ADDRESS

Timisoara, Romania
Gospodarilor Street, nr. 42
Tel: +4-0256-439441
cod 300778
e-mail: boiaeugen@yahoo.com

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EVALUATION OF PHARYNGEAL AIRWAY VOLUME USING CONE – BEAM COMPUTED TOMOGRAPHY – CASE REPORT

Ștefania Dinu[1], Emilia Brândușa Brăilă[2], Răzvan Mihai Horhat3, Mariana Păcurar[4], Hajosman Isam Osma[4], Vlad Grigore[4], Simina Boia[5], Eugen-Radu Boia[6], Magda Mihaela Luca[1], Mălina Popa[1]

Abstract

Background: Visualization and calculation of the airway dimensions are important because an increase of airway resistance may affect the development of dentofacial structures by altering the breathing pattern of growing patients. The aim of this study is to shed light on the resources provided by cone – beam computed tomography in the diagnosis of possible physical barriers that may reduce upper airway permeability by presenting one case report. Material and method: A patient clinically diagnosed with oral respiratory syndrome initially underwent a profile teleradiography and orthopantomography. For a better assessment of the airway space, it was recommended to perform a cone – beam computed tomography. Results: On demand 3D software program automatically provides the total area and volume of any predefined region as well as the location and size of the narrowest portion of airspace. Conclusions: On demand 3D software allows rapid segmentation of the upper respiratory tract. Segmentation can be checked on 2D sections (axial, frontal and sagittal). Three – dimensional measurements of airway volume and most constricted surface can be accurately performed.

Keywords: Cone – Beam Computed Tomography, teleradiography, pediatric dentistry, upper airway.

Introduction

Cone beam computed tomography (CBCT) is probably one of the most revolutionary innovations in the field of pediatric dentistry and offers a new platform for orthodontic diagnosis and treatment planning.

Nowadays, the use of cone beam computed tomography (CBCT) is increasing in orthodontic practice due to its 3D diagnostic ability with the continued reduction in cost and radiation exposure. [1]

Different three – dimensional (3D) imaging modalities are available to investigate airway morphology and the surrounding soft tissues. This allows for the quantification of volumetric, area and linear measurements. [2]

Upper airway space assessment is a routine procedure in orthodontic diagnosis and treatment planning. Most studies have been based on profile teleradiography because such radiographs are part of the usual records for good planning of orthodontic treatment. Although it provides a wealth of information, teleradiography is limited in the sense that it produces two – dimensional images (height and depth) of a three – dimensional structure, thus preventing the correct assessment of the size and complexity of this structure.

Although numerous methods with 2-dimensional (2D) cephalograms, providing limited data such as linear and angular has been proposed for upper airway studies, there were studies that evaluate the airway have introduced the use of CBCT, which made the 3D diagnosis of the patient became more accessible in dentistry. The segmentation of the airway can be done manually or automatically. Manual segmentation seems to be the most accurate method and allows for the most operator control. [2]

[1] Department of Pediatric Dentistry, Faculty of Dental Medicine, "Victor Babeș" University of Medicine and Pharmacy Timisoara, Romania, Pediatric Dentistry Research Center (Pedo-Research)
[2] Department of General Dentistry of Municipal Emergency Clinical Hospital, Timișoara, Romania
[3] Department of Endodontics, Faculty of Dental Medicine, "Victor Babes" University of Medicine and Pharmacy Timisoara, Romania, TADERP Research Center
[4]Department of Orthodontics, Faculty of Dental Medicine, University of Medicine and Pharmacy Targu Mures, Romania
[5]Department of Periodontology, Faculty of Dental Medicine, "Victor Babeș" University of Medicine and Pharmacy, Timișoara
[6]Department of ENT, Faculty of Medicine, "Victor Babeș" University of Medicine and Pharmacy, Timișoara

Email: dinu.stefania@umft.ro; braila.emilia@umft.ro; razvanhorhat@yahoo.com; mariana.pacurar@umftgm.ro, hajosman.isam@gmail.com; dr.ec.vlad.grigore@gmail.com; simina.boia@umft.ro; eugen.boia@umft.ro; popa.malina@umft.ro

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Manual segmentation needs the operator to delineate the airway slice by slice and render the data into a 3D volume for analysis. [3]

In the study about developing pediatric three-dimensional upper airway normative values, the authors, insisted that clinicians should utilize the proposed-there upper airway normative values for screening and assist in the timely diagnosis and management of pediatric sleep apnea. [4] CBCT made it possible to obtain 3D images with the volumes of all structures in the maxillofacial complex. With the use of specific software and procurement protocols based on individual needs, these digital volumetric scans can be transformed into multiple flat images (transverse, frontal and sagittal). The software also allows measurements of bone structures to be obtained, as well as 3D evaluation of soft tissues and shapes, volumes and features of the face and upper respiratory tract.

CBCT has contributed to bringing new information in orthodontics regarding the space of the upper respiratory tract, by acquiring three-dimensional images, which allows professionals to accurately determine the narrowest area, where the greatest resistance to air passage occurs.

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Objectives

The aim of this study is to shed light on the resources provided by CBCT in the diagnosis of possible physical barriers that may reduce upper airway permeability by presenting one case report

Materials and Methods

A patient clinically diagnosed with oral respiratory syndrome initially underwent a profile teleradiography (figure 1) and orthopanthomography (figure 2). For a better assessment of the airway space, it was recommended to perform a CBCT examination covering the neck region. CBCT examination for airway assessment has a specific image acquisition protocol. Patients should be placed in the maximum intercuspid position, with the mid-sagittal plane perpendicular to the horizontal plane, the Frankfurt plane parallel to the horizontal plane. Upon completion of the CBCT examination, some manipulations may be performed using the software provided by the scanner manufacturer. The raw image (raw data) has been reconstructed to allow visualization of 3D reconstruction and multiplanar sections. These two-dimensional images can be viewed from any direction. The most commonly used are sagittal, coronal and transverse images. Images are best viewed with the help of specific tools. Images can be rotated and magnified to allow a better evaluation of a particular region. Images can also be played back from any angle, at any scale or position. We applied different filters thus allowing the differentiation between tissues with different densities and the use of transparency that allows the visualization of hard tissue among soft tissue. A linear measuring instrument is available, which can measure the height, depth and width of any part of the pharynx.

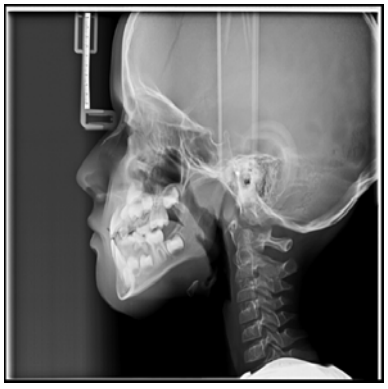

Fig. 1. Profile teleradiography of patient

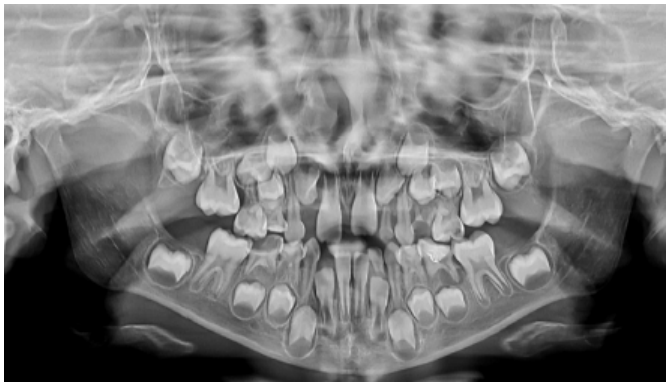

Fig. 2. Orthopantomography of patient

These images were transformed into DICOM (Digital Imaging and Communications in Medicine) files that allowed export to other assessment software, which in turn allow a wider range of resources useful in assessing airspace.

The On demand 3D version is an airway space analysis tool that not only allows you to evaluate the shape and contour of the upper airways in 3D, but can also calculate the volume, sagittal areas and the smallest predefined cross-sectional area in the airspace upper respiratory tract. It provides segmentation of upper airway space through rotatable and amplifiable images. The program has two threshold filters: for hard tissue and soft tissue, displaying the airway space along with the bone tissue or separately.

To evaluate the images in the program, we first had to import the DICOM format files from the CBCT images. Once imported, the three-dimensional image of the patient's head was oriented in virtual space, similar to the cephalostat, so that the horizontal Frankfurt plane is parallel to the transverse plane, the medioagital plane coincides with the midline of the individual and the cranial plane is oriented so that it passes beyond from the lower edge of the orbits. In asymmetric cases, the orientation should be as close as possible to these reference plans. This virtual orientation allowed the head to rotate properly so that the bilateral

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structures coincided. Once an instrument is selected for the assessment of the upper airway space, it was necessary to define, on the sagittal section, the area of interest in the upper airway space.

Results

The program automatically provides the total area and volume of any predefined region as well as the location and size of the narrowest portion of airspace.

In order to segment the airway space, we open Fine Tuning and select from Load Preset, Airway in Opacity Preset to have optimal viewing conditions. We selected from the segmentation menu (Segmentation Menu) the 3D Picker icon and marked several points on the sagittal section, in the area of interest of the neck, which will represent the opacities (gray level) corresponding to the airway space where we need to measure volume. After we pressed Start, and the program determines the patient airway space and determine the most restricted area of the airway (figure 4).We can adjust the gray level with the More and Less buttons. Select Operation - Select as a New Object, and then press the Ok button. You can see the segmentation of the airway space from a 3D perspective (figure 3). In the list of objects, the volume of the airway space will appear at the level of the newly created object.

With the On demand 3D program we performed an endoscopy of the upper airways (figure 6). From the Task we chose CPR and placed the points for the airway space through which the endoscopic image will be reconstructed and then by pressing the Airway 1 button and the endoscopy can be run (figure 7).

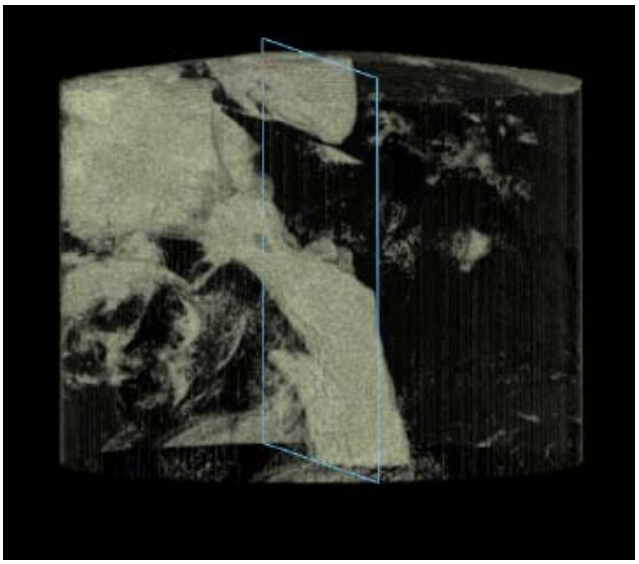

Fig. 3. Three-dimensional reconstruction of the upper airways

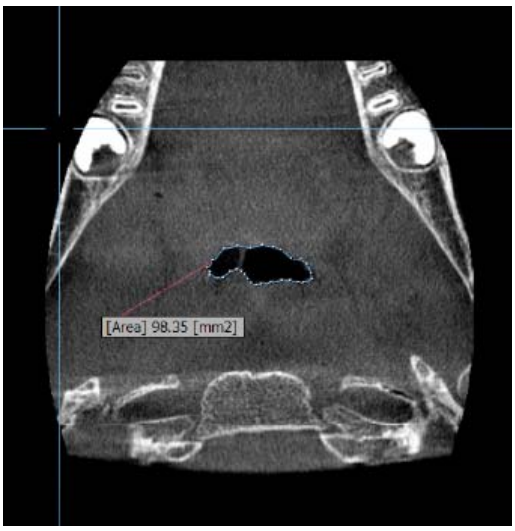

Fig. 4. Determination of the cross-sectional area of the airway in the most restricted area (98.35mm²))

Fig. 5. Determination of points of interest on the sagittal section

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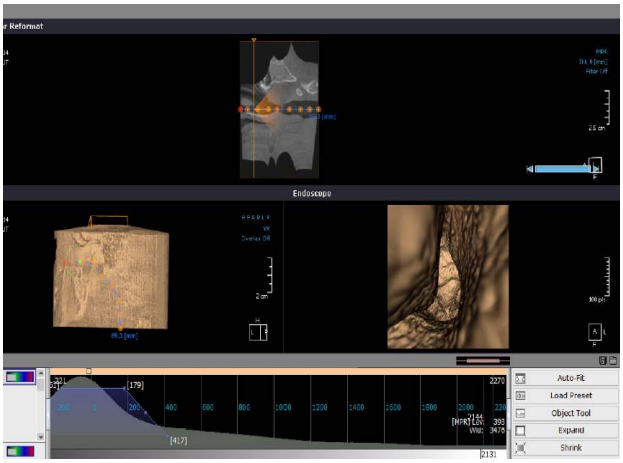

Fig. 6. The way to acquire an endoscope with the help of images provided by CBCT

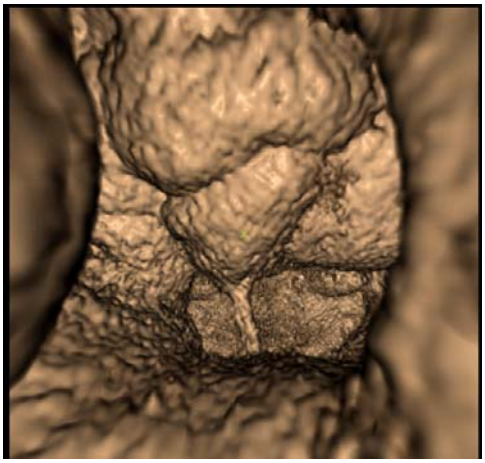

Fig.7. The endoscopy provided by CBCT

Discussion

CBCT systems have been developed specifically for the maxillofacial region with the advantage of the reduced radiation doses compared with conventional CT. [5]

Clinicians who order or perform CBCT for orthodontic patients are responsible for interpreting the entire image volumes, just as they are responsible for interpreting all regions of other radiographic images that they order. [6]

With advances in medical care, the pharyngeal airway space of orthodontic patients is beginning to attract attention. The pharyngeal airway can be divided into three sections, namely the nasopharyngeal, oropharyngeal, and laryngopharyngeal airways. The nasopharyngeal and the oropharyngeal airways are demarcated by the retro palatal region of maxilla, whereas the oropharyngeal and the laryngopharyngeal airways are demarcated by the tip of the epiglottis. [7]

Over the past century, a large number of tests have been proposed to evaluate the upper respiratory tract on profile teleradiographs using linear and angular measurements and sagittal areas between cephalometric points. [8, 9] These points are defined by the overlapping projections of the different structures.

In the study about developing pediatric three-dimensional upper airway normative values, the authors, insisted that clinicians should utilize the proposed-there upper airway normative values for screening and assist in the timely diagnosis and management of pediatric sleep apnea. [4]

In a comparison between CT and profile teleradiography in the assessment of pharyngeal airspace, Aboudara et al. [10] found a significant correlation between the sagittal surface obtained by cephalometry and the volume obtained by CBCT, although the latter showed greater variability in patients with airway space similar to profile teleradiography. This was to be expected since only height and depth can be measured on profile teleradiography and therefore does not allow cross-examination (ie width).

Accuracy and reliability of airway measurements for volume and minimum area in CBCT images have been tested. Lenza et al. [11] had compared the linear, area, and volumetric measurements by two examiners and found no significant differences.

Aboudara et al. [10] did that study to compare the nasopharyngeal airway size between a lateral head film and a CBCT scan in adolescent subjects and found that there is a significant positive relationship between nasopharyngeal airway size on a head film and its true volumetric size from a CBCT scan.

Ghoneima & Kula [5] did had investigated the accuracy of CBCT airway measurements by scanning the actual volume of an airway model. The results of their study showed that the CBCT digital measurements of the airway volume and the minimum area of the airway are reliable and accurate. [3]

The size of the airspace and the morphology vary when the patient inhales and exhales. [12]

The acquisition time of CT scans is about 20 – 40 seconds, too long for the individual to control their respiratory movements. Hopefully, in the near future, the time required will be shorter in order to prevent the patient's movements (breathing, swallowing and involuntary movements) from interfering with the results. Several imaging software programs are currently available for upper airway assessment. In addition to On demand 3D, Dolphin 3D, InVivo Dental, Mimics, OsirX, ITK-Snap, etc. can also be used.

Because the technology develops, the efforts to reduce exposure and to improve image quality have led to new innovations. These can include flat panel detectors with greater photon sensitivity, automatic exposure control with photon counting, customizable FOV collimation and image quality settings. Several studies have accumulated valuable data on technology assessment, craniofacial morphology in health and disease, treatment outcomes and efficacy of CBCT. Currently, the main limiting factor for widespread use of CBCT in orthodontics is the radiation dose especially in children. CBCT is a supplementary diagnostic aid with lot of radiation risk. It is not an essential diagnostic aid so it is unwise at present to make it mandatory for all patients. It is suggested that routine radiographs as well as 3D radiographs should not be prescribed routinely [14].

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CBCT examinations must not be carried out unless a clinical examination have been performed. CBCT examinations must be justified for each patient.

Conclusions

CBCT allows clinicians to assess the airspace and surrounding structures and determine nasal, oro- and hypopharyngeal measurements, such as the most constricted area, volume, and smallest antero-posterior and lateral dimensions of the pharynx in patients with respiratory problems. It is also possible to assess changes that may be induced by the treatment modality itself, and to identify which patient could benefit from such treatment. CBCT will be able to guide orthodontic diagnosis and planning by showing clinicians about the effects of mechanotherapy applied to the airway space and the consequences of these effects. On demand 3D software allows rapid segmentation of the upper respiratory tract. Segmentation can be checked on 2D sections (axial, frontal, and sagittal). Three – dimensional measurements of airway volume and most constricted surface can be accurately performed.

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Correspondence to:

Horhat Răzvan Mihai
Department of Endodontics, Faculty of Dental Medicine,
"Victor Babes" University of Medicine and Pharmacy
Timisoara, Romania,
TADERP Research Center
Bv. Revolutiei din 1989, nr. 9
E-mail: razvanhorhat@yahoo.com

POSTERIOR URETHRAL VALVE, PARTE OF CONGENITAL OBSTRUCTIVE UROPATHIES; PROGNOSTIC FACTORS IN LONG TERM FOLLOW UP

Roxana Alexandra Bogos[1], Radu Russu[2], Iuliana Magdalena Stârcea[1,2], Mihaela Munteanu[2], Maria Adriana Mocanu[1,2], Doina Nedelcu[3], Iulia Ciongradi[1,3], Ioan Sârbu[1,3], Georgiana Scurtu[1], Mirabela Smaranda Alecsa[1], Ingrith Crenguța Miron[1], Ovidiu Ionel Bărbuță[3]

Abstract

Background: The posterior urethral valve (PUV) is an important cause of lower urinary tract obstruction in boys, with a wide spectrum of presentations, different degrees of severity, and in 25-45% of patients end with stage kidney failure. Objective: Monitoring the children diagnosed and operated for PUV and identifying the predictive factors for the evolution towards chronic kidney failure. Material and method: Retrospective analysis of children treated for PUV at Children' Hospital "St. Mary" Iasi during 2004-2014. We followed: age, clinical presentation, recurrences of urinary tract infection (UTI), association with/without vesicoureteral reflux (VUR), serum creatinine levels (at diagnosis, after valve resection and at the end of follow-up) and correlation with the degree of impaired of renal function over time. Results. Of the 18 boys diagnosed between 2 days and 12 years old; 11 were admitted for recurrent UTI, and 5 were presented for the investigation after antenatal diagnosis of hydronephrosis.11 cases presented grade IV and V VUR, bilateral in 6 cases. Impairment of renal function was present at initial diagnosis in all patients in various degrees and at the end of follow-up period 5 patients were with end stage kidney disease with creatinine clearance less than 60 ml/min/1.73 sqm. Two of them were in end stage of renal insufficiency under dialysis and one in the predialytic stage. Unfavorable prognostic factors were late diagnosis with recurrent UTI, association with VUR, and persistent increased creatinine after valve resection. Conclusion. The study reveals the persistence of recurrent urinary tract infection as the main criteria to identify the posterior urethral valve (11/19). Late diagnosis along with the persistence of increased creatinine after valve resection were the main factors of unfavorable prognosis of renal function.

Keywords: posterior urethral valve, children, urinary tract infection, chronic kidney diseases

Introduction

The posterior urethral valves (PUV) are the leading cause of lower urinary tract obstruction in male children as a 1 in 8000 – 25000 live births (1). The severity spectrum and the clinical presentation are variable. Severe forms are presented with urinary tract abnormalities; a few are life-threatening condition in neonatal period. Many of these patients have long-term complications regarding urinary continence and impaired kidney function even under a correct and continuous management. It is known that 25-40% of cases develop chronic kidney disease (CKD) at different ages (2). The causes of renal injury in PUV are: associated irreversible dysplasia, respectively persistent obstructive aeropathy, scars after repeated/recurrent UTI and detrusor dysfunction that can be influenced by early and correct medical-surgical treatment.

Objective

Monitoring the evolution of children operated for the posterior urethral valve and identifying the factors that influence the development of renal failure.

Material and method

Retrospective analysis of observation records of 18 children who were diagnosed and treated for the posterior urethral valve at Pediatric Nephrology and the Pediatric Surgery Division "St. Mary" Children's Hospital Iasi during 2004-2014. We followed: the clinical presentation; main complain at diagnosis, age at diagnosis, recurrences of urinary tract infection (UTI), association with vesicoureteral reflux (VUR), association with dysuria, serum creatinine level (at diagnosis, the minimum value in the first year after surgery and at the end of follow-up). We studied the association of above mentioned parameters with the level of impairment of renal function. The patients were classified based on the creatinine clearance calculated by the Schwarz formula, in stages III (GFR: 60-30 ml / min / 1.73 sqm), stage IV (GFR: 30-15 ml / min / 1, 73 sqm) and V (GFR < 15 ml / min / 1.73 sqm) of chronic kidney disease at the end of follow-up.

[1] Mother &Child Department, „Grigore T. Popa „University of Medicine and Pharmacy Iasi, Romania
[2] Nephrology Division, St. Mary's Emergency Children Hospital Iasi, Romania
[3] Second Pediatric Surgery Division, St. Mary's Emergency Children Hospital Iasi, Romania

Email: bogos.roxana@gmail.com, radurussu@yahoo.com, magdabirm@yahoo.com, mihaelamunteanu2001@gmail.com, scurtugeorgiana8@gmail.com, ingridmiron@hotmail.com, adriana_baltag@yahoo.com, iuliaciongradi@gmail.com, ioansarbu@yahoo.com, doinanedelcu2002@yahoo.com, subotnicu_mirabela@yahoo.com, ovidiubarbuta74@gmail.com

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Results and discussion

The series includes 18 boys aged between 4 days and 3 years at diagnosis, followed by 6 to 120 months. All patients received primary endoscopic resection of the valve except in one case where initially vesicostomy was performed and after 2 months the resection. At diagnosis creatinine was increased > 1 mg% in all patient at diagnosis, except for one, and at the end of follow-up 5 patients (27.7%) had stage III CKD or greater, of whom 2 patients (11.1%) entered the extra renal dialysis and 1 (5%) before starting dialysis. Severe VUR was noted in 12 cases (66%) bilateral in 7 of 12 cases. Recurrent UTI were present in 13 of 18 cases (72%). Micturition dysfunction was identified clinically and by ultrasound in 9 of 18 cases (50%).

The age at diagnosis shows that 38.9% of patients were diagnosed in the neonatal and infant period, 27.8% were diagnosed between 1 and 2 years, and 33.3% after the age of 2 years, results that attest to a late diagnosis.

By analyzing the average age at diagnosis differentiated for the years of the studied period (fig.1) it is noted the improvement in diagnosis after 2010; so in 2014 the average age of diagnosis was 0.9 months. These data reflect the improvement the early diagnosis in the recent period.

Age at presentation: in 61% of patients were diagnosed after having at least one episode of UTI and only 27.8% of cases by evaluation of antenatal hydronephrosis (ANH). By analyzing the way of clinical presentation separately for the years studied (fig.2) there is a sharp increase in cases of PUV that are diagnosed after investigating newborns with ANH. This tendency towards early diagnosis is probably also due to the increase number of pregnancies that benefit from antenatal echographia with the more frequent detection of antenatal hydronephrosis. Results are close to literature data which reveals that in the last 20 years antenatal ultrasound identification has become predominant in developed countries (3).

Analysis of postoperative serum creatinine indicates a significant association of its increased value with the advanced stages of CKD at the end of follow-up. (fig.3)

The literature reveals that the minimum value of creatinine in the first year after valve resection (≤0.8 mg / dL) correlates with good long-term renal function (4). Other studies have found creatinine threshold value of ≤ 1 mg / dL (6). In patients who presented more than 3 recurrent UTIs, it was noted a significant association with the evolution to CKD stages III-V (p = 0.00224 - Spearman Rank R). The presence of severe bilateral VUR was significantly associated with CKD stages III-V (Chi-square = 19.25, p = 0.032103). The role of reflux in PUV is debatable. Some authors consider that bilateral IV-th and V-th grade VUR correlates significantly with the prognosis (7). Analysis of the presence of micturition dysfunction showed a significant association with CKD stages III – V (Chi-square = 8.45, p = 0.016777).

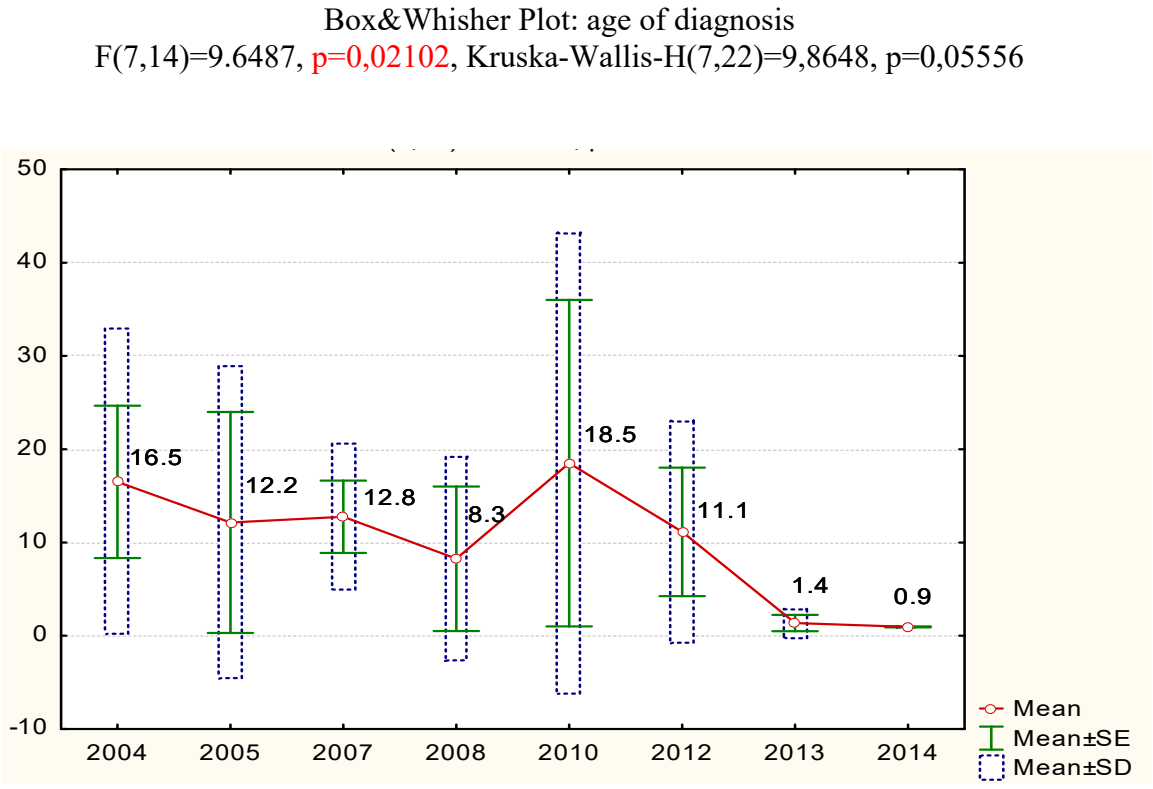

Fig.1. Age at diagnosis in the studied period

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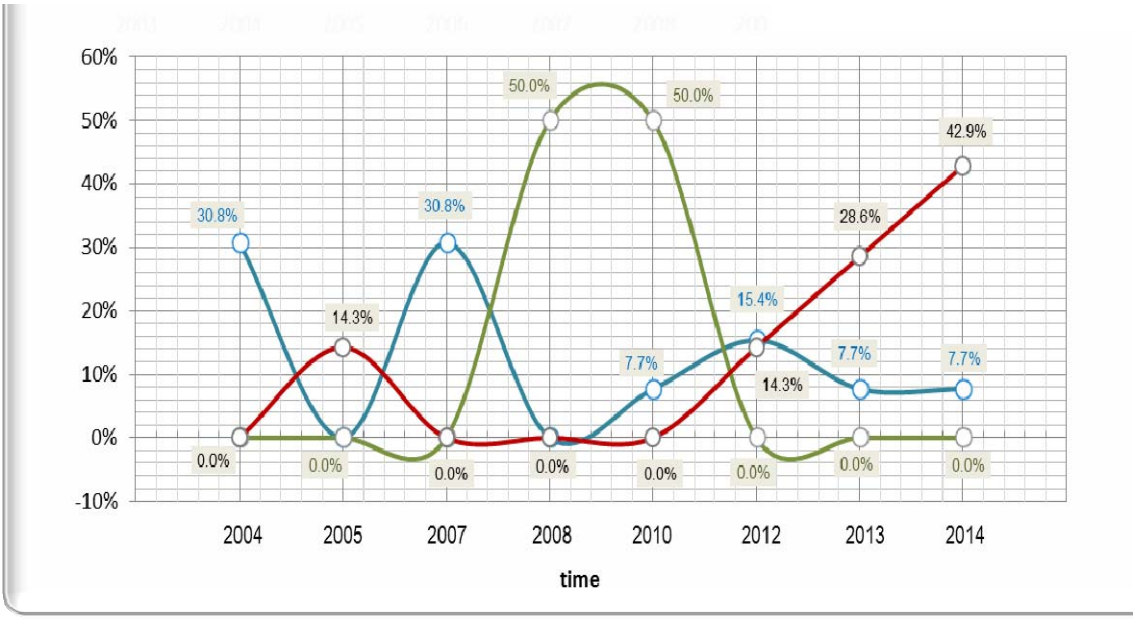

Fig.2. Ways of presentation depending on the period studied

Red – AHN, green – urinary ascites, blue – UTI

Box&Whisher Plot: age of diagnosis
F(4,13)=5,1755, p=0,0102, Kruska-Wallis-H(4,18)=12,0699, p=0,0168

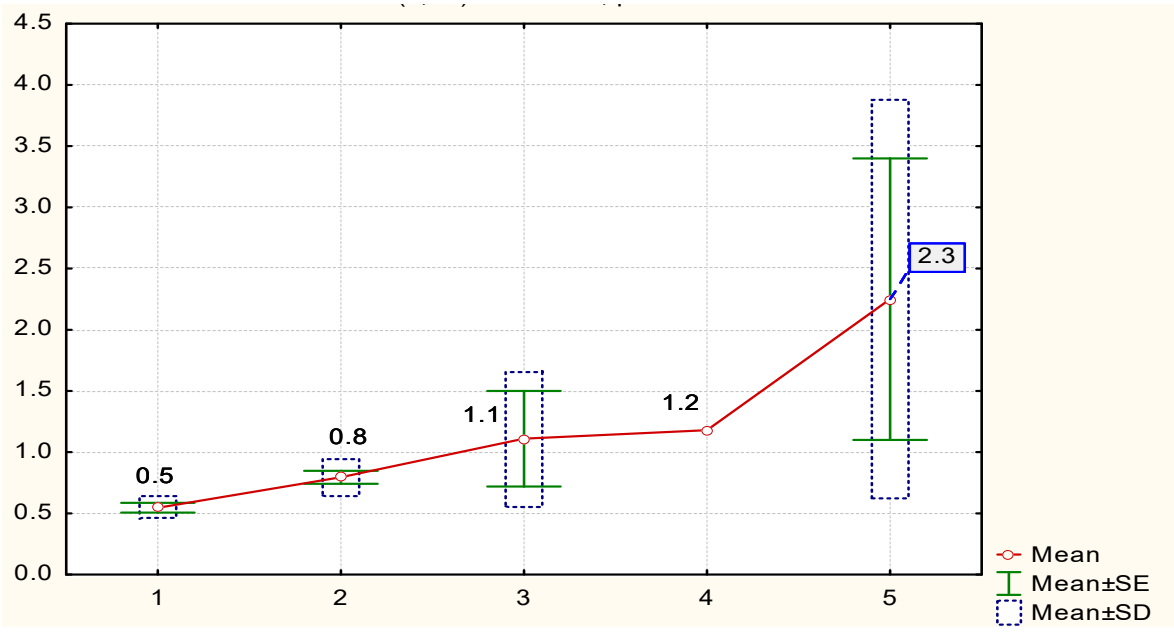

Fig.3. Relationship between postoperative serum creatinine – CKD stage at the end of follow-up

MULTIVARIATE ANALYSIS	Beta	SE	Wald	Sig. p	Hazard Ratio Exp(β)	95% CI for Exp(B)	
						Lower	Upper
Increased creatine	5.002	0.047	11.57	0.001	**5.147**	2.987	6.987
Post-diagnosis UTI number	4.871	0.024	9.846	0.002	**4.806**	2.241	5.091
VUR	4.969	0.256	7.817	0.034	**4.548**	1.946	6.724
urinary dysfunction	1.568	0.155	5.681	0.021	**2.645**	1.987	3.541
old age at diagnosis	5.871	0.241	6.884	0.037	**3.461**	1.764	5.975
ways of clinical presentation	1.664	0.367	1.578	0.069	1.576	0.579	2.564

χ^2 statistical *test = 5.691 (*the *degree of fit of the model); df = 5; p = 0.0178; 95%CI.*

CI – confidence interval, df- degrees of freedom , HR- hazard rate (risk ratio), SE- standard error

Fig.4. Multivariate analysis

The patterns of micturition dysfunction described in children with VUP are diverse and changes over time: in infants it is characterized by low compliance, after 1 year, bladder instability, and after puberty the muscular insufficiency of the detrusor is noticed. Along with the ultrasound examination (detrusor thickness, post-micturition residue), the assessment of micturition behavior through urodynamic studies is necessary in order to assess the effectiveness of treatment (8, 9). In children with severe urinary dysfunction, with recurrent UTI and risk of early deterioration of renal function, the solution of Mitrofanoff vesicostomy and intermittent catheterization is viable. Multiple studies have supported this (10, 11).

Multivariate analysis indicated that the prognostic factors for CKD severity were increased creatinine (HR = 5.1), post-diagnosis UTI number (HR = 4.8), VUR (HR = 4.5), urinary dysfunction (HR = 2.6), and old age at diagnosis (HR = 3.46) (fig.4). The literature indicates as predictive factor the plasma renin activity, increased in children with obstructive nephropathy secondary PUV, but the assessment was not accessible to this series of patients (12).

Conclusions

Urinary tract infection was the main way of diagnosing VUP, but in recent years the detection by antenatal echography of gravida as well as postnatal evaluation of ANH has increased significantly the early diagnosis. Severe bilateral VUR, the high number of recurrent UTIs and the presence of micturition dysfunction were significantly associated with the advanced stages of CKD. The main unfavorable prognostic factor for CKD was creatinine level in the first postoperative year > 0.8mg%. Children with PUV, including those operated in neonatal age, require long-term follow-up to identify and treat early complications of CKD.

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All authors approved the final manuscript and agree to be accountable for all aspects of the work. This original study was performed in accordance with Declaration of Helsinki (the latest revision) and approved by the local hospital ethics committee. Informed consent was obtained from the parents of reported pediatric patient. All the data presented can be available upon request. We would especially like to thank Prof. Dr Gabriel Ionescu for his guidance in writing of this paper.

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Correspondence to:
Iuliana Magdalena Stârcea
Nephrology Division, St. Mary's Emergency Children Hospital Iasi, Romania
E-mail: magdabirm@yahoo.com
Tel: +40726704612

IRON DEFICIENCY IN CHILDHOOD OBESITY

Orsolya Olah[1], Cristina Loredana Pantea[1], Teofana Otilia Bizerea-Moga[1,2], Raluca Corina Tamasanu[1,2], Raluca Asproniu[1], Giorgiana Flavia Brad[1,2], Vatistas Theodoros[2], Otilia Marginean[1,2]

Abstract

Introduction: Iron deficiency (ID) is one of the most common causes of anemia in children. Although it is frequently encountered in a clinician's daily practice, the multifactorial etiology of ID still represents a challenge in terms of long-term management. In overweight and obese children, adiposity related inflammation causes ID by decreasing transferrin saturation on one hand and by increasing hepcidin production on the other hand, which in turn decreases iron absorption. Dietary uptake of iron and other micronutrients is also impaired in these children. Aim of the study: To investigate the link between overweight, obesity and iron deficiency in pediatric patients. Materials and methods: A retrospective observational study was conducted over a 1-year period (1st April 2018-31th March 2019), in the Endocrinology Department of "Louis Turcanu" Children's Emergency Clinical Hospital Timisoara. After applying the inclusion criteria, a total of 78 overweight and obese children were enrolled in the study. The Ethics Committee of the "Louis Turcanu" Children's Emergency Clinical Hospital approved the study. Results: The CDC BMI- charts matched for age and sex were used in order to define overweight and obesity (overweight 85th - 95th and obesity > 95th percentiles). According to age patients were divided in 3 groups: toddlers 6% (age 1-5 years); preadolescents 40% (age 5-12 years) and adolescents 54% (age 12-18 years). Overall, the overweight/ obesity ratio in the studied groups was as follows: 20:80 in toddlers, 13:87 in preadolescents and 45,6:54,4 in adolescents. The highest percentage of ID- patients was found in toddlers (60%), followed by preadolescents with half as much patients (32%), and the lowest percentages was observed in adolescents (14%). Although there was a correlation between iron levels and BMI throughout our sample, these obese and overweight children did not associate significant anemia. Conclusions: The negative correlation between BMI and iron levels, even in the absence of anemia, should raise awareness with regard to the micronutrient imbalance that exists in these children from a very young age. Children with elevated BMI may need to be screened for iron deficiency. There is an acute need to expand the studies to establish the cause of ID among children and adolescents.

Keywords: obesity, body mass index, iron deficiency

Introduction

Iron deficiency (ID) is one of the most common causes of anemia in children. Although it is frequently encountered in a clinician's daily practice, the multifactorial etiology of ID still represents a challenge regarding long-term management (1).

Childhood obesity continues to spark the interest of researchers worldwide. It is estimated that the global prevalence of obesity in pediatric patients is 16-31% (2) However, it has been observed that despite the high prevalence in the western countries, there are countries like Poland and Russia where it is not as frequent (3), a possible explanation could be the easier access to fast-food in develop countries in spite of dietary education.

Excess weight during childhood determines the development of several conditions such as elevated blood pressure and dyslipidemia which leads to cardiovascular disease. Also, type 2 diabetes can develop due to insulin resistance. In short, these patients have a significant increased risk to develop metabolic syndrome. Another issue is the weight gain which leads to breathing issues such as sleep apnea, joint and musculoskeletal problems and, also fatty liver disease (4).

In overweight and obese children, adiposity related inflammation ultimately leads to ID by two different/separate mechanisms: the increase production of hepcidin, TNF-α, IL-1, IL-2 and adipokines (resistin and leptin) alters iron homeostasis and iron sequestration in the enterocytes, macrophages and hepatocytes determine a decrease in transferrin saturation (5-8).

It seems that there is also a dietary imbalance, rich in carbohydrates and poor in micronutrients in these children (9). Therefore, obese and overweighed patients are iron deficient. ID usually appears before the onset of anemia.

In preadolescents ID is often linked to a combination of an imbalanced diet, poor in micronutrients/iron with sedentary lifestyle. Adolescents, especially girls, due to increased menstrual bleeding are also at higher risk for ID, as it is known that requirements are yet again increased in this age group (1). Adolescents may also have diminished socio-economic circumstances.

[1] 1st Pediatric Clinic, "Louis Turcanu" Children's Clinical and Emergency Hospital, Timisoara, Romania
[2] Department XI of Pediatrics - 1st Pediatric Discipline, "Victor Babes" University of Medicine and Pharmacy Timisoara, Timisoara, Romania

Email: olah.orsi@yahoo.com, cristina.pantea13@gmail.com, bizerea.teofana@umft.ro, tamasanu.raluca@umft.ro, brad.giorgiana@umft.ro, raluca_asproniu@yahoo.com, theovatistas@hotmail.com, marginean.otilia@umft.ro

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ID has durable effects such as: neurodevelopmental and behavior issues, reduced motor development, disruptions of attention and communication (10). The causes leading to ID are different by age group. Among toddlers, lack of iron in the diet is associated with the increased needs in iron during the fast process of growth as well as a dietary imbalance in consumption of cow's milk.

If the iron requirements are not covered, at the initial stage the iron deposits are reduced, ferritin and iron transferrin saturation are decreased. If the iron balance remains negative, after depletion of iron reserves, hemoglobin, hematocrit decrease followed by reductions of VEM and CHEM, thus installing microcytic hypochromic anemia.

Aim of the study

The aim of the study is to investigate the link between overweight/obesity and iron deficiency in children and to explore age-specific variations.

Material and method

A retrospective observational study was conducted over a 1-year period (1st April 2018-31th March 2019), on 78 pediatric patients admitted for overweight or obesity in the Endocrinology Department of "Louis Turcanu" Children's Emergency Clinical Hospital Timișoara.

Inclusion criteria: overweight and obesity as defined by CDC, children aged 1-18 years. Exclusion criteria: genetic and/or iatrogenic obesity.

According to the CDC, overweight is defined as a BMI for sex and age between the 85th and 95th and obesity as a BMI equal or greater than the 95th percentile (11). WHO defines ID as serum ferritin levels <12 µg/L in children under the age of 5 years and <15µg/L in those over 5 years of age, and anemia as a condition in which there is a reduction of either red blood cells, hemoglobin or hematocrit under age-appropriate thresholds. Anemia is defined as Hemoglobin level lower than the normal thresholds as shown in Table 1.

An electronic database consisting of anonymized patient files was created using Microsoft Excel and the correlations between the predictable variable (BMI) and the independent one (Iron level) was assessed.

The retrospective study was approved by the Ethics Committee for Research of the "Louis Turcanu" Children's Clinical Emergency Hospital from Timisoara

Results

A total of 78 pediatric patients admitted for overweight or obesity were enrolled and analyzed in the study, after applying the inclusion criteria. According to age patients were divided in 3 groups: toddlers 6% (age 1-5 years); preadolescents 40% (age 5-12 years) and adolescents 54% (age 12-18 years). The CDC BMI- charts matched for age and sex (12) were used in order to define overweight and obesity (overweight 85th - 95th and obesity > 95th percentiles).

In each group, the incidence of overweight and obese patients according to BMI-CDC charts was analyzed. Thus, obesity in the group of toddlers was 80%, in the pre-adolescents 87% and among the adolescents group 54,4%. Whereas, the complementary percentages of overweight children were as follows: 20% in the group of toddlers, 13% in the preadolescents group and among the adolescents 45,6 %.

It was surprising that although obesity predominated in the group of adolescents, an almost equal number of overweight children was found. The highest prevalence of obese patients was observed among children aged 5 to 12 years.

Figure 1 shows the prevalence of ID in the studied groups. The highest prevalence of ID was observed among children 1 to 5 years, with a percentage of 60%. As age increases, the prevalence of ID decreases by approximately a half, 32% in the preadolescents and 14% in the adolescent patients, respectively. Therefore, it seems that young age increases the risk for ID.

ID was evaluated through serum iron and ferritin and the relation between adiposity and iron levels was investigated, as depicted in Figure 2.

A negative correlation was observed in all age groups as supported by the slightly decreasing slope of the lines and the negative coefficient representing the slope. However, R2 levels supports a weak negative correlation between studied parameters: in toddlers R2=0,0101, in preadolescents R2=0,022 and adolescents R2=0,0189, as described in Figure 2.

It was also important to evaluate the correlation of hemoglobin (Hb) levels with overweight /obesity because a decrease in Hb levels defines anemia, and ID is a precursor state. We calculated the prevalence of low Hb levels in our predetermined age groups. Figure 3 shows Hb levels among the studied patients according to age groups. Out of the total children up to the age of 5 whose Hb levels were obtained, considering a threshold of 11g/dL, none of them had anemia.

Table 1. **Hemoglobin and Hematocrit threshold levels for anemia in children adapted from WHO [7]**

Age group	Hemoglobin(g/dL)	Hematocrit (%)
Toddlers (1-5 years)	11	33
Preadolescents (5-12 years)	11,5	34
Adolescents (>12years)	12	36

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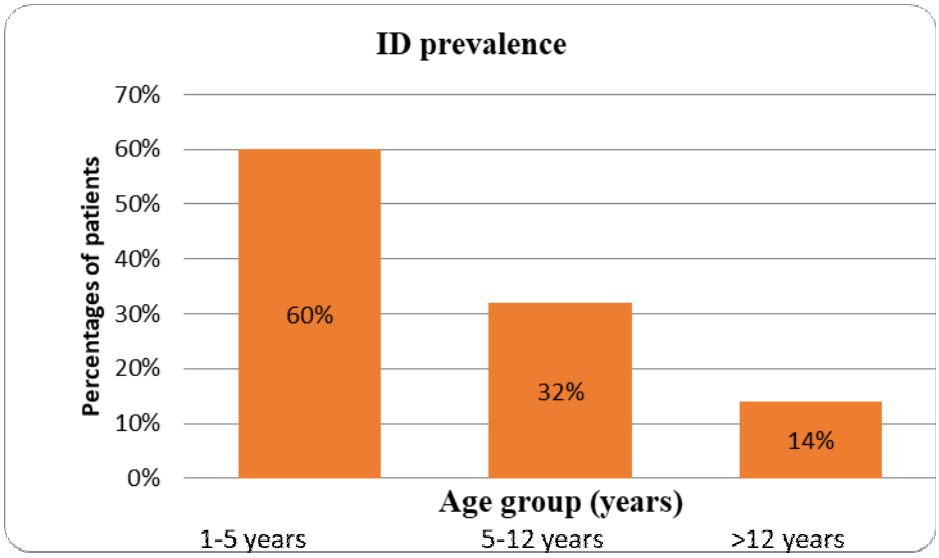

Fig.1. Comparison of iron deficiency between three groups

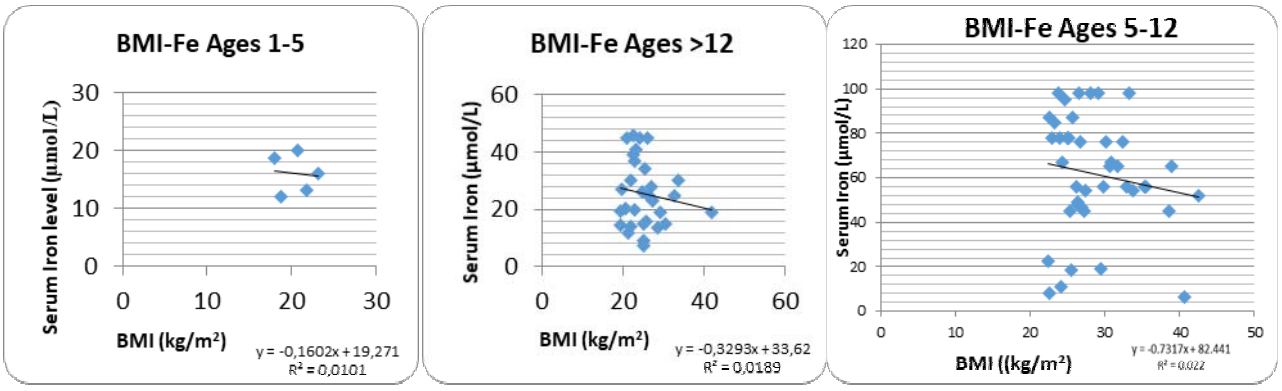

Fig. 2. Correlation of iron levels with BMI in age groups.

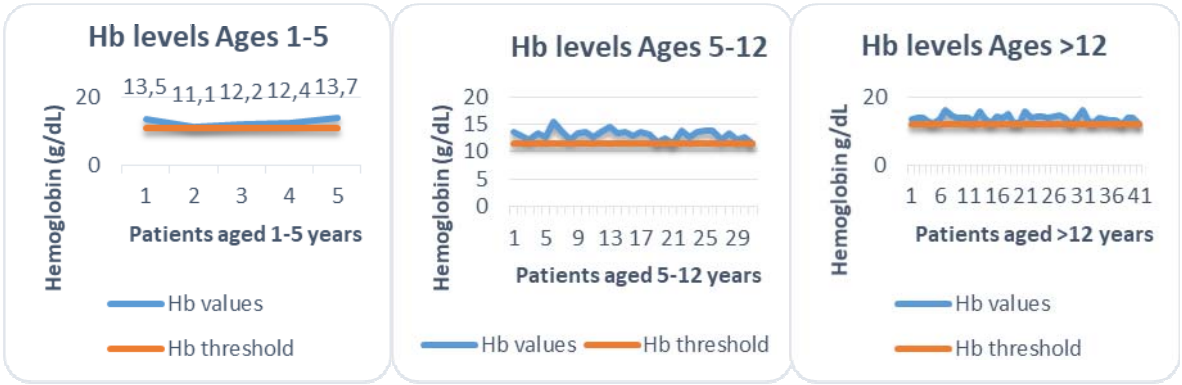

Fig. 3. Hb levels in age groups

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In the preadolescents group, one in 31 children had a decreased level of Hb, while among the adolescents two had low Hb levels, as depicted in Figure 3.

3.22% of obese and overweight children aged 5-12 years had low Hb level, although there were another 5 patients with Hb within 0.5 g/ dL from the threshold. Among adolescents 5% had Hb level below the threshold, and 6 adolescents were with Hb within 0.5 g/dl from the threshold. There were no significant differences in Hb of obese and overweight children between adolescents and adolescent groups. Several of these children may be at risk of developing anemia.

Although iron deficiency was most common in children aged 1-5 years, none had low hemoglobin levels. These results demonstrate that the combination of low serum iron and normal hemoglobin is common among obese and overweight children. In the same time there is a significant number of children throughout our sample with marginal hemoglobin values. The correlation coefficient does not support a connection between BMI and hemoglobin. Thus, it can be stated that negative correlation between BMI and ID does not necessarily imply the same relation between adiposity and anemia.

Discussion

World Health Organization defines obesity and overweight as a disequilibrium between the calory intake and the consumption (13). In this study it was observed that in the group of children aged 5 to 12 years the proportion of obese patient related to overweight ones was the highest compared to the other studied groups (87% compared to 80% in toddlers and 54,4% and adolescents respectively). Obesity and iron deficiency remain two of the most common nutritional disturbances in childhood. Iron deficiency is the principal factor in the development of microcytic anemia (14).

Studies have reported that excess weight has an adverse effect on iron metabolism. In obesity there is a chronic subclinical inflammation associated with reduced iron availability due increased levels of hepcidin and low iron absorption (15-17). There is data that suggests that adipocytes are also capable of producing hepcidin (18). Baumgartner, J, et al. demonstrated that children who are overweight or obese have a two-fold risk of remaining ID after iron supplementation (19, 20)

An important number of studies have considered that ID in obese pediatric patients is more common than in healthy ones. The data collected by American National Health and Nutrition Examination Survey III, from the pediatric population demonstrated the widespread presence of ID. There are studies that indicate that overweight children from America were twice more likely to be iron deficient than normal-weight children. Thu emphasizing the negative correlation between iron levels and BMI. ID simultaneous rose with BMI (5, 6, 9, 21)

In this study obesity was associated with higher ID risk. A negative correlation between BMI and serum iron was observed (toddlers R2=0,0101, in preadolescents R2=0,022 and adolescents R2=0,0189).

ID was present in all of the studied groups, but children ages 1 to 5 were the most affected. 60% of obese and overweight toddlers had ID and the presence was significantly decreased in the other 2 groups, 32% of the preadolescents and 14% of the adolescents respectively had ID, whereas the prevalence of decreased by nearly a half in preadolescents and again in adolescents (32% and 14% respectively).

Similar results were found in a cross-sectional Canadian study on 1607 children, aged 1-3 years, which concluded that the z-score of BMI was rose inversely proportional to ferritin levels and it was associated with a higher risk of iron deficiency (22). Another study, from China that included over 5000 patients 7-11 years old observed that obesity increased the risk of ID, even though it did not apparently amplify the risk of anemia (23).

A chronic inflammatory caused by obesity leads to hepcidin overproduction which could be the link between excessive adiposity and low iron levels, by decreasing ferroportine-1 from enterocytes (24, 25) .It also determines a decrease of transferrin saturation leading to ID.

A study on a large cohort of Greek children showed that obesity increased the risk of ID [20]. However, in children from western societies in spite of an adequate nutritional reserve, the prevalence of ID is significantly increased. This might be due to poor nutritional habits and education, as well as easy access to fast-food (5). Obese children may be at increased risk of micronutrient deficiency (26).

Conclusions

The negative correlation between BMI and iron levels, even in the absence of anemia, should raise awareness with regard to the micronutrient imbalance that exists in overweight and obese children from a very young age. Children with high BMI may need to be screened for iron deficiency especially in the toddler group.

As iron deficiency has a lot of negative effects on the course of obesity- related conditions, screening of iron deficiency is justified and treatment is warranted for the long- term management. There is an acute need to expand the studies to establish the cause of ID among overweight and obese children and include additional markers such as hepcidin.

Early intervention in case of obesity and routine monitoring of a healthy growth and development are important in order to prevent iron deficiency. In this respect knowing the prevalence of ID among overweight and obese children as a predisposing state for anemia, is important order to counteract its long- term consequences on growth and neurodevelopment (14, 27, 28).

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Correspondence to:
Cristina Loredana Pantea
Vadul Crisului 1, 300613
Timisoara, Romania
E-mail: cristina.pantea13@gmail.com
Tel: +40 721 246 369

INDIVIDUALIZED TREATMENT OF INFANTILE HAEMANGIOMA: A CASE REPORT

Anca-Maria Raicu[1], Ionuț Fernando Secheli[2], Dana Galieta Mincă[1]

Abstract

The treatment of infantile hemangiomas has been greatly modified in the last 15 years, starting from the passive attitude, from "wait and see", to complex surgical procedures. Currently, the vast majority of infantile hemangiomas are treated with Propranolol, however there are cases where monotherapy is not sufficient, requiring a combination of existing treatment methods. The complexity of the therapy is determined by the complexity of the infantile hemangioma: an extended or exposed area, local complications as ulceration etc. In the present case, a clinical situation is described in which we added to the drug treatment (with oral Propranolol) the local treatment (with Timololum gel) and the surgical procedure of partial excision of hemangioma. Our goal is to highlight the importance of knowing the treatment methods and their possibilities of combination, for a better aesthetic and functional result.

Keywords: infantile hemangioma, Propranolol, infantile hemangioma treatment, complications of infantile hemangioma.

Introduction

Infantile hemangioma (HI) is the most common benign tumor of the child, with an average incidence of 4% to 5% (1-3) and a maximum incidence of 10% -12%, found in non-Hispanic Caucasian infants. At the same time, infantile hemangioma is considered not only the most common benign tumor of the child, but also the most common vascular tumor, which occurs by rapid division of endothelial cells, its growth being attributed to hyperplasia of these cells. The pathogenesis of infantile hemangiomas is complex and little understood and known. Risk factors include prematurity and placental abnormalities (4).

Infantile hemangiomas most commonly occur on the skin but can also affect the viscera (the liver is most often involved). Facial hemangiomas can be impressive in appearance, disfiguring, sometimes affecting visual function, with eating disorders, and those in the airways can be life-threatening, especially in the proliferative phase (5-6).

The treatment of childhood hemangiomas includes a wide range of approaches, from conservative monitoring - "wait and see", to emergency surgery for severe morbidity and complications. Early treatment can reduce complications. However, there are so many therapeutic protocols (β systemic or topical blockers, corticosteroids, laser therapy, etc.) (7-8) that it is almost impossible for clinicians to choose the best therapeutic method.

Given the high heterogeneity of hemangiomas, the decision on who needs treatment as well as when to start treatment requires a detailed knowledge of the natural history and clinical indicators of high risk.

Aim

Our goal was to highlight the importance of knowing all the methods of treatment of infantile hemangiomas and adapting the therapeutic approach according to the complexity of the case, for an aesthetic and functional result as good as possible.

Material and method

We present the case of a little girl, who addressed the paediatric surgery service of the Emergency Clinical Hospital for Children „M. S. Curie", at the age of 3 months, for a vascular abnormality that included two lower thirds of the arm and two upper thirds of the left forearm, appeared at 3 weeks postnatal (Fig. 1), with rapid and unfavorable evolution, towards ulceration on the arm (Fig. 2).

Following the clinical examination, corroborated with the anamnestic data (moment of appearance, evolution, etc.), the diagnosis of infantile hemangioma is made, and it is decided to hospitalize for specialized investigations, in order to establish the treatment as soon as possible.

Since 2008, the treatment of infantile hemangiomas has been revolutionized by the introduction of Propranolol, a beta blocker, with superior results and much lower side effects compared to previously used drugs (9-17), a method quickly approved and implemented in our country.

Although there is currently no generally accepted infantile hemangioma management protocol, in our team, Propranolol treatment is not instituted until a detailed paediatric, cardiology, surgical and imaging examination, which includes a complete biological assessment , an electrocardiogram, a heart ultrasound, a soft tissue ultrasound, a trans fontanel ultrasound (for hemangiomas in the cephalic extremity), an abdominal ultrasound (for thoraco-abdominal hemangiomas) and for selected cases of an MRI. Following the investigations performed and clinical data, no pathological changes were found, which would contraindicate the start of oral treatment with Propranolol.

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] "M.S. Curie" Clinical Emergency Hospital for Children, Bucharest, Romania

Email: anca.raicu@drd.umfcd.ro, tacclo@hotmail.com, dana.minca@umfcd.ro

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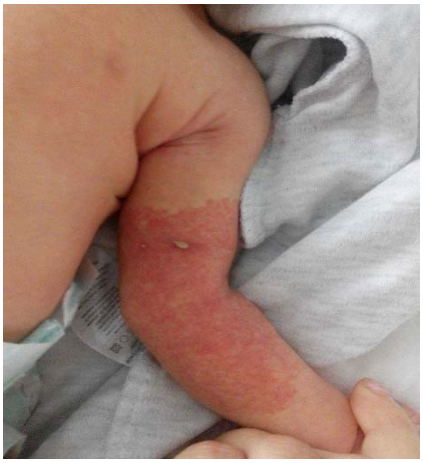

Fig. 1. Aspect of the hemangioma at 3 weeks of age

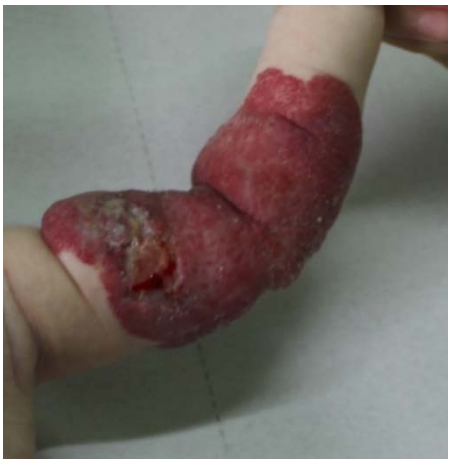

Fig. 2. Aspect of the haemangioma at 3 months of age

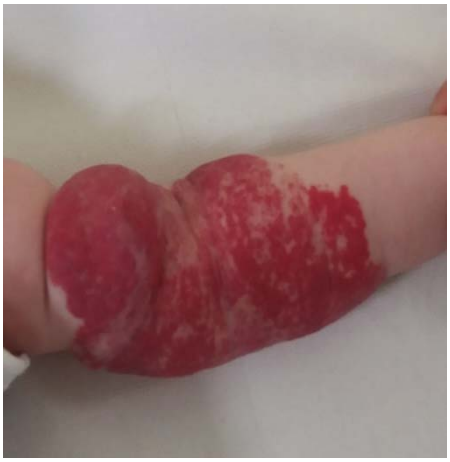

Fig. 3. Aspect of the haemangioma after 3 months of treatment with Propranolol

Fig. 4. Aspect of the haemangioma after 13 months of treatment with Propranolol

Discussions

Infantile hemangiomas remain the most common vascular tumors of the child, which appear in the first month of life and which often involve spontaneously, gradually, after the age of 1 year in their vast majority. Their clinical presentation varies from minimal skin lesions to impaired vital functions (example: hemangiomas that cause respiratory or visual disturbances) or disfiguring lesions. The most common complication of infantile hemangiomas is ulceration (20-23), who's healing by re-epithelialization is most often done with unsightly and disabling scars.

Infantile hemangioma is a great clinical challenge, from diagnosis to treatment (Should we treat or should we wait and see? If we decide to treat the hemangioma, what type of treatment should we recommend? How long?).

Although the introduction of Propranolol in the treatment of infantile hemangiomas, which is currently the first line of treatment, no consensus has been reached on the optimal time to initiate treatment or its duration. There are authors who specify that the duration would be 6 to a maximum of 12 months for high-risk hemangiomas (18), but as we present, in selected cases this period can be extended until the complete remission of the lesions. Regarding the time of initiation, it is recommended to be done at the age of 5 weeks of life, but this term can be advanced in situations where the evolution of hemangioma is rapidly unfavorable and if the bio-humoral status of the patient allows us. In this

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case, the initiation of treatment was made from the presentation, at 3 months of age (approximately 12 weeks), when he addressed our service (presentation determined by the appearance of ulceration and less by the increase in size of the hemangioma). An early treatment could have limited the spread of hemangioma, prevented the onset of ulceration, decreased the duration of subsequent treatment, perhaps even the need for surgery. It would also have reduced treatment costs, both for the health care provider and for the family. But most importantly, the child's suffering would have decreased.

Conclusions

Establishing the correct diagnosis, as early as possible, by the multidisciplinary team is the first step in approaching these patients. Choosing the appropriate treatment for the case, under close monitoring, can prevent complications, and their correction as close as possible to normal, in terms of appearance and function of the affected organ.

Knowing all the treatment methods, the possibilities of combining them, teamwork, as well as adapting the approach according to the particularities of the case is the key to success in these complex situations, with good results.

We also consider that it is necessary to develop a standardized protocol for the management of cases of infantile hemangiomas, which should come to the aid of the clinician whose object of activity is this pathology.

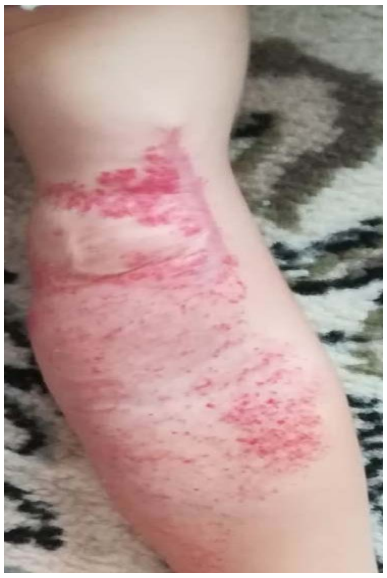

Fig. 5. Aspect of the haemangioma after 1 year and 6 months of treatment with Propranolol and 3 months after surgery

Fig. 6. Hemangioma at the age of 2 years, after 20 months of oral Propranolol, 4 months of Timololum gel, and one surgical intervention

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Correspondence to:

Anca Raicu
"Carol Davila" University of Medicine and Pharmacy37
Dionisie Lupu Street, 2nd Sector, Bucharest
Phone: 0721 681 280
Email: anca.raicu@drd.umfcd.ro

GENETICS IN ANOREXIA NERVOSA

Iulia Maria Sabau[1,2], Nicoleta Ioana Andreescu[1,2], Adela Chiriță-Emandi[1,2], Iulia Jurca-Simina[1], Meda-Ada Bugi[2,3], Maria Puiu[1,2]

Abstract

Anorexia Nervosa (AN) in defined by restriction of energy intake leading to low body weight, an intense fear of gaining weight, as well as body image disturbance. AN has the highest mortality rate of any psychiatric disorder and unfortunately, treatment methods are often inefficient. Genetic factors have a substantial role in the etiology of AN. The purpose of this review is to make a brief synthesis of the current knowledge regarding the genetic factors involved in AN disorder. Several studies that have an impact in understanding the role of genetics in the AN architecture were discussed and chronologically presented. As AN represents a difficult treat-to treat illness, all the research that has been made until now was led by the motivation and goal of finding specific pharmaceutical targets for the treatment and prevention of AN. Although there has been made substantial progress in understanding the genetic architecture of AN and its relation to other disorders, further investigation still needs to be done with hope and determination.

Keywords: Anorexia Nervosa, GWAS, SNPs, genes

Introduction

According to DSM-5 (The Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders) the definition of Anorexia Nervosa must include the following criteria: restriction of energy intake leading to low body weight for age, sex, physical health and developmental trajectory, an intense fear of gaining weight (even though the person may be underweight), as well as body image disturbance. People who meet the AN criterion but are not underweight have atypical anorexia. It has been proved that there is no difference in the psychological and medical impacts between anorexia and atypical anorexia. [1]

Anorexia can affect people of all genders, ages, races, sexual orientations and ethnicities. The prevalence of AN is around 4% and usually, females are more affected with this disorder than males. [2]

Unfortunately, statistical epidemiology has shown that AN has the highest mortality rate of any psychiatric disorder, being associated with medical complications and comorbidities. [2]

Aim

As we have witnessed remarkable advances regarding the implication of genetics in many disorders, it has been proved that genetic factors are involved in the etiology of AN as well. The purpose of this review is to make a brief synthesis of the current knowledge regarding the genetic factors involved in AN disorder.

Material and method

The search platform used was PubMed and the searched terms were “anorexia nervosa”, “GWAS”, “genes” (August 2021). There were no filters added, except the fact that were taken into consideration only the articles published in the last 5 years.

Results

History of Genetics in Anorexia Nervosa

Among the first studies that demonstrated the implication of genetic factors in the development of Anorexia Nervosa were the family studies and the twin studies. By their contribution, it has been proved the familial aggregation of AN. In addition, the twin studies suggested that there might be a common genetic risk between AN and other psychiatric disorders such as eating disorders, major depression and obsessive-compulsive disorder. [3]

The candidate gene studies are based on the examination of the allele frequency of a selected SNP (single nucleotide polymorphism) in individuals that represent or not a trait of interest. In trying to reveal the risk genes for AN, the candidate gene studies did not add too many improvements to the genetic knowledge in AN. However it is important to mention that meta-analysis studies came to the conclusion that serotonin genes may be involved in the etiology of AN. They found a significant association between HTR2A polymorphism (specially, the A allele) and AN. There also was found an association between AN and short allele of 5-HTTLPR and a 5-HTT polymorphism. Unfortunately, these findings were not confirmed in further studies. [4]

There are many genes that contribute to the development of AN and as there are more and more advances of genomic experiments, genome-wide association studies have an important role in understanding the relationship between AN and genetics.

In 2010 a GWAS of both CNVs and SNPs in AN performed by Wang et al, confirmed that SNPs in OPRD1 gene and also SNPs near HTR1D confer risk for AN. Also, the study observed a recurrent 13q12 deletion (1.5 Mb) disrupting SCAS in two cases, and CNVs disrupting the CNTN6/CNTN4 region present only in AN cases. However, the study was not able to find genome-wide significant signals but emphasizes the importance of genomic studies in order to identify disease genes. [5]

[1.] Centre of Genomic Medicine-“Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
[2.] “Louis Turcanu” Emergency Hospital for Children, Timisoara, Romania
[3.] “Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
Email: iuliamariasabau@gmail.com, andreescu.nicoleta@umft.ro, adela.chirita@umft.ro, jurca.iulia@gmail.com, nutritiapentrutoti@gmail.com, maria_puiu@umft.ro

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In 2014 Boraska and partners were able to identify variants in SOX2OT and PPP3CA genes that when significantly associated with AN, but these genes were previously known for association with Alzheimer's disease.[6] In 2015 a smaller GWAS confirmed that there is association between SOX2-OT gene and eating disorders, even though it could not reach genomic significance due to its limited size (only 184 cases). [7]

In 2017 a large and rigorous GWAS made on 4000 AN cases and 11000 controls was published. The study found a genome-wide significant locus on chromosome 12 (rs4622308), a region that was previously associated with some autoimmune diseases such as type I diabetes, asthma, rheumatoid arthritis. 6 genes from this specific region with genomic-wide significance were identified: ERBB3, RPL41, PA2G4, RPS26, IKZF4 and ZC3H10. The top SNP was found in ERBB3 gene. The study also made a LDSC (linkage disequilibrium score regression) which is a method used to discover genetic overlaps between disorders. Thus, there was observed significant correlation between AN and other disorders. More exactly, positive correlation was found between AN and schizophrenia, educational attainment, and high-density lipoprotein cholesterol and neuroticism and also, negative correlation between AN and glucose, insulin, and lipid phenotypes and body mass index. [8]

Also in 2017, it was published another GWAS that tried to reduce the phenotype heterogeneity by excluding the cases with AN that migrated to or from bulimia nervosa or binge eating disorder, making the assumption that this method will enhance gene discovery. The study managed to identify a genome-wide significant risk in EBF1 (Early B-Cell Factor 1) gene variants. This gene is known to encode a transcription factor necessary for the development of both osteoblast and adipocyte, mutations in this gene leading to low levels of circulating leptin. Therefore, this study suggested that a dysregulation in leptin signaling may have a role in the etiology of AN. [9]

In addition, an exome chip-based GWAS was conducted on more than 2000 cases of AN. The study also put emphasize on low frequency and rare variants. Although there were no findings that reached genomic-wide significance, there were identified two novel common variants rs10791286, an intronic variant in OPCM and rs7700147, an intergenic variant. [10]

Copy number variants also play an important role in developing psychiatric disorders. Therefore in 2017 was conducted the largest CNV genome-wide study in order to help to understand the role of CNVs in AN. It was investigated whether CNVs previously associated with psychiatric disorders were also present in AN. There was observed 2 cases of CNV in AN, one of them was previously associated with developmental delay, schizophrenia, and autism, and the other one was associated with AN in a previous pilot study. Moreover, there were also identified 40 new cases of large CNVs (more than 1Mbp size) from which five of them did not have any associated reports in CNV databases until then. [11]

Moving forward, in 2019 it was published the first GWAS that focused on de novo variants (DNVs) possibly involved in the risk genes of AN. DNVs represent mutations that are not found in the genome of the parents, but are found in the probands. Using the whole exome sequencing, it was analyzed a cohort formatted from nice females (aged 13-43) plus their families (mother and father). Focusing on de novo variants, it was discovered seven missense variants in potential genes: CSMD1, ZFHX2, PTPRD, CREB3, CYP4A11, TNFRSF6B, and GAB1. It is important to mention that four of these genes (CSMD1, CREB3, PTPRD and GAB1) are known for their presence in the same signaling pathways, specifically neuron differentiation pathway and dopamine pathway. Interestingly, PTPN11 (gene known to be involved in the etiology of Noonan syndrome) also belongs to this pathway and it was reported a case with a variant of PTPN11 in a patient with AN. PTPRD and CSMD1 were previously associated with addictions and psychiatric disorders. [12]

The largest GWAS ever made included 33 databases with almost 17000 cases of AN and 55 000 controls. Using meta-analysis for autosomes and chromosome X, the study was able to identify eight risk loci that reached genome-wide significance. Making the connection from loci to specific genes is not an easy task and, in order to achieve that, the study used three different perspectives: relationship to brain expression loci, regulatory chromatin interactions and the gene location within a GWAS locus. A number of 58 genes were identified by all three methods. Four of the single-gene loci identified were CADM1, MGMT, FOXP1 and PTBP2, concluding that these genes may contribute to the etiology of AN. Also, the study showed that AN shared genetic variations with some metabolic phenotypes (insulin resistance, type 2 diabetes, HDL cholesterol) and proved a bidirectional causal relationship between AN and BMI: AN risk alleles could increase the risk for low BMI and also the low BMI risk alleles could increase the risk for AN. In other words, the study suggested that metabolic dysregulation contribute to the difficulty of the patients with AN to maintain a healthy BMI. [13]

Lin Z. et al conducted a study that used the information provided from the previous GWAS meta-analysis mentioned above, suggesting that SNP (rs6589488) in CADM1gene might be in linkage disequilibrium with functional intronic variants or unknown variants. Therefore, in a cohort of 51 cases of AN, CADM1gene was screened by Sanger sequencing. There were found 13 SNPs from which 2 missense, 2 synonymous, 2 located at 5'-UTR and 7 intronic variants (including rs6589488). The conclusion was that the missense variants were not deleterious and that the initial intronic variant was not causative. However, the study encourages for further investigations as the causative variant might be in the vicinity of CADM1 gene, within 1Mb. It is interesting that one of the closest genes to CADM1 is NNMT (the nicotinamide N-methyltransferase) which is known to be associated with obesity. [14].

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Author	Publishing Year	Type of Study	Reached Genome Significance	Study Size	Main conclusions
Wang et al	2010	GWAS (SNPs)	no	1033cases AN; 3733 controls	HTR1D gene
Boraska et al	2014	GWAS (SNPs)	no	2907cases AN; 14860 controls	SOX2OT; PPP3CA
Duncan et al	2017	GWAS (SNPs)	yes	3495cases AN; 10982 controls	locus chromosome 12; ERB3;correlation with other diseases
Li et al	2017	GWAS (SNPs)	yes	692 females AN	EBF1;dysregulation leptin signaling
Huckins et al	2017	exome-chip based GWAS	no	2158 cases; 15485 controls	2 common variants
Yilmaz et al	2017	genome-wide CNV	no	1983 females	2 pathogenic CNVs; 40 new large CNVs
Bienvenu et al	2019	GWAS (DNVs)		9 females	7 missense variants in CSMD1,ZFHX2, PTPRD, CREB3,CYP4A11, TNFRSF6B, GAB1
Watson et al	2019	GWAS	yes	17000 cases; 55000 controls	8 risk loci; metabolic dysregulation
Lin et al	2020	GWAS	no	51 cases	variants in CADM1 gene

Table1. The main characteristics of the GWASs that were conducted regarding the genetic variants related to AN disorder.

Another study that is worth to be mentioned is about the association that was found between AN and OCD (Obsessive–Compulsive Disorder). Published in March 2021, the study used the information provided by the previous GWAS that were made on both AN and OCD and collected the tops SNPs for the risk genes of both disorders. Then, it was explored the phenotype, functional, spatiotemporal, and cell-specific patterns of these genes. What was found was that AN and OCD might have similar functional pathway, as the risk genes involved in both disorders led to alteration of the synapse transmission, by influencing the prefrontal cortex expressions. [15]

An important progress regarding genetics in AN is ANGI (Anorexia Nervosa Genetics Initiative), an international collaboration that collected information from 13 000 cases of AN. The countries involved in the trial are United States (US), Sweden (SE), Australia/New Zealand (ANZ) and Denmark (DK). The aim of this cooperative was to expand the samples for GWAS, and to provide efficient phenotyping regarding the phenotype. In addition, information provided could also be used for SNP-based genetic correlations and cross-disorder meta-analyses to identify variants shared with other psychiatric disorders. [16]

A step forward in the progress of genetics is made by EDGI: The Eating Disorders Genetics Initiative. EDGI represents an international organization whose aim is to explore the role of genes and environment in three major eating disorders: anorexia nervosa, binge eating disorder and bulimia nervosa. The countries that are taking part in the investigation are United States (US), Australia (AU), New Zealand (NZ), and Denmark (DK). The GWAS will include 14 500 cases of eating disorders and 1500 controls, becoming the largest genetic study ever conducted. [17]

Epigenetics is referring to all kind of biochemical mechanisms that result in changes in the activity of genes, but without changing the DNA sequence. The study of epigenetics is increasingly developing and methods in which epigenetics modifications can occur include DNA methylation, changing the chromatin conformation or non-coding RNAs. Although histone acetylation as an epigenetic method has not been studied too much, by this process the chromatin conformation is regulated, controlling the expression of many genes. Recently, a research published in 2019 discovered a potentially component in the etiology of AN- activity of the histone deacetylase 4 (HDAC4). HDAC4 is a member of the family of epigenetic modifier enzymes called histone deacetylases and is known to be implicated in the formation of the bone, central nervous system (CNS), muscle, and metabolism. The activity of HDAC4 might be altered either by genetic predisposition, fighter by environmental conditions such as: diet, increased levels of estrogen, physical activity. As these conditions could be potential "triggers" of AN, in this way HDAC4 may be involved in the cognitive factors of AN. Several studies

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demonstrated that there are significant methylation differences in HDAC4 locus in peripheral tissues of the patients with AN. [18]

Clinical Implications

The goal of all of this work and research regarding the implications of genetics in AN is that all the information will be used for the clinical care of the patients affected with the disorder.

The understanding of the role of genetics in AN can be used, first, for the psychoeducation of the patients and families. All the patients should be educated so that they will be aware of all the factors that can contribute to the etiology of their disease, including the genetic factors. A step forward was made by the Academy of Eating Disorders and other eating disorder organizations, when releasing the document "Nine Truths About Eating Disorders" in which Truth 7 and Truth 8 are stating "'Genes and environment play important roles in the development of eating disorders", respectively, "Genes alone do not predict who will develop eating disorders".[19]

Another aspect to be taken into consideration is that by identifying the genetic markers of risk, we would be also able to identify those who are at high risk. Once we identify we can put all our efforts towards prevention because is always better to stop the disease before it starts.

Furthermore, all the genetic correlations that were found between AN and other diseases can be used for further investigations and for a better understanding of the genes that can be specific pharmaceutical targets for the disorder. As AN is a difficult-to-treat illness, all the information provided by GWAS can help in finding pharmaceutical agents that will innovate the treatment for AN. [2]

Conclusions

To conclude, there has been made substantial progress in understanding the genetic architecture of AN and its relation to other disorders, but there is still room for more. AN represents a difficult treat-to treat illness and there is a desperate need to discover an efficient therapeutic method for patients with this disorder. Therefore, all the research that has been made until now should lead to motivation and encouragement for further investigations and follow-up studies. The main goal is that all the genetic information to be used directly in the treatment and prevention of AN.

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Correspondence to:
Meda-Ada Bugi, PhD student
"Victor Babes" University of Medicine and Pharmacy
"Louis Turcanu" Emergency Hospital for Children
Iosif Nemoianu Street, No 2,
Timisoara, Romania
E-mail: nutritiapentrutoti@gmail.com
Mobile: 0040 752 199 354

KETOGENIC DIET AND GENETIC DISORDERS

Iulia Maria Sabau[1,2], Nicoleta Ioana Andreescu[1,2], Adela Chiriță-Emandi[1,2], Iulia Jurca-Simina[1], Meda-Ada Bugi[2,3], Maria Puiu[1,2]

Abstract

Ketogenic Diet (KD) represents a specific type of diet which is based on the process of ketosis. Even since 1925, KD began to be used as a treatment for drug-resistant epilepsy but recently, KD has begun to take part in the treatment of many chronic diseases. In this review we look at the role and the implications of KD in some genetic disorders: pharmacoresistant epilepsy, Alzheimer's disease, Angelman syndrome, glucose transporter type 1 deficiency syndrome (Glut1-DS), glycogen storage diseases (GSDs) and pyruvate dehydrogenase complex deficiency (PDCD). The review aims to provide clinicians a snapshot of the genetic factors that could have an impact on the response to patient's response to KD. As genetic variants may influence the response to KD, the implementation of nutrigenomics in the personalized nutrition of the patient with KD would be the key for the best patient care.

Keywords: ketogenic diet, genetic disorders, epilepsy, gene

Introduction

Ketogenic Diet Therapies represent a group of high-fat, low-carbohydrate diets which are based on the process of ketosis. Currently, there are four types of ketogenic diet therapies: the classical ketogenic diet (KD), modified Atkins diet (MAD), medium chain triglyceride (MCT) and, also, low glycaemia index treatment (LGIT). [1]

During ketosis, in the human organism is produced a form of starvation, a state that deviate from the traditional source of energy-the glucose to fats. By limiting the carbohydrate intake to a total amount per day of 10 to 50 grams (5% to 10% of total caloric intake), the human body is forced to use fats as a source of energy for cells, tissues, and organs. [1]

Even since 1925, KD began to be used as a treatment for drug-resistant epilepsy. Recently, KD has begun to take part in the treatment of many chronic diseases such as diabetes, cancer, obesity, polycystic ovary syndrome, neuromuscular and neurological diseases, and many studies demonstrating the positive effects of KD. [2]

Genetic factors may influence the body's response to KD, by affecting the metabolism of carbohydrates and fats. Common genetic variation consisting in single-nucleotide polymorphism (SNPs) may interact with individual differences and impact the response to KD.

Aim

The aim of this review is to discuss the implications of KDs in a few selected genetic disorders. Although there are several genetic disorders in which KD has a huge impact as a therapy, the diseases chosen to be discussed in this review are epilepsy, Alzheimer disease (AD), Angelman syndrome (AS), glucose transporter type 1 deficiency syndrome deficiency (GLUT1-DS), glycogen storage diseases (GSDs) and pyruvate dehydrogenase complex deficiency (PDCD). By making a brief synthesis of the current implications of KD in the treatment of these disorders, we would like to gain a better understanding of the importance of KD and the way it interacts with genetic factors. Also, the review aims to provide clinicians a snapshot of the genetic variants that could have an impact on the response to KD in the genetic disorders that were taken into consideration.

Material and method

The browse platform used was PubMed and the search terms were "ketogenic diet", "genetic disorders", "genes" (August 2021) The articles used as references were filtered by data publication as there were only taken into consideration those published in the last 5 years.

Results

Cell physiology

The energy of the cell is produced in the organelle called mitochondria. The mitochondrial metabolism involves the oxidation of pyruvate, the citric acid cycle, β-oxidation of fatty acids and the oxidative phosphorylation. In the presence of oxygen, the energy source of the cell is glucose. Through glycolysis, glucose is transformed into pyruvate and then, inside mitochondria, takes places the oxidation process through oxidative phosphorylation which lead to ATP production. In the absence of glucose, the cell is taking energy from the degradation of fatty acids and proteins, which results in generation of the ketone bodies. The three most important ketone bodies are acetone, acetoacetate and 3-β-hydroxybutyrate. Ketone bodies are produced when there is not sufficient glucose in the organism, for instance during fasting process, prolonged exercise, or when following a ketogenic diet. In the mitochondria of the liver cells takes place the ketogenesis process with the generation of ketone bodies, which are transported via blood to different organs of the body. [3]

[1.] Centre of Genomic Medicine-"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2.] "Louis Turcanu" Emergency Hospital for Children, Timisoara, Romania
[3.] "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Email: iuliamariasabau@gmail.com, andreescu.nicoleta@umft.ro, adela.chirita@umft.ro, jurca.iulia@gmail.com, nutritiapentrutoti@gmail.com, maria_puiu@umft.ro

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In normal conditions, the concentration of the ketone bodies in the blood is very low (<0.3 mmol/L). Following a ketogenic diet, when ketone bodies' concentration in the blood reach around 2-4 mmol/L, the tissues begin to use the ketone bodies as a source of energy. What is interesting is that ketone bodies produce an even higher quantity of energy compared to glucose and this is due to the modifications in the ATP's production they can induce. Moreover, it has been demonstrated that ketone bodies have pleiotropic actions, being implicated in pathways and gene expression of different processes in the body such as oxidative stress, inflammation, immune function, cell signaling, membrane health and antioxidant status. [4, 5]

Precision Nutrition and Ketogenic Diet

As personalized nutrition is becoming more and more popular nowadays, the personalized approach of KD would maximize the effectiveness as a therapy and would ensure long-term safety for the patients. Although several clinical trials proved the efficacy of KD, the therapeutic response to KD has proven to be different for each individual. Besides the variability regarding sex and age, there is the interaction between genetic factors and lifestyle which include diet, activity level, and insulin resistance. Genetic factors may influence the body's response to KD, by affecting the metabolism of carbohydrates and fats. Common genetic variation consisting in single-nucleotide polymorphism (SNPs) have an effect that depend on the interaction with environmental factors and other genetic variants. In the past years, there are a few GWAS (genome-wide association studies) that managed to identify SNPs associated with individual response to KD. [5]

Epilepsy

It is estimated that there are around 50-60 million people that suffer from epilepsy, 25-30% of these being resistant to any pharmacological treatment. Over the last years, concerns about side effects of the medications, the negative effects that seizures have on the brain development and also, concerns about treatment failure, has led to a revolutionary growth in the use of KD as a therapeutically alternative for non-responsive epilepsy in children, adolescents and adults. Studies demonstrated that after 3 months, half of those on KD had more than 50% reduction in seizures. Moreover, patients reported improvements in the quality of life and, also, possibility to reduce or interrupt medications. [3]

Certain types of epilepsy such as tuberous sclerosis, myoclonic-atonic seizures, Dravet syndrome are known to have a good response to KD. [6]

A review published in February 2021 mentioned that 6 randomized control-trials proved the efficacy and safety of different KDs in patients with intractable epilepsy. The positive effect of KD that was reported by all the 6 studies, was the reduction in seizures frequency. The side effects reported were constipation, diarrhea, vomiting, hypercalciuria, hyperlipidemia and weight loss. [1]

As we live in the era of genomics, evidence is showing that identifying specific mutations in the genome is relevant both for diagnosis and prognosis as well as it is for treatment selection. This is applicable in epilepsy as well. For instance, in Dravet Syndrome due to mutations in SCN1A, KD proved to be efficient as an adjuvant therapy. On the other hand, in patients with epilepsy caused by autosomal dominant variants in KCNT1 (a gene that encodes the potassium channel) response to KD is quite poor. Moreover, two retrospective studies showed that patients with CDKL5-related epilepsy, either were completely unresponsive to KD, or their response was quite favorable, reducing the seizures frequency. [7, 8]

A GWAS published in 2018 aimed to determine whether common genetic variation influences the response to KD in children with epilepsy and discovered that a SNP within CDY1L (chromodomain Y 1 ligand) may affect KD response to seizure. The patients with epilepsy received KD and after a 3 month follow up, the GWAS which included 123 responders to KD vs 112 no responders identified an association locus of CDYL (rs12204701) at 6p25.1. Patients carrying at least one copy of CDYL1 A allele had a lower response to KD compared with non-carriers. CDY1L is a protein and acetyltransferase which is very important in the brain, in the epigenetic regulation of genes expression. [9]

Alzheimer's disease (AD)

Alzheimer's disease is one of the top ten causes of death in USA and, unfortunately, is still the only one without a specific treatment. At least 99% of drug candidates fail. [10]

Although AD cannot be considered a rare disease, it has been established that genetic factors may contribute to its etiology. The greatest genetic risk factors for AD is represented by the mutations of apolipoprotein E (ApoE). Apo E is a protein synthesized primarily by astrocytes but also by other glial cells and has a very important role in the metabolism and transport of lipids in the body. It is estimated that around 20% of the normal population carry ApoE4 allele and around 40-65% of AD cases, ApoE4 allele representing the genetic factor that led to late-onset AD. [11]

Ketogenic diet, by increasing 3-β-hydroxybutyrate so that it can be an alternative source of energy to glucose, has shown to be efficient in treating the patients with AD. For instance, a recent randomized crossover trial conducted on 26 patients from which 21 followed KD, wanted to determine whether the KD followed for 12 weeks would improve daily function, cognition, or quality of life of patients with AD. The study concluded that KD proved high rates of retention, safety, and adherence and that the quality of life and daily function of patients with AD greatly improved. [12]

The biological mechanism through which KD can help reduce the risk for AD implies the fact that β-hydroxybutyrate can reduce oxidative stress, inflammation, and mitochondrial dysfunction. Moreover, Qi et al described three mechanisms that can explain the benefits of KD to patients with AD. Firstly, KD increases lipophagy in neurons, protecting against lypotoxicity. Secondly, KD improves lipid transport, decreasing the lipoprotein glycation. Moreover, β-hydroxybutyrate represents an alternative source of acetyl-CoA, which is needed for sustaining brain's metabolic needs. [13, 14]

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A review published in December 2020 remarked that ApoE4 variant could influence the response to KD regarding the cognitive performance. A placebo-controlled trial conducted on 20 patients with AD or mild cognitive impairment showed that administration of medium chain triglyceride (MCT) improved cognitive performance only in ApoE3 homozygous but not in ApoE4 carriers. Also, ApoE4 carriers had more prolonged elevations in ketone levels after MCT administration which suggest that ApoE4 carriers may have a lower cellular utilization of ketogenic agents. This information was further investigated by a larger randomized, placebo-controlled, double-blind study that tested the administration of MCT supplement for a period of 3 months on 152 patients with AD. Interestingly, both carriers and non-carriers ApoE4 showed improvements in cognitive performance, but the effects were better and significantly correlated with β-hydroxybutyrate blood levels only in ApoE4 non-carriers. [¬5]

Angelman Syndrome (AS)

Angelman Syndrome is a genetic neurodevelopmental disorder, which is caused by the deficiency of maternally inherited UBE3A (ubiquitin E3 ligase). Angelman Syndrome is characterized by motor dysfunction, severe developmental delay, language and cognition deficits, frequent smiling and laughter, seizures, as well as autism-like behavior. In most tissues UBE3A gene is expressed from both alleles, whereas in neurons is expressed only the maternally inherited UBE3A allele (the paternally copy being silent). It is known that the maternal deficit in UBE3A gene can have four genetic etiologies: deletions of the maternal 15q11–q13 region (approximatively 70% of cases), paternal uniparental disomic of chromosome 15 (5%), imprinting defects or mutations in UBE3A (10%). [15]

The main physiological pathways that explain the use of KD in patients with Angelman Syndrome involve deregulated GABAergic and dopaminergic neurons, abnormal mTOR signaling, excitation/inhibition imbalance, impairment in synaptic plasticity. Moreover, it has been tested on mice with Angelman Syndrome that KD can improve the hippocampal deficits by stimulating mitochondrial biogenesis. [16, 17]

KD and low-glycemic-index diets proved to have benefic effects in the treatment of drug-resistant seizures in patients with Angelman syndrome, improving the quality of life, cognition, sleep, mobility and, also, the gastrointestinal health. As KD is based on ketosis, it was wanted to know whether the administration of exogenous ketones would have a similar effect as KD. In 2016, a study showed that supplementation with exogenous ketones in mice improved memory, learning, motor coordination and synapse plasticity in mice with AS and was also. Therefore, the study suggested that supplementation with exogenous ketones can produce sustained ketosis and can ameliorate AS phenotype. [18]. Recently, a randomized, placebo-controlled, double-blind, crossover study is being conducted on pediatric population with AS (ages 4-11 years) to study the potential benefits of nutritional intervention with exogenous ketones (β-hydroxybutyrate). The study offers a unique design, providing data for the nutritional approach of patients with AS, helping them to overcome the disease. [19]

Glucose transporter type 1 deficiency syndrome (Glut1-DS)

Glucose transporter type 1 (Glut1) is a protein located in the blood–brain barrier and its main role is to assure the facilitative transport of glucose into the brain, an energy-independent process. Glut1 protein is encoded by SLC2A1 gene, which is located on chromosome 1p34.2. [20]

The glucose transporter type 1 deficiency syndrome (Glut1-DS) was described for the first time in 1991. As the understanding of the pathophysiology mechanism of this disease has significantly improved, the clinical features of Glut1-DS involve transient movement disorders, paroxysmal exertion-induced dyskinesia (PED), myoclonic astatic epilepsy (MAE), absence epilepsies particularly with an early onset absence epilepsy (EOAE), childhood absence epilepsy (CAE), episodic choreoathetosis and spasticity (CSE) and, also, focal epilepsy. [20]

KD, as precision medicine therapy should be started in the early stages of the Glut1-DS. A general review about Glut1-DS explained the mechanisms through KD can have beneficial effects. These mechanisms include stabilization of synaptic function, reduction in the generation of reactive oxygen species, boosting energy production, seizure reduction. Regarding the cognitive functions and neurodevelopment, there is not enough evidence for positive effects of KD. [21]

The classical KD assume that the serum ketones should be maintained around 3–4 mg/dl, but at this level, side effects such as fatigue or diarrhea might be intolerable. Therefore, in cases of noncompliance to KD or when the patients are reluctant, a modified KD like Atkins diet might be better option. The modified Atkins diet imply that 65% of total calorie intake is provided by high food fats, restricts carbohydrates at 10g/day (15g for adults), but does not restrict protein or calorie intake. Although there is enough data that suggests the benefits of the modified Atkins diet, its effect has not been tested on huge number of patients with GLUT1-DS [20, 21].

A recent observational descriptive study, published in March 2021, was conducted on 18 patients with GLUT1-DS (with or without mutation in SLC2A1) to investigate the beneficial effects of KD. The conclusions of the study were that KD, as well as the Modified Atkins Diet were effective for the patients enrolled in the study, from which six were SLC2A1 positive. Also, the most frequent side effects were constipation, hyperlipidemia and hypercalciuria. [22]

Regarding the genetic testing in GLUT1-DS, the SLC2A1 gene mutations are detected only in 70-80% of patients with the disease. For instance, in a Japanese study published in 2011, 33% of patients with clinical symptoms of GLUT1-DS, were not found to have mutations in exons of SLC2A1 gene. [23] Furthermore, in 2016 a study suggested that low cerebrospinal fluid glucose levels might be associated with pathogenic variants in SLC2A1, which also include the deep intronic variants. By this, the study encouraged the extension to non-coding regions, enabling the

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diagnosis of GLUT1-DS so that the patients can benefit from KD therapy. [24]

The idea that the absence of pathogenic mutation in SLC2A1 gene (common variation) does not exclude GLUT1-DS, was sustained by some case reports. For instance, in 2017 it was reported a novel heterozygous variant in the exon 5 of SLC2A1 gene, detected by Sanger sequencing.[25] Also, in children, there were found de novo and heritable paternal mutations of SLC2A1 gene, including amino acid insertion and point mutations. [26]

Recently, by whole genome-sequencing, rare homozygous missense variants were detected in SLC45A1 (second cerebral glucose transporter) which can cause epilepsy and intellectual disability. Regarding the treatment, KD might be effective in SLC45A1 mutations as well, but it needs further investigations. [26, 27]

Glycogen Storage Diseases (GSDs)

The hepatic glycogen storage diseases represent a group of diseases characterized by an inborn error of metabolism, more exactly abnormalities of the enzymes implicated in the degradation or the synthesis of the glycogen. [28]

The first GSD was described in 1929 by Edgar von Gierke. Until now, we know that there are about 16 GSDs (type 0 to type XV). All the types of GSDs are characterized by hypoglycemia due to an abnormal conversion of glycogen into glucose. [28]

Although the treatment recommendations in GSDs are based on the specific enzyme defect in each type, nutritional therapy remains the primary treatment for GSDs. The goal of managing all the hepatic GSDs is to prevent hypoglycemia as well as to minimize acidosis. High-carbohydrate diets could prevent fasting hypoglycemia, but the main issue is that increases glycogen storage and, also, the progression of muscular and cardiac manifestations. [28, 1]

Recently, there are several publications that emphasized the positive outcomes of KD in the management of GSDs. For instance, several case reports documented beneficial effects of KD in GSD III even since 2014. GSD III represents an autosomal recessive disease and is caused by the deficiency in glycogen debranching enzyme which is encoded by AGL gene. Clinically, GSD is characterized by affected liver, skeletal muscle, and heart. In 2019 a case report showed that Modified Atkins Diet was very efficient in treating a patient with GSD IIIa, improving quality of life, physical activity, cardiomyopathy, unlike other hyper carbohydrate diets. [29] Also, in 2020, a 4-year follow-up case report, concluded that KD is safe and could reverse the cardiomyopathy and improve quality of life in patients with GSD III. [30, 1]

GSD V, also called McArdle disease is caused by genetic defects of glycogen phosphorylase, a muscle specific isozyme, which lead to incapacity of glycogen to be converted in ATP in skeletal muscles. Patients with GSD V present exercise intolerance. In 2020, a pilot study that a modified KD (consisted of 75% fats and 10% carbohydrates) induces ketosis, leading to improvements in exercise tolerance and fatty acid oxidation. [31]

GSD VII, or the Tarui disease, is caused by a deficiency in muscle phosphofructokinase (PFKM) and is characterized by myalgia and exercise intolerance. The first study that showed a long-term effect of KD in this disease, was represented by a case report with 5 years follow up on modified Atkins diet. Published in 2020, the study concluded that KD alleviated the muscle symptoms, had beneficial effects on breathing and improved exercise performance and oxygen uptake. [32]

Pyruvate Dehydrogenase Complex Deficiency (PDCD)

The pyruvate dehydrogenase complex deficiency (PDCD) represents a rare neurodegenerative disorder which is caused by genetic alterations in any of the genes encoding the enzymes involved in the complex. The enzymes involved in the pyruvate dehydrogenase complex (PDHc) have the role of catalysts in the decarboxylation of pyruvate into acetyl-CoA. The pyruvate dehydrogenase complex deficiency (PDCD) is, actually, a metabolic disorder and clinically, is characterized by progressive neuromuscular and neurological degeneration and also, lactic acidosis. [1]

Ever since 1976, KD was proved to be beneficial in pyruvate dehydrogenase complex deficiency (PDCD). Since then, the efficacy of KD has been shown by several case reports. [1]

Recently, an article released in October 2020 concluded that identifying the causing mutations for PDCD and understanding the structural and functional mutant variants, would allow to have an insight of the clinical phenotype and also to select the best option for treatment. The study was conducted on thirteen Portuguese patients and the mutations found among them were in PDHA1, PDHX and DLD genes. All the patients received treatment which included ketogenic diet, antiepileptic drugs and also thiamine supplementation. Three patients with PDHX mutations and three patients with PDHA1 mutations clearly showed beneficial effects following KD. [33]

Conclusions

KD has an important role in the treatment of epilepsy, Alzheimer's disease, Angelman syndrome, GLUT1-DS, GDSs and PDCD. As there is evidence regarding the benefits of KD, medical practitioners should take into consideration KD as adjuvant therapy for these disorders. Also, as the response to KD is highly correlated with genetic variants, implementation of nutrigenomics in precision medicine would be the key for the best management of the patient.

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Correspondence to:
Meda-Ada Bugi, PhD student
"Victor Babes" University of Medicine and Pharmacy
"Louis Turcanu" Emergency Hospital for Children
Iosif Nemoianu Street, No 2,
Timisoara, Romania
E-mail: nutritiapentrutoti@gmail.com
Mobile: 0040 752 199 354

DIAGNOSTIC AND THERAPEUTIC CHALLENGE IN A CHILD WITH OSTEOGENESIS IMPERFECTA-CASE REPORT AND LITERATURE REVIEW

Maria Daniela Trăilescu[1,2], Adrian Ionel Pavel[1,2], Alexandru Mircea Pop[1]

Abstract

The treatment of fractures in children with osteogenesis imperfecta depends on several factors: the patient's age, the type and location of the fracture, the degree of fracture displacement and the type of osteogenesis imperfecta. Operative management varies and evidence is limited. We present a case report of operative treatment in an 8-year-old boy, admitted to our hospital within two years with displaced femoral shaft fractures. The past medical history was significant for multiple fractures managed conservatively. During the first hospitalization, after osteosynthesis of the right femoral shaft fracture, we extended the investigations for bone fragility. The history, clinical signs, low bone mineral density (BMD) level and genetic test, all led to the diagnosis of osteogenesis imperfecta type IV. After 1 year and 3 months from the first osteosynthesis with titanium elastic nails the patient returns to our emergency department with left displaced femoral shaft fracture. This time we stabilized the shaft fracture with the same type of osteosynthesis with elastic titanium nails. At two years after surgery, we found no inequalities of the lower limbs or joint stiffness.

Keywords: minimally invasive osteosynthesis, titanium elastic nails, genetic test, osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI) is a group of genetic disorders characterized by bone fragility. The most well-known consequence of OI is the occurrence of multiple and recurrent fractures without major trauma. Since 1979, the classification by Sillence is the most widely used and it is based on modes of inheritance, radiological and clinical findings and includes OI types I (mild non-deforming), II (perinatal lethal), III (severe), IV (moderate to severe) [1]. It has been known for three decades that the majority of individuals with OI have mutations in COL1A1 or COL1A2, the two genes coding for collagen type I alpha chains, but in the past 10 years defects in at least 17 other genes have been linked to OI [2]. There's no cure for OI and the management is multidisciplinary. The goals of therapy are to reduce fracture rate, prevent long bone deformities, minimize chronic pain, and maximize functional capacity [3]. Orthopedic treatment is part of the multidisciplinary approach providing correction of long bone bowing, rotational malalignment, angular deformity and preventing fractures [4–6]. Fractures in OI are treated with orthopedic procedures appropriate for the type of fracture and the age, the evolution towards healing of the fractures being also dependent on the medical treatment of the bone fragility. The aim of this paper is to present our experience in a child late diagnosed with osteogenesis imperfecta.

Material and method

We present the case of a boy of 8 years 3 months old (height 91 cm, weight 20.1 kg) presented in our emergency room with acute pain and functional failure of the right leg, after falling from roughly the same height. Prior to the clinical examination, the patient's mother informed us that in the last three years the boy had multiple non-displaced fractures involving the right clavicle, bilateral radius - buckle fractures, radial head and which fractures had been treated conservatively. Even in the last year, before this presentation in our hospital, at the age of 7 years, he was treated conservatively with casts immobilization for similar proximal tibial fractures, produced by falling from the same height, fractures occurring at 6-month intervals. The only radiographs with the previous child's fractures, owned by the patient's mother and presented to us, confirmed fractures of the proximal metaphysis of the bilateral tibia and plastic deformations of the tibia underlying the fractures (Figure 1).

Examination of the right lower limb revealed its shortening by 3 centimeters, obvious deformation at the level of the right thigh with external rotation of the lower extremity. At the clinical examination we did not find any deformities in the segments affected by the previous fractures. On palpation we found the interruption of the bony continuity of the right femur and bone crackling.

His radiographs revealed displaced right femoral shaft fracture and moderate osteopenia (Figure 2a). The complete blood count of the child was unremarkable. All usual parameters: white blood cell count, red blood cell count, platelet count, hemoglobin and hematocrit, were in normal limits. Two titanium elastic nails (TEN) of 3mm diameters were inserted retrograde through two distal short incisions, proximal to the distal right femoral growth plate (Figure 2 b). The postoperative evolution was favorable with analgesic medication and cast immobilization maintained for 30 days.

[1]Department of Pediatric Surgery and Orthopedics, Emergency County Hospital, Arad, Romania
[2]Faculty of Medicine, "Vasile Goldiş" Western University of Arad, Romania
E-mail: trailescumaria@yahoo.com, adipavel72@yahoo.com, alexanpop@yahoo.com

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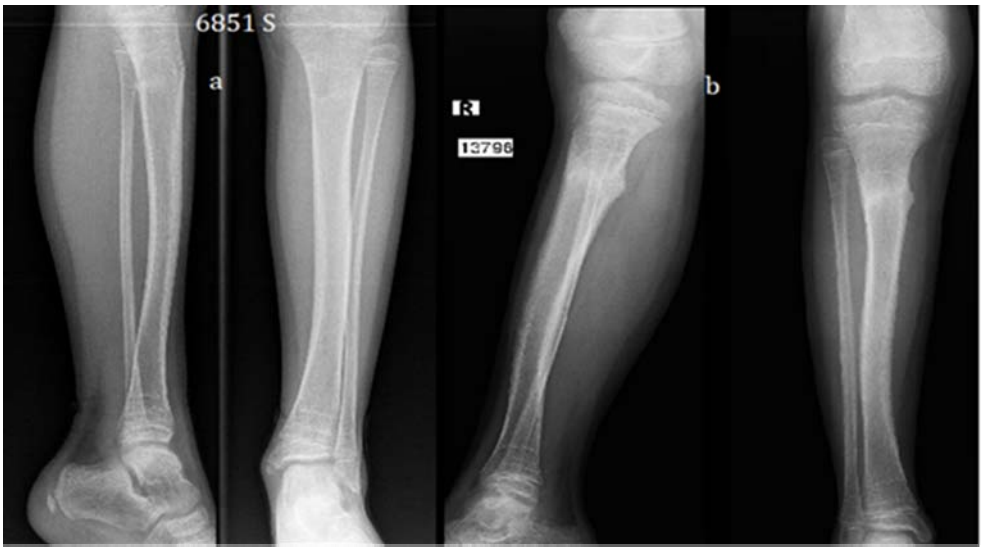

Fig.1. Fractures of the proximal metaphysis of the bilateral tibia (left tibia - a, and right tibia - b) and plastic deformations of the tibia underlying the fractures.

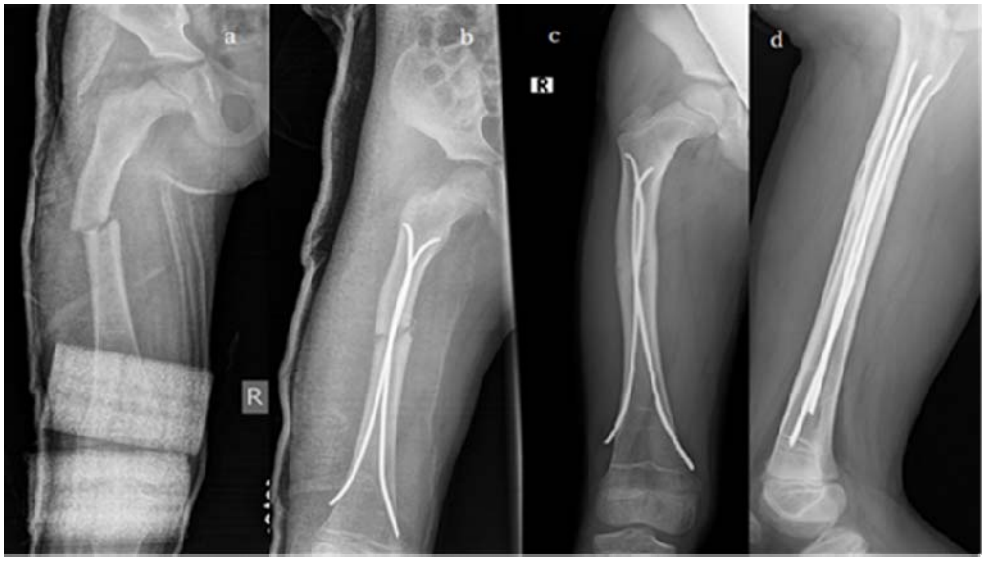

Fig.2. Radiological aspect of right femoral shaft fracture preoperatively (a), immediately after osteosynthesis with TEN (b) and postoperatively at 9 months (c, d).

Based on the medical history, clinical and radiographic data, a provisional diagnosis of an osteogenesis imperfecta was made.

Due to the stature-weight retardation (waist age of 5 years and 7 months) and the multiple fractures existing in the patient's past, we extended the investigations. Serum creatinine, magnesium, PTH, TSH, and free thyroxine were normal. Serum vitamin D levels and gonadotropin levels identified severe hypovitaminosis D (21 nmol/L) and growth deficit due to low growth hormone level (0.05ng/mL). The bone osteodensitometry of the lumbar spine (L1-L4) made with GE Lunar DPX (GE Healthcare) at dose 5μSv allowed the calculation of the T score (bone density relative to that of a healthy patient of the same age and sex) and the diagnosis of imperfect osteogenesis, the T score being of -3.02 (low bone density) in the presence of several fractures in the antecedents.Considering the importance of the genetic test to confirm the diagnosis of imperfect osteogenesis type, it was recommended for the patient. The sequencing was performed in collaboration with the Center for Genomic Medicine Timisoara, research laboratory, using the Illumina TruSight One Sequencing Panel kit, a large panel that includes 4813 genes.

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Mean Region Coverage Depth	Uniformity of Coverage (Pct > 0.2*mean)	Target Coverage at 1X	Target Coverage at 10X	Target Coverage at 20X	Target Coverage at 50X
110.8X	97.5%	99.9%	99.2%	98.0%	90.6%

Fig. 3. Enrichment sequencing report - Coverage level for target nucleotides in the patient sample

The next generation sequencing technique was used using the MiSeq Illumina platform, which allows the analysis of coding sequences in genomic DNA. In the first stage, the fragmentation of the genomic DNA was performed, followed by the amplification of the coding sequences and the generation of libraries using the Illumina TruSight One Sequencing Panel kit. The coverage level for the target nucleotides in the analyzed sequences is shown in Figure 3.

End-to-end bioinformatics algorithms have been implemented, including nitrogen base alignment, primary filtration of lowquality readings and probable artifacts and annotation of variants, using Isis (Analysis Software) 2.5.2.3; BWA (Aligner) 0.7.9a-isis-1.0.1; SAMtools 0.1.18 (r982: 295); GATK (v1.6-23-gf0210b3) 1.7. The data analysis was performed at the level of current knowledge, using the UCSC Genome Browser, OMIM (Online Mendelian Inheritance in Man), DGV (Database of Genomic Variants) databases. All variants that may cause diseases reported in HGMD®, ClinVar (class 1), as well as all variants with a minor allele frequency (MAF) of less than 1% in the ExAc database were considered.

The patient began treatment with subcutaneous injections with Somatotropin 0,025 mg/kg/day, a regular intake of calcium (1000 mg/day), and an adequate intake of vitamin D (1000 IU/day).

Due to low bone density, we allowed the progressive loading of the right lower limb after one month from osteosynthesis.

At 9 months postoperative, radiological healing of the fracture stabilized by osteosynthesis with titanium elastic nails was confirmed, healing without hypertrophic osseous callus (Figure 2c, 2d). We observed a decrease in the degree of osteoporosis and a general mineralization of the femur with the thickening of the femoral cortex. The titanium elastic nails removal was performed 1 year postoperatively and we recommended limiting physical activity due to the bone fragility characteristic of the disease.

After 1 year and 3 months from the first osteosynthesis surgery (3 months after the removal of titanium elastic nails from the right femur) the patient returns to our emergency department with left displaced femoral shaft fracture, produced by falling from bed (Figure 4 a, 4b). Two titanium flexible nails of 3,5 mm diameters were inserted retrograde through two distal short incisions, proximal to the distal left femoral growth plate (Figure 4c).

The postoperative evolution was favorable with radiological healing of the fracture at 9 months postoperative (Figure 4d). The titanium elastic nails removal was performed 1 year postoperatively

The patient continued treatment with subcutaneous injections with Somatotropin 0,025 mg/kg/day, a regular intake of calcium (500 mg/day), and an adequate intake of vitamin D (1000 IU/day).

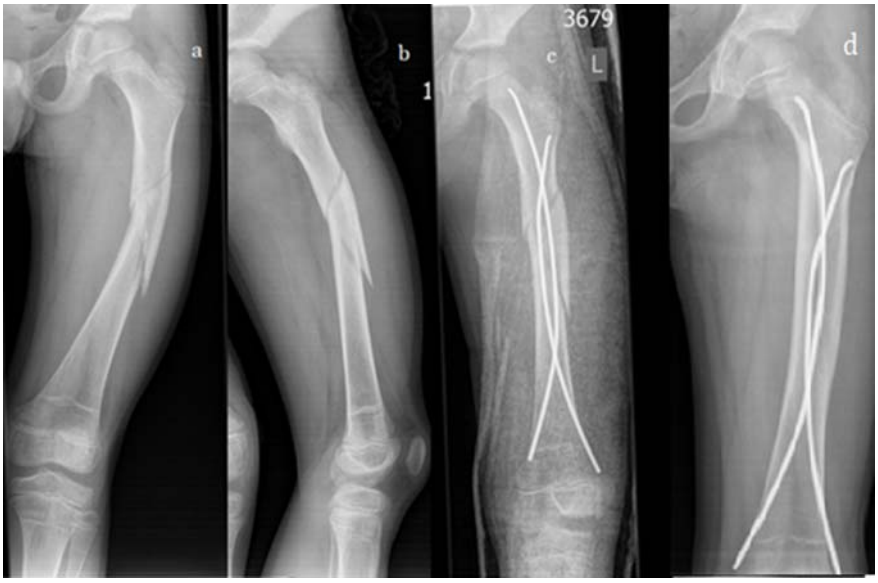

Fig.4. Radiological aspect of left femoral shaft fracture preoperatively (a and b), immediately after osteosynthesis with TEN (c) and postoperatively at 9 months (d).

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Discussion

Originally named "osteomalacia congenita," osteogenesis imperfecta was first medically described by Ekman in 1778 and classified 200 years later by Sillence [1].

The term OI encompasses a broad range of clinical presentations that may be first apparent from early in pregnancies to late in life, reflecting the extent of bone deformity and fracture predisposition at different stages of development or postnatal ages [7]. Depending on the age of presentation, OI can be difficult to distinguish from some other genetic and nongenetic causes of fractures, including nonaccidental injury [8]. In childhood, in the absence of a positive family history, most children newly diagnosed with OI are identified after one or more fractures. The differential diagnosis for frequent fracture in childhood is relatively limited and includes both inherited and acquired conditions. Hypophosphatasia, osteopetrosis with renal tubular acidosis, hypophosphatemic osteomalacia and nonaccidental injury should be considered [9-11].

Undisplaced fractures are treated by standard orthopedic measures appropriate for the age of the patient and the type of fracture.

The purpose of the surgical treatment of fractures is the elimination and prevention of fragments displacement, pain reduction, and immobilization terms reduction with the possibility of early activation. The basic principle of surgical treatment is restoring limb anatomy and intramedullary splinting at the maximum extent of the bone. The use of multiple long bone osteotomies secured with intramedullary rod fixation is the treatment principle described by Sofield in the 1950's and this continues to be used in the present [12-15].

The literature describes using the following structures for fixing bone fragments: non-telescopic (Rush nail, Kuntscher's pin), titanium elastic nails (TEN), Kirchner pins, telescopic internal fixation devices (Bailey–Dubow, Sheffield, Fassier–Duval rods), plates, and external fixation devices [16, 17].

In children, telescopic rods such as the Fassier-Duval and the Sheffield telescopic intramedullary rod system have become known and accepted, although reoperation and complication rates are high [18, 19].

The current methods of orthopedic surgical treatment described and reported in the literature in fractures children with osteogenesis imperfecta refer especially to osteogenesis imperfecta type I [13, 15-17].

The use of TEN may be considered as a less invasive approach compared to telescopic nail surgery, however only temporarily, as it will still most probably require a surgical revision a few years down the line, in moderate or severe osteogenesis imperfecta types [20].

Other authors consider that flexible intramedullary nails have specific contraindication in growing OI children although they can be used in young OI adults with good cortical bone [21].

Like other authors, we consider the selection of surgical techniques is dependent on surgeon experience, type of OI and patient function, and availability of specific instrumentation [22].

Because our department does not have telescopic rods, the only intramedullary rods we can use in children are the titanium elastic nails and that is why we used them in the osteosynthesis of the case presented. We chose this type of osteosynthesis for the minimally invasive nature of the surgical technique and for the stability of site fracture produced by the intramedullary insertion of the curved titanium nails. Although opinions are divided, by the favorable evolution of the case presented, we demonstrated that the minimally invasive osteosynthesis with titanium elastic nails is the optimal method of surgical treatment for femoral shaft fractures in children with osteogenesis imperfecta type IV.

We have shown that flexible intramedullary rods have no specific contraindications in raising OI type IV children.

In childhood, the clinical examination is the key first step in evaluation of the child with suspected OI. The evaluation requires familiarity with the natural history and variation in clinical presentation of OI, particularly in the infant or toddler [23]. Mild forms of OI may go unnoticed by even experienced general clinicians. Referral to an experienced physician familiar with the range of clinical expression of OI is relatively inexpensive in comparison to laboratory testing and may be all that is necessary to secure the diagnosis [7, 24, 25].

The peculiarity of this case consists in the late diagnosis of imperfect osteogenesis in a child who until the presentation in our service had a suggestive history for this disease and suggestive radiological signs such as tibial fractures accompanied by plastic deformities. Based on the medical history, clinical and radiographic data, a provisional diagnosis of an osteogenesis imperfecta was made but was difficult to differentiated a form a mild form of OI or OI type IV (with white sclerae) from non-accidental injury, juvenile idiopathic osteoporosis or the some other genetic and nongenetic causes of fractures [7,26 -29].

Therefore, we recommended additional investigations that confirmed the type of osteogenesis imperfecta, very important for the treatment, monitoring and prognosis of the patient.

By sequencing analysis using a large panel of 4813 genes (Illumina TruSight One Sequencing Panel), a variant, in heterozygous status, was detected in the COL1A2 gene located on chromosome 7q21.3. The missense variant c.1009G> A, shows coverage on the spot 150X variant. This sequence change replaces glycine with serine at codon 337 of COL1A2 protein (p.Gly337Ser). The glycine residue is highly conserved and there is a small physicochemical difference between glycine and serine. This variant is not present in the bases of population data (ExAC, GnomAD without frequency). This variant has been reported in several individuals affected by imperfect osteogenesis types I, III and IV [30-35].

Pathogenic variants in heterozygous status in the COL1A2 gene have been associated with several phenotypes, of which osteogenesis imperfecta type IV (OMIM 166220) is the most relevant for the patient [36].

In our country, especially in rural areas, parents find it difficult to accept the existence of a rare disease and special treatment for these patients, hoping that these fractures occur only due to carelessness or physical activity characteristic of age.

In the present case, the patient's parents were compliant, cooperative and understood the importance of continuing the treatment instituted in hospital for the correction of hypovitaminosis D, for the recovery of growth retardation and calcium deficiency.

Conclusions

Diagnosing and treating a child with imperfect osteogenesis requires further investigation and a multidisciplinary team approach for a good therapeutic outcome. The treatment of fractures that occur on the basis of bone fragility, characteristic of imperfect osteogenesis, is not standardized and continues to be a challenge for the orthopedic physician. In case of patients with multiple fractures in the medical history, young orthopedic surgeons on duty and emergency department physicians should take these symptoms seriously and be highly suspicious of OI. Osteosynthesis with titanium elastic nails in children with osteogenesis imperfecta type IV and femoral shaft fractures can be a good solution in association with a suitable treatment of bone fragility. Genetic counseling plays an important role in this case because the risk of developing the disease in another pregnancy or other children of the patient's parents is theoretically 1%, due to a possible gonadal mosaicism but the risk of developing the disease in the patient's descendants is 50%, regardless of gender.

Conflicts of Interest: The authors declare no conflict of interest

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Correspondence to:

Maria Daniela Trăilescu

Department of Pediatric Surgery and Orthopedics,

Emergency County Hospital, Arad, Romania

Andreny Karolly Street, No.2 – 4,

Arad, 310037, România

Phone: +40-257- 220 000

Email: trailescumaria@yahoo.com

APPENDICITIS IN PRESCHOOL CHILDREN - A CONTINUING CLINICAL CHALLENGE

Diana Benchia[1], Klara Sârbu[2], Ștefan Popa[1,3], Ioan Sârbu[1,3], Irene Paula Popa[4], Carmen Iulia Ciongradi[1,3]

Abstract

Introduction: Acute appendicitis is one of the most common causes of acute abdominal pain in pediatric population. The condition most commonly requiring emergent surgery in children still retains its diagnostic challenges, especially in preschoolers, despite significant advances in therapeutics and medical imaging, due to the variety of symptoms and the rapid development of complications. The purpose of this study is to determine the prevalence of appendicitis in preschool children, the preferred route of management, as well as to comparative evaluate the data obtained from children of other ages, in terms of time from admission to surgery, length of surgery and length of hospital stay. Materials and Methods: Retrospective analysis of children admitted with the diagnose of acute appendicitis at Emergency Children Hospital „Sf. Maria" Iasi between January 2012 and July 2018 and analysis of demographics, preoperative, intraoperative, and postoperative data of three age groups: preschool (less than 6 years of age), school children (6 to 11 years) and teenager (12-17 years). Results: Of 2165 patients selected for this study, 5.35% patients were preschool children, with a gender distribution not significantly different respect to the other two groups. From 99 patients receiving the final diagnosis of appendicitis in the preschool group, 95 were operated, mainly open (78 cases). The surgery was done in the first day after admission in 59.8%, with a longer duration of surgery, both in open and laparoscopic appendectomy, respect to the other two groups. In the preschool group, the frequency of peritonitis was much higher compared to other ages and the hospital stay was longer. There was no link between a longer time to appendectomy and poorer outcomes. Conclusions: Despite progresses in diagnose and treatment, acute appendicitis in preschool children is a continuing challenge.

Keywords: preschool children, acute appendicitis, peritonitis, laparoscopic surgery

Introduction

First described in 1886 by Reginald Fitz, acute appendicitis is one of the most common surgical causes of acute abdominal pain in pediatric patients [1, 2]. The peak incidence is considered between the first and the second decade of life, albeit it is rarely considered in children younger than five years of age [3]. Unlike school-aged and adolescent children, younger children do not exhibit the classic clinical picture of anorexia and peri-umbilical pain that migrates to the right lower quadrant, followed by nausea or vomiting and fever [4].

Despite significant advances in therapeutics and medical imaging, the condition most commonly requiring emergent surgery in children still retains its diagnostic challenges. The non-specific clinical presentation of acute appendicitis in preschool children is thought to be responsible for diagnosis delay and therefore for a higher rate of complications [5].

The purpose of this study is to determine the prevalence of appendicitis in preschool children, the preferred route of management, as well as to evaluate the time from admission to surgery, the length of surgery and hospital stay. Furthermore, the aim is to analyze and compare the results with the data found in the literature.

Material and method

A retrospective analysis was carried out for all children less than 18 years old with the main diagnosis of acute appendicitis, using the International Classification of Diseases (ICD-10) codes for appendicitis. Between January 2012 and July 2018, a total of 2165 patients admitted at the "Sf. Maria" Emergency Clinical Hospital for Children, Iași, Romania with acute appendicitis were charted and retrospectively reviewed. Demographics, preoperative, intraoperative, and postoperative data were collected from patient's medical records and added to Microsoft Excel for further analysis. The patients presented with common symptoms of acute appendicitis, including right lower quadrant pain, fever, anorexia, nausea, and vomiting.

The biological findings, such as leukocytosis and elevated C-reactive protein, were taken to consideration during the diagnosis of the selected patients.

[1] „Sfânta Maria" Emergency Children Hospital Iași
[2] Klara Sârbu MD Office, Târgu-Neamț, Neamț
[3] „Grigore T. Popa" University of Medicine and Pharmacy Iași
[4] „Prof. Dr. George I.M. Georgescu" Institute of Cardiovascular Diseases Iași

E-mail: diana_benchia@yahoo.com; paula.cioban@gmail.com; klarasarbu@yahoo.com; dr_popastefan@yahoo.com; dr.sarbu@gmail.com; iuliaciongradi@yahoo.com

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The particular focus of this study was on the group of preschool children, which were defined by < 6 years of age. For a better comparison, the rest of the patients were divided into two further groups of age, from 6 – 11 and from 12 – 17, representing roughly the school children and "teenager".

The age at diagnosis, management, duration of each type of surgery, the duration of hospital stay, and the meantime between the admission and the surgery for each subgroup were obtained and analyzed.

Results

A total of 2165 patients were selected for this study, based on all inclusion criteria. 116 patients were preschool children, having an age less than 6 years. The group of 6 – 11 years had 721 patients, while the group 12 – 17-year-old ones was represented by 1328 patients. This makes the group of 12 – 17 years of age the most represented with a percentage of 61,3% and the group of preschool children the least represented with a percentage of 5,35% of all registered cases. (Table I)

When it comes to gender, we observed an almost even distribution, with no statistical significance differences.

In the group of preschool children, 73 patients were diagnosed with appendicitis on admission. The group of 6 to 11 years included 630 patients that were diagnosed as such. The oldest patients, the group of age between 12 and 17 years had 1028 cases of appendicitis, according to the ICD-10 on admission. This led to a distribution of 3.37% for the age 0 – 5 years, 29% for the age 6 – 11 years, and 47.4% for the age of 12 – 17 years.

The diagnose of appendicitis was further divided into 3 subgroups: acute appendicitis with peritoneal abscess, acute appendicitis with generalized peritonitis, noncomplicated appendicitis

In total there were 99 cases with final diagnosis of appendicitis in preschool children. 31 of them had acute appendicitis with peritoneal abscess, 65 patients had acute appendicitis with peritonitis and only 3 had acute appendicitis. The group of 6 to 11 years included 644 with final diagnosis appendicitis, 421 with noncomplicated appendicitis, 159 with acute appendicitis with peritoneal abscess, and 64 with acute appendicitis with peritonitis. The oldest patients, the group of age between 12 and 17 years had 1194 cases of appendicitis, 706 of them had noncomplicated appendicitis, 337 had acute appendicitis with peritoneal abscess and 151 had acute appendicitis with peritonitis (Figure 1).

AGE (y)	NUMBER OF CASES	%
0-5	116	5,35%
6-11	721	33,5%
12-17	1328	61,3%
Total	2165	100,0%

Table I. Number of cases admitted as appendicitis

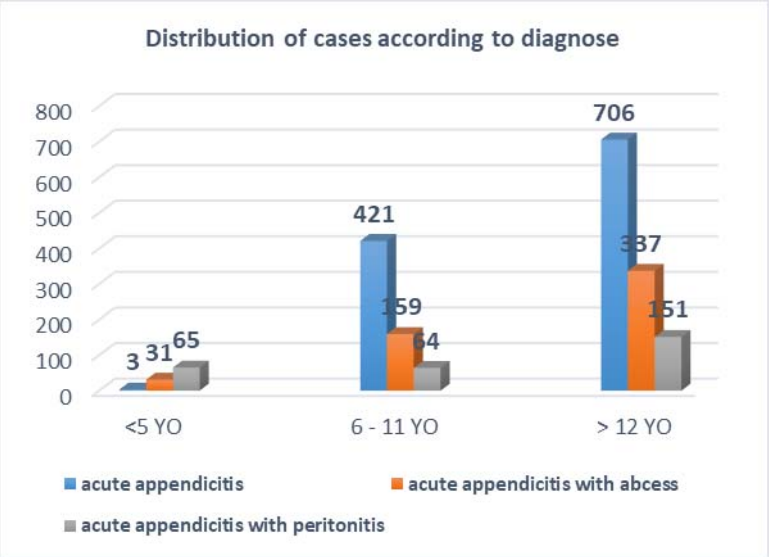

Fig. 1. Distribution of cases according to the type of appendicitis

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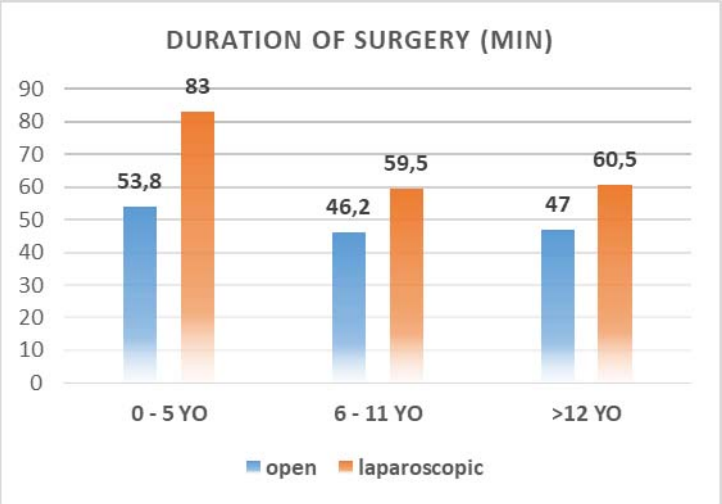

Fig. 2. Duration of surgery

Group of age	Open appendectomy	Laparoscopic appendectomy
0-5	78	17
6-11	463	114
12-17	837	229
Total	1378	360

Table II. Type of surgery

AGE (y)	MEAN DURATION OF HOSPITALIZATION (d)
0-5	**8,14**
6-11	**5,45**
12-17	**5,79**
Total	**5,81**

Table III. Mean duration of hospitalization

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Out of a total of 2165 patients included in this study, 1937 had a final diagnosis of appendicitis, and 1738 of them underwent surgery. The surgical interventions were divided into open appendectomy (OA) and laparoscopic appendectomy (LA). All patients with surgical intervention received also medical treatment, consisting mainly of antibiotic coverage.

In the group of preschool children, we had 95 surgical interventions. The vast majority of them were OA with a count of 78 and 17 patients had LA. The group of 6 to 11 years included 463 OA and 114 LA. And the group of age between 12 and 17 years had 229 LA and 837 OA (Table II).

Out of 2165 patients from the study, 228 had a different final diagnosis such as gastro-enterocolitis, mesenteric lymphadenitis, Meckel diverticulitis, urinary tract infections, and intussusceptions. Out of 1937 who were diagnosed with appendicitis, 199 received conservative, non-surgical management.

Due to invalid values during data analyze look over, the meantime between the admission and the surgery of the patient, compared first by each group, then focused on the group of preschool children, a certain number of cases had to be excluded. The vast majority of patients (61 out of 95) between 0 – 5 years of age were operated on the same day of admission. This represents a distribution of 64,2% of all patients in this group. 26 patients (27,3%) received surgical intervention one day after being admitted to the hospital and 8 patients (8,5%) underwent the intervention two or three days after admission.

Considering the duration of surgery, data from only 1153 patients were obtained. We observed that the group of preschool children had the longest mean duration of all groups, as well as in OA as in LA. With a total of 48 minutes operation time in average in OA, the group of 6 – 11 years old patients and the group of 12 – 17 years old were slightly below average with 46,2 minutes (6 – 11 years) and 47 minutes (12 – 17 years). The group of 0 – 5 years old on the other hand exceeded clearly the total mean duration, with an average of 53,8 minutes per OA surgery. In LA, the mean duration in 6 – 11-year-old patients was with 59,5 minutes, almost similar with the total average time of the group of 12 – 17-year-old with 60,5 minutes, clearly lower than the total average time of 64,8 minutes of surgery, while just like in the case of OA, the meantime of surgery in the patients below 6 years exceeded the total average time with 83 minutes per surgery on average (Figure 2).

A look at the mean duration of hospital stay for the patients involved in this study, shows a higher mean time, with 8,14 days for the group of preschool children than the others. The group of 6 -11 and 12 – 17 had a comparable mean duration of hospital stay with 5,45 days for the group of 6 – 11 and 5,79 days for the group from 12 – 17 years of age. This resulted in a total mean duration of hospital stay of 5,81 days. (Table III)

Discussion

Acute appendicitis is a relatively uncommon illness in children under the age of six, and it is frequently detected late in this age group [6]. Indeed, appendicitis diagnosis in preschool children is challenging, with a significant probability of misinterpretation due to atypical clinical symptoms and the trivialization of abdominal pain [7,8]. The clinical manifestation is frequently variable, and the diagnosis may be misinterpreted by other medical conditions. This observation is consistent with the findings of our study, which show that appendicitis is uncommon in preschool children and peaks during adolescence. In this study, 116 preschool children with suspected appendicitis were involved, with 99 receiving a final diagnosis of appendicitis. Preschool children were in the minority when compared to the other groups, with 12–17-year-olds constituting the vast majority.

The differential diagnosis of acute appendicitis includes gastro-enterocolitis, mesenteric lymphadenitis, Meckel diverticulitis, inflammatory bowel disease, right lower lobe pneumonia, urinary tract infections, and intussusception, particularly in young pre-verbal children [9].

Misdiagnosis in preschool-age children ranges from 19 to 57 percent due to its atypical clinical features, resulting in a high rate of complications [10,11]. The high prevalence of complicated appendicitis in young children is due to a combination of factors. The inability of a young child to communicate with his or her parents, as well as atypical presentation and other associated illness, may cause a delay in diagnosis [12–14]. In these young patients, anatomic immaturity and a lack of an adequate omental barrier may contribute to the rapid progression to perforation and peritonitis. Perforation may already be present in 30 percent to 75 percent of children when the diagnosis is made, with young children being at higher risk [13]. This was demonstrated in our study, which found a high rate of appendicular abscess (31%) and peritonitis (66%). Since both, acute appendicitis with peritoneal abscess and acute appendicitis with peritonitis, are defined as complicated appendicitis, this gives us high percentage of complicated appendicitis in the group of preschool children, underlying the importance of this pathology in the particular group of lower age children.

In the pediatric population, complicated intraabdominal infections are most commonly caused by appendix perforation and may be one of the leading causes of morbidity [15, 16]. A complicated appendicitis usually requires a significantly longer hospital stay. A look at the average length of hospital stay for the patients involved in this study, reveals that the group of preschool children has had a higher mean time, with 8,14 days, than the others (5,45 and 5,79).

In terms of surgery duration, we observed that the preschool age group had the longest mean duration of all groups, both in OA and LA, possibly due to complicated appendicitis and anatomical particularities [15,17].

This study also looked at the time it took from presentation to surgery. Despite the fact that the majority of

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patients aged 0 to 5 years were operated on the same day of admission or one day later, there was no link between a longer time to appendectomy and poorer outcomes in terms of total time of surgery procedure and length of hospital stay. Recent studies investigating the time to appendectomy relative to the onset of symptoms found no association, implying that the timing of appendectomy has no effect on adverse event rates, that appendectomy in the middle of the night is no longer justified, and that appendectomy should be considered an elective procedure once antibiotic therapy has been initiated [18-21].

Conclusion

These study results point out that, despite major breakthroughs in treatments and medical imaging, diagnosing appendicitis in preschool children remains challenging. Despite the low number of incidences, an early diagnosis of acute appendicitis in preschool children is mandatory. It requires a high level of suspicion, a thorough medical history, and periodic physical examinations, due to the variety of symptoms and the rapid development of complications.

Conflicts of Interest: The authors declare no conflict of interest.

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Correspondence to:

Ioan Sârbu

„Grigore T. Popa" University of Medicine and Pharmacy
16 University Street, 700115
Iași, Romania

Phone: +40745760716

Email: Dr.sarbu@gmail.com

INCIDENCE OF ASSOCIATED TRAUMATIC INJURIES AND COMORBIDITIES IN RELATION TO LONG BONE FRACTURES IN CHILDREN – PROSPECTIVE ANALYSIS OF 291 CASES

Maria Daniela Trăilescu[1,2], Adrian Ionel Pavel[1,2], Alexandru Mircea Pop[1]

Abstract

Background and objectives: The study's objective was to investigate the incidence of associated traumatic injuries and comorbidities in relation to long bone fractures among children aged 5–18 years. *Materials and Methods:* The study population consists of children aged 5–18 years and included 291 patients with long bone fractures hospitalized and operated in a single institution, over the period 2015–2018. *Results:* Our results show an increased incidence of traumatic injuries associated with long bone fractures in children, as well as an increased prevalence of comorbidities. Compared to the number of long bone fractures, the associated injuries were found in 85.22% of cases. Compared to the number of patients studied, the percentage of comorbidities in the group studied is 24.74%. Iron deficiency anemia, obesity and ADHD syndrome, sequelae of rickets and insulin-dependent diabetes mellitus were the most common comorbidities. *Conclusions:* The myth that the fracture in children occurs in a healthy field, without comorbidities, raises questions in the case of these concrete data. Thus, it is necessary to diagnose the injuries associated with fractures in children, as well as comorbidities by correct historical clinical and paraclinical examinations that are extremely important in the preoperative evaluation of the patient and in the subsequent evolution towards healing.

Keywords: children; fractures; injuries; comorbidities

Introduction

Commonly encountered in pediatric traumatic pathology, the incidence of fractures in children has become high in the conditions of modern life, where road accidents, sports and play occupy the first place and are of particular interest to children.

It is realistic to accept that "all children are sometimes prone to accidents" as Gusstafson states [1] and as medical practice demonstrates daily. Pediatric fractures account for approximately 25% of all pediatric traumatic injuries [2,3]. According to a recent report, trauma is the 28th leading cause of death globally [4].

Various studies have identified the young population as the most vulnerable group affected by fall-related injuries, with boys being affected twice as often as girls.

Falling from a height has also been recognized as one of the most common mechanisms of trauma in low-income countries [5].

Some studies report that the risk of having a fracture during childhood is almost 50% for boys and 30% for girls [6-14]. Recent studies [15-17] have evaluated and established that attention deficit hyperactivity disorder (ADHD) is a risk factor for fractures in children with this condition in which the daily condition is permanently characterized by attention deficit and inadequate hyperactivity or impulsivity, which affects all aspects of social life.

Our study aims to investigate the prevalence of associated traumatic injuries and comorbidities in relation to long bone fractures among children aged 5–18 years hospitalized in our department which required surgery to stabilize the long bone fractures.

Material and method

This is a prospective study that aims to analyze and investigate the prevalence of associated injuries and comorbidities in relation to long bone fractures among children aged 5–18 years. The study population consists of patients with long bone fractures hospitalized and operated in a single institution.

The study was conducted in accordance with the ethical principles from the Declaration of Helsinki and it respects ethical demands that are required by research with human subjects. Before starting the study, approval from the Human Research and Ethics Committee of the "Vasile Goldiș" Western University of Arad and from the Emergency County Hospital, Arad, Romania, was obtained (number of approval 2/19.07.2018 and 128/7.12.2018).

The study was carried out at the Pediatric Surgery and Orthopedics Department, Emergency County Hospital, Arad, Romania, between 2015-2018, and included 291 children with long bone fractures hospitalized for surgical treatment.

All patients and/or parents of patients were interviewed for personal medical history of the child, family history, the context of traumatic injury. In addition, imaging scans focusing on obvious traumatic injuries were performed to establish the definite diagnosis of traumatic injuries, supplemented by laboratory tests.

[1]Department of Pediatric Surgery and Orthopedics, Emergency County Hospital, Arad, Romania
[2]Faculty of Medicine, "Vasile Goldiș" Western University of Arad, Romania
E-mail: trailescumaria@yahoo.com, adipavel72@yahoo.com, alexanpop@yahoo.com

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For all the cases studied we used coding related to fractures, classified by ICD-10 (The International Classification of Diseases - The tenth Revision), of humerus (S42.2 - S42.4, S42.7), femur (S72.0 - S72.9), radius and /or ulna (S52.0 - S52.9) and tibia and /or fibula (S82.1–S82.9). For all associated injuries and/or comorbidities we used the same coding classified by ICD-10.

2.2. Identification of the type of fracture

X-rays of the limb with clinical signs of fracture, anteroposterior and lateral views, were performed in all patients studied. Based on the radiological examination, the type of fracture and the indication for treatment were established. Radiography of other anatomical regions, as well as ultrasound or CT examination were indicated in polytrauma patients. The obtained results allowed the identification of lesions associated with fractures of long bones in children.

2.3. Laboratory investigations

The preoperative biological balance for all cases with surgical indication complied with the protocol adopted at the hospital level: complete blood count, urea, creatinine, blood glucose, transaminases, urine examination. In patients with associated traumatic injuries or in polytrauma patients, the biological balance has been extended, including blood group, Rh, bleeding time (BT), clotting time (CT), prothrombin time (PT), activated thromboplastin time (aPTT) and thrombin time (TT).

Results

Clinical examination of patients with diaphyseal fractures revealed clinical signs of probability in all patients, while clinical signs of certainty were identified in only 251 cases. In 40 cases, the externalization of the fractured fragment by the solution of skin continuity established the definite diagnosis of open fracture and made it unnecessary to perform local examination maneuvers, which would have accentuated the suffering of young patients. From a radiological point of view, the diagnosis of diaphyseal fractures was made in 100% of cases, without the need for further investigations.

The distribution of patients among gender, different age and count of associated injuries and comorbidities is presented in Table 1.

In polytrauma patients, the clinical examination identified in addition to certain clinical signs of fracture and signs of cerebral distress in 65 cases (drowsiness, amnesia, vomiting, headache), as well as signs of hemorrhagic shock in 49 cases, in which the diagnostic strategy was focused on the major lesion (hepatic rupture, splenic rupture), as well as the therapeutic conduct (Figure 1).

Compared to the total number of diaphyseal fractures, the associated injuries were found in 85.22% of cases.

Figure 1 shows the traumatic injuries associated with patients with long bone fractures at the time of admission in hospital.

It can be observed that the associated minor injuries, represented by wounds, hematomas and contusions, were the most common traumatic injuries associated with diaphyseal fractures in 97 cases accounting for 39% of injuries.

Closed acute craniocerebral injuries that required pediatric neurological consultation and specific medication accounted for 26% of injuries, intraabdominal parenchymal organ injuries that required specific treatment accounted for 20% of injuries, while other types of fractures associated with diaphysis fracture accounted for 15% of injuries, followed in frequency.

The coexistence of major traumatic injuries required the stabilization of the patient by medical or surgical therapeutic methods, the stabilization of fractures being performed in a secondary time. Monitoring of patients in the pediatric intensive care unit was essential, the operative moment being established by agreement with the anesthetist.

Out of the total number of operated patients, 72 cases presented comorbidities (Figure 2).

Study population	***Patients (no.)***	***Age (yrs.)***	***Count of associated injuries (%)***	***Count of comorbidities (%)***
Long bone fractures in children			85.22%	24.74%
Female	91	12 (5,17)		
Male	200	14 (5,18)		

Data for distribution of patients among gender, different age and count of associated injuries and comorbidities. The patients' age is shown as median values and minimum and maximum values (in parenthesis).

Table 1. The measured values of count of associated injuries and comorbidities in relation to long bone fractures in children and according to gender.

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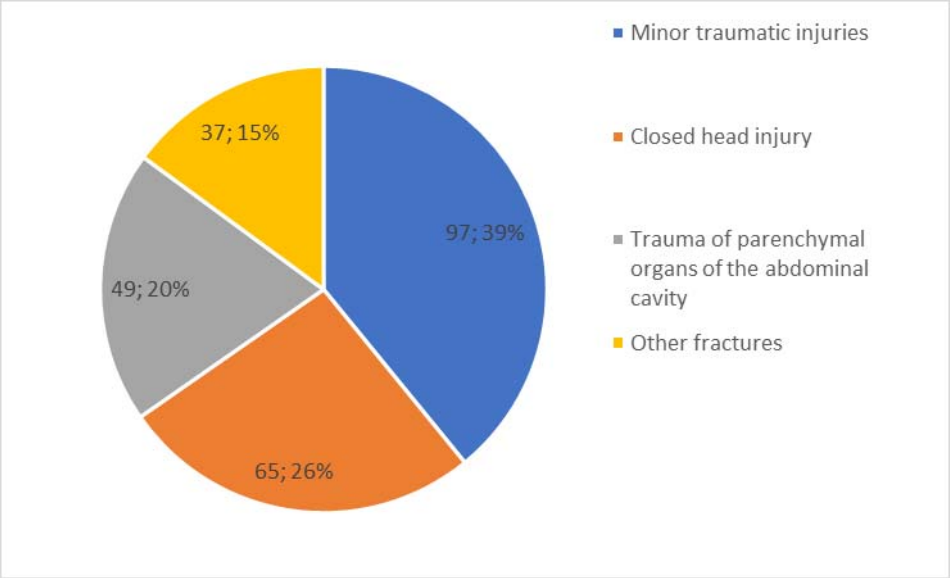

Fig. 1. Associated injuries in relation to long bone fracture in children.

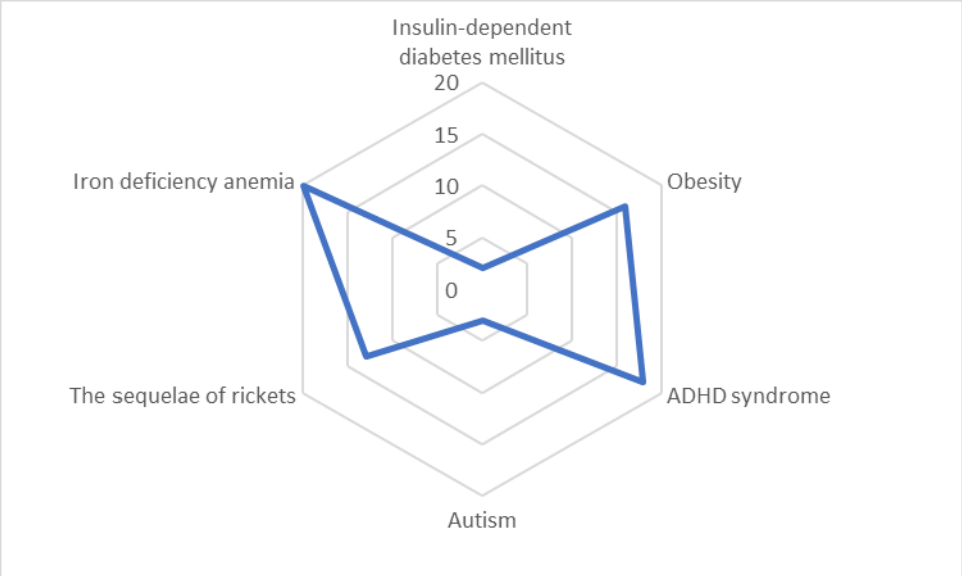

Fig. 2. Associated comorbidities in relation to long bone fracture in children according to the study group.

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Compared to the number of operated patients, the percentage of comorbidities in the group studied is 24.74%. Iron deficiency anemia, obesity and ADHD syndrome were the most common comorbidities. Thus, the myth by which the fracture in children occurs in a healthy, untreated ground, raises questions in the case of these concrete data.

Compared to the number of operated patients, the percentage of comorbidities in the group studied is 24.74%. Iron deficiency anemia, obesity and ADHD syndrome were the most common comorbidities. Thus, the myth by which the fracture in children occurs in a healthy, untreated ground, raises questions in the case of these concrete data.

Discussion

To our knowledge this study examined for the first time in Romania the prevalence of associated traumatic injuries and comorbidities in relation to long bone fractures in children. Our research results expand the knowledge about the associated injuries and comorbidities of fractures in children and offer new data regarding correct diagnosis approach in pediatric patients with long bone fractures. Our study focused on the determination of associated injuries and comorbidities in children with long bone fractures.

Although our study focuses on the young body, with the peculiarities of the musculoskeletal system, the frequency and complexity of fractures in children is a global problem, especially when recent studies show that 25% of traumatic pathology in children are fractures [6, 18, 19].

It is well known that, in pediatric traumatology, conservative orthopedic treatment allows certain degrees of angulation or displacement, permissiveness due to the physiological process of accentuated bone remodeling after indirect healing with initial hypertrophic callus. If we omit the unique ability of immature bone to reshape and correct displacements or angles described, demonstrated and accepted by pediatric orthopedists, osteosynthesis can be performed on any type of fracture in a comprehensive manner, with disastrous results.

The increased prevalence of cases with indication for orthopedic surgical treatment in our department demonstrates complex traumatic mechanisms of production, resulting in complex fractures of long bones in children and multiple associated traumatic injuries.

The incidence of traumatic pathology by sex groups, respectively 69% male and 31% female, corresponds to the data in the literature and is explained by the concern and involvement of males in extreme sports and physical activities.

Clinical and paraclinical investigations demonstrated that the long bone fractures in children highlight two important aspects that should be considered in the future by every pediatric orthopedist.

Firstly, the diagnosis of injuries associated with long bone fractures is mandatory, in the case of polytraumas taking priority patient stabilization and treatment of organ injuries, with surgical stabilization of fractures being performed later. In our study, monitoring of patients in the pediatric intensive care unit was essential in 20% of cases which demonstrates the association of major traumatic injuries (traumatic intra-abdominal injuries) associated with fractures.

Secondly, the diagnosis of comorbidities requires the establishment of appropriate treatment after surgical stabilization of fractures [20].

Compared to the number of operated patients, the percentage of comorbidities in the groups studied is 24.74%. The anatomical healing of the fracture in the child is directly dependent on the orthopedic treatment, but the coexistence of some undiagnosed pathologies can adversely influence the healing. Thus, it is necessary to diagnose comorbidities in close collaboration with pediatricians.

Our paper has some weaknesses. Firstly, the observation is made over a relatively short period of time in a single hospital and includes patients with long bone fractures that require surgery. In this situation, we do not have a study of associated lesions or comorbidities in patients with long bone fractures who were treated on an outpatient basis, in which case, the percentage of associated traumatic injuries and comorbidities could have been higher.

This paper also has several strengths. First of all, our study includes a significant number of children with long bone fractures. Secondly, the medical care of children with fractures is provided within a centralized system, involving a limited number of qualified physicians. This gives credibility to the diagnosis, on the one hand, and makes the collection of information quite easy and complete, on the other hand. Finally, the methodology used to collect information has been the same for over 10 years, namely direct contact with the pediatric orthopedic surgeon managing these children, being well developed and contributing to the reliability of the information.

Conclusions

Our data demonstrated an alarming incidence of associated traumatic injuries and comorbidities in long bone fractures in children. To confirm this, however, collecting information from larger populations from different geographical regions and monitoring the incidence over a period of several years are needed.

Conflicts of Interest: The authors declare no conflict of interest

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Correspondence to:

Maria Daniela Trăilescu

Department of Pediatric Surgery and Orthopedics,

Emergency County Hospital, Arad, Romania

Andreny Karolly Street, No.2 – 4,

Arad, 310037, România

Phone: +40-257- 220 000

Email: trailescumaria@yahoo.com

CLINICAL MODEL OF IMMUNOLOGICAL TRANSFER FROM THE MOTHER TO THE NEWBORN AFTER VACCINATION AGAINST SARS-COV-2 DURING PREGNANCY

Daniela-Eugenia Popescu[1,2], Cristina Jura[3*], Dan Navolan[1], Nicoleta Lungu[1,3], Zaharia Dariana[3], Maria Terebenț[4], Corina Cristea[5], Valerica Belengeanu[6], Mărioara Boia[1,3]

Abstract

Coronavirus disease represents a new and extremely contagious infectious entity, declared a pandemic in March 2020. Pregnant women confirmed with COVID-19 can develop severe forms of disease, being at greater risk of ICU admission, preterm birth occurring 3 times more frequently for this category. Initially, pregnant women were excluded from phase 3 vaccine clinical trials, thereby not enough data about the safety and efficiency of vaccination against COVID-19 is available. Currently, the producing companies have several ongoing studies. Under these circumstances, we present the case of a newborn from a young mother with no known pathologies, with no reported infection throughout the pregnancy and vaccinated with Pfizer-BioNTech vaccine at 31 and 34 weeks of pregnancy, respectively. Anti-spike antibody serum and breast milk concentrations were determined. This case indisputably demonstrates the existence of an important specific antibody transfer from the mother to her offspring, both by transplacental and human milk passage.

Keywords: SARS-CoV-2, pregnancy, vertical transmission, newborn, vaccine, spike protein

Introduction

Coronavirus disease appeared in China by the end of 2019 and rapidly spread throughout the world, being declared a pandemic in March 2020.

Many scientists joined forces to discover a vaccine that could put an end to pandemic evolution as quickly as possible and save the population. Generally, the main purpose of vaccines is to create a host immune response (defense), so that it can develop B and T cell immunological memory against an infectious agent (in the case being, SARS-CoV-2 virus). The development of immunological memory after vaccination is the one that will protect from further infections [1]. All scientist efforts led to the production of 6 vaccines, using different technologies (classical and modern methods). The COVID-19 pandemic set out the development of new vaccine production technologies, some of which had never been human tested before, such as DNA and mRNA based. Until recently, most vaccines were working by infectious agent inoculation into the human body, in order to induce immune response. The antigen was represented either by the inactivated (prior to inoculation) infectious agent, or by a purified protein belonging to the pathogen. Using the modern biotechnology and genetic engineering, large quantities of viral DNA and RNA can be obtained, requiring only the sequence of genetic material of the SARS-CoV-2 virus, this being made public by the Chinese researchers on 11th of January 2020 [1,2]. Unlike classic vaccines, the ones produced by Pfizer-BioNTech and Moderna work by transporting the genetic information required for the synthesis of SARS-CoV-2 spike protein, which can be naturally found on the viral surface. After vaccine inoculation, the muscle cells produce the spike protein, which is then recognized by the immune system. After a couple of days, the mRNA is degraded into the cytoplasm and does not enter the nucleus, which means it is not integrated in the cellular DNA [3,4]. The Astra-Zeneca Oxford and Janssen-Johnson and Johnson vaccines use a modified viral vector that can deliver the spike protein into the cell, triggering the immunologic response. These 4 vaccines are largely used across the USA and Europe and so, with the help of vaccination, millions of people have been able to protect themselves against this disease [1].

[1]Department of Obstetrics-Gynecology and Neonatology "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania
[2]Department of Neonatology, Première Hospital, Regina Maria Health Network, Timișoara, Romania
[3]Department of Neonatology, "Louis Țurcanu" Children Emergency Clinical Hospital Timișoara, Timișoara, Romania
[4]Regina Maria Health Network, Timișoara, Romania
[5]Department of Epidemiology, Première Hospital Timișoara – Regina Maria Health Network, Timișoara, Romania
[6]Department of Genetics, Institute of Life Science, Faculty of Medicine, "Vasile Goldiș" West University of Arad, Romania

E-mail: popescu.daniela@umft.ro, maciu.cristina@gmail.com, navolan@yahoo.com, nico_lungu2001@yahoo.com, darianaramona@gmail.com, maria.terebent@reginamaria.ro, corina.cristea@reginamaria.ro, belvtim@yahoo.com, marianaboia@yahoo.com

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Pregnant women that develop COVID-19 can present with severe forms of disease, especially if comorbidities are present, or associated to pregnancy (high blood pressure, diabetes, obesity, asthma etc.). These cases have higher risks of ICU admission and preterm delivery risk is 3 times higher compared to pregnant women who did not contract or develop the infection [5]. Initially, pregnant women were excluded from the vaccines clinical trials, this being the main reason why there is still insufficient data reported about the efficacy and safety of vaccinating against COVID-19 during pregnancy [6]. At this time, there are several ongoing studies, done by the producing companies. During pregnancy, most vaccines can be administered if the benefits overcome the risks [7]. Vaccines against flu, tetanus, diphtheria and pertussis are frequently used during pregnancy, due to the protection they, by transplacental antibody transfer from the mother to the fetus/newborn [5]. Starting from these unanimously approved results, we expect the vaccine against COVID-19 to offer the same anti-infectious protection to both the mother and the fetus/newborn [5,6,7].

Material and method

After maternal vaccination during pregnancy, anti-Spike (S) protein antibody titer was determined, from the maternal and neonatal blood, as well as from breast milk. For anti-S protein antibody determination, the ECLIA (electrochemiluminescence) method was used, an immunologic test that allows the quantitative analysis of IgG antibodies against SARS-CoV-2 S protein receptor binding domain (RBD) in both human serum and plasma, as well as human milk. The test is suggested as an adjuvant for the evaluation of humoral immune reaction to SARS-CoV-2 S protein.

Case report

We present the case of a 24 years old pregnant woman from Timișoara, Romania, Gravida 1, Para 1, with no history of SARS-CoV-2 infection and who decided, together with the family and obstetrician, to vaccinate against COVID-19.

The pregnancy developed as a physiological process, within normal parameters, with no preexistent pathologies or complications. The fetal evolution and development were normal, both before, as well as after vaccination. The main reason for vaccine uptake was due to the fearful complications the disease can cause, having a husband who was working in an environment with high infection risk and also for being a General Medicine student.

By 31-weeks gestational age, the first dose of Pfizer-BioNTech vaccine was administered, and by 34-weeks the second dose, as well. No adverse effects were reported other than local pain surrounding the inoculation area. No analgesics or antipyretic medication was administered neither before nor after vaccination. Following vaccination, the evolution of pregnancy developed within normal ranges, with on-time check-ups and prenatal care, which showed normal fetal growth and development.

By 39-weeks gestational age, spontaneous labor occurred, followed by normal vaginal delivery, in cephalic presentation, from which resulted a newborn with appropriate gestational weight (3500g), length (51cm), head circumference (35cm) and an APGAR score of 10. The neonatal adaptation to the extrauterine life was normal. According to the hospital's protocol, the pregnant woman was tested against COVID-19 on admission, by polymerase chain reaction (PCR), with a negative result.

After delivery, the usual laboratory tests of the mother and neonate were normal, with no pathologic findings. In the 5th day after delivery, both the mother and her newborn came into our clinic for a usual check-up, which showed a normal newborn evolution and for several tests, which included specific anti-SARS-CoV-2 antibodies (IgG and IgM) testing from the venous blood, that were negative, meaning the infection never occurred. At the same time, the anti-Spike (S) protein antibody titer was determined, from the maternal and neonatal blood, as well as from breast milk. For anti-S protein antibody determination, the ECLIA (electrochemiluminescence) method was used, an immunologic test that allows the quantitative analysis of IgG antibodies against SARS-CoV-2 S protein receptor binding domain (RBD) in both human serum and plasma, as well as human milk. The test is suggested as an adjuvant for the evaluation of humoral immune reaction to SARS-CoV-2 S protein. The minimum detection limit, under which the result is negative for the presence of antibodies against the S protein represents 0,80U/ml, above this value the result being positive.

Results

The antibodies against Spike protein of SARS-CoV-2 evaluated 5 days after delivery from the maternal and neonatal serum were increased, the maternal titers were of 624U/ml and the neonatal ones of 470U/ml. The titers from human milk were lower, of only 1.34U/ml, but above the minimum detection limit. A follow-up of anti-spike antibody titer dynamics, 6 weeks after delivery (and 5 weeks after the first determination) was done. The antibody titers from the maternal and infant blood and from human milk were once again determined. The results were increasingly higher for the mother, with values of 737.2U/ml (serum value) and 1.61U/ml (breast milk value), which translates to a more important antibody transfer via human milk. Although the infant's antibody titer was lower (164.9U/ml), its value is still appropriately increased for offering a sufficient anti-infectious protection by 4 months of age, when the infant's immune system starts to produce its own antibodies. The finding of this type of antibodies in human milk is both important and benefic due to the fact that this transfer can never be a passive one, but one that contributes to the anti-infectious mucosal defense, taking into account that an exclusively breastfed newborn can ingest up to 800-1000 ml of human milk in 24 hours.

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Antibody titer (U/ml)		
	5 days	**6 weeks**
Mother serum	624	737.2
Breast milk	1.34	1.61
Newborn/Infant serum	470	164.9

Table 1. Table demonstrating antibody titers from the maternal, neonatal/infant serum and breast milk

Discussion

The development and apparition of mRNA based vaccines stands upon research initiated since 2006 and finished after 15 years, with the launch of 2 vaccines, Pfizer-BioNTech and Moderna, respectively. These vaccines represent a premiere in vaccinology and the pressure exerted by the SARS-CoV-2 pandemic represented a good opportunity for this type of vaccines, so they could contribute significantly and put an end to this pandemic [3,4].

The vaccination of pregnant women leads to cellular and humoral mediated immunity, which increases the resistance against infection and reduces the vertical transmission rate [3,7,8]. Furthermore, vaccination produces IgG antibodies, which can cross the placental barrier and IgG, IgA and IgM antibodies which have a role in mucosal immunity and are secreted in colostrum/mature breast milk, and then ingested by the newborn during breastfeeds [9,10,11].

Anti-Spike antibodies acquired after vaccination and found in human milk, even if they appear in reduced quantity, are accumulated by administration repetitivity, when the newborn and infant is exclusively breastfed. As mentioned above, the breastfed newborn can ingest around 800-1000ml of milk per day, which ensures an immunologic overprotection if we add the antibodies transferred through the placenta during pregnancy [11]. The anti-Spike antibody transfer via breastmilk is followed by a subtler cell transfer, with cells both involved in anti-infectious defense as well as memory cells, which will contribute to the infant's future immune mechanisms. Lately, affirmations regarding the colostrum and mature milk cellularity, based on scientific arguments, strongly suggest that no milk contamination takes place, but a highly-selective immunological transfer with an essential role in the mucosal anti-infectious defense, including respiratory mucosa, which is greatly affected by the coronavirus infection [12,13].

In the above presented case we indubitably demonstrated that the anti-Spike antibodies acquired after vaccination against SARS-CoV-2 virus can cross the placental barrier from the maternal blood to the fetus. The pregnant woman was vaccinated with 8 and 5 weeks prior to delivery, which allowed enough time for the production, development and transfer of protective antibodies. During the first determination (5 days after birth) the plasmatic antibody quantity present in newborn represented 75% of the maternal plasmatic antibody titer, which leads to the conclusion that there exists a significant and sufficient placental and breastmilk antibody transfer for the protection of both the newborn and infant, at least until 1 year of age, which determines ab initio the exclusion of vaccination during the first year of life. The maternal plasma antibody titer had an increase of 18,1% from the first determination, fact that directly correlates to an equal increase in maternal breastmilk antibody titer, which was 20% since the first determination.

Conclusions

The most authorized recommendations for vaccination against COVID-19 during pregnancy come from the American College of Obstetrics and Gynecology (ACOG), which recommends that the vaccine should not be contraindicated during pregnancy and the decision must be taken together with the obstetrician.

World Health Organization considers there are no specific risks that outweigh the benefits of vaccination for pregnant women. The pregnant women at high risk of SARS-CoV-2 exposure (health care workers), or the ones with associated comorbidities (conditions that can lead to death) can be vaccinated after an accurate assessment done by the obstetrician, with interdisciplinary collaboration, if the case presents, with other specialties.

This paper illustrates that vaccination during pregnancy and breastfeeding provides the infant immunity during the first 4-6 months of life.

There is a significant and urgent need of research regarding the effectiveness and safety of vaccination against SARS-CoV-2 during pregnancy and establishing the optimal period of time for the vaccine administration, both for the mother as well as her fetus/newborn.

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Correspondence to:

Cristina Jura

Doctor Iosif Nemoianu Street, No. 2

300011, Timişoara România

Email: maciu.cristina@gmail.com,

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The manuscript must be in English, typed single space, one column on A4 paper, with margins: top – 3 cm, bottom – 2, 26 cm, left – 1, 5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author's correspondence address.