about FMF and MEFV mutations in Georgia have been published [8,10]. The aim of our study was to review existing data and to analyze the spectrum and frequency of twelve common MEFV mutations among Georgian newborns.

Fig. 1. Geographical map of Geogia

Materials and methods. Blood was obtained from 202 unselected newborns at various hospitals in Tbilisi (Georgia) and collected on filter cards (903 Sample Collection Cards, GE Healthcare, UK) for further analysis. DNA was prepared using the GenXtract Blood DNA Extraction System (ViennaLab Diagnostics, Austria). Multiplex PCR and reverse-hybridization teststrips (FMF StripAssay; ViennaLab Diagnostics) [13] were applied to simultaneously analyze twelve common MEFV mutations.

Results and their discussion. We found 30 neonates to be heterozygous and one to be E148Q/M694V compound heterozygous or carrier of a complex allele (both mutations in cis). The most frequently observed variants were E148Q (N=15), M680I G/C (N=5) and M694V (N=4). Five other MEFV mutations were found at lower incidence (V726A, A744S, R761H: N=2; P369S, F479L: N=1).

LINE	PROBE SPECIFICITY	LINE	PROBE SPECIFICITY
RML	red marker line (top)	13	wild type codon 148
CTL	positive control	14	wild type codon 369
1	mutant E148Q	15	wild type codon 479
2	mutant P369S	16	wild type codon 680
3	mutant F479L	17	wild type codon 692-695
4	mutant M680I (G/C)	18	wild type codon 726
5	mutant M680I (G/A)	19	wild type codon 744
6	mutant I692del	20	wild type codon 761
7	mutant M694V	GML	green marker line (bottom)
8	mutant M694I		
9	mutant K695R		
10	mutant V726A		
11	mutant A744S		
12	mutant R761H		

Fig. 2. Oligonucleotide probe specificities

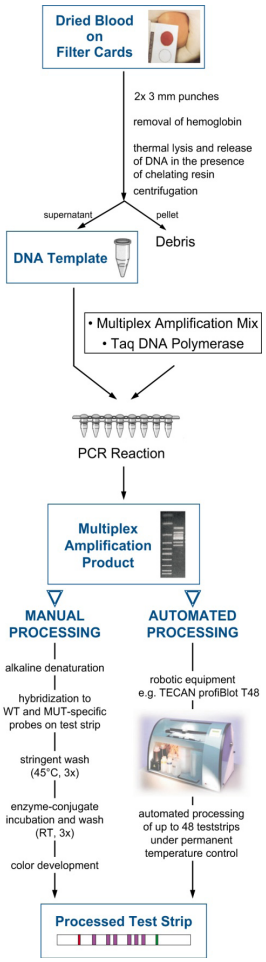

Fig. 3. StripAssay procedure: DNA isolation, in vitro amplification (PCR), hybridization and detection

Table. Spectrum and frequencies of MEFV mutations in newborns from Tbilisi

MUTATION	E148Q	P369S	F479L	M680I (G/C)	M694V	V726A	A744S	R761H	total
Total Newborns: (n=202)									
Heterozygous	15	1	1	5	4	2	2	2	32
Homozygous	0	0	0	0	0	0	0	0	0
Allele Frequency (%)	3.7	0.2	0.2	1.2	1.0	0.5	0.5	0.5	7.9
Armenian Origin: (n=9)									
Heterozygous	2	0	0	1	2	0	0	0	5
Homozygous	0	0	0	0	0	0	0	0	0
Allele Frequency (%)	11.1	0	0	5.6	11.1	0	0	0	27.8

The carrier rate of MEFV mutations (31/202; 15.3%) was remarkable, although lower compared to data reported from neighbouring Turkey and Armenia (approx. 20%). This reflects the about two thousand years long neighbourhood of Georgians and Armenians and the high frequency of interethnic marriages, particularly in Eastern Georgia. Although low in number, newborns of parents with known Armenian origin had a substantially higher carrier rate of MEFV mutations (5/9; 55,6%) compared to the Georgian population overall.

We identified only six existing publications dedicated to the issue of FMF in Geogia. One of them is a description of 18 cases of child renal amyloidosis as a complication of periodic fever [15]. Three other reports analyze the HLA antigen prevalence in FMF patients and its comparison with Armenian data [20-22]. They demonstrate a positive correlation between clinically defined FMF according to the Tel-Hashomer criteria and certain HLA antigens, in particular B5 (RR=2.4) and B7 (RR=3.5) in females. A1 (RR=2.7) and B7 (RR=5.7) in males, to A9 (RR=2.7) and B5 (RR=2.9). None of these studies included MEFV genotyping. One study confirms the efficacy of colchicin treatment for FMF and the prevention of amyloidosis in adults [8]. Twelve among 52 patients were genetically tested, but mutations were specified for only five (M694/M694V: N=3; M6801/M694V: N=2). One paper provides a clinical description of pediatric cases, including the results of genetic testing [10]. Five of the patients were M694V/M694V homozygous and one was M680I/M694V compound heterozygous. One of the patients (M694V/M694V) had developed amyloidosis. The authors of this study state that their patients have no Armenian roots, while this question is not discussed in all other publications.

Conclusions.

The results of our literature survey indicated a lack of research on FMF in Georgia. Our own data indicate that MEFV mutations, including severe ones such as M680I and M694V, are fairly common in the Georgian population. Based on these new findings, the awareness for FMF and the availability of appropriate testing should be further promoted in Georgia, especially among people with Armenian roots.

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SUMMARY

FAMILIAL MEDITERRANEAN FEVER IN GEORGIA

[1]Pagava K., [2]Rauscher B., [1]Korinteli I.A., [1]Shonvadze[1] D., [2,3]Kriegshauser G., [2]Oberkanins Ch.

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Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder caused by mutations in the MEFV gene. Carrier rates are known to be particularly high among Sephardic Jews, Turks, Armenians and Arab populations. Our literature survey regarding FMF and MEFV mutations in Georgia revealed a lack of existing studies. We applied multiplex PCR and reverse-hybridization teststrips (FMF StripAssay) to simultaneously analyze twelve common MEFV mutations in DNA samples from dried blood on filter cards, which had been obtained from 202 unselected newborns at various hospitals in Tbilisi, Georgia. We found 30 samples to be heterozygous and one to be compound heterozygous or carrier of a complex allele (two mutations in cis). The carrier rate of MEFV mutations (15.3%) was remarkable. The most frequently observed variants were E148Q (15x), M680I G/C (5x) and M694V (4x). Five other MEFV mutations were found at lower prevalence (V726A, A744S, R761H: 2x each; P369S, F479L: 1x each). Based on these new findings, the awareness for FMF and the availability of appropriate testing should be further promoted in Georgia.

Keywords: Familial Mediterranean Fever, MEFV mutations, frequency, spectrum, Georgia.

РЕЗЮМЕ

СЕМЕЙНАЯ СРЕДИЗЕМНОМОРСКАЯ ЛИХОРАДКА В ГРУЗИИ

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Семейная средиземноморская лихорадка наследственное аутовоспалительное заболевание, обусловленное мутациями гена MEFV. Известно, что частота носительства данных мутаций наиболее высока среди евреев-сефардов, турок, армян и арабов. Анализ литературы выявил недостаточность исследований по семейной средиземноморской лихорадке и мутациям гена MEFV

в Грузии. Обследовано 202 новорожденных из различных клиник города Тбилиси на наиболее частые 12 мутаций гена MEFV. Пробы ДНМ взяты из засохшей крови, консервированной на специальных фильтровальных карточках и исследованы посредстсвом PCR и специальными тестстрипами (FMF StripAssay). В 15,3% случаев установлено наличие мутаций. Наиболее частыми вариантами были E148Q (15x), M680I G/C (5x), M694V (4x). Частота других 5 мутаций была ниже (V726A, A744S, R761H: каждая 2x; P369S, F479L: каждая 1x). Полученные данные указывают на актуальность семейной средиземноморской лихорадки в Грузии и на необходимость повышения доступности соответствующих генетических исследований.

რეზიუმე

ოჯახური ხმელთაშუაზღვის ცხელება საქართველოში

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ოჯახური ხმელთაშუაზღვის ცხელება მემკვიდრეობითი აუტოანთებითი დაავადებაა, გამოწვეული MEFV გენის მუტაციებით. ცნობილია, რომ მათი მტარებლობის სიხშირე განსაკუთრებით მაღალია სეფარდ ებრაელებში, თურქებში, სომხებსა და არაბებში. ჩვენს მიერ შესრულებულმა ლიტერატურის მიმოხილვამ გამოავლინა კვლევების სიმცირე ოჯახური ხმელთაშუაზღვის ცხელებისა და MEFV გენის მუტაციების შესახებ საქართველოში. 202 ახალშობილი თბილისის სხვადასხვა კლინიკიდან შემოწმებული იქნა MEFV-ის 12 უხშირეს მუტაციაზე. დნმ-ის სინჯები მიღებული იქნა სპეციალურ ფილტრის ქაღალდებზე დაკონსერვირებული გამშრალი სისხლიდან. დნმ-ის სინჯები შემოწმდა რთული PCR და შებრუნებითი ჰიბრიდიზაციის ტესტსტრიპებით (FMF StripAssay). 15.3%-ში დადგინდა მუტაციის მტარებლობა. უხშირესი ვარიანტები იყო E148Q (15x), M680I G/C (5x), M694V (4x). დანარჩენი 5 მუტაციის სიხშირე იყო შედარებით დაბალი (V726A, A744S, R761H: თვითოეული 2x; P369S, F479L: თვითოეული 1x). მიღებული მონაცემები მიუთითებს ხმელთაშუაზღვის ოჯახური ცხელების აქტუალობაზე საქართველოში და შესაბამისი გენეტიკური გამოკვლევების ხელმისაწვდომობის აუცილებლობაზე.

SOME PERSONAL VIEWS ON PEDIATRICS AND NOT ONLY ...

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Pediatrics is usually defined as a branch of medicine, dealing with the development, care and diseases of children. A definition developed by the American Academy of Pediatrics [4] is more comprehensive; it encompasses a broad spectrum of health services ranging from preventive health care to the diagnosis and treatment of acute and chronic diseases, is handling with biological, social and environmental influences on the development. Main accent is done on the healthiness, main activities of pediatricians seem to be diagnostics and treatment (including prevention, prophylaxis and rehabilitation as well). One must entirely agree with the opinion, that health is a main target of medicine. Health is of great value, but it has a subordinate importance in comparison to the complete self-realization, particularly regarding the childhood. Pediatrics is unique discipline which contains both medical and humanitarian components. Going back to the co-founder of modern pediatrics Adalbert Czerny (I would like to mention only the title of his world-known book – "The physician as an educator of the child") [3], I suppose that today the pediatrician besides performing a routine clinical work must be more involved in protecting of minors, optimization of their development and **being the main advisor** to the society, school and family in the matter of their education, not only restricted by healthy life style simple rules but covering the problem how to reach the optimum of the emotional, intellectual, social, ethical and esthetic maturation of the young generation.

I fully agree with the opinion upon more concentration on the development of moral issues in young generation [8], chivalric values stay of eternal importance.

Concerning the sexual education – to think that its main goal is teaching to the youth the principles of safe sex is an impermissible oversimplification. Efforts must be focused on the identification of gender roles, a boy must become a man, and a girl – a woman, as well as to learn the assimilate gender responsibilities.

In all age periods of life, especially in adolescents we encounter depressiveness (in elderly people it has its explanation) and aggressive behavior. The depressiveness should not be present in children and adolescents. What can we, parents, teachers and pediatricians do? Firstly to help youth to find the stage in the life theater where they would be able to play the best role, to get the applause. Regarding the aggressiveness, I suppose, that to some extent, especially in males it is necessary to some degree, it can be considered as a display of activity, even of courage, readiness to be winner. Of course, social demands restrict aggressiveness. Sport is the best tool of sublimation. Both types of sport could be greeted – individual ones for boosting of individual development, and collective ones to contribute to team feelings and ability to behave in team.

I like very much health education and am involved in this activity. Nevertheless, taking into account its necessity, I guess that traditional ways of its promotion by summonning the youth and whole population to follow the healthy life style are not so efficient as we want, they are a little bit dead-ended. We need innovative technologies, new ways, maybe the help from marketing professionals.

We all witness increasing globalization in the modern age. Globalization might not be exclusively associated with worldwide economic integration and creation of a borderless global market. Perhaps more important things happen on the social, cultural and political terrains. Contradictory processes of homogenization and universalization on the one hand and differentiation on the other take place. Cultural codes have a great role in the process of identity formation on all levels, beginning from individual to supranational levels. We are far to discuss the advantages and disadvantages of these tendencies, what is better for civilization's development, prevention of hidden and manifested conflicts, caused by forcible coercion to cultural similarity. Nevertheless, realizing the crucial role of media and information and communication technologies we think that the corresponding efforts must focus on the early developmental stages (according to imprinting theory by Conrad Lorentz) and the schools (centuries old experience of Jesuits education system, Ignacio (Íñigo) López de Loyola, Claudio Aquaviva). Here the role of pediatricians must be also taken into account. Idea of imprinting and cultural code is presented in the narrative "What has the lullaby done?" by Georgian writer and teacher of XIX century Jacob Gogebashvili. It tells a story of a girl who was kidnapped and grew up faraway from her family, native land. The sounds of the lullaby help her find her identity, parents, mother country and mother tongue. About two thousand years long debate what is correct - *ubi patria ibi bene* or *ubi bene ibi patria* still remains undecided. But **the imprinting of cultural codes should be considered as a biological basis of patriotism**.

One sad tendency is being observed almost everywhere – parents spend less time with their off-spring. Maybe that is a reason of raising frequency of psychosomatic, psychological, social and even psychiatric disorders. The love, caress and kindness to children must not have frames (of course it does not mean permissiveness, lack of restraint); such approach is similar to the "banking behavior" – the more kindness will be given to children, the more generous and self-confident they become in the future.

Child development – what is better, to overload them or to give more freedom, how to optimize it, how to find the golden mean? We need criteria in order to judge whether our pedagogical efforts are the best for the individual.

I don't think that to be healthy must be the main aim in the life, but healthiness is really one of main prerequisites for maximal self-realization of the person.

To speak about stagnation of adolescent health sounds as a triviality today. Nevertheless, the problem exists indeed. How to change the behavior of youth, make it more healthy? Maybe it has a sense not to be afraid to touch **"sacred cows" – inadmissibility of censure** and restrict access to harmful information and examples?

Ipsa sientia potestas est. Scientific research is considered as a major prerequisite for the development of medicine, incl. pediatrics as well. (It is being used more and more widely in the medical education too). Nobody doubts the importance of epidemiological studies and different clinical trials (evaluation of safety and efficacy of new diagnostic methods and medications) in pediatrics. At the same time I think **it would be purposeful to give more consideration** to the fundamental research, particularly **to the problem of age-related morphological and functional peculiarities of growing organism in the conditions of norm and pathology**. It would be also very desirable to join efforts of colleagues working in this area and create the appropriate net.

A lot of known and new, maybe yet unknown environmental factors are causing the increase of different diseases, like leukemia, cancers, deafness, congenital diseases, bronchial asthma; they can contribute also to the development of new clinical entities, with their pathogenesis, pathology and necessity of specific treatment. One should have in mind the importance of combination of harmful factors, their pathogenic effect even in case when separately their concentration are within the accessible frames.

We experience the "Renaissance" of clinical genetics. More and more diseases, conditions and even predisposition to diseases, differences in clinical course of diseases, suscepti-

bility to treatment are found to have causative genetic mutations and/or their combinations. All the above-mentioned is the theoretical basis of individualized medicine. Yes, we are only in the beginning of the way, but it is really a magnificent perspective. "Forewarned is forearmed".

The main goals of medical education, incl. pediatric one are following: giving the information, sharing the attitude, training in skills, contributing to raising of students' knowledge and their ability to use all this in real life. Attitude must be empathic, **despite of marked tendency of some industrialization of medical care, patients and parents prefer the empathic approach**. I suppose also that the main importance especially in the concluding period of teaching must be given to the elaboration of intellectual skills – problem solving and decision making.

For me it was always difficult to understand what does the functional disease mean, I suppose it must be some pathologic morphological changes and/or pathological molecule. Of course, we are aware that often it is impossible to reveal them, but still we must try.

Psychosomatic interrelationships still stay unclear, nevertheless there are sufficient number of cases were the psychological treatment of somatic disorders is effective. Is it only contingency?

A great majority of physicians think skeptically of different kinds of alternative/complementary medicine, incl. homeopathy, acupuncture, herbal therapy, hypo oxygenation etc. At the same time the cases of their clinical efficacy, just anecdotic, really happen. Maybe classical clinical trials are not appropriate to prove their usefulness and the new methods, approaches must be elaborated. There is a same situation regarding the psychotherapy, nobody argues about its necessity for neurotic disorders, but sometimes we have results with somatic disorders also.

Medical Guidelines are considered and absolutely justly as a basis of a good clinical practice, but can they cover all possible cases of real life? There is also another problem – their creation (compilation of data and opinions from different sources) and selection among the number of options [9]. Due notice should be paid to the methodology of meta analysis. Importance of national and regional peculiarities, availability of health resources, epidemiological situation etc. have to be taken into account. The mechanism of approximate reasoning seems to us advisable in order to deduce necessary recommendations. Principles – how to choose and how to rank "the experts" are crucial. Due attention must be paid to the level of evidence (having in mind regional epidemiological data as well), connectivity strength, level of invasiveness, price and availability, severity of diseases confirmed or refuted by means of special investigations and so on.All our life is vague, everything runs according fuzzy logic regularities. It seems to be an universal rule. Thus, these principles should be used everywhere, incl. medicine, especially child and adolescent medicine, dealing with the most complex system – permanently changing human organism [6]. According to the modern description [10], evidence-based medicine is the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients,…..integrating individual clinical expertise with the best available external clinical evidence from systematic research". It is not a slavish adherence to external evidence or mindless extrapolation of trial results to the clinical setting. Clinical judgment, the key element of evident-based medicine can be considered as the sum total of all the cognitive processes involved in clinical decision making [5]. Having in mind the great portion of uncertainty in the content of both above-mentioned mainframe principles of modern medicine, I would like to emphasize **the necessity of implementation of probability approaches in the daily medical activities**.

Natura abhorret vacuum (Aristotle) – from the physics point of view, now this proposition is not considered as a truth, but in medicine it has some assertion. The desire and practical steps to reach sterile environment plays a malicious trick: we encounter an epidemics of multi-drug resistant bacterial infections, dramatic increase of allergic and autoimmune diseases, decrease of the organism's natural resistance (gnotobiont animals can be used as the best illustration, evidence of the above-mentioned). Who knows, maybe the other changes in morbidity (e.g. inflammatory bowel disease) are also caused by essential changes of bacterial flora around us, both in quantitative and qualitative senses. Nobody should call upon to be dirty, but I suppose **we need to enrich our environment**, especially environment of children, even clinical settings **with probiotics**, our potential "friends" among bacteria. **The sweeping usage of pro- and prebiotics in nutrition could be also hailed**.

Rare diseases – the emergency of the last decade. There are about 7500. Nobody can know them comprehensively, even narrow specialists. Very often we have the overlapping of symptoms and signs, indicating on the damage of different organs and systems. Due to rareness, the clinical trials are restricted, very often the treatment is not clear, the pharmaceutical industry is not interested in development and production of the specific drugs. Everything must be investigated, but coming from "All animals are equal, but some animals are more equal than others", some sequence is necessary; I think that primarily we must study the comparatively more prevalent diseases and the ones where the early intervention is most successful. The point is diagnostic of rare diseases, in the overwhelming majority of cases in order to treat them first of all we need to suspect them in time, afterwards the road is open. It sounds paradoxically, but **in order to recognize the rare diseases we must know very well the clinical course of the common diseases;** if the clinical manifestations are atypical, deviations are expressed significantly, one should think about certain rare diseases and administer appropriate investigations [7].

Results of epidemiological studies indicate that the world trends of morbidity, mortality and even health-related behavior follow the changes in developed countries. Thus analysis of their data and efficacy of relevant measures can be used for prognosis and elaboration of preventive actions in the rest of the world.

Discovery of antibiotics can be considered as the biggest victory of medicine. But now we see that there are a lot of factors which potentially restrict their usage (different side effects, bacterial resistance, allergy, price etc.). Now the modern bacteriophage therapy (BT) is the only one alternative option. The best way is to use bacteriophages against preliminary culturing of causative bacterial pathogens and finding of most effective bacteriophages (this approach is expensive). It is possible also to use commercial phages (mixture of a great number of them) and include them in treatment either empirically or after preliminary testing. Phages were administered intravenously, orally, rectally, locally, as aerosols or intrapleural injections. Virtually no serious complications were reported. Orally given phages could enter internal environment of the organism. Production of neutralizing antibodies could restrict clinical efficacy of BT. Despite of more than hundred years old history of BT a lot of questions are still unanswered. Numerous publications reported improved clinical outcomes associated with BT, particularly in cases of intestinal infections and cutaneous purulent infections, practically without any side effects [1,2,10,12]. Only a handful of studies have been fulfilled in compliance with modern requirements to clinical trials. There is some regulatory conundrum of BT. I suppose, that **the bacteriophage therapy can be considered as a safe and effective antibacterial treatment**: complementary to antibiotic therapy (to overcome the bacterial resistance to antibiotics), or replacing antibiotic therapy (when associated with severe adverse reactions). Nevertheless additional research is needed.

Spiro spero – I believe, it must be the main device (motto) of physicians and not only, there are so much achievements in medicine, so everybody can hope for a positive outcome of the disease, so first of all **never to give up**.

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SUMMARY

SOME PERSONAL VIEWS ON PEDIATRICS AND NOT ONLY...

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In the paper there are presented author's personal views on youth education, medical education, child and adolescent physiology, some other common medical and pediatric issues. The role of the physician as an educator of the child is underlined. The pediatrician must be the main advisor to the society, school and family in the matter of youth education, contribute to their optimal self-realization. The importance of moral values, gender peculiarities and cultural codes are emphasized. The imprinting of cultural codes should be considered as a biological basis of patriotism. The effectiveness of the implementation of healthy life style is discussed. The opinion regarding the protection of youth from potentially negative effects on their development and behavior is expressed. It would be purposeful to give more consideration to the fundamental research, particularly to the problem of age-related morphological and functional peculiarities of the growing organism in the conditions of norm and pathology.

One should have in mind the importance of research of the combination of harmful factors for the organism. The elaboration of empathic and optimistic attitudes should be considered as the very important goals of medical education. The differential usage of clinical guidelines is discussed. It is mentioned the purposefulness of more wide application of fuzzy logic approaches in medicine. The items of rare diseases, individualized medicine, alternative medicine and bacteriophage therapy are discussed as well.

Keywords: youth education, medical education, fuzzy logic, rare diseases, bacteriophage therapy.

РЕЗЮМЕ

ЛИЧНЫЕ МНЕНИЯ И СУЖДЕНИЯ О ПЕДИАТРИИ И НЕ ТОЛЬКО...

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В статье представлены личные мнения и суждения о воспитании детей, медицинском образовании, физиологии детей и подростков, ряде общемедицинских и общепедиатрических вопросах. Подчеркивается роль педиатра как воспитателя ребенка, указывается что педиатр должен быть главным советником родителей и педагогов в области развития детей и подростков, способствовать их максимальной самореализации. Подчеркивается роль моральных ценностей, гендерных особенностей личности, культурального кода, значение импринтинга как биологической основы патриотизма. Обсуждается вопрос эффективности имплементации здорового образа жизни. Обсуждаются целесообразность определенного ограничения детей и подростков от потенциально негативно воздействующей на их развитие и поведение информации, необходимость интенсификации научных исследований в области физиологии детей и подростков, подчеркивается значение комплексной оценки вредных экологических факторов на организм. В медицинском образовании следует придавать большее значение развитию эмпатического отношения к пациентам и оптимистического настроя. Рассматривается вопрос клинических гайдлайнов и необходимость их дифференцированного применения. Рассматриваются вопросы, касающиеся редких болезней, индивидуализированной терапии, альтернативной медицины, бактериофаготерапии. Автор рекомендует более широкое использование методов нечеткой логики в повседневной клинической работе.

რეზიუმე

პირადი შეხედულებები პედიატრიაზე და არა მხოლოდ ...

ყ. ფაღავა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

სტატიაში წარმოდგენილია ავტორის პირადი შეხედულებები ბავშვთა აღზრდაზე, სამედიცინო განათლებაზე,ბავშვთა და მოზარდთა ფიზიოლოგიაზე,ზოგიერთ ზოგადსამედიცინო და ზოგადპედიატრიულ საკითხზე. მითითებულია, რომ პედიატრი უნდა იყოს მშობლებისა და პედაგოგების მთავარი მრჩეველი, ხელს უწყობდეს მოზარდი თაობის ოპტიმალურ თვითრეალიზაციას. ხაზგასმულია მორალური ფასეულობების,პიროვნების გენდერული თავისებურებების, კულტურალური კოდის მნიშვნელობა; მითითებულია,რომ იმპრინტინგი პატრიოტიზმის ბიოლოგიურ საფუძვლად შეიძლება იყოს მიჩნეული. განიხილება ჯანსაღი ცხოვრების წესის იმპლემენტაციის ეფექტურობა. გამოთქმულია მოსაზრება ბავშვებისა და მოზარდების განვითარებასა და ქცევაზე პოტენციურად უარყოფითად მომქმედი ინფორმაციისგან დაცვის მიზანშეწონილობაზე. აღნიშნულია, რომ სასურველი იქნებოდა ბავშვთა და მოზარდთა ფიზიოლოგიის დარგში სამეცნიერო კვლევების ინტენსიფიკაცია. მავნე ეკოლოგიური ფაქტორების ზემოქმედება ორგანიზმზე უნდა ფასდებოდეს ჯამურად. სამედიცინო განათლებაში მეტი ყურადღება უნდა ეთმობოდეს ემპათიური და ოპტიმისტური მიდგომის განვითარებას. განიხილება კლინიკური გაიდლაინების დიფერენცირებული გამოყენების აუცილებლობა. განხილულია იშვიათი დაავადებების, ინდივიდუალიზირებული თერაპიის, ალტერნატიული მედიცინისა და ბაქტერიოფაგოთერაპიის საკითხები. ავტორი მიუთითებს არამკაფიო ლოგიკის მეთოდების უფრო ფართოდ გამოყენების მიზანშეწონილობაზე ყოველდღიურ კლინიკურ პრაქტიკაში.

KARAMAN PAGAVA ON THE OCCASION OF HIS 65TH BIRTHDAY

Professor Karaman Pagava is a distinguished Georgian pediatrician, a stellar representative of his *Alma Mater* – Tbilisi State Medical University.

Karaman Pagava is a disciple of Simon Gogitidze and Mariam Ugrelidze scientific school, his mentors were Academician Vladimer Bakhutashvili, Professor Meri Gelovani, Professor Gita Kagan, a winner of the highest academic distinction in the former Soviet Union – Lenin Prize, and first of all – his father, Professor Irakli Pagava. Professor K. Pagava received his PhD in 1974 from the Tbilisi State Medical Institute; the study of the thesis was partially conducted at the Gamalei institute of Epidemiology and Microbiology of the Academy of Medical Sciences in Moscow, Russia. He received his DSc degree in 1990 from the All-Union Institute of Pediatrics in Moscow (research was conducted in Tbilisi, Georgia). He rose through the ranks and has been holding a position of Full Professor in child and adolescent medicine since 1992.

It is worthy to mention that K. Pagava's family (incl. himself, father, grand-father Nikolai Aspisoff, Professor of otology-rhinology-laringology and brother – Gaioz Pagava, Docent/Associate Professor of dermatology) has been contributing to the service of medicine and medical education, in particular, at our University, for over 120 years.

Professor Karaman Pagava is a pediatrician and a child physiologist of broad clinical and scientific skills. In addition to the general pediatrics, his scientific expertise lay in: low intensive laser radiation effects, bacteriophage therapy, fuzzy logic and diagnosis supporting expert systems, child deprivation, adolescent medicine, medical decision making, functional asymmetry and biorhythmology, infectious diseases, autoimmune and autoinflammatory diseases, rare diseases. He has authored well over 400 scientific publications, including manuals and monographs, supervised 23 PhD theses; participated and presented his scientific studies at more than 40 international congresses. He is a member of the editorial boards of scientific Georgian and international journals, incl. Modern Pediatrics (Kiev, Ukraine) and Italian Journal of Adolescent Medicine. As a guest editor he has regularly prepared special issues of the Journals - "Georgian Medical News" and "Georgian Medical Bulletin". He has reviewed WHO editions in the field of pediatrics, participated in WHO meetings as an invited temporary expert. He organized more than 20 scientific conferences, including the international ones as well. He is actively involved in the activities of international networks, such as EuTEACH, PRINTO, Brighton Group, etc…

While being the Chief Pediatrician at the Ministry of Labour, Health and Social Affairs of Georgia, Professor Pagava contributed essentially to development and implementation of health care reforms in Georgia.

Professor Pagava is distinguished by passion and enthusiasm for teaching. At 1998 as a result of the high rating and outstanding lectures he was awarded with the title of the Best Teacher of the Tbilisi State Medical University. Professor Pagava promotes learning innovations. He is doing presentations and interactive seminars for students and practitioners both in Georgia and abroad; is delivering lectures on healthy life style, child development and care, youth problems and school healthcare issues in radio and TV broadcasts; is publishing papers in mass-media on pediatrics, medical education and other pressing topics.

Karaman Pagava is not just a typical University Professor, he is patriot, *pater familiae*, sportsman, "Reliable Knight of Ahura Mazda", true to his convictions, – he is a gentleman and a scholar.

Zurab Vadachkoria
Professor & Rector
Tbilisi State Medical University

Научно-редакционный совет и Научно-редакционная коллегия журнала "Georgian Medical News" от всей души поздравляют профессора Карамана Ираклиевича Пагава с 65-летним юбилеем и желают ему дальнейших творческих успехов, здоровья и счастья.