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INFLAMMATORY AND IMMUNOLOGIC BIOMARKERS CORRELATED WITH THERAPEUTIC OUTCOME IN JUVENILE IDIOPATHIC ARTHRITIS

Andrea Somogyi Militaru¹,²*, Otilia Marginean¹,², Camelia Daescu¹,², I Sabau¹

Abstract

Introduction: Juvenile idiopathic arthritis (JIA) is the most important rheumatic disease of childhood. Aim: To study the correlations between biomarkers and the therapeutic response in JIA. Material and methods: In 58 children, diagnosed and classified according to ILAR (International League of Associations for Rheumatology), evaluation consisted in clinical and laboratory examination (ESR, CRP, RF-rheumatoid factor, alpha2-and gamma-globulins, total IgM and IgG, immunoglobulins, anticyclic citrullinated peptide antibody- ACPA, antinuclear antibodies-ANAs, interleukins – ILs). The outcome was assessed by ACR Pedi (American College of Rheumatology) score. Results: Patients distribution regarding diagnosis was: of patients was: 1 systemic JIA, 17 polyarthritis, 18 oligoarthritis, 22 spondyloarthropathies. There was a good, but inverted correlation between the ESR, CRP, serum immunoglobuline values and the ACR Pedi30 scores on NSAID treatment. ACPA was found positive in 6 cases, all associating important inflammation at the onset, but no correlations with ACR scores. ANAs was found positive in just 3 cases of extended oligoarthritis, all associating ocular complications. Plasma levels of IL-1alpha, IL-1beta, IL-6 pro-inflammatory interleukins was determined in 8 cases. Both fractions of IL-1 were increased in two cases of reactive arthritis and one juvenile spondylitis (with normal IL-6 levels). Enhancement of IL-6 (and normal IL-1 values) was observed in 3 children with polyarthritis. Conclusions: Important biologic inflammatory syndrome at the moment of JIA diagnosis suggests a highly active disease, indicating a more aggressive therapeutic approach. Positive ACPA is less prevalent than in rheumatoid arthritis, but its positivity denotes an erosive course of JIA. ANAs were correlated with extended oligoarthritis and ocular complications. Interleukins could be correlated with clinical form of JIA (IL-1 with spondyloarthropaty, IL-6 with polyarthritis) and could suggest the timing of biological therapy withdrawal. Further studies are needed to sustain these observations.

Keywords: juvenile idiopathic arthritis, biomarkers, ACPA, pro-inflammatory interleukins, ACR Pedi score

Introduction

Juvenile idiopathic arthritis (JIA), with a prevalence varying from 16 to 150 per 100,000 (1) is the most common chronic rheumatic condition in childhood and represents an important cause of short and long term disability. It is not a disease, but an exclusion diagnosis that gather together all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown origin.

Laboratory examination in JIA

Although the laboratory may provide support for a diagnosis of chronic arthritis, no laboratory test or combination of studies can confirm the diagnosis. The laboratory can be used to provide evidence of inflammation, to support the clinical diagnosis and as a research tool to understand more completely the pathogenesis of the disease. ESR and CRP. The Westergren erythrocyte sedimentation rate (ESR) is a useful but not totally reliable measure of active disease at onset and during follow-up of children with arthritis. It is occasionally helpful in monitoring the therapeutic efficacy of treatment, although it does not correlate with the articular response to medication.(2) The C-reactive protein (CRP) level may be a more reliable monitor of the inflammatory response; at least it is less often increased in a child in whom no clinical inflammatory disease can be found.(3)

Rheumatoid factor.

The diagnostic importance of RF seropositivity in a child with possible chronic arthritis is mitigated by the frequent occurrence of abnormal titers in the other connective tissue disorders of childhood.(4) RFs are common in children with later onset age and polyarticular disease and is associated with articular erosions, or a poorer functional class.(5)

¹“Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
²“Louis Turcanu” Children's Emergency Hospital Timisoara, Romania
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E-mail: andreamilitaru@yahoo.com, otiliamarginian@yahoo.com, camidaescu@yahoo.com, idsabau@yahoo.com
Serum immunoglobulins.

Elevated levels of immunoglobulins are correlated with activity of the disease and reflect the acute-phase response. Extreme hypergammaglobulinemia is present in the sickest children and returns toward normal with clinical improvement. In general, persistent hypergammaglobulinemia is an important hallmark of deteriorating clinical course and poor therapeutic response. Significantly increased concentrations of IgG, IgA are present in children with active disease, whereas elevated IgM levels are characteristic of the disease itself. (6)

Antinuclear antibodies.

Tests for ANAs are more useful than those for RF in diagnostic and classification. Standardized serum dilution titers are usually low to moderate. The frequency of ANAs is highest in girls of younger age of onset, especially in those with oligoarticular disease, and lowest in older boys and whose with systemic-onset disease. ANAs reach their highest prevalence in children who have oligoarthritis and uveitis. Therefore, determination of ANA seropositivity is supportive of the diagnosis and is important in identifying children with the highest risk for chronic uveitis. (7)

Anti-cyclic citrullinated peptide.

Biomarkers with the potential to differentiate those patients with aggressive JIA early in their disease have recently included anticyclic citrullinated peptide antibodies (ACPAs). Although ACPAs have been studied extensively in rheumatoid arthritis (RA), their significance in JIA has been evaluated only recently. Anti-CCP antibodies have a specificity of 98% and a sensitivity of 48% for RA, providing a useful diagnostic tool in RA. (8) They seem to play an important role in the pathogenesis of RA inflammation, because RA patients with ACPA have a more aggressive disease course with joint erosion and damage. (9,10) Citrullinated proteins may be targets of the local immune response in patients with RA and perpetuate a persistent state of synovitis leading to joint destruction. Role of ACPA in JIA remains controversial. Several studies have generated varying results regarding its significance in the disease process. They showed no statistically significant correlation between ACPA positivity and ESR or radiographic damage was detected. (Another study suggested that anti-CCP antibodies in JIA were not as prevalent as in adult RA, but could be useful in predicting joint damage. (5,11,12)

Interleukins.

Although onset and disease course may differ, the subtypes of JIA share the occurrence of chronic inflammation of joints. Monocytes, macrophages, fibroblasts and T cells within the inflamed microenvironment secrete many mediators that interact directly with the surrounding tissue and tend to have a proinflammatory character. (12-14) The produced interleukins (IL) regulate the production of inflammatory mediators from the surrounding tissue, whereas secreted chemotactic cytokines (chemokines) function as regulatory molecules that attract and direct the differentiation of new potent inflammatory cells to the site of inflammation. (11,14,15) Evidence of an imbalance of pro-inflammatory cytokines in patients with inflammatory diseases includes the positive correlation of serum and synovial cytokine concentrations with JIA disease activity, an increase in antagonists or soluble receptors with a flare of arthritis (14) and the effectiveness of JIA therapies that involve cytokine modulation. The pro-inflammatory cytokines that have been reported to play a major role in JIA include interleukin 1-beta (IL-1β), tumor necrosis factor alpha and interleukin 6. (16,17)

Circulating cytokines correspond to the activation status of immune-competent cells, and it could be instrumental to monitor changes in this profile during treatment. Evaluating cytokines in plasma might help in identifying surrogate parameters for disease activity, disease severity, risk of side effects and treatment outcome. (16,18)

Therapy in JIA

Recently the ACR has issued recommendation for the treatment of JIA (19). Recommendations are based on a step up approach which requires the subsequent use of drugs with greater power once the previous treatment(s) failed. Recommendation are proposed for five functional categories of JIA and according to the level of disease activity (low, moderate, and high) and the presence of poor prognostic features specific for each JIA group. In addition the recommendations provide guidance for the safety monitoring of NSAID, methotrexate (MTX) and TNF-α inhibitors.

Assessment of therapeutic answer in JIA.

The validated criteria to evaluate response to therapy in JIA were adopted by the ACR and are now known as the ACR Pediatric 30. According to the ACR Pediatric 30, patients are considered responders to a given therapy if they demonstrate at least 30% improvement from baseline in at least 3 of any 6 JIA core set variables, with no more than 1 of the remaining variables worsening by more than 30%. Commonly, patients also are evaluated for higher level of improvement (ACR Pediatric 50, 70, 90, and 100). Variables included in the JIA core set variables include: (1) the number of joints with active arthritis, (2) the number of joints with limited range of motion; (3) the physician’s global assessment of disease activity; (4) the parent assessment of child’s overall well-being; (5) a validated measure of functional ability, usually measured by the disability index of the Childhood Health Assessment Questionnaire (CHAQ), (6) a laboratory measure of inflammation, either the ESR or CRP.

Objectives

The main goals of this study were to analyze inflammatory and immunologic biomarkers in a pediatric cohort with chronic arthritis, and to investigate the predictive role of these biomarkers by studying the interrelation between the lab tests at the disease’s onset and the therapeutic response in different subtypes of JIA.
Material and methods

It was a retrospective study, followed by a prospective one. We enrolled 58 children with chronic arthritis, assessed in the First Pediatric Clinic from “Louis Turcanu” Emergency Hospital for Children, Timisoara during the period of May 2005 –October 2011. All the patients were diagnosed and classified according to ILAR (International League of Associations for Rheumatology) criteria.

The study had full ethical approval of the department. Informed consent was obtained either from parents or from the individuals directly if they were older than 12 years.

Evaluation of the patients consisted in complete medical history, clinical assessment, functional evaluation and lab tests. Demographic and clinical characteristics of the patients included: age at the onset of JIA, sex, body weight, duration of JIA prior to diagnosis.

Clinical parameters involved: number of swollen joints, of tender joints and of joints with limitation on passive motion. Presence of extra-articular symptoms and signs (ocular, gastrointestinal, dermatological, cardiovascular etc.) had been assessed.

Functional assessment included: physician’s and parent’s global assessment of disease activity (with a 100-mm visual analogue scale -VAS, in which higher scores indicated more active disease); Disability Index score in Childhood Health Assessment Questionnaire -CHAQ, in which scores range from 0 (best) to 3 (worst) and parent’s or patient’s assessment of pain (through a 100-mm visual analogue scale in which higher scores indicated more severe pain).

All patients were assessed through laboratory exams, consisting in evaluation of: 1) inflammatory syndrome (blood cells count, ESR, CRP, plasma alpha2- and gamma-globulin levels, serum IgM and IgG levels); and 2) immunologic assessment (RF, ANA, ACPA, and, IL-1alpha, IL-1beta, IL-6 in 13.6% of cases).

Routine assay, consisting in latex agglutination, measured 19S IgM RFs, but enzyme-linked immunosorbent assays (ELISAs) have provided significantly more positive results than the routine ones. This is the reason why in our study we performed the measurement of IgM RF by ELISA.

ACPA, ANAs and plasma levels of ILs levels were determined by ELISA also.

Imagistic evaluation was performed in every long lasting form of JIA and included x-ray and, in some cases, magnetic resonance investigation. Genetic assessment included HLA-B27 gene testing in the spondyloarthropathy group.

Active disease was defined by the presence of joint swelling or limitation of movement with either pain on movement or tenderness. Non-active disease (remission) was defined by the absence of joint swelling or limitation of movement with no pain on movement or tenderness.

The patients have been treated according to ACR Pediatric recommendations, and the therapeutic response has been assessed according to the ACR Pediatric criteria at one month (on treatment with NSAIDs), at 3 months (on DMARD therapy) and at 6 months (on biological treatment only or combined with DMARD, according to the form of JIA).

Analysis of the results was performed with SPSS16 software. The correlations were estimated using linear regression models.

Results

Characteristics of the cohort

Clinical data permitted the division of cohort into four major subgroups: (persistent) oligoarthritis, polyarthritis (including three extended oligoarticular JIA), systemic JIA and spondyloarthropathy (or enthesitis-related arthritis-ERA). Distribution of the patients is summarized in table I. The spondyloarthropathy group included: 4 cases of arthropathies associated with Crohn disease, 4 juvenile ankylosing spondylitis, 5 reactive arthritis and 9 patients with undifferentiated arthritis.

Table 1 summarizes the characteristics and descriptive statistics of our cohort. Female patients were predominant, both in oligoarticular and polyarticular JIA, but in the spondyloarthropathy group were more boys than girls. In our studied group, the highest medium age was found in spondyloarthropathy (12.4 years).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort</th>
<th>Oligo JIA</th>
<th>Poly JIA</th>
<th>Systemic JIA</th>
<th>SpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients number</td>
<td>58</td>
<td>18</td>
<td>17</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Gender ratio F:M</td>
<td>32:26</td>
<td>12:6</td>
<td>10:7</td>
<td>1:0</td>
<td>10:12</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>8.9</td>
<td>6.8</td>
<td>8.6</td>
<td>5.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Mean ESR (mm/1h)</td>
<td>54.6±30.6</td>
<td>33.4±18.6</td>
<td><strong>68.3±21</strong></td>
<td>110</td>
<td>28.6±24.3</td>
</tr>
<tr>
<td>Mean CRP (mg/dl)</td>
<td>18.1±14.74</td>
<td>12.8±8.7</td>
<td><strong>24.8±12.6</strong></td>
<td>48</td>
<td>18.3±10.5</td>
</tr>
<tr>
<td>Mean VAS score</td>
<td>5.61±1.85</td>
<td>4.43±1.56</td>
<td><strong>6.8±2.2</strong></td>
<td>7</td>
<td>5.3±2.7</td>
</tr>
<tr>
<td>Mean CHAQ score</td>
<td>10.73±5.23</td>
<td>6.56±2.87</td>
<td><strong>14.86±4.6</strong></td>
<td>16</td>
<td>8.2±4.64</td>
</tr>
<tr>
<td>IgM RF positive (no)</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anti-CCP ab (no)</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>ANA positive (no)</td>
<td>3</td>
<td>0</td>
<td>3 (extended oligo JIA)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the cohort and subgroups
IgM RF detection
IgM RF has been evaluated in all 58 cases by ELISA. In 4 patients, (6.9%), elevated levels of IgM RF were found, all belonging to polyarticular JIA. RF detection permitted the sub-classification of the polyarticular JIA (RF positive and RF negative polyarthritis). All these cases, had important inflammation with severe functional disability at the onset of the disease and had radiographic evidence of joint damage at the moment of diagnosis, including joint space narrowing and joint erosion.

Inflammatory biomarkers evaluation
The values of ESR and CRP levels at disease’s onset were divided up into two groups: moderate (less than five times of normal values) and important biologic inflammation (more than five times the normal value: above 50 mm/1h for ESR, and more than 25mg/dl for CRP). Distribution of cases according to the biologic inflammatory syndrome and JIA forms are illustrated in figure no 1 and no 2 (revealing that the systemic JIA and the 70% of polyarticular cases presented an important inflammatory syndrome at disease onset). We studied the interrelations between the inflammatory biomarkers’ values (ESR, CRP, fibrinogen, alpha2-, and gamma-globulins, IgM, IgG) at disease onset and therapeutic response.

We found a significant negative correlation between both ESR ($r = -0.70, p <0.001$) and CRP ($r = -0.74, p <0.001$) values and ACR score obtained on NSAID therapy (Figure no 3 and 4).

Very similar results were obtained in the study of correlations between fibrinogen ($r = -0.63, p <0.001$), serum alpha2-globuline levels ($r = -0.59, p <0.001$), gamma-globuline ($r = -0.67, p <0.001$), IgM ($r = -0.41, p =0.002$), IgG ($r = -0.59, p =0.002$) and ACR Pedi30 score on NSAID therapy at one month.
IMMUNOLOGIC BIOMARKERS EVALUATION

Anti-CCP antibody detection

In 43 cases ACPAs presence was assessed. Positive, but very low levels were found, in just 9 children, with the following distribution: 6 polyarticular JIA (4 RF-positive and 2 RF-negative polyarthritis), 1 oligoarticular JIA, 2 cases of ERA (an ankylosing spondylitis and 1 patient with Crohn disease associating arthritis). We found no correlation of ACPA positivity and the clinical form of JIA.

100% of ACPA positive cases had important inflammatory syndrome at onset of JIA, had no improvement on NSAIDs at 1 month (under ACR Pedi30), poor evolution on DMARD treatment (average ACR Pedi35 score) and all cases needed aggressive treatment (DMARD and biological association) in evolution. We found no correlation between ACPA values and ACR Pedi score at one, three or six months (p>0.05).

In five cases from the six patients with borderline positive ACPA, radiographic evidence of joint damage was found on disease onset. The exception was the patient with arthropathy associated to Crohn disease, with an aggressive evolution of the intestinal inflammation, but no joint damage.

ANAs detection

Antinuclear antibody detection was found positive in just three cases (5,1% of total cases), but in all children disease's history revealed an oligoarticular onset, extended to polyarticular JIA. Ocular complications were checked, and we found in all cases uveitis (in two cases asymptomatic iridocyclitis).

Interleukin plasma level evaluation

Plasma levels of IL-1alpha, IL-1beta, IL-6 pro-inflammatory interleukins were determined by ELISA in 9 cases, but in different disease activity status of the patients. (Figure no 5)

We observed a possible interrelation between IL type elevation and clinical form of JIA. Both fractions of IL-1, with normal IL-6 levels, were increased in spondyloarthropathies: two cases with reactive arthritis and one juvenile ankylosing spondylitis. Enhancement of IL-6 (and normal IL-1 values) was observed in 3 children with polyarthritis: 2 with clinical active disease, one in clinical remission on treatment, but high ACPA level and positive RF. All three ILs plasma levels were found elevated in the active systemic JIA case.

Discussions

ESR and CRP are important biomarkers in assessment of disease activity and response to treatment, with good correlation with functional indexes and have an important role in prognosis of the each individual case. (13,20-22) One of the questions raised in consequence of our study's results is if a high disease activity at onset of JIA, reflected by an important increase of inflammatory biomarkers, could or could not be a predictive factor for an aggressive course? For answering, we observed that in our cohort 44% of cases with highly elevated values of inflammatory biomarkers belonged to polyarticular JIA. This issue is highlighted by the newest ACR recommendations, which proposed concerning the polyarticular JIA treatment to over leap NSAIDs, and to start treatment with the DMARDs. (19)

The other inflammatory biomarkers (serum globulins and immunoglobulins) presented less sensitivity in comparison with CRP in appreciation of disease activity in our cohort. The significantly elevated serum levels of both IgG and IgM at the moment of diagnosis reflected a highly active disease, though IgM plasma concentration remained increased even in cases with improving outcome. (6)

In diagnostic of rheumatoid arthritis, ACPA is an important biomarker, with higher specificity than RF and may better predict erosive disease. (11,23) Because of this diagnostic and prognostic value of ACPA, recently. RA is reported to be sub-classified into two subsets by ACPA
positivity, sub-division which could be useful in JIA as well. (23-27) Though, in JIA significance of ACPA remains to be determined. The low prevalence of ACPA in our cohort of JIA is in concordance with the result of other studies. (13,15,27,28) This point could support the supposition of the similarity between JIA and the ACPA negative RA, assumption with therapeutic and predictive implications in the management of JIA.

Numerous studies have shown that IgM RF-positive polyarthritis patients have a higher prevalence of ACPA, observation which was confirmed in our cohort. (5,12,15)

The pathogenic pathways of different subtypes of JIA are still up to debate. The correlation between IL and the form of JIA in our cohort is in concordance with the results of some studies, but in discordance with the outcome of others. (29,31-33)

Studies (34) raise the issue that all the available scores (ACR Pedi 30, the 3 versions of the Juvenile Arthritis Disease Activity Score based upon 10-, 27-, and 71-joint counts JADAS,) used in the assessment of disease activity in JIA can lead to a miss-classification of active versus inactive disease. These scores apply ESR or CRP as inflammatory biomarkers, but the researchers continue to detect more sensitive biomarkers. A possible solution could be the interleukins. Elevated level of proinflammatory interleukins in clinical remission JIA cases could support the concept of a sub-clinical, immunological disease activity. (31,34-37) This observation could have a practical importance as well, in answering the question: “When to stop biological therapy in clinical remission JIA”. Normal interleukins values could be markers for withdrawal of biological therapy, while, in contrary, high levels of IL could suggest the continuation of the anti-TNF treatment. Nevertheless, high levels of pro-inflammatory interleukins could also be the result of other inflammatory condition out of articular area.

Limitation of the present study consists in the relatively low number of cases.

Conclusions

ESR and CRP correlate closely, show similar test characteristics and are feasible and valid tools for assessing disease activity in JIA. Higher values of ESR and CRP at the first study visit significantly predicted physical disability, damage, no remission on NSAID medication, and use of DMARDs during the disease course.

IgM RF and anti-CCP antibody are not reliable markers in appreciation of disease activity or treatment response. However, the measurement of the mentioned biomarkers early in the course of JIA may be beneficial to distinguish aggressive disease and possibly initiate more aggressive treatment earlier in those patients.

Prevalence of ANAs was low in our cohort of JIA, but determination of ANA seropositivity is important in identification of children with the higher risk for chronic uveitis.

ACPA, even if is much less prevalent than in RA, represents a reliable biomarker for an aggressive form of JIA, underlying the necessity for a complex therapeutic approach.

Interleukins could be correlated with clinical form of JIA (IL-1 with spondyloarthropaty, IL-6 with polyarthritis). The interleukins could be more sensitive markers of the disease activity than the routine inflammatory markers or the functional indexes.

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Correspondance to:
Somogyi Militaru Andrea
First Pediatric Clinic,
“Louis Turcanu” Clinical Emergency Hospital
Iosif Nemoianu street No 2,
Timisoara,
300011,
Romania
Tel.+40-730-618838
E-mail: andreamilitaru@yahoo.com
REALITY OF ASSESSMENT PAIN IN PEDIATRIC SURGERY

Mihaela Coșofreț¹, Nida Boșnac¹, Asan Rucni¹, F Enache¹, C Tica¹

Abstract
Post operatory pain assessment study monitored a group of patients using assessment scales according to the protocol used painkiller category, minor and major surgery. The study group consisted of 47 patients aged 0 - 192 months, divided into four age groups and two categories according to surgical complexity.

The measurement scales used in the post operatory pain evaluation study are: DAN, EVA, and CHEOPS.

At the age category, the assessment shows DAN lower score averages in children treated with meperidine and paracetamol compared to those treated with paracetamol, statistically significant differences due to surgical category. For the categories A, B, and C age group there were found statistically significant differences in pain scores according to the protocol used analgesic, but no clinical differences were found due to different type of surgical procedures (major, minor, plastic).

Pain scores were significantly lower with epidural analgesia than the others following the analgesic protocol, in the D age group.

Key words: scales, evaluation, post operatory pain.

Introduction
Acute postoperative pain (DPO) is a particular form of acute pain that occurs in response to tissue injury, visceral distension or disease. DPO is that expression of autonomic responses, psychological and behavioral causes unpleasant, undesirable sensory-emotional experience.[2]

Post operatory evaluation strategy is complex in children. Post operatory pain assessment and treatment is essential because the effectiveness of a patient and a particular type of surgery, it is impossible to predict the amount of felt pain and analgesic consumption.[6]

To treat pain adequately, it is essential to evaluate it in terms of prevalence and severity of the child and response to treatment. Assessment tools are reliable, valid and clinically sensitive and are available for infants and children by adapting pain assessment instruments to teenagers [10].

Purpose
The aim is to evaluate effective means implemented to control postoperative pain of children in pediatric surgery service in Constanța County Emergency Hospital, as well as to compare the requirements imposed by the reality of pain management, in order to identify specific targets for improving clinical practice with positive effects on patient satisfaction and the cost of hospitalization (reduce the medication doses, use of available medication, hospitalization period).

Materials and methods
The research sample consisted of 47 children aged between 0 -192 months with an average of 71 months. The weight of the children in the study was from 2 kg to 97 kg, with an average weight of 23.200 kg.

The period in which the study was conducted was between December 2008 and January 2009.

The criteria for their inclusion in the study were as follows:
→ Surgery patients are subjected to general or loco regional anesthesia;
→ After surgery patients are monitored in the intensive care unit;
Children were divided into four categories according to age, as follows: Category A: neonates and infants between 0-6 months, B: infants and young children between 6 and 24 months; Category C: early childhood: 2 to 6 years; category D: children over 6 years.

The assessment of pain in our study was performed mostly on patients undergoing major surgery and receiving complex analgesic. Table I contains the distribution of population according to the age group and category of surgery. All the children treated with paracetamol were evaluated alone or in combination with other methods of providing analgesia.

The average dosage of paracetamol reported to the average weight of the included children, was 15 mg/kg on body weight and grip. Paracetamol was prescribed up to 4 injections in 24 hours. The average dosage of meperidine reported to the average weight of children was 1 mg / kg. It wasn’t prescribed systematically but according to the patient’s needs.

Morphine dosage was 0.1 mg / kg as a bolus, possibly repeated every 5 minutes as a re-injection of 0.025 mg / kg to achieve adequate analgesia. [ 5,9 ]

¹Constanța County Emergency Hospital, Department of Pediatric Surgery and Orthopedics
E-mail: mihaela.cosofret@yahoo.com, nida_bosnac@yahoo.com, rucni.asan@yahoo.com, doctor.enache@gmail.com, tica.constantin@yahoo.com
Table I –The population distribution according to age and surgical category.

<table>
<thead>
<tr>
<th>Age category</th>
<th>Minor surgical</th>
<th>Major surgical</th>
<th>Plastic surgical</th>
<th>Total number of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categ. A</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Categ. B</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Categ. C</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Categ. D</td>
<td>0</td>
<td>17</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>5</strong></td>
<td><strong>32</strong></td>
<td><strong>8</strong></td>
<td><strong>47</strong></td>
</tr>
</tbody>
</table>

0.125 to 0.25% bupivacaine dosage was about 2 to 2.5 mg epidural / kg initial bolus followed by an infusion of 0.25 -0.4 mg / kg / hour during the operation.[ 7]

Table II. contains the study of population distribution by type of post operative analgesia.

Table II – Distribution of population by type of post operatory analgesia administration.

<table>
<thead>
<tr>
<th>Age category</th>
<th>No. all children</th>
<th>Paracetamol</th>
<th>Paracetamol+ meperidin</th>
<th>Morfin + paracetamol</th>
<th>Epidural analgesia (bupivacain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

In 72% of the cases, the pain assessment scales were used for opioid analgesia and post operatory epidural analgesia.

The peripherals analgesics used in the study were paracetamol and those with centrally acting morphine and meperidine.

The distribution of pain assessment protocol based on the painkiller used is shown in Figure 1.

The assessments were made immediately after surgery at each nurses shift change, over a period of 48 hours. The evaluation of post operatory pain in our study was performed with EVA scale as a reference tool after 6 years (group D), the CHEOPS scale for age groups B and C and DAN scale for children under 18 months (group A). All the pain assessments were made for the case the patient is at rest.

The validation of the results was done by statistical analysis: Student t test.

**Results**

![Figure 1](image1.png)

*Figure 1 – The distribution of pain assessment according to the protocol used painkiller.*

![Figure 2](image2.png)

*Figure 2 – Pain score Eva.*

1. The post operatory pain assessment for category D age group children

It is noted that the pain seems well controlled for the analgesia with morphine in the epidural but the analgesia with acetaminophen and meperidine for pain control is of inferior quality, as highlighted by the values of EVA score above 3 in the first 36 hours post operatory. The pain control is better when using epidural anesthesia methods compared with other methods, the average score obtained was 28% lower. To check whether this difference is statistically significant we compared the mean score obtained for EVA pain therapy with morphine, meperidine and epidural anesthesia, using student t test.

The result shows that there is no significant difference between the mean pain score EVA, epidural analgesia in children compared to children treated with other analgesics protocols, (p <0.05), in the sense of better control of pain with epidural analgesia (Figure 2).
2. Post operatory pain assessment in the category A age group children

It is noted that, the mean pain intensity is below the minimum which leads to a required additional therapy and surgical category regardless of the used analgesia.

We compared the mean score obtained DAN meperidine therapy and the painkiller peripheral and the peripheral therapy. It is noted that the DAN pain score was 47% lower when using peripheral painkiller only due to the differences in the complexity of the surgery. The statistical interpretation of the results shows a significant difference between the two groups at a p < 0.01. However, because the two groups of patients were undergoing various surgeries, the interventions that major and minor difference in terms of pain control, represented by the values obtained with DAN pain score can not be regarded as significant (Figure 3).

3. Post operatory pain assessment in categories B and C age group children

From Figure 4 we see that the mean pain intensity is below the minimum (3) the additional therapy is required. Patients were treated postoperatively with an average score painkillers peripheral Cheops less than 50% compared with those who received treatment with opioids. The difference recorded between the mean pain score for children treated with opioids and the peripheral pain relievers (1.82), respectively peripheral pain relievers (0.92), is highly statistically significant (p<0.001), which is also due to the difference the complexity of the surgery. But the difference is explained by the fact that patients were treated according to the type of painkiller that the surgery was subjected to (opioids for major, minor peripheral pain relievers).

Conclusions

Due to the differences in the emotional and cognitive development, the evaluation is more difficult for children.

The EVA self-assessment is reliable and accurate in many studies and has the advantage of being able to be reproduced in time [10]. Manifestations due to child fear (crying, agitation) often present even before puncture less influenced by the child the value of the scale proposed by maneuver.

The maximum average of the pain intensity for children over 6 years (4.1) was recorded in the first post operatory day for both groups, a fact which I attributed to mobilize children. The average values EVA decrease in the pain scores after 36 hours post operatory probably due to the natural resolution of the inflammatory phenomena, but in the meperidine analgesia with paracetamol and still remains higher than 3, suggesting that the dose of opioid seemed adequate was often too small to be useful in severe pain.

In our study, the Cheops and DAN scores fall in the same trend of over estimation of pain management by the medical staff, they are falling below the minimum which is required in the therapeutic intervention, regardless of the type of analgesia used.

Pain assessment within the 48 hours after the surgery should be performed systematically at small intervals of time (4-6 hours), regardless of the clinical situation and the therapies used, which is the only available means to refine observations [8].

The pain assessment must be made by qualified and constant training in pain therapy [4].

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Correspondance to:
Mihaela Coșofreț,
33A 1 Mai Blvd., PF8 Bl., Sc. B, flat 35
900117 Constanta,
Romania
Phone: 0040721538146
E-mail: mihaelacosofret@yahoo.com
THE VALUE OF FAECAL CALPROTECTIN ASSESSMENT IN CHILDREN WITH CHRONIC GASTROINTESTINAL SYMPTOMS

Oana Belei¹, Camelia Daescu¹, Tamara Marcovici¹, Andreea Militaru¹

Abstract

Background: Various studies have described fecal markers as powerful markers of inflammation of the intestinal mucosa in patients with inflammatory bowel disease (IBD). Calprotectin is a calcium-binding protein found in abundance in neutrophils, where it accounts for 60% of the protein in the cytosol. Aim: Several studies have compared fecal calprotectin with activity indexes and/or endoscopic/histological evaluation to confirm intestinal inflammation in IBD patients. This study proposed to assess the accuracy of fecal excretion biomarker calprotectin in children with chronic gastrointestinal manifestations. The objective was to assess calprotectin as indicator of IBD activity using a commercial rapid semi-quantitative test (Cal Detect). Material and methods: 82 children (aged 18 months -18 years), presenting at least one of the following symptoms: diarrhea, rectal bleeding, recurrent abdominal pain, weight loss, constipation or alternative bowel habits were clinical and biological examined. Stool samples were collected from all of them and tested for calprotectin using a commercially available kit. In parallel, all patients were referred to colonoscopy. Results: 14 children were diagnosed with IBD (9 associating Crohn’s disease – CD and 5 ulcerative colitis – UC). The remaining of 68 children formed the control lot, and their diagnoses included: chronic constipation, rectal and/or sigmoidan polyps, eosinophilic proctitis associated with cow’s milk protein allergy or irritable bowel syndrome. The overall specificity (Sp) for IBD was 66% for a positive cut off point of 15 µg/g, and became 100% when raising the positive cut off point to 60 µg/g (p= 0.0003). Conclusions: Raised fecal calprotectin more than 15 µg/g should prompt endoscopic assessment in children with chronic intestinal symptoms, since an organic bowel disorder is likely. Being an invasive method, colonoscopy can be avoided in children with gastrointestinal symptoms and low positive levels of fecal calprotectin between 0 and 15 µg/g. Fecal calprotectin detected by this rapid semi-quantitative test represents a sensitive and specific marker for detection of intestinal inflammation in children with CD and UC at a positive cut off point of 60 µg/g.

Key words: Crohn’s disease, ulcerative colitis, calprotectin, inflammation, children

Introduction

Endoscopic evaluation with histopathological sampling is generally considered indispensable in the investigation of patients with suspected inflammatory bowel diseases (IBD). In a relatively large proportion of children with chronic gastrointestinal symptoms and suspected IBD, the results of endoscopy will be negative. Laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum fibrinogen level and haematocrit, among others, are not specific to active IBD, so those can not be used routinely as markers of inflammatory activity in clinical practice (1), (2). In order to avoid invasive investigations, several noninvasive markers have been suggested to distinguish functional gastrointestinal disorders from organic diseases. Among these, fecal calprotectin concentrations have been shown to be a good marker of intestinal mucosal inflammation, being higher in patients with IBD than in controls (3). Calprotectin constitutes ~60% of the soluble cytosol proteins in neutrophil granulocytes and plays a central role in neutrophil defense. (4) Consequently, its concentration in stool correlates with the intensity of neutrophil infiltration of the intestinal mucosa and with the severity of inflammation. Furthermore, its in vivo and in vitro resistance to degradation allows fecal samples to be assayed for a reliable calprotectin determination (5). Faecal calprotectin is found elevated in adults and children with various gastrointestinal infections, but the concentrations are lower than in persons with IBD. (6), (7) Calprotectin is present in plasma, and the faecal calprotectin concentrations might be increased with any bleeding into the gastrointestinal tract (8). Elevated concentrations of faecal calprotectin have been described in cystic fibrosis, rheumatoid arthritis, Crohn's disease (CD), ulcerative colitis (UC) and bacterial infections, as well as neoplastic conditions (9). This new approach to the diagnosis of IBD - fecal calprotectin testing - is a useful tool for identifying patients who are most likely to need endoscopy for suspected IBD, thereby reducing the number of unnecessary endoscopies especially in children.

¹First Pediatric Clinic, University of Medicine and Pharmacy “Victor Babes” Timisoara
E-mail: oana22_99@yahoo.com, camidaescu@yahoo.com, t_marcovici@yahoo.com, andreamilitaru@yahoo.com
Objectives of the study
Several studies have compared fecal calprotectin with activity indexes and/or endoscopic/histological evaluation to confirm intestinal inflammation in IBD patients. The results of these studies are promising, demonstrating that these markers are useful in detecting inflammation and differentiating it from other diseases as well as in predicting recurrence for periods of up to one year. This study proposed to assess the accuracy of fecal excretion biomarker calprotectin in children with chronic gastrointestinal symptoms. The objective was to assess calprotectin as an indicator of IBD activity using a rapid semi-quantitative test – Cal Detect.

Material and methods
The study was developed between October 2009 and December 2011 and included 82 consecutive patients presenting one or more of the following symptoms: diarrhea, rectoragia, recurrent abdominal pain, constipation, alternating constipation / diarrhea, fever, pallor, fatigue, weight loss, continuous or intermittent symptoms present at least one month before study entry. The patients’ age varied between 1 year 6 months and 18 years old. One mandatory criteria for inclusion in the study was the written informed consent of children’s legal tutors, accepting all the clinical and biological tests, including the lower ± upper digestive endoscopy followed by intestinal biopsy sampling.

Exclusion criteria were the presence of hepatitis B, C or HIV, bacterial or viral (Rotavirus or Adenovirus) diarrhea and intestinal parasitosis.

We performed to all children a complete initial clinical examination, followed by biological evaluation (CBC, CRP, ESR, fibrinogen, serum iron, blood glucose, liver and renal tests), assessment of total and specific IgE to food allergens - in some selected cases and viral markers such as HBsAg / HBsAb, HCVAb and HIV test for the exclusion of positive cases. Stool samples were taken in order to identify the Rotavirus and Adenovirus fecal antigens. Three consecutive coproparasitological exams were needed to exclude children with parasitic diarrhea from the study. Fecal calprotectin was assessed in all children. Coloscopy ± colonic biopsy was performed after blood and stool sample examination to all patients who fulfilled the inclusion criteria in the study.

Calprotectin determination from feces was done using Cal Detect test, a rapid immuno-chromatographic semi-quantitative test. Calprotectin (MRP 8 / 14) is a heterodimer of two proteins that are linked by calcium (MRP 8 and MRP 14), present in the cytoplasm of neutrophils and expressed by the membrane of monocytes. The physician can distinguish the value of calprotectin thanks to the presence of three strips proportional with the inflammatory level. Fecal sample should be placed directly on the foil tape included in the kit. According to the manufacturer's instructions, the test shows a strip which represents the control. The first strip indicates that calprotectin concentration is less than 15 µg/g, value that is not representative in cases of intestinal inflammation and may indicate the presence of intestinal bacteria. The presence of a second strip indicates that calprotectin concentration is between 15 and 60 µg/g, which indicates an acute inflammation of the intestinal mucosa. The appearance of a third strip shows that the concentration of calprotectin is greater than 60 µg/g and displays a high degree of inflammation of the intestinal mucosa.

We performed to all children from our study a colonoscopy after a short-term sedation with Propofol and Midazolam. According to macroscopic appearance of mucosa we performed only sigmoidoscopy, partial, or total colonoscopy with the examination of the first 10 cm of terminal ileum. Endoscopic biopsies were taken in patients with affected areas. When the colonoscopic appearance was typical for Crohn's disease, upper (gastrointestinal) endoscopy was done to quantify the extension of lesions.

Statistical analysis was performed using SPSS 16 (Statistical Package for Social Sciences for Windows version 16).

Results and discussions
Out of the 82 patients, which were clinical, biological and endoscopic examined, 14 children were diagnosed with inflammatory bowel disease (IBD) based on endoscopic aspect and on the results of colonic biopsies. Of these, 9 patients had ileo-colic form of CD and the rest were diagnosed with hemorrhagic ulcerative colitis (UC).

The rest of patients without inflammatory bowel disease that was excluded based on colonoscopy ± biopsies, were diagnosed as follow:
- 23 cases were diagnosed with irritable bowel syndrome (IBS) according to third Rome criteria,
- 31 children had functional constipation (FC) and some of them associated anal fissures
- 8 children had singular and benign sigmoid polyps (BSP)
- 6 cases presented eosinophilic proctitis (EP) in association with cow’s milk protein allergy (Figure 1).

---

**Figure 1**: Distribution of diagnosis after colonoscopy was performed.
To assess the accuracy of calprotectin detected due to the intestinal inflammation at patients with CD and UC, sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (VNP) were calculated according to statistical formulas listed below (Table I).

### Table I: Definition of statistical parameters used in this study.

<table>
<thead>
<tr>
<th></th>
<th>Present Disease (D+)</th>
<th>Absent Disease (D-)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Test (T+)</td>
<td>a</td>
<td>B</td>
<td>a+b</td>
</tr>
<tr>
<td>Negative Test (T-)</td>
<td>c</td>
<td>D</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

- **Sn** = \( \frac{a}{a+c} = \frac{\text{true positive subjects (RP)}}{\text{total B +}} \)
- **Sp** = \( \frac{d}{b+d} = \frac{\text{true negative subjects (RN)}}{\text{total B –}} \)
- **PPV** = \( \frac{a}{a+b} = \frac{\text{true positive subjects (RP)}}{\text{total B +}} \)
- **VNP** = \( \frac{d}{c+d} = \frac{\text{true negative subjects (RN)}}{\text{total B –}} \)

Our study lot consisted in 14 patients with IBD. It was analyzed in terms of the distribution by age and sex. The average age of patients was 14.5 years and sex ratio F / B was 5 / 9 (36% girls and 64% boys). The rest of 68 patients without endoscopic aspects and/or histological characteristics of CD or UC, were considered to be the control group. All 14 patients with histologic aspects characteristic for IBD showed positive values of calprotectin. In three cases the titer was between 15-60 µg/g, while the rest had values greater than 60 µg/g, according to cut off values established by the manufacture company of Cal-Detect kits (Figure 2). None of the 68 patients from the control group (without inflammatory bowel disease) had positive values of calprotectin greater than 60 µg/g. There were negative values of calprotectin (0-15 mg / g) in 45 patients, while in 23 of the children without inflammatory bowel disease it was detected, however, a positive value of calprotectin between 15 and 60 µg/g, underlining by the presence of inflammation in the gut due to other conditions than IBD (chronic constipation, anal fissures, polyps traumatized by sigmoid passage of faeces, eosinophilic proctitis) (Figure 3).

**Figure 2:** Semi-quantitative assessment of fecal calprotectin determined by Cal Detect kits in patients with inflammatory bowel disease and in control group.
We calculated the values of Sn, Sp, PPV and NPV of calprotectin in patients diagnosed with IBD, with a positive cut-off set at 15 µg/g first and then with a positive cut-off set at 60 µg/g and then we compared the datas.

Table II: Sn, Sp, PPV and NPV values of calprotectin using Cal Detect kits for the diagnosis of IBD at a positive cut-off set at 15 µg/g

<table>
<thead>
<tr>
<th>Test with positive cut-off &gt; 15µg/g</th>
<th>Sn</th>
<th>Sp</th>
<th>VPP</th>
<th>VPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin</td>
<td>100%</td>
<td>66%</td>
<td>37%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table III: Sn, Sp, PPV and NPV values of calprotectin using Cal Detect kits for the diagnosing of IBD at a positive cut-off set at 60 µg/g

<table>
<thead>
<tr>
<th>Test with positive cut-off &gt; 60µg/g</th>
<th>Sn</th>
<th>Sp</th>
<th>VPP</th>
<th>VPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin</td>
<td>78%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Statistic analyze was performed using SPSS 16 programme. We used chi-square test for comparison of specificity and positive predictive values of calprotectin considered positive first at a cut-off of 15 µg/g, and then 60 µg/g. We obtained a statistically significant difference p = 0.0003.

Although this study evaluated calprotectin at a positive cut-off of 15 µg/g, it showed a good sensitivity. The lower value of its specificity at this cut-off was responsible for a significant lower PPV.

None of the 68 patients from the control group showed positive values of faecal calprotectin in titers greater than 60 µg/g, but, however a moderate value of calprotectin between 15 and 60 µg/g was detected in 23 of the children without IBD due to the presence of inflammation in the gut because the underlying disease. This fact lowers the specificity of Cal-Detect kit in diagnosis of IBD at moderate values between 15 and 60 µg/g. If the threshold is increased and we consider values of calprotectin greater than 60 µg/g significant for IBD, the specificity of this test will increase to 100%. So, we can diagnosed pediatric patients with inflammatory bowel based on clinical and biological picture suggestive for this disease, which associates calprotectin values greater than 60 µg/g. In children with clinical and biological data characteristics for IBD, calprotectin values between 15 and 60 µg/g, colonoscopy and serial biopsies are needed for the diagnosis. Colonoscopy ± upper digestive endoscopy investigations are mandatory in all children with IBD, because it helps to establish the extension of the disease, makes the differences between CD and UC and contribute to the pursuit of therapeutic effectiveness (10). Semi-quantitative rapid Cal-Detect test for detection of calprotectin in the faeces has a high negative predictive value of great importance in the selection of pediatric patients with intestinal symptoms (abdominal pain, diarrhea, rectoragia, stagnation weight, etc.) for colonoscopy. Tests with values below 15 µg/g can exclude the colonoscopy in children, sparing pediatric patients of the discomfort of an invasive, traumatic exploration.

Conclusions

Fecal calprotectin detected by a rapid semi-quantitative test using Cal Detect kits represents a sensitive and specific marker for detection of intestinal inflammation in children with CD and UC at a positive cut off point of 60 µg/g. Raised faecal calprotectin more than 15 µg/g should prompt endoscopic assessment in children with chronic intestinal symptoms, since an organic bowel disorder is likely. Being an invasive method, colonoscopy can be avoided in children with gastrointestinal symptoms and low positive levels of fecal calprotectin between 0 and 15 µg/g. Recent studies reported an increasing of IBD prevalence in children. A lot of other bowel disorders can present with similar clinical manifestations (cow’s milk protein allergy, eosinophylic
Therefore, it is useful to promptly detect intestinal inflammation by rapid fecal markers, in order to select the referral to endoscopy of pediatric patients. Due to its high negative predictive value, fecal calprotectin assessment using quick test Cal Detect can avoid unnecessary colonoscopy in children, making this a cost/efficient test in pediatric digestive pathology.

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Correspondance to:
Belei Oana,
Heinrich Heine Street no 4,
code 300041,
Timisoara,
E-mail: oana22_99@yahoo.com
DIFFUSE GIANT INFLAMMATORY POLYPOSIS 
AT THE ONSET OF ULCERATIVE COLITIS, 
PRESENTING WITH PROTEIN-LOSING 
Enteropathy and Masquerading 
As Intestinal Intussusception

Elena Daniela Serban¹,³, P Florescu²,³

Abstract
Inflammatory polyposis (IP) in ulcerative colitis (UC) appears most often over the course of the disease, being very rarely described as a presenting feature. Giant IP (> 1.5 cm in diameter or length) is very uncommon and most reported cases have had a localized form. We report a case of a male teenager, who was admitted in our clinic after 16 days of abdominal pain and bloody diarrhea. He was found with palpable abdominal mass, protein-losing enteropathy and anemia. Intestinal intussusception was considered in the surgical department; however, laparotomy did not reveal any abnormality. Readmitted to our department two months later, he was diagnosed by colonoscopy and histology with giant diffuse IP and moderate-to-severe ulcerative pancolitis. Therapy with Mesalazine and Prednisone led one month later to histological remission of the UC and reduction in the number and size of the polyps. Being a steroid-dependant UC, Azathioprine was added 3 months later and he has remained in microscopical remission since (5.6 years later). We discuss our case in relation to the literature and highlight the current concepts in managing the treatment, given also the high risk of colorectal cancer (CRC).

Case report
A 14-year 1-month-old male, without any significant personal/family medical history, presented to our clinic in April 2006, with diffuse abdominal pain and bloody diarrhea (3-6 diurnal and nocturnal daily stools), for 16 days. He had been previously admitted into two hospitals and treated with antibiotics for presumed gastroenteritis, without any effect. In our clinic, the physical examination revealed pathologically pallor, palpebral edema, intense diffuse abdominal tenderness, palpable mass in the right lower paraombilical area (~4/8 cm), with diminished abdominal sounds in that region, and bloody loose stools at the digital rectal examination. Somatic development was within the normal range (weight 46 kg, p10-25; height 161 cm, p50; BMI 17.7 kg/m², p10-25).

Clinically, the following hypotheses have been considered: persistent infectious diarrhea, antibiotic-associated diarrhea, inflammatory bowel disease or diverticulitis, associated with possible tumor. Inflammatory markers were normal (ESR, fibrinogen, CRP, no neutrophilia). Basic blood tests have shown hypochromic microcytic hyposideremic anemia (Hb 10.3 g%, VEM: 75.5 fl, HEM: 24.5 pg, Fe=9 µg/dl) and hypoalbuminemia – 1.8g% [n 3.5-4.5 mg%]; liver, pancreatic, hemostasis and urinary tests were normal. Immunologic panel (including antinuclear antibodies, antidSDNA, serum immunoglobulins, pANCA, cANCA, ASCA) was normal. HIV, cytomegalovirus Ig M and Epstein-Barr virus Ig M antibodies were negative.

¹Second Pediatric Clinic, Emergency Children’s Hospital, Cluj-Napoca
²Department of Pathology, Emergency Children’s Hospital, Cluj-Napoca
³University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca
E-mail: danitiserban@yahoo.com
Neither pathogens nor dysbiosis were detected in the stool (including toxins against Clostridium difficile). On the next day, the patient’s condition worsened, with insupportable abdominal pain. A colonoscopy was planned, but the surgeons suspected an ileo-colonic intussusception, requiring the patient to be transferred to their department. Two days later, a laparotomy was performed, however, without revealing any pathology. The patient was subsequently treated with antibiotics (Amikacin, Cefuroxime, Clindamycin), for an associated mandibular osteomyelitis and was dismissed from the surgery department 6 weeks later. In the hospital, as well as at home, he continued to present intermittent bloody diarrhea and abdominal pain. Readmitted in our clinic 2 months after the first visit, we found the same physical characteristics, except for the absence of the abdominal mass and the presence of weight loss (1 kg). Laboratory results were not much different than the first admission, except for the worsening of anemia (Hb 9.9 g %). Lower endoscopy revealed, surprisingly, hundreds of diffuse colonic polyps, sized between 0.5 and 2 cm, most of them being sessile, with various shapes. The intervening mucosa (difficult to be appreciated given the density of polyps) showed erythema, loss of vascular pattern, ulcerations, friability and petechiae (Fig. 1). All lesions (including polyps) were much less pronounced in the rectum. Terminal ileum was normal. Upper digestive endoscopy was normal. The endoscopic diagnosis considered a diffuse colonic polyposis (with rectal sparing), inflammatory and/or adenomatous, in the settings of a possible active ulcerative colitis with relative rectal sparing. The histopathology report (a few days later) showed typical features of inflammatory polyposis (Fig. 2) and chronic active diffuse colitis, without any adenomatous feature. Our final diagnosis was moderate-to-severe ulcerative pancolitis, with diffuse GIP. A treatment with Prednisone and Salofalk was administered, according to the existing guidelines.

One month later, the follow-up visit showed triple clinical, endoscopic and histological remission of the UC, with marked reduction in the number and size of the polyps. After tapering the steroids, 3 months later, colonoscopy showed remission of the UC, but with microscopical activity. To prevent the clinical flare-up, we restarted the steroid therapy, adding Azathioprine, given the steroid-dependency. The patient had 18 follow-up visits in our clinic (last in April 2010), with at least 2 colonoscopies/year. He remained in histological remission for 5.6 years, with only a few diffuse scattered inflammatory polyps and a good somatic development (18 year-old male, weight 70 kg, p50-75; height 170 cm, p10-25; BMI 24.22 kg/m², p75-85). He did not develop any severe infection or side effects related to the therapy. Afterwards, he was transferred to an adult IBD clinic.

**Discussions**

Many aspects could be considered in this patient: the probable diagnosis at the first presentation - intestinal...
intussusception due to GIP, with spontaneous resolution; the extreme rarity and also the severity of the diffuse GIP at the disease onset, with protein-losing enteropathy; the uselessness of the serological inflammatory markers in assessing the activity of the disease, contrasting with other reports; the relative macroscopic rectal sparing (atypical in adult UC, but present in up to 30% of pediatric patients); the patient’s high risk of developing CRC; the crucial role of the colonscopy in monitoring disease activity/surveillance for dysplasia and/or CRC.

Inflammatory polyps appear as intraluminal projections of inflamed or regenerated mucosa, covered by normal/ulcerated epithelium. The classification of the inflammatory polyposis was made more than 30 years ago, considering the following types: localized multiple polyposis (small polyps, < 5 mm with focal distribution), giant polyposis (large polyps, >1.5 cm, generally with focal distribution), generalized polyposis (small polyps with diffuse distribution) and filiform polyposis (elongated slender polyps, with diffuse or random distribution). Our case is peculiar, since he presented with a giant polyposis, but in a diffuse form, which is not included in the above classification.

An outstanding review of published cases with GIP in inflammatory bowel disease (1965-2007) found only 81 GIP in 78 patients, attesting the rarity of this entity. Moreover, as the authors stated, they had only one case in 10 years, out of 1921 patients with UC. GIP has been found to be very rare both at the CU onset (no case in children and 3 in adults, these all being localized) and during the course of the disease (4 pediatric cases, 2 with total colectomy and 2 with partial colectomy, all being localized) and less than 40 cases in adults. We believe that in our case the polyps were already expressed at the first admission, with protein-losing enteropathy and intestinal intussusception, which resolved spontaneously. This makes our case very intriguing, with respect to the very short time of developing the GIP (16 days). Even if we consider 2 months (until the colonoscopy), the period is still unusually short, most cases developing these polyps in years. That is why we considered also the possibility of another type of polyposis (e.g. adenomatous), superimposed on an active colitis. We found in the literature one case associating adenomatous polyposis coli and UC, so that our supposition during the colonoscopy could have been right. In the classical differential diagnosis of the GIP, adenomatous polyp is included, but the main fear is that of an adenocarcinoma. Other entities to be excluded are dysplasia-associated lesion or mass secondary to cytomegalovirus or other infections.

Most cases with GIP had extensive UC, but with localized polyps – especially in the descending and transverse colon; there has been only one published case of pancolonic GIP in adults. Our case is also unique in this respect in children, with GIP arising almost throughout the entire colon (only relative rectal sparing).

The clinical expression of GIP may appear as intestinal obstruction, intestinal intussusception, abdominal pain, diarrhea, lower hemorrhage, and abdominal palpable mass. Three cases presented with protein-loss enteropathy, as was our patient.

We consider that monitoring this patient by periodic colonoscopy with biopsies (2-3/year) was the best choice, both for detecting the microscopical activity/remission and for the surveillance for dysplasia/CRC.

Indeed, if before 2005 the aim of the therapy in UC was to induce and maintain the clinical remission, afterwards, the obtaining of the endoscopic mucosal healing started to be considered. Moreover, many clinicians have lately included as a therapeutic goal the achievement of the microscopical mucosal healing. The detection of an active microscopical inflammation has been associated with a 2-3-fold increased risk of a clinical relapse after 1 year. By performing colonoscopy in clinical remission, we were able to detect this microscopical activity of the UC and start a treatment that avoided the patient to have another clinical flare-up. By maintaining the microscopical remission of the disease, we consider that the risk of CRC was diminished, since a significant association between the degree of histological inflammation and progression towards CRC has been reported in the literature. Chronic inflammation increases oxidative stress, promotes repeated cycles of injury, regeneration, and repair, and accelerates the accumulation of oncogenic mutations. Conversely, especially in adult data, mucosal healing has been associated with long-term remission rates, reduction of disease-related complications and of hospitalization and surgery, and this was true in our patient as well. Our patient was fortunate to keep the remission for such a long time, only with Salofalk and Azathioprine, with marked reduction in size and number of polyps, while most patients with GIP in IBD required colectomy (85%). It is also true that very often surgery has been performed as a security precaution, given the possibility of the confusion of a GIP with an adenocarcinoma.

Nowadays, surrogates of the microscopical healing could be considered the fecal inflammatory markers, like calprotectin. According to the recent ECCO/ESPGHAN Consensus in pediatric UC, calprotectin levels >100-150 µg/g indicate mucosal inflammation, however its role in predicting clinical relapse needs to be further studied. The same Consensus has stated that, in a patient in clinical remission, endoscopic evaluation is not routinely recommended, aside from cancer surveillance. Investigation by inflammatory fecal parameters was not available at that time in our patient.

We highlight that, even if the colonic inflammation in our patient disappeared, he still has risk factors for developing dysplasia and CRC. Generally, in patients with UC, the relative risk of developing CRC is 5.7-fold increased compared with the general population. High risk factors include young age at the UC onset, longstanding disease (cumulative risk of 1.6%, 8.3% and 18.4% after 10, 20 and 30 years of disease, respectively), extensive colitis (relative risk 2 times higher), family history of CRC (risk 2.5 times higher), inflammatory polyps (2-2.5-fold greater risk), colonic strictures, association with sclerosing cholangitis (relative risk 4.8-fold higher than in UC without
sclerosing cholangitis), severe endoscopic/histologic inflammation, detection of dysplasia. Protective factors include: normal colonoscopy[2–6,31], therapy with 5-aminosalicylates[32,33] (although recently controversial[34]), therapy with Azathioprine[35] (but carrying a 4 times higher risk of developing lymphoma[36]), therapy with ursodeoxycholic acid in those with sclerosing cholangitis[28,29], smoking (reduced risk by 50%)[28,29] and prophylactic colectomy[37]. Probable decreasing risk factors are adherence to therapy and surveillance colonoscopies (especially chromoendoscopy and endoscopy with magnification)[28,29]. Given all this data, we consider that for the future, even if calprotectin is available, colonoscopic surveillance is mandatory in our patient, in an adult clinic.

In conclusion, we have reported an unusual case presenting with short-time bloody diarrhea and abdominal pain, who was found with a palpable abdominal mass and was considered as having intestinal intussusception. The association of ulcerative pancolitis and diffuse GIP (expressed with protein-losing enteropathy) at the onset of the disease represents, to the best of our knowledge, the first case in the pediatric literature. The patient was closely monitored by colonoscopy with biopsies and was kept in long microscopical remission. The presence of factors increasing the risk of CRC requires a close follow-up of this patient in the adult clinic.

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Correspondance to:
Elena Daniela Serban
Second Pediatric Clinic
Emergency Hospital for Children
University of Medicine and Pharmacy “Iuliu Hatieganu”
Cluj-Napoca
Romania
E-mail: danitiserban@yahoo.com
USE OF ANTIBIOTICS IN PAEDIATRICS,
WHAT PARENTS THINK

Simona Dumitra, Liana Precup, Daniela Răpan, I Precup,
Andreea Radu, Sabina Morgovan, D Lazăr

Abstract

Background – The exaggerated use of antibiotics led to high rates of antibiotic resistance in our geographical area. Objective – to map the parents’ attitudes and their knowledge regarding the antibiotic therapy in Paediatrics. Materials and methods – A questionnaire was used, comprising 20 questions that would probe the parents’ attitude towards the introduction of antibiotic therapy, the criteria for introducing the antibiotic therapy, the frequency of antibiotic consumption in the family, elements of antibiotic resistance, the frequent consumption of antibiotics, etc. 500 parents of children admitted to the Paediatrics Clinic of the Arad County Hospital answered the questionnaire and the data were analysed statistically by the SPSS 10 software. Results and discussions – the parents consider that the antibiotic reduces the fever and that it must be introduced against the fever. The parents introduce the antibiotic following advice from unauthorized persons and sometimes administer the therapy at their own initiative. Conclusions – The questionnaire highlights the lack of medical education in a large percentage of parents. A large proportion considers the main effect of the antibiotics to be hypothermal. Quality sanitary education is a must, through mass-media campaigns and school workshops. Key words: antibiotic resistance, antibiotic therapy, sanitary education

Introduction

The treatment of bacterial diseases has entered a new stage with the discovery of antibiotics. They were initially regarded as a true universal panacea that can solve any type of bacterial infection. Their abusive use have led to a serious phenomenon called antibiotic resistance, which is natural or an acquired ability of a microorganism to withstand the effects of one or more antibiotics (1, 2,3).

Research of the phenomenon of antibiotic resistance is a permanent activity for the most modern laboratories and research centers worldwide. To avoid this phenomenon go out of control, there were introduced stringent preventive measures but, also, produced new antibiotics which provided to clinicians an effective treatment and a modern solution.

Because the antibiotic resistance is a phenomenon which resemblance with a devastating avalanche, the question is put to empower and aware users and traders of antibiotics so they are used only after a proper scientific advice, argued for a biological criteria and not a random one.

In this sense, it was designed and submitted all information provided by research institutes through the media, Internet, magazines, newspapers or other documents and were made available to the public through special programs of medical information.

What is the result of this information? What is the information that a parent has in relation to antibiotics administered to the child which he has under care?(4,5,6,7,8,9,10,11).

What are the most common mistakes that are related managing antibiotics and how they can be corrected? What is the information gap and how it should be corrected? (4,5,6,7,8,9,10,11).

Objective

In our study, we sought to emphasize parents attitude and knowledge about antibiotics and antibiotic resistance and to outline factors related to self medication.

Materials and methods

It was designed a questionnaire with 20 questions focused on parents attitude towards the introduction of antibiotics in treatment of children, self-medication, antibiotic entry criteria, knowledge of doses and treatment period, the source of information, the result of antibiotic therapy, knowledge of the concept of antibiotic resistance, who prescribed the treatment and how it was obtained (with or without a prescription or purchased stock in the house); with these data it was analyzed the profile of respondents (residence, education level, age of parents and children, the affection of children, fear related to the occurrence of complications and hospitalization. There were interviewed a total of 500 parents of children hospitalized in the Clinic of Pediatrics Arad County Emergency Hospital, aged between 1 and 18 with acute diseases which required antibiotics, from January to April 2011, data being statistically processed.

1Department of Pediatrics, Vasile Goldiș Western University of Arad E-mail: dumitrasimona@yahoo.com, precup_l_d@yahoo.com, daniela_ripan_elisabeta@yahoo.com, precup_l_d@yahoo.com, hadassa4yhw@yahoo.com, sabina_myx@yahoo.com, dorinlazar@ymail.com
Results and discussions

Results obtained after statistical processing outlined the following:
1. Respondents residing in urban areas 282 cases (56.4%) and 218 (43.6%) in rural areas, no significant differences in percent balance;
2. Education level of parents of respondents were: enrolled: 12 cases (2.4%), less than 8 grades, 292 cases (58.4%) were high school, 107 cases (21.4%), higher education 89 cases (17.8%), the highest percentage is recorded by parents who have secondary education;
3. Age of children treated ranged from 1-3 years: 214 cases (42.8%) 4-10 years 230 cases (46%), and more than 10 years 56 cases (11.2%); the group between 1 and 3 years is with a higher vulnerability in terms of illness especially in winter-spring;
4. In principle, parents do not agree with the introduction of antibiotic therapy only when strictly necessary: 482 (96.4%) versus 18 (3.6%) didn’t consider as dangerous the use of antibiotics for their child. This high percentage of parents who responded that they have a firm stance against antibiotics should give us some satisfaction in terms of their conviction.
5. The question towards the administration of antibiotics to their own children at least once in life, without medical advice, 412 (82.4%) responded affirmatively, compared to 88 (17.6%) who denied this;
6. The criteria behind the decision of parents to treat children on their own initiative with antibiotics were: for fever 318 (77.18%) and cough 94 (22.81%);
7. Doses administered by parents, without medical advice, adjusted to the age and weight of children in 283 cases (68.68%), compared with 28 (6.79%) who received a dose lower than the normal child.
8. Duration of administration of antibiotics, without medical advice, was 1-2 days in 274 cases (66.50%), 3-5 days in 130 cases (31.55%) and less than 5 days in 8 cases (1.94%). High percentage of cases who stopped antibiotics after symptoms improved in 1-2 days could prove that the antibiotic was not necessary, although it is difficult to assess retrospectively;
9. Source of information for parents for administering medication to children was the internet in 58 cases (14.07%), entourage in 102 cases (24.75%) and previous experience in 252 cases (61.16%), all 252 cases were treated with the same antibiotic that the child received at the last visit to the doctor, which is correlated with the fact that, although the choice of antibiotic can often be inappropriate for the child condition, however, parents rarely get the wrong dose because of a recent past experience;
10. In self-medication, diseases treated had a favorable outcome in 321 cases (77.91%) and unfavorable in 91 cases (22.08%), these cases requiring medical intervention; favorable evolution in a significant percentage makes us believe again that many viral diseases are treated with antibiotics, in the wrong way;
11. The first motivation for the introduction of antibiotics to treat the condition of the child was fear of complications and hospitalization in 482 cases (96.4%);
12. Of all respondents, the concept of antibiotic resistance was unknown, exactly in 276 parents (52.2%), while 224 (44.8%) have heard about this phenomenon. The percentages are similar and contrasts with the high percentage of parents who are against the administration of antibiotics to those who do not have a strong opposition;
13. Anamnysis revealed that the patient received antibiotic treatment for the condition which required hospitalization, current treatment being recommended by the family doctor in 172 (34.4%) cases, 111 cases by pediatric specialist (22.2%), pharmacist 103 cases (20.6%) and 114 cases (22.8%) antibiotics were administered on its own initiative; again, in response to the high percentage recorded “from initiative” which contrasts with that of the general beliefs;
14. Diagnosed disorders that were treated with antibiotics from the recommendation of the physician and from it’s own initiative were: bronchitis 291 (58.2%), laryngitis 88 (17.6%), pneumonia 62 (12.4%), enteritis 7 (1.4%), otitis 52 (10.4%);
15. The data obtained clinically, paraclinically and from biological laboratory results at hospitalization were found 201 cases of bronchitis that would not have required treatment with antibiotics, 51 cases of laryngitis and 12 cases of otitis.

Conclusions

Survey shows lack of certainty and a difference between informal medical education of a large percentage of parents and how to action when are confronted with their children disease.

Parents require from the pharmacist for an advice for a recommended antibiotics or administrates on it’s own the antibiotics from the entourage advice or after previous experience.

Antibiotics continue to be administered for symptoms such as fever or cough.

The favorable evolution of some cases who received antibiotics for a short period of time may encourage parents practice, they being convinced that the antibiotic may have not been necessary but they have successfully treated their children.

It requires a sustained and continuous health education, spreading information materials through the media and organized workshops at school sites to train from early age and have strong skills to work outside the subjectivity related to their child illness. It should also ban the marketing of antibiotics in pharmacies at the request of patients who do not have prescription, with sanctions for not following these decisions.

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Correspondance to:
Dumitra Simona,
Clinica de Pediatrie Arad,
Victoriei 1-3,
310158,
Arad
România
E-mail: dumitrasimona@yahoo.com
IMAGISTIC ASPECTS OF THE INTRACRANIAL MENINGIOMA

Elena Pop¹, Monica Vaida¹, Corina Matu¹, Roxana Folescu¹, Izabella Șargan¹, S Bolintineanu¹, A Motoc¹

Abstract

Meningioma is a benign tumor which derives from meninges. The retrospective study has been carried out on a group of 29 hospitalized patients, diagnosed and treated in County Emergency Clinical Hospital of Timisoara (Romania). The paraclinical diagnosis of the intracranial meningiomas, in the case of our group, was based on CT examination: both native and with contrast substance. The exact diagnosis was established by the histopathological examination, in all cases (hematoxylin –eosin staining).

Key-words: intracranial meningiomas, CT, CT with contrast substance, histopathological diagnosis

Introduction

Meningiomas are frequent tumors; they are found in proportion of 13%-19% of the intracranial tumors, thus being on the second position after gliomas. The notion of benignity should not be taken in the strict sense of the word. Although from a histopathological point of view these are benign tumors, the neurosurgical experience proves that a part of the meningiomas, especially those in case of children, behave like malign tumors, having the tendency to quickly and permanently recur, even after a total extirpation. Meningioma is also an expansive tumor, which does not invade, but comprimes the nervous texture around it, during its expansion. Because of this, the disturbed neurological function recovers after the tumor is extirpated, in most of the cases (1,2,3).

Material and method

The retrospective study has been carried out on a group of 29 hospitalized patients, diagnosed and treated in County Emergency Clinical Hospital of Timisoara (Romania), between 2009-2010, aged 18-64. All the patients had been operated upon, and the diagnosis of meningioma was established after the histological examination.

The paraclinical diagnosis of the intracranial meningiomas, in the case of our group, was based on the CT examination: both native and with contrast substance.

The native CT scan aimed at:
- the localization of the generally well defined tumour which had been outside the parenchyma;
- it indicated a round or a flat tumour, either isodense, or discretely hyperdense (frequent), homogeneous;
- frequently there were indicated punctiform or massive intratumoral calcifications;
- there were identified bone abnormalities with the help of bone window at the level of the implementation base;
- peritumoral edema was objectified through a perilezional hypodensity less or more important;
- indirect signs: mass effect;
- indirect signs: mass effect on the medial line, on the ventricular system or/ and on the tanks from the brain base (4,5,6).

The CT with contrast substance:
- the injection of the contrast substance determined a highly increased tumoral hyperdensity (generally, the SDC impregnation was homogeneous; in some cases there were highlighted meningiomas with necrotic center, which took the contrast substance in a scratchy way or in cockade);
- the injection of the contrast substance allows a clearer highlight of the large implementation base of the tumour and also a net differentiation of the peritumoral edema tumour (7,8,9).

Results and discussion

We studied on 29 patients diagnosed with intracranial meningiomas (21 men and 8 women) (Chart 1), with the age 18-64; 15 patients came from urban, while 14 patients came from rural; to all the patients the diagnosis was established on the base of the clinical criteria, biochemical, imagist (TC) and morphological.

Meningiomas may develop on both sides of the dura mater, especially on its inner face. There are cases of meningiomas without dural attachment. These develop on the endothelial cells of the arachnoid. Meningiomas take two forms: round and flat ("en plaque"). The round meningioma is come across on the brain’s convexity or intraventricularly, where the growth in all directions is free. It has a spherical or ovoid form, with a smooth or nodular surface. The insertion base may be large or small, according to the tumour’s size.

¹Anatomy and Embriology Department, University of Medicine and Pharmacy „V. Babes”, Timisoara
E-mail: alexandra_2987@yahoo.com, monicaadrianavaida@yahoo.com, matu_corina@umft.ro, roxanafolescu@yahoo.com, dr.sarganizabella@yahoo.com, bolint@upcnet.ro, amotoc@umft.ro
Tabel 1: The distribution of the cases depending on age and sex.

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<tr>
<th>Age groups</th>
<th>Female</th>
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<th>Number of patients</th>
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<tr>
<td>18 – 30</td>
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<td>31 – 40</td>
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<td>5</td>
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<td>&gt; 60</td>
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The flat meningioma is flattened and stretched and accedes to the dura master on a large surface, while its thickness is small in relation with its insertion base (10). It develops especially at the base of the skull, in this case being accompanied by a marked hyperostose, thus the patient presenting a cranial deformation. At the level of the insertion place of the meningioma, the bone may be modified: either in the sense of thinning due to the process of lysis by pressure, or in the sense of a hyperostosis, which is more frequent in the case of “en plaque” meningiomas. Sometimes, the tumour may invade the bone and overcome the skull, exteriorizing itself under the teguments (11, 12).

The intracranial disposition topography of the meningioma conditions the neurological semiology and is at the origin of the anatomo-clinical classifications (Chart 1).

According to these criteria, the meningiomas are classified into:
- hemispheric convexity meningiomas (4 cases);
- meningiomas of the cranial base (11 cases);
- para-saggital meningiomas;
- meningiomas of the scythe brain, with unilateral or bilateral development (2 cases);
- meningiomas of the tentorium;
- meningiomas of the posterior cerebral fossa (12 cases).

The exact diagnosis, in all the cases, was brought by the histopathological examination (hematoxylin- eosin staining).

The histological classification of the World Health Organization divides the meningiomas into 3 main types (Chart 2):
- menigothelial meningioma (14 cases);
- fibrolastic meningioma (5 cases);
- psamomatous meningioma (10 cases).

Case 1 (Figures 1,2): Meningioma in plaque, of approximately 5/4 , 2/4 cm, developed at the level of the sphenoidal corpus, on clivus, left cavernous sinus, suprasellar , which includes left internal carotid artery in the cavernous portion, it marks the basilar artery and it moves the optic chiasm. Aneurism dilatation of 4 mm, sessile of left intracavernous ICA. Without other cranial-cerebral changes.

Case 2 (Figures 3,4): Meningioma does not always have different imagistic characters from the benign one; the unclear margins, the scratchy contrast setting, the necrosis’ presence and the osteolysis at the implementation base are indicative criteria.
Figure 1: Case 1: T.N. patient, 49 years old, Diagnosis - Meningioma in sphenoidal plaque.

Figure 2: Psamomatous meningioma (HE x 200) and detail: hematic extravasated (HE x 400).

Figure 3: Case 2: R.A. patient, 61 years old: Diagnosis- Meningioma in plaque.

Figure 4: Meningothelial meningioma, oval cells, arranged in compact vortex and isles and focal myxoid degeneration (HE x 100).
Conclusions

- we identified meningiomas in 3 cases which presented fatty degeneration with native hypodense aspect;
- there appeared difficulties in identifying isodense tumours with cortical localization (meningiomas of convexity);
- the best TC examination was performed in a spiral way, fact which led to a shorter examination period and brought maximum information which could be obtained through the processing (post-processing) of the scanned volume;
- CT- scan and NMR are imaging examinations which accurately specify the topography of brain tumors. These appear as hyperdense, space-replacing formations. A tumoral biopsy is essential in order to highlight the histological type and to establish the treatment.

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Correspondence to:
Elena Pop,
Anatomy and Embriology Department
University of Medicine and Pharmacy „V. Babes”
P-ta Eftimie Murgu Nr. 2,
300041,
Timisoara
România
E-mail: alexandra_2987@yahoo.com
PHYSICAL DEVELOPMENT (WEIGHT AND HEIGHT) IN CHILDREN WITH CONGENITAL HEART DISEASES

Maria Elena Veronica ¹, Antonia Popescu², Georgeta Cornițescu¹, Ileana Puiu¹

Abstract

Introduction: Children with congenital heart defects (CHD) are prone to malnutrition and growth disorders, both due to reduced food intake, and increases in energy needs. Objective: Assessment of physical development in children with CHD and identification of significant factors that influence z scores. Methods: Anthropometric data have been registered in a group of children with CHD and z score has been calculated for weight/age, height/age and weight/height. It has been used the Mann-Whitney statistical test to compare the z scores. Results: Weight-for-age z-score was ≤ -2 for 75 children (44.38%), weight-for-size for 48 children (28.4%) and height-for-age for 72 children (42.6%). Comparing z scores we have identified a significant difference (p <0.01) between averages of height-for-age z-scores and statistically highly significant (p <0.001) for weight-for-age z-scores between children born prematurely and eutrophic children. The presence of heart failure (HF) influenced negatively the physical development in children with CHD, p = 0.0001 in weight-for-age z-score, and p = 0.015 in height-for-age z-score. Inappropriate food selection has been negatively correlated with physical development (p <0.05, 95% CI). Conclusions: Physical deficit is frequently found in children with CHD, and chronic malnutrition affects both length and weight in children. Nutrition counseling is an important part of every child’s recovery process.

Keywords: physical deficit, congenital heart defect, children.

Introduction

The essential element which distinguishes the adult from the child is the complex process of growth and development, a highly dynamic process, that begins at conception, continues in intrauterine life, and then throughout childhood and adolescence. The growth process is a highly biological energy consumer used in the synthesis of plastic substances, tissue organization, and cell mitosis.

Children with congenital heart defects (CHD) have frequent disturbances of growth and development. In these children, multiple factors are incriminated in the development of these disturbances and the understanding and control of these factors can prevent the deterioration of nutritional status and therefore increased morbidity. It creates a vicious cycle between malnutrition, heart failure and respiratory infections.

Half of children with CHD require surgery in infancy, and postoperative evolution is negatively influenced by malnutrition.

Objective

The objective of this work is to appreciate the physical development in children with CHD and to identify the significant factors that influence z scores.

Materials and methods

The study included 169 children with CHD hospitalized in Pediatric Clinics I and II of the Emergency County Hospital of Craiova, in January 2007 - December 2010.

In all cases patients were assessed using demographic factors, socioeconomic factors, and history of nutritional intakes. Anthropometric data were recorded and weight-for-age, height-for-age, and weight-for-size z-scores were calculated using as reference values from WHO growth tables (The WHO Child Growth Standards 2007).

An alternative way to express height, weight, and weight for height is z score, which denotes units of standard deviations from the median. It allows the clinician to locate an observation on the normal curve by the number of standard deviations it is from the center of the curve, and thus detect movement toward or away from the median, which is more sensitive than percentile changes.

For the statistical analysis we used the Data Analysis module of Microsoft Excel 2003 (Microsoft Corp., Redmond, WA, USA) together with the XLSTAT 2009 for MS Excel (Addinsoft SARL, Paris, France), to process the data.

The original database was created by using all data of the subjects. From it we extracted only the important aspects for this study.

The actual processing was done using the Pivot Tables, Functions-Statistical, Chart commands and the Data Analysis module of MS Excel and commands for statistical tests from the XLSTAT add-in.

¹University of Medicine and Pharmacy, Craiova
²University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj Napoca
E-mail: veronica17nico@yahoo.com, tonypopescu@yahoo.com, constantincornitescu@email.com, vipuiu@yahoo.com
We used the Mann-Whitney statistical test to compare the z scores.

**Results**

From 169 children with CHD 97 (57.40%) were boys, and 72 (42.60%) girls (Figure 1).

Figure 1. Distribution of cases by sex.

Weight-for-age z-score was \( \leq -2 \) for 75 children (44.38%) (Figure 2), weight-for-height for 48 children (28.4%) (Figure 3) and height-for-age for 72 children (42.6%) (Figure 4).

Figure 2. Weight-for-age z-score.

Figure 3. Height-for-age z-score.

Figure 4. Weight-for-height z-score.

Using the statistical test Mann-Whitney we identified a significant difference \( (p <0.01) \) between averages height-for-age z-scores and statistically highly significant \( (p <0.001) \) for weight-for-age between children born prematurely and eutrophic children (Figure 5).
The presence of heart failure (HF) influenced negatively the physical development in children with CHD, p = 0.0001 for weight-for-age z-scores, and p = 0.015 for height-for-age z-scores (Figure 6).

We could not demonstrate any other statistically significant differences in case of surgery, pulmonary hypertension (PH) and cyanosis.

Poor nutrition diet was negatively correlated with physical development, the average value of weight-for-size z-scores in patients who had an improper diet is significantly lower than those that had a proper diet (p = 0.028, 95% CI) (Figure 7).

Discussion

Children with congenital heart defects are prone to poor physical development no matter what are the nature of cardiac malformation and the presence/absence of cyanosis.

In these children there is a degree of functional and structural damage to organs (reduced stomach capacity, anoxia, circulatory congestion, changes in intestinal motility, decreased absorption), but inadequate caloric intake is the major cause of poor growth. Reducing food intake following a strict control of fluid necessities is often associated with inadequate intake of nutrients due to fatigue or tachypnea, or low socioeconomic level of the family.

Hyper catabolic status, given by the increased cardiac and respiratory activity, makes that caloric needs used for optimal growth to be 50% higher than in normal children.

In a study made by Varan, Kurs, Tokel, and Yilmaz regarding children with CHD, 65% were below the 5th percentile for weight, 41% were below the 5th percentile for height.
both height and weight, 63% of children showed low weight for height. (1,2)

In our study group z score was ≤ 2 in almost half of children with impairment of both waist and weight.

Premature healthy babies have an accelerated growth rate, at 8-9 months catching those children born at term. Also children who were born dysmature, if intrauterine malnutrition was due to maternal causes, after birth they will show an accelerated growth.

Children born with impaired weight and CHD, included in our study, presented poor physical development, the mean Z scores for eutrophic subjects being significantly higher than those for preterm subjects with 99% confidence.

Cardiac malformations associated with cyanosis, pulmonary hypertension and congestive heart failure cause a more severe damage to weight and size, with worsening nutritional deficit. (1,2,3)

In our study the average z scores were lower in children with cyanogen congenital heart diseases, PH and HF, but only in cases with HF the difference between Z scores was statistically significant.

In developing countries, due to limited resources, many times the intervention for correction of CHD is made late, realizing a vicious circle, frequent respiratory infections and heart failure promoting and worsening malnutrition. (4)

Several studies have shown normalization of somatic growth if corrective surgery is performed early. (5,6)

Regarding the intervention, we could not demonstrate a significant influence of it in terms of z scores making a correlation between patients with surgery and patients with no surgery. This is explained by the small number of patients who were operated on, only 27, but also by the advanced age when surgery was performed.

A group of doctors from the Instituto Coração do Hospital DAS Clinicas - FMUSP - São Paulo, SP - Brazil, assessed dietary intake in children between 0 and 24 months, with CHD. The results of this study showed inadequate food consumption during hospitalization and the probability of deepening power failures at home. (7,8)

In our study group food history has shown 39% of children with inadequate diet. Average value of weight-for-height and weight-for-age z-scores for patients who had incorrect diet was significantly lower than those who had a proper diet.

Conclusions
1. Physical deficit is frequently found in children with CHD, and chronic malnutrition affects both size and weight.
2. CHD associated with HF causes a more severe damage to weight and size.
3. Birth weight represents a negative prognostic factor for subsequent development of children with CHD.
4. Nutrition counseling is an important part of every child’s recovery process.

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Correspondence to:
Maria Elena Veronica
Strada Independenței, Nr. 1, Bl. 6A, Sc. 1, Ap. 3,
Craiova,
Județul Dolj,
E-mail: veronica17nico@yahoo.com
SEPTIC SHOCK IN A SCHOLAR MALE PATIENT

Laura Marinăș1, Ileana Puiu1, Carmen Niculescu1, Anca Maloș2, Simona Răciulă3

Abstract
Septic shock can be defined as a severe sepsis with low blood pressure, prolonged over an hour, which does not respond to intravenous administration of fluids and requiring vasoactive substances management. The authors report the case of a scholar Ş.M., a male patient, aged 10 years, who was admitted to the Intensive Care Department of Pediatric Clinic I Craiova presenting with coma, severe hypotension, occurred due to fever, vomiting and diarrhea emission. Laboratory investigations revealed: infectious anemia, leukopenia (2900/mm3), followed by leukocytosis (>13000/mm3), six days), thrombocytopenia (<85000/mm3) which lasted for 7 days and altered coagulation, elevated serum ALT, AST (100-500u/l), hypoglycemia, metabolic acidosis and transient hyponatremia, hypokalemia. Being comatose, with O2 saturation (determined by pulse oximeter) of 76%, it has been required assisted ventilation for 5 days. Severe hypotension (40/30 mm Hg) in the second day of admission imposed both an adequate fluid rebalancing and proper administration of Dopamine 5µg/kc/min. These are antibiotics that were sequentially used: Sulcef, Meropenem, and Ceftriaxone associated with Metronidazole and Ciprofloxacinum. Clinical evolution was favorable, fever reducing gradually in 4 days. Five days later, he regained consciousness without disabling motor deficits. Due to mechanical ventilation, he presented subcutaneous emphysema as a transient incident. Because of the lesions diagnosed “dry gangrene” to toes, he has been transferred on the 14th day to Pediatric Surgery Department, where he received antibiotics, local treatment, being discharged on the 18th day from admission. In conclusion, our patient was admitted in the Emergency Room for septic shock, a redoubtable complication of sepsis, due to a gastroenteritis. His evolution was a favorable one, unto healing, but with disabling ischemic lesions in the legs caused by microcirculation disturbances in the context of a septic shock low blood pressure. The particularity of this case was a “restitutio ad integrum” healing of the organ damage and his complete recovery after septic shock with life-threatening hypotension.

Key words: septic shock, hypotension.

Introduction
Sepsis is defined as a systemic inflammatory response syndrome (SIRS) induced by infection. Severe sepsis can be diagnosed when an organic injury occurs, as a sign of hypo-perfusion and / or hypotension. Septic shock is defined by the maintenance of hypotension (SBP <85mmHg) over an hour, according to the correct fluid and electrolyte rebalancing, requiring vasoactive drug administration(1). If it does not respond to any injection of vasopressors, it is a refractory shock. Septic shock is a medical condition as a result of severe infection and sepsis, though the microbe may be systemic or localized to a particular site. Its most common victims are children. It can progress to death within the first 24-48 hours, due to multiple organ failure (MOF)(1), or to reversible multiple organ dysfunction syndrome (MODS) and healing, often with sequels.

Case report
We present the case of a male scholar, named Ş.M., aged 10 years, from rural environment, who has been hospitalized in Intensive Care Department of First Pediatrics Clinic of Craiova, then moved to the ward. Afterwards, he has been transferred to the Department of Pediatric Surgery. The month of admission was november 2011.

Reasons for admission to Intensive Care Department were: the abolition of consciousness, with cold and cyanotic hands and feet, hypotension (SBP decreased from 90 to 40 mm Hg) occurred due to fever, vomiting and diarrhea emission. Family history reveals that he is the 6th child of a poor family, whose mother undergoes therapy for pulmonary tuberculosis. Past medical history includes a hospitalization for gastroenteritis, a year ago and a trauma of skull 6 days ago.

On admission, there were described as it follows: a10-years-old patient, delay of staturo-ponderal growth, abolished consciousness, unresponsive to verbal or painful stimuli, fever 39 C, cyanosis of the face and extremities, pale skin, dehydration, dry mucous membranes, hypotonia of ocular globes , respiratory acidosis, at chest auscultation: rough lung-breathing, HR= 130 b / min, TCR> 3 sec., aloin tongue, adhering to spatula, flushing pharynx, excavated stomach, emesis, watery and fetid diarrhea, at the palpation of the scalp, in frontal area, is decaled a sutured wound, neck stiffness.

Initially, his BP was 90/57 mm.Hg. On the second day of hospitalization, in despite of hydration and fluid rebalancing, he presented extreme hypotension: 40/30 mmHg, with HR = 142-170 b / min.

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1University of Medicine and Pharmacy Craiova, First Pediatric Clinic, Emergency County Hospital
2Critical Care Department, Emergency County Hospital
3Student of University of Medicine and Pharmacy Craiova
E-mail: mlaurad@yahoo.com, vipuiu@yahoo.com, drcarmen@yahoo.com,
anacamalos2003@yahoo.com, simona89@live.com
Blood pressure measured one hour later after administration of Dopamine, Norepinephrine was 77/39 mmHg. He presented fever (39 to 40.5°C) for another three days, but 2nd level coma lasted for 5 days (requiring intubation with mechanical ventilation). On the sixth day he regained consciousness and breathed spontaneously.

**Laboratory findings:**
First and second days of hospitalization (22-23-11-2011):
There were diagnosed anemia, leukopenia, thrombocytopenia.

- **HL + FL:** E = 3900000/mm³, Hb = 10.7 g / dl, Ht = 33%, HEM = 28pg/cell, MCHC = 36%, MCV = 76fl,
- **Platelets** = 53000/mm³, White blood cells = 2900-3800/mm³, FL: PMNs = 81%, basophils = 17%, Mo = 2%.

The smear: anisocytosis, hypochromic red blood cells. INR = 3.38. Quick Time = 20%. APTT = 41%. pH = 7.17; pO₂ = 157.3 mmHg, pCO₂ = 10.8 mmHg, HCO₃act = 7.6 mmol / l; HCO₃std = 13.6 mmol / l. BE = - 13.8 mmol / l, serum urea = 53mg/dl, serum creatinine = 1.26 mg / dl, Na = 126-132 mEq / l, K = 3.2 - 4.9 mEq / l, Cl=114mEq / l. Blood glucose = 42-89 mg / dl; PVC = 5cmH₂O; AST = 61u / l, ALT = 47u / l

ECG revealed tachycardia, HR = 142b/min, and shortening PR interval to 92 ms.

Blood tests run on the third day of hospitalization revealed: anemia, thrombocytopenia and leukopenia replaced by leukocytosis. E = 3230000/mm³, Hb = 8.8 g / dl, Ht = 25% ; HEM, HEM = 27pg, MCHC = 36%, MCV = 76.

- **Platelets** = 68000-84000/mmc, White blood cells = 13700-19400/mmc: in 24-11, Fl: PMNs = 76%, LF = 7%, Mo = 4%, basophils = 13%, then 25-11, FL: PMNs = 11% PMNs = 80%, LF = 6%, Mo = 3%

- **Glucose** = 89mg/dl, serum urea = 35.8-50mg / dl, serum creatinine = 1.05 mg / dl; PVC-13cmH₂O; AST = 524-675u / l, ALT = 128-346 U / l. AST, ALT returned to normal in 12/01/2011.

Clinical evolution was favorable, fever reducing gradually in 4 days. After the first day of hospitalization, he has not presented vomiting anymore, but had diarrheic stools still three days. Five days later, he regained consciousness without disabling motor deficits. Due to mechanical ventilation, he presented subcutaneous emphysema as a transient incident. In evolution, he presented hepatomegaly for 7 days and ischemic skin lesions, consecutive septic shock status.

Because of the lesions diagnosed „dry gangrene” to toes, he has been transferred on the 14th day to Pediatric Surgery Department, where he received antibiotics, local treatment, being discharged on the 18th day from admission.
Discussion

Shock means acute circulatory deficiency, which leads to a poor tissue perfusion, inadequate for cellular needs.

Septic shock is a pathogenic form having in substrate intricate mechanisms (hypovolemic, vasogenic).

Sepsis - concept that refers to those situations in which a clinically proven or suspected infection localized or disseminated, is accompanied by a systemic inflammatory response in the body (SIRS) (2). SIRS includes at least two of following: fever (or hypothermia), leukocytosis (or leukopenia), tachypnea, tachycardia (14).

In this case has been a SIRS (presence of fever, leukopenia/leukocytosis, tachycardia) induced by an infection-gastroenteritis.

As a particularity of this case we can mention a large percentage of basophils. It may appear in various inflammatory diseases as: inflammatory bowel diseases (in this patient was acute gastroenteritis), upper airway disease, chronic dermatitis, in viral infections, infectious endocarditis.

Sepsis with negative cultures means SIRS and empiric antibiotic treatment for clinically suspected infection, but that all cultures are negative(11). In this case, infection was clinically suspected, not proven by laboratory investigations. Leukocytosis with increased of PMNs is usually induced by a microbial infection. We suspected a gram negative infection.

Due to coma and hypotension, even a severe one, 40/30mmHg (second day of admission), in despite of proper fluid rebalancing and due to its persistence more than an hour of SBP<80mmHg, we can diagnose septic shock (SS).

SS is a serious clinical -biological syndrome triggered by different pathogens and / or their products (especially endotoxins). Free LPS attaches to a circulating LPS-binding protein, and the complex then binds to a specific receptor (CD14) on monocytes, macrophages, and neutrophils. Engagement of CD14 (even at doses as minute as 10 pg/mL) results in intracellular signaling via an associated "Toll-like receptor" protein 4 (TLR-4), resulting in profound activation of mononuclear cells and production of potent effectors cytokines such as IL-1 and TNF-α. These cytokines act on endothelial cells and have a variety of effects including reduced synthesis of anticoagulation factors such as tissue factor pathway inhibitor and thrombomodulin.Endotoxins play leading role as trigger in sepsis, septic shock and MODS, adhering to platelets by PAF, by vasoactive Kinines, inducing DIC- with thrombocytopenia, consumption of coagulation factors → a marked alteration of organs infusion→ small thromboses→ installation of septic shock → MODS (multiple organ dysfunction syndrome) and eventually death (9). In clinical analysed case, MODS was developed and proved by hepatic cytolysis syndrome, by need for prolonged mechanical ventilation (more than three days) and by second level coma that lasted for five days (5;7).

Endotoxins lead to activation of proinflammatory cytokins (especially IL-1, IL-6, TNFα), which, released in bloodstream, produce vasodilators and damaging to the capillary endothelial cells. Vasodilators lead to hypotension and hypoperfusion of skin and abdominal viscera. The capillaries can be obstructed by proliferation of WBC that have invaded area to attack bacteria and will cause further cell damages, creating area of tissue ischemia, with insufficient infusion of tissue, that characterizes septic shock.(3) This is the explanation of „dry gangrene” at patient’s feet. It is, also, released nitric oxide (NO) by damaged vascular endothelial cells. NO was shown to reach high levels in septic shock, producing vasodilation and vasoplegia(4). NO and vasoplegia may be the explanation for life-threatening low blood pressure (40/30 mmHg) measured in our analysed patient, who was enough hydrated in the second day of admission. It was not a hypovolemic shock, but a certain septic shock.

Altered microcirculation is central pathophysiological factor of shock’s progression to MODS (11). Low flow syndrome induces ischemic lesions. Extensive lesions of the soft parts may be a trigger that activate humoral systems. They precede the activation of cellular systems, as in sepsis. Thus, disturbances of peripheral irrigation are amplified,
showing a genuine "vicious circle" infection - ischemic lesions – infection (12).

Syndrome "low flow" produces an increased pulmonary release of mediators that contribute to severe endothelial cell damage, especially in the lungs (6). This might explain low oxygen saturation (76%) in a patient without respiratory infection.

DIC was proven by clinical and laboratory findings (INR = 2.23, TQ = 33%, TH = 42 sec, thrombocytopenia). DIC’s activation by endotoxins and other humoral factors will produce small thromboses that aggravate hypoxia, contributes to the morphological substrate of organ failure(4).

There was a transient and minor injury of kidneys (a high serum urea and creatinine level). The damage of liver (which became enlarged for 7 days) was more important, proven by high levels of ALT, AST, for a week.

Conclusion

In conclusion, our patient was admitted in the Intensive Care Unit with sepsis due to a gastroenteritis, followed by septic shock (a redoubtable complication) and reversible MODS. However, his evolution was a favorable one, unto healing, but with disabling ischemic lesions in the legs caused by microcirculation disturbances in the context of a septic shock low blood pressure. One particularity of the case was: the presence of a large percentage of basophils.

“Happy-end” particularity of this case was a "restitutio ad integrum" healing of the organ damage and his complete recovery after septic shock with severe hypotension.

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Correspondance to:
Laura Marinău,
Str. Rîului, no.177,
Craiova,
Jud. Dolj,
România,
Telephone: 0763417076,
E-mail: mlaurad@yahoo.com
TRANSVERSE TESTICULAR ECTOPIA: A CASE REPORT AND REVIEW OF LITERATURE.

Muhammad Riaz ul Haq¹, Bagir Uthman¹, Adel Mutwalli¹, Sami Nasr¹

Abstract
Transverse testicular ectopia, also called Crossed testicular ectopia, is an uncommon congenital anomaly in which both testes migrate through a single inguinal canal towards the same hemiscrotum. A few more than 100 cases have been reported in the literature. This rare syndrome is commonly associated with abnormalities of genitourinary development, especially inguinal hernia and defective Mullerian regression. A conservative approach is recommended, now performed via laparoscopy. Long-term follow-up is required for assessment of fertility and early detection of testicular malignancy. The authors report a new case of crossed testicular ectopia in a 4-year-old boy operated in King Faisal Hospital Saudi Arabia, who presented with right inguinal hernia and bilateral undescended testes.

Key words: testis crossed testicular ectopia, transverse testicular ectopia, testicular migration, ectopic

Introduction
Transverse testicular ectopia (TTE) in an extremely rare entity in which both testes migrate along the same inguinal canal towards the same hemiscrotum, while the opposite inguinal canal and hemiscrotum are empty. The ectopic testis may be located on the inner inguinal ring, in the inguinal canal, or in the contralateral hemiscrotum [1]. The clinical findings are usually symptomatic inguinal hernia on one side to which the ectopic gonad has migrated, and an impalpable testis on the other side. TTE is usually associated with abnormalities such as persistent Mullerian duct syndrome (PMDS). PMDS is a rare form of male pseudohermaphroditism characterized by the persistence of Mullerian duct structures (uterus, fallopian tubes) in phenotypically normal boys [2]. Majority of patients are of a very young age, around 1–2 years old. In 65% cases the exact diagnosis is not determined prior to surgical intervention. Patient often undergoes unsuccessful inguinal exploration and the ectopic testis is usually discovered during the repair of an inguinal hernia [3]. Classically, in TTE the two testes are identical in size and appearance; each has its own epididymis, vas deferens and testicular vessels; the vascular supply and vas deferens of the crossed testis are derived from the appropriate side; the processus vaginalis is patent on the side of the two testes and there is no hernia on the side of the undescended testis [4]. In the pre-laparoscopic era, unilateral TTE was most often diagnosed during herniotomy or following inguinal exploration for contralateral impalpable testis. However, with the increasing use of laparoscopy for the evaluation of impalpable testis, patients with TTE are diagnosed prior to inguinal exploration [5].

In this case, our aim is to raise awareness of this uncommon condition with review of literature on different aspects of management.

Case Report
A 4 years old child was referred to our outpatient department by a general practitioner with the history of bilateral absence of testes in the scrotum since birth and an occasional bulge in the right inguinal canal for a few months, as noticed by the parents. There was no significant family history and other two male children were quite healthy. On physical examination child was found to be in a good state of general health. Scrotum was underdeveloped and cough impulse was positive in the right inguinal region. Scrotum was empty and nothing could be palpated in the left inguinal area while testicular tissue and inguinal hernia were clinically appreciated on the right side. So, with the clinical diagnosis of right inguinal hernia with bilateral undescended testes. Ultra sound was requested. Report was consistent with the presence of both testes in the right inguinal region with patent process vaginalis. After necessary blood work up, patient was placed on elective operative list. Under general anesthesia, right side was explored through a transseptal approach. Post operative course was uneventful and patient did well on follow up.

¹King Faisal hospital Taif, Saudi Arabia
E-mail: riaz_rao@hotmail.com
Discussion

In 1886, von Lenhossek described the first case of transverse testicular ectopia and, in 1895, Jordan described the syndrome of transverse testicular ectopia with persistent Mullerian ducts [6]. Transverse testicular ectopia is a rare anomaly in which the testis is seen either in the contralateral inguinal canal or in the hemiscrotum. This anomaly is also called "testicular pseudo duplication", "unilateral double testis" or "transverse aberrant testicular maldescent". An inguinal hernia is invariably present on the side to which the ectopic testis has migrated. About 100 well-documented patients with this condition have been reported. Usually the right testis is ectopic, but, as in the present case, the left side has also been reported [7].

On the basis of the presence of various associated anomalies, transverse testicular ectopia has been classified into three types: those associated with inguinal hernia alone (40–50%); those associated with persistent or rudimentary Mullerian duct structures (30%); and those associated with other anomalies without Mullerian remnants, e.g. inguinal hernia, hypospadias, pseudohermaphroditism and scrotal abnormalities (20%) [4]. Our case is the most common variety of TTE.

The etiology of this condition is incompletely understood. Various theories have been put forward, such as: (a) Failure of the gubernacular mechanism and, consequently, failure to open the inguinal canal and the descent to the opposite side is due to adhesions to the testes with normal gubernacular mechanism and inguinal rings, (b) Rupture of the gubernaculum and dysfunction of the genitofemoral Nerve, (c) Both testes arising from the same genital ridge,(d) True crossover of the testes,(e) Adhesion and fusion of the Wolfian duct in early embryonic life and the subsequent descent of both testes on the same side,(f) An aberrant ring on the normal side, (g)Both testes lying in the same processus vaginalis prior to descent [8].

There are many theories attempting to explain the etiology of the isolated TTE. The first serious explanation was given by Lockwood through multiple insertion theory [9]. Gupta and Das assumed that merging of the developing Wolf canals is taking place early and that descent of one testis stimulated the other to follow. However, Gray and Skandalakis consider that crossed ectopia occurs later, since the testes have separate sperm canals [9]. Berg states that the real crossed ectopia occurs only if special sperm canals reach each testis [9]. In a patient with TTE and PMDS, it is thought that a MIF does not have a direct role in the descent of the testes. Therefore, it is likely that the mechanical effect of the persistent Mullerian duct structures produce cryptorchidism by preventing normal testicular descent [10]. It seems possible in some cases that this mechanical effect also leads to both testes being located on the same inguinal side. With anatomical point of view, usually there is separate blood supply for both testes and vas deferens is also separate as in our case but anomalies such as common vas deferens with proximal fusion and unilateral absence of vas have been reported in TTE [11].

Literature review shows that most of the cases are diagnosed during surgery for a hernia or exploration for undescended testis. TTE can rarely present with torsion of the testis, while some children present with obstructed inguinal hernia [12]. Although diagnosis of TTE is usually made during an inguinal hernia repair, nonoperative diagnostic modalities, such as ultrasonography, computerized tomography, magnetic resonance imaging, and magnetic resonance venography, have also been used to identify the testis.

The aim of surgical management is fixation of the testes into the scrotum, a search for Mullerian duct remnants and other anomalies, and long-term follow-up due to the risk of malignancy. Fixation is accomplished either by transeptal orchiopexy or extraperitoneal transposition of the testis [13]. Presently, laparoscopy for both the diagnosis and management of this presentation and even a combined approach of an inguinal method assisted by laparoscopy has been described [14]. Till the recent past it was mentioned in the literature that no malignancy arises from the Mullerian structures, hence, surgical management being orchiopexy, leaving the uterus and fallopian tubes in situ. Recently some cases of malignancy have been detected in the Mullerian remnants so the optimal strategy in these patients is to
closely followup these patients if the Mullerian remnants have been left behind[15].

**Conclusion**

TTE is an uncommon variety of undescended testis. Patients with bilateral undescended testes and symptomatic inguinal hernia must receive due attention and necessary investigations should be carried out. If Mullerian duct remnants are discovered, laparoscopic management should be the first choice and follow up for any remnant structures is mandatory.

**References**


**Correspondance to:**
Muhammad PS Riaz ul Haq,
Department of pediatric surgery
King Faisal Hospital, Taif-KSA
Mobile: 00966507567662
E-mail: riaz_rao@hotmail.com
ASPECTS OF MUSHROOM INTOXICATION IN CHILDREN

Liana Precup¹, Simona Dumitra¹, I Precup¹, Sabina Morgovan¹, D Lazăr¹

Abstract

Background – Mushroom intoxication remains a current issue in the paediatric pathology, both as morbidity and as clinical expression. The aim of this work is to define the clinical aspects at the onset of the intoxication in children in our geographical area. Materials and method – the retrospective longitudinal study of the medical files of children admitted between 1st-Jan-2008 and 31st-Dec-2011 to the Paediatric Clinic of Arad with a diagnosis of acute mushroom intoxication. Results and discussions – Out of the 11 children who were monitored, 8 showed a short incubation period and 3 showed a long incubation period. The intoxication appeared in other family members in only 5 cases, the other 6 were isolated cases. Clinically, the children presented: altered clinical condition, vomiting, diarrhoea, nausea, abdominal pain, dizziness, headache, somnolence, delirium. Conclusions – The most prevalent cases were with short incubation periods, in children from a rural area. The onset symptoms were dominated by digestive issues and not so much by neurological ones. The rapid onset of vomiting with the modification of the general state in children from a rural area must point the anamnesis towards mushroom intoxication, even in the absence of symptoms in other family members – in this study, there were 6 cases without a family history.

Key words: Mushroom intoxication, symptoms, child

Introduction

Although not very common, mushroom poisoning is characterized by the severity of symptoms that often requires hospitalization, but also by unpredictable evolution, especially when it comes to poisoning by mushrooms with long incubation period.(1)

In Romania there are approximately 50 species of poisonous mushrooms and are known the world over 4000 species of mushrooms.(2)

Depending on the debut of symptoms related to poisoning, when talking about mushroom poisoning, these are classified into two categories:
- short incubation intoxication
- intoxication long period of incubation.

In the first case, the symptoms of poisoning occur 15 minutes to 3 hours after ingestion, and in the second case, the symptoms appear after 12 hours of ingestion.

Symptoms vary, depending on the type of mushroom ingested, the chemical structure of their toxins, mechanism of action, severity of visceral lesions produced.(3,4,5)

Thus, mushroom intoxication with short incubation period can develop: cholinergetic syndrome, atropine, resinoidian, hallucinatory, coprinian and for mushroom poisoning with long incubation it might develop giromitrian syndrome, orelian, faloision. The worst case scenario, with the reserved prognosis and mortality up to 80-90% are given by Amanita phalloides poisoning, classified among the mushrooms with long incubation period.(6,7,8)

Materials and method

The study was conducted by retrospective longitudinal analysis of observation sheets of the children admitted between 01.01.2008-31.12.2010 in Arad Pediatrics Clinic with a diagnosis of acute mushroom poisoning.

Tracked parameters were: incubation period, the presence of symptoms in other family members, symptoms at onset, progress with treatment, days of hospitalization, complications occurred, first aid measures, awareness of the disease by the entourage.

The study group consisted in 11 children: 1 child (9.09%) less than three years, six preschool children (54.54%), 3 children with age between 7 and 14 (27.27%) and one over 14 years (9.09%); 8 (72.72%) children were from rural areas and the remaining 3 children were living in urban areas.

Data were processed with SPSS 10.

Results and discussions

Of the 11 children monitored, 8 (72.72%) had symptoms that appeared after a short period of time (under 6 hours), which was a landmark for intoxication with short incubation and 3 (27.27%) of them showed symptoms after a longer incubation (more than 6 hours). This parameter is essential to be included in history because it is the most important benchmark in terms of medical attitudes.

¹Department of Pediatrics, Vasile Goldiș Western University of Arad
E-mail: precup_l_d@yahoo.com, dumitrasimona@yahoo.com, precup_l_d@yahoo.com, sabina_myx@yahoo.com, dorinlazar@ymail.com
Only in 5 cases (45.45%), poisoning occurred in other family members, the remaining 6 (54.54%) being isolated. We believe that this difference is rather related to the preparation of mushrooms than individual reactivity to toxins; in all 5 cases of poisoning in the family, the cooking was made by boiling or roasting small pieces of mushrooms, mixed in homogeneous composition, as opposed to isolated cases where history has shown the consumption in large quantity or by consumption of large mushrooms, roasted entirely of breaded fried.

Clinically, the children presented: general state changed: 11 cases (100%), vomiting: 11 cases (100%), diarrhea: 5 cases (45.45%), nausea: 8 cases (72.72%), abdominal pain: 8 cases (72.72%), vertigo: 3 cases (27.27%), headache: two cases (18.18%), somnolence: 3 cases (27.27%), delirium: 2 cases (18.18%).

From these data we see an associative relationship between changing the general condition and vomiting which was present in all 11 cases (100%), between nausea and abdominal pain the 72.72% of cases, whereas neurological symptoms can be linked to the interest of the nervous system (vertigo and delirium) found in a lower percentage, 27.27% and 18.18%. Headache and somnolence were related to dehydrated patients with some neurological signs.

Regarding the development therapy, all cases have progressed to healing without lesions. The most frequent complication was acute dehydration syndrome in 5 cases (45.45%) and urinary retention with bladder globe, in one case (9.09%).

Days of hospitalization ranged from 7 to 10 days in 90.90%, one patient was discharged the 6th day (9.09%).

All 11 cases admitted had received first aid measures granted by medical personnel as part of pre-hospital care, even in the 6 isolated cases of intoxication.

A particularly important aspect is related to these 6 cases of isolated intoxication, cases in which parents have not noticed the relationship effect between the consumption of mushrooms and the illness of children, so they weren’t aware of the phenomenon; in 4 cases only the detailed history emergency room revealed this fact; questioned about the use of mushrooms, parents have denied that this would be the cause the child illness, bringing as an argument that the whole family has consumed the mushrooms.

Conclusions

The most prevalent cases were with short incubation periods, in children from a rural area. The onset symptoms were dominated by digestive issues and not so much by neurological ones. The rapid onset of vomiting with the modification of the general state in children from a rural area must point the anamnesis towards mushroom intoxication, even in the absence of symptoms in other family members – in this study, there were 6 cases without a family history.

By all means of information and health education in must be made public the danger posed by consumption of mushrooms gathered from the forest, even by traditional connoisseurs and collectors.

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Correspondance to:
Liana Precup,
Clinica de Pediatrie Arad,
Victoriei 1-3,
310158,
Arad
România
E-mail: precup_l_d@yahoo.com
STUDY ON PRIMARY OBESITY IN SCHOOL CHILDREN

Cristina Singer¹, Polixenia Stancu¹, Simona Coșoveanu¹, Camelia Cristea²

Abstract
We carried out a retrospective epidemiologic-clinical study, regarding primary obesity in school children (6 to 16 years old), who were admitted with different illnesses to 2nd Pediatric Clinic of the County Emergency Hospital Craiova, between 01.01.2010 and 31.12.2010. We calculated the body mass index (BMI); BMI=G (kg)/T² (m²). The results we obtained by taking anthropometric measurements were reported to the normal values for age and sex, according to the CDC 2000 nomograms. There were admitted, in this period of time, a number of 435 children, aged 6 to 16 years, among which 91 (20.9%) were obese and overweight. We studied the distribution of the overweight and obesity cases according to their social origin, sex, age groups, birth weight, feeding regime in the first 6 months of life, and parents’ educational level.

Keywords: obesity, overweight, children

Introduction
Obesity is a complex, multi-factorial illness, characterized by an increase of the body mass on the basis of the adipose tissue.

In the last decades, it has become one of the most frequent nutrition illnesses in the world, resembling a pandemic, according to the WHO 2011 report, being considered the 21st century illness (1).

Material and method
We carried out a retrospective epidemiologic-clinical study regarding obesity in school age children (6 to 16 years old), admitted to the 2nd Pediatric Clinic of the County Emergency Hospital Craiova with various illnesses, throughout a one-year period (01.01.2010 - 31.12.2010).

Inclusion criteria: children aged 6 to 16 years, with a body mass index (BMI) ≥ 95 percentile/sex/age for obesity, 85 percentile/sex/age for overweight. The information taken by means of anthropometric measurements was reported to the normal values for age and sex, according to the CDC 2000 nomograms.

Results
In this period of time, there were admitted a number of 435 children, aged 6 to 16 years, among which 91 were overweight and obese, representing 20.9%. Overweight was registered in 35 children, representing 8% of the 435 children admitted, aged 6 to 16 years, while obesity was registered in 56 children, who represented 12.9% of the total number of admitted children (fig.1).

Fig.1 Prevalence of overweight and obesity in the admitted children.

The specialty literature and the performed studies have revealed a doubling of the obesity prevalence in children, throughout the world, in the last 30 years, both in the developed, highly industrialized countries, and in the developing countries as well (2).

1University of Medicine and Pharmacy Craiova, 2nd Pediatric Clinic, County Emergency Hospital Craiova
22nd Pediatric Clinic, County Emergency Hospital Craiova
E-mail: mendelson.ltd@gmail.com, stancu.poli@yahoo.com, mendelson.ltd@gmail.com, scosoveanu@yahoo.com
The distribution of the overweight and obesity cases according to sex showed: in the overweight children - 22 girls (62.9%) and 13 boys (37.1%); in the obese children: 32 (57.1%) girls and 24 (42.9%) boys (table 1).

Table 1. Distribution of overweight and obesity cases according to sex.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Overweight</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>62.9</td>
</tr>
<tr>
<td>M</td>
<td>13</td>
<td>37.1</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100</td>
</tr>
</tbody>
</table>

The distribution of the overweight and obesity cases according to their social origin was as follows: in overweight children - 18 (51.4%) children from urban areas and 17 (48.6%) from rural ones; in obese children - 32 (57.1%) came from urban areas, while 24 (42.9%) from rural ones (fig.2).

According to age group criterion, the distribution of the cases was: in overweight children - 7 (20%) children belonged to the 6-10 years group, 17 (48.6%) to the 10-14 years group, 11 (31.4%) to the 14-16 years group; in obese children – in the 6-10 years group there were 16 children (28.5%), in the 10-14 years group 31 (55.4%) while in the 14-16 years group 9 children (16.1%) (fig.3).
The birth weight (BW) in the overweight children showed: BW 2500-2800 g in 6 cases (17.1%), BW 2800-4000 g in 20 (57.2%), BW > 4000 g in 9 (25.7%) cases. In the obese children we recorded: 5 (8.9%) had a BW between 2000 and 2500 g, 14 (25%) between 2500 and 2800 g, 26 (46.5%) between 2800 and 4000 g and 11 (19.6%) BW > 4000 g (fig.4).

![Fig.4 Birth weight in obese and overweight children.](image)

The feeding in the first 6 months of life in overweight children: breastfeeding in 21 (60%), bottle feeding in 10 (28.6%), mixed in 4 (11.4%). Bottle feeding was done with powder milk in 7 children (70%) and cow’s milk in 3 (30%). In the obese children: breastfeeding in 36 (64.3%), bottle feeding in 15 (26.8%), mixed in 5 (8.9%). In the bottle-fed children, 7 (46.7%) received powder milk and 8 (53.3%) cow’s milk (table 2).

<p>| Table 2. Feeding in the first six months of life in the overweight and obese children. |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Feeding type</th>
<th>Overweight</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>21</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Bottle feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LP</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>LV</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Mixed</td>
<td>4</td>
<td>11.4</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100</td>
</tr>
</tbody>
</table>

Feeding diversification in overweight children was done before the age of 4 months in 12 (34.3%) children, between 4 and 6 months in 15 (42.9%) and after the age of 6 months in 8 (22.8%) children. In obese children, diversification before the age of 4 months was done in 20 cases (35.7%), between 4 and 6 months in 24 (42.9%) children, while in 12 (21.4%) diversification started after the age of 6 months (fig.5).

![Fig.5 Feeding diversification in overweight and obese children.](image)
Discussions

Among the 435 school children who were admitted, 91 were obese or overweight, representing 20.9%; we registered a number of 35 overweight children (8%), and 56 obese children (12.9%).

A study which was carried out by Prof. I. Popa and colab in the western part of the country in children aged between 3 months and 16 years identified 14.7% obese children: 18.6% infants, 15% preschool children and 14.2% between 3 months and 16 years identified 14.7% obese children (12.9%).

A study carried out in the 2005-2006 period in the children aged between 11 and 15 years, and published in a report of The International Association for the Study of Obesity (IASO), London 2009, showed that, in Romania, the overweight prevalence was 14.4% in girls and 8.8% in boys (4).

Another study carried out in the 2005-2006 period in the children aged between 11 and 15 years, and published in a report of The National Study “Health and Nutrition Examination Survey” (NHANES III (1976-1980 and 2003-2004) shows an increase of the overweight prevalence in the 6-11 years age group from 6.5% to 18.8%, while in the 10-14 years age group from 5% to 17.4% (5).

The results obtained in our study revealed that the prevalence of overweight and obesity in school children had values close to those published on obesity in children in our country.

The National Study “Health and Nutrition Examination Surveys” (NHANES III (1976-1980 and 2003-2004) shows an increase of the overweight prevalence in the 6-11 years age group from 6.5% to 18.8%, while in the 10-14 years age group from 5% to 17.4% (5).

Our study revealed a prevalence of obesity (12.9%) higher than that of overweight (8%). The obesity prevalence was 1.6 times higher than the overweight prevalence.

The distribution of the overweight and obese children according to sex showed a higher frequency in girls, both regarding the overweight (62.9%) and the obesity (57.4%).

The information in the specialty literature (IASO, 2009) showed a higher prevalence of overweight in girls (14.7%) rather than in boys (8.4%) (6).

Numerous studies showed that an increasing number of children do not exercise, girls being more numerous than boys (7).

We registered a prevalence of the overweight and obesity in the urban children.

An explanation could be the fact that, in urban areas, children have an easy access to sweet soft drinks with a high level of sugars and calories, to food with high energy content (fast-food type), instead of consuming milk, fruits and vegetables (8).

Children, especially those in the urban areas, spend more time in front of the TV set and the computer rather than doing physical activities.

There are studies that show that 83% of the children spend, daily, more than 5 hours watching TV, 34% more than 4 hours daily in front of the computer, 25% of the children are completely sedentary and only 26% take part in sport activities organized by school.

Sports, walking, biking, outdoor games are all replaced by car driving, using the elevator, indoor games, playing on the computer, watching TV (9).

The age group distribution in the overweight children showed a higher frequency (55.4%) in the 10-14 year-age group, followed by the 14-16 year-age group, 31.4% and the 6-10 year-age group 20%. Most of the obese children (55.4%) belonged to the 10-14 year-age group, followed by the 6-10 year-age group (28.5%) and the 14-16 year-age group (16.5%).

The preschool and primary school period is extremely important for the prediction of a future obesity.

The excessive food intake undoubtedly represents the main exogenous factor, with a role in the genesis or perpetuation of the obesity (10).

The analysis of birth weight showed, in the overweight children: more than half of the children had a normal weight at birth. It is worth mentioning that 25.8% (1/4 of the children) had a birth weight more than 4000 g. 46% of the obese children had a normal birth weight. About a quarter of the obese children had the birth weight more than 4000 g.

High birth weight is considered a risk factor for obesity.

Feeding in the first six months of life in the overweight children was breastfeeding for 60% of the children and mixed for 40% of them. Most of the obese children (64.3%) were breastfed, while 30.2% had bottle or mixed feeding.

The diversification of food in the overweight children was correctly done in most of the cases in the 4-6 month-age group (42.9%), in 34.3% of the cases was done before the age of 4 months, and in 22.8% of the cases after the age of 6 months. The diversification in the obese children was done, in most of the cases, in the 4-6 month-age group (42.9%), before the age of 4 months in 35.7%, while in 21.4% of the children after the age of 6 months.

Breastfeeding represents a protection factor against obesity. The protective role of breastfeeding was not
correlated with the social class and lifestyle differences (10).

Promoting a longer period of breastfeeding, in the industrialized countries, may lead to a decrease of obesity prevalence among children.

The analysis of parents' educational level showed, both in the overweight and in the obese children, that, in most of the cases, parents had high school studies (57.1% in the overweight and 53.6% in the obese); in 28.6% of the overweight and obese cases parents had secondary school studies, while 14.3% of the overweight children and 17.8% of the obese children had their parents with higher education studies.

The familial environment has, among the environmental factors, the greatest impact upon the nutritional status of children.

Children depend on their parents in providing food, and feeding habits are constrained and modulated by the food selections of the parents who, at their turn, are influenced by the cultural, economic context, including the cost, advantage, taste and accessibility of the food (7).

Conclusions
1. Prevalence of overweight and obesity in admitted school children was 20.9%.
2. Prevalence of obesity was 12.9%, while of overweight 8%.
3. Obesity had a frequency of 1.6 times more than overweight.
4. Overweight and obesity were more frequent in girls, in urban children and in the 10-14 year-old group.
5. 1/4 of the overweight and obese children had a birth weight more than 4000 g.

Creating certain healthy food habits since an early age is important for keeping a good health in the long run and for preventing obesity.

References
GIANT MUCINOUS OVARIAN CYSTADENOMA IN 13-YEAR-OLD PREMENARCHAL GIRL

I Skondras, S Gavera, O Achilles, G Kapouleas, Th Aivazoglou, A Passalidis

Abstract
Ovarian tumors represent less than 2% of all tumors in girls under 16 years of age. Mucinous cystadenomas (MCs) generally occur in adult life and are an extremely rare finding before menarche. To the best of our knowledge, only 19 cases have previously been reported in the literature. We present the rare case of a 13-year-old premenarchal girl who was admitted to the hospital with lower abdominal pain, fever and a palpable abdominal mass. Abdominal ultrasonography disclosed a multilocular cystic mass measuring 10x30x25 cm that virtually occupied the entire abdomen. Neither ultrasonography (U/S) nor magnetic resonance imaging (MRI) could identify the origin of the mass, due to its enormity. At laparotomy, the giant tumor was found to originate from the left ovary, which contained a small amount of gelatinous peritoneal fluid. Unilateral oophorectomy with tumor removal was performed. Histology revealed a benign mucinous cystadenoma of the left ovary. Regular follow-up with ultrasonography has shown no sign of recurrence. Albeit a rare entity, this diagnosis should be considered in young girls aged 11-15 years who present with a very large abdominal mass.

Key words: ovary, mucinous cystadenoma, premenarchal girl

Introduction
Ovarian tumors account for less than 2% of tumors in young girls under 16 years of age. Mucinous cystadenomas (MCs) are benign and represent 15% of ovarian tumors. They contain mucinous fluid and differ in size. Usually unilateral, they are more prevalent in women aged between 20 and 40 years but have also been reported in postmenopausal women. Their incidence is exceptionally rare in young, premenarchal girls. Like serous cystadenomas, MCs are considered as non-functional childhood tumors. They vary greatly in diameter, often occupying a considerable part of the peritoneal cavity and are described as encapsulated, multilocular cystic lesions with a smooth surface, without adhesions to neighboring organs. A mucinous cystadenoma can cause discomfort, particularly if it compresses adjacent organs, such as the bladder, rectum and ureters. Other complications include torsion, supputation and perforation. Malignant transformation is not common; it has been reported in just 5-10% of cases. Herein, we describe the rare case of a young, premenarchal girl aged 13 years who presented with a mucinous ovarian cystadenoma.

Patient-method
A 13-year-old girl presented to the outpatients department at Aglaia Kyriakou Children’s Hospital with a 4-day history of intermittent lower abdominal pain, bloating and a fever reaching 38.5°C. The patient reported that for the past 4 months, she had experienced recurrent lower abdominal pain, constipation and a gradual increase in swelling of the abdomen.

Clinical examination revealed considerable abdominal distension and a large, palpable mass that occupied the entire abdominal cavity. Laboratory tests showed WBC: 7.4x10/µL (64%NE, 27%LE), CRP: 92mg/L, LDH: 212U/L, β-HCG: 0.0U/L and AFP: 1.7ng/mL. Ultrasonography and MRI (pics 1,2,3) identified a sizeable multilocular cystic mass that occupied the entire abdomen and lesser pelvis, extending upward between the abdominal paracolic sulcus toward the anterior liver surface. A mild dilatation of the pyelocaliceal system of both kidneys was also detected, while a chest x-ray showed elevation of the diaphragm. It was not possible to identify the origin of the mass, due to its enormity.

At laparotomy, a huge multilocular cystic mass was found to arise from the left ovary. The cyst had caused a slight tear to the lower part of the ovary, from which exuded gelatinous fluid. Sample fluid was obtained for cytologic examination, which proved negative for cancer cells. The patient underwent en bloc resection of the mass and the fallopian tube was preserved. The patient’s postoperative course was uneventful. She was discharged from hospital on the 9th postoperative day. Histologic examination of the mass confirmed a benign ovarian cystadenoma, measuring 40cm at its greatest diameter and weighing 11.5 kg.

12nd Department of Pediatric Surgery, Aglaia Kyriakou Athens Children’s Hospital
E-mail: skondras@yahoo.gr, gkavera@hol.gr, acho@otenet.gr, kapouleas@gmail.com, alpassal@gmail.com
Picture 1: Patient showing the abdominal distention.

Picture 2: Ultrasound scan showing a large cystic mass containing multiple septa.

Picture 3,4: MRI scan of the abdomen.

Picture 5: Large multicystic tumor originating from the left ovary.

Picture 6: Mucinous cystadenoma of the left ovary.
Ovarian tumors in children constitute an unusual entity. Sixty-four percent of these tumors are malignant and derive from mesenchymal cells, while just 10-17% stem from epithelial cells. The most common of epithelial tumors are benign cystadenomas, of which 75% are serous and 25% mucinous. The latter constitute an extremely rare finding in premenarchal girls. Mucinous cystadenomas are sizeable tumors, often multicellular, containing sticky gelatinous fluid. Microscopically, they comprise a tall columnar epithelium that produces mucus. Histopathologically, MCs fall into three categories:

1) Benign cystadenomas without cellular stratification and without stromal infiltration
2) Borderline malignancy with cellular stratification up to 2-3 layers, without stromal infiltration
3) Mucinous carcinoma with extensive cellular stratification exceeding 3 layers, and stromal infiltration

Prognosis is favorable, with malignant transformation occurring in only 5-10% of cases. In 2003, Morowitz et al presented a 14-year retrospective study of epithelial ovarian tumors in patients with a mean age of 13.9 years. Borderline malignancy was reported in just 4 cases of serous tumors in patients with a mean age of 13.9 years. Borderline presented a 14-year retrospective study of epithelial ovarian tumors in children. In 2003, Morowitz et al described 4 cases of epithelial carcinoma in premenarchal girls. Flosho et al reported a similar case. In 1984, Morris et al described 4 cases of young girls under 15 years of age and 6 cases of malignant cystadenomas out of 172 cases of ovarian tumors in patients under 15 years of age.

The main clinical symptoms of ovarian tumors include chronic lower abdominal pain and, in 55% of cases, a palpable pelvic mass. Among the more serious complications is ovari torsion, which demands urgent surgical intervention.

Ultrasoundography is the examination modality of choice. In cases where it is difficult to identify the origin of the mass, computed tomography (CT) and MRI can help establish diagnosis. In the case of the patient presented herein, it was not possible to identify the origin preoperatively due to the enormity of the mass. Transvaginal U/S would appear to be more accurate.

The preferred treatment for MCs is cystectomy, either with preservation of ovarian tissue or an oophorectomy. In cases of suspected borderline MCs, in line with the Clinical Practice Guidelines of the Society of Obstetricians and Gynecologists of Canada (SOGC), treatment includes resection of all visible disease, an omental biopsy and appendectomy. According to the International Federation of Gynecology and Obstetrics and the American College of Obstetricians and Gynecologists (ACOG), treatment can either involve a salpingo-oophorectomy or just a cystectomy if the patient wishes to remain fertile. There are several reports in the literature of patients managed by simple cystectomy showing excellent fertility rates ranging from 40-70%. The rate of recurrence in cases of fertility preservation varies from 12-37.5%. Infiltration at the surgical margin of the resected tumor is conducive to an increase in the risk of recurrence. As reported by the ACOG, laparoscopic surgery is contraindicated if malignancy is suspected. Postoperatively, the SOGC proposes annual follow-up with ultrasonography and testing for CA-125 only in the presence of poor prognostic factors. In contrast, the International Federation of Gynecology and Obstetrics recommends annual U/S for all patients in whom the ovary was preserved. Unfortunately, it has not yet been possible to determine the required duration of follow-up with any degree of certainty, given that recurrences have been reported as late as 10 years after surgery, particularly in cases of borderline MCs. A recurrence rate of up to 60% has been reported for borderline MCs, mainly within the first year.

Conclusions

The mucinous ovarian cystadenoma is a rare disease among premenarchal girls under 15 years of age. Oophorectomy is considered the treatment of choice. While ovarian preservation for fertility reasons is considered a safe method, it demands a far more rigorous follow-up after surgery. In cases that do not present a risk for malignancy, follow-up with U/S is adequate.

References

Correspondance to:
Ioannis K Skondras
Ivis 11, Chalandri,
Athens
15234
Tel/Fax: 210-6825625, 6932572226, 2106834338
E-mail: skondras@yahoo.gr
CROSSED ECTOPIC KIDNEY – A CASE REPORT

Sonia Tanasescu¹, Ioana Ciucă¹, Mirela Soare², Carmen Stanculet², L Pop¹

Abstract
Renal ectopia is characterised by congenital abnormal renal position as a result of the migration disorders during embryogenesis. There are 2 types of Renal Ectopia: simple renal ectopia or direct renal ectopia and crossed renal ectopia. The incidence of this affection is approximately the same in both sexes (1:900). The authors present the case of a 8 years old child, admitted to the Clinic II Pediatrics from Timisoara, with fever (39 C), shiver, polaki-disuria. After the clinical and biological investigations, as well as the ultrasound exam, the diagnostic of crossed ectopic kidney was applied.

Key words crossed ectopic kidney, migration disorders, diagnosis.

Introduction
Renal ectopia is characterised by congenital abnormal renal position as a result of the migration disorders during embryogenesis (1).

Normally, the kidneys start developing in the pelvis and migrate to their anatomical position in the upper abdomen. The kidneys’s ascension precedes the gonades’s descent in the pelvis. Genetic and teratogenic factors can determine abnormal kidney migration resulting in Renal Ectopia (2).

There are 2 types of Renal Ectopia: simple renal ectopia or direct renal ectopia and crossed renal ectopia. Simple renal ectopia may be unilateral or bilateral and the kidneys may have various positions: thoracic, high lombar, ileo-lumbar, iliac or pelvine. In the crossed renal ectopia, the kidney develops in the opposite side, usually in the lower lumbar region, the ureter crosses the spine, the ureter orifice having a normal opening site in the bladder (3,4,5). The incidence of this affection is approximately the same in both sexes (1:900); in 10% of the cases, renal ectopia may affect both kidneys (6,7,8).

Although pelvic renal ectopia can be associated with hydronephrosis and vesicoureteral reflux, in most cases it’s asymptomatic and is often a random discovery (9,10).

Case presentation
The authors present the case of a 8 years old child, admitted to the Clinic II Pediatrics from Timisoara, with fever (39 C), shiver, polaki-disuria.

There are no significant data in the patient’s history. His physiological history reveals: the 4-th child, natural term birth, BW=3050 g, L=54 cm, APGAR score = 10, physiologic jaundice – 3 days, breast fed. Pathological history: 1 hospitalisation for Pneumonia.

History: 8 years old child, with no significant pathologic history, is presenting 7 days before admittance with fever and polaki-disuria.


Laboratory findings:
WBC = 8.530/mm³ ; N = 44%, Ly = 47%, M = 7,01%, E = 1,01%, Ba = 0,972%, RBC = 4,470.000/mm3, Ht = 37,8%, Hb = 12.5 g%, ESR= 25mm/h, RCP= 47mg/l, urea, creatinine, uric acid – in normal range.

Urine analysis: 15-20 leukocytes, erythrocytes – absent, crystals – absent, microbial flora – present. Urinalysis (3 days consecutively) revealed over 100.000 germs/ml – E. coli (sensible for Gentamicin, Cefuroxim, Amikacin).

Abdominal ultrasound: liver with normal dimensions and structure, PV=1,2 cm, gallbladder – no lithiasis, spleen = 7,3 cm, right kidney = 6,5/7cm, normal structure; the absence of the left kidney in the renal fossa (Fig 1).

Urography: bilateral urinary excretion; in the right kidney: double basinet. The left kidney is situated in the upper pelvic region with axial rotation (Fig 2).

Surgical examination: crossed renal ectopia with axial rotation. It does not require surgical intervention.

Corroborating the clinical and the paraclinical investigations we established the diagnosis: High Urinary Tract Infection, Left Crossed Renal Ectopia with axial rotation. In consequence, during the hospitalization the patient received antibiotics for urine sterilization: Gentamicin for 10 days, followed by consolidation treatment with Ciprofloxacin for 7 days. Renal ectopia does not require treatment in the absence of complications.

This case had a favorable evolution, with complete healing of the urinary tract infection and urine sterilization. The immediate prognosis is good and the future prognosis depends on the evolution of the renal malformation on which the UTI episode developed.
Discussions

Pelvic Renal Ectopia is the most frequent form of renal ectopia and must be differentiated from renal ptosis (the ptotic kidneys have normal-length ureters and renal arteries with a normal origin from the abdominal aorta). The ectopic kidney can be localized in the ileo-lumbar region, high lombar, iliac, pelvine, in the thorax (extremely rare) and in a few cases on the opposite side, also known as crossed ectopia.

In the case of pelvic renal ectopia, the kidneys are situated in the pelvis, and the diagnosis is based on the ultrasound examination. Most of the cases of renal ectopia are asymptomatic and do not have a higher risk for UTI, renal lithiasis or hydronephrosis.

The diagnosis of pelvic renal ectopia is of great clinical importance and must be considered while evaluating unknown pelvic structures, to avoid a nephrectomy or mistake a renal colic for acute appendicitis.

Renal ectopia is often associated with other malformations as kidney agenesis, vascular malformations or genital anomalies. In this particular case, no genital anomalies were present.

The treatment depends on the clinical manifestations and on the presence of complications. If the renal function is normal and there are no other associated renal anomalies, only routine follow-up is required.

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Correspondance to:
Janine Lazăr,
Clinica II Pediatrie,
Str. Paltinis 1-3,
Timisoara, România,
Telephone: 0723859841
E-mail: sonia.tanasescu@yahoo.com

Fig. 1. Abdominal ultrasound: the absence of the left kidney in the renal fossa. Fig. 2. Urography.
HYPERGLYCEMIA: „TRICK OR TREAT” – CASE REPORT

Mirela Mogoii1, I Velea2, Simona Dumitriu3, Corina Paul2, Georgeta Noditi1

Abstract

Hyperglycemia is a condition characterized by excessively high levels of glucose in the blood: fasting glucose higher than 7 mmol/l (> 126 mg/dl), or random glucose higher than 11,1 mmol/l (> 200 mg/dl) (1). Temporary hyperglycemia is often asymptomatic, but when glucose levels are extremely high is a medical emergency and can rapidly produce serious complications. Usually when we say „hyperglycemia” we think of diabetes or a prediabetic state. The paper presents the case of an adolescent girl, admitted for pseudoneurological symptoms and abnormal capillary blood glucose values (> 11,1 mmol/l). Her medical history is remarkable for repeated episodes of neurological symptoms accompanied with pathological glucose blood levels. She had two other hospital admissions for impaired glucose tolerance, overweight and loss of consciousness. The initial laboratory tests showed: high levels of fasting blood glucose without glycosuria or ketonuria, abnormal Oral Glucose Tolerance Test (positive for diabetes mellitus) and no clinical symptoms related to the high glycemic levels. Further investigations revealed an unexpected „cause” of hyperglycemia: the somatoform disorder.

Key words: hyperglycemia, somatoform disorder, medically unexplained symptoms, fabricated or induced illness.

Introduction

The origin of the term „hyperglycemia” is Greek: hyper- meaning „over, beyound, overmuch, above measure”; -glycys-, meaning „sweet”; and –emia from „haima” meaning „of the blood” (2). So hyperglycemia is a condition characterized by excessively high levels of glucose in the blood: fasting glucose higher than 7 mmol/l (> 126 mg/dl), or random glucose higher than 11,1 mmol/l (> 200 mg/dl) (1). Temporary hyperglycemia is often asymptomatic, but when glucose levels are extremely high is a medical emergency and can rapidly produce serious complications. Usually when we say „hyperglycemia” we think of diabetes or a prediabetic state. The following conditions can also cause hyperglycemia in the absence of diabetes:

a) endocrinopathies (especially those affecting the thyroid or adrenal and pituitary glands);

b) another exocrine pancreas diseases (cystic fibrosis, pancreatitis, trauma / pancreatectomy, haemochromatosism, neoplasia);

c) certain infections, sepsis;

d) terminal stages of many diseases;

e) neurological pathology: encephalitis, brain tumors (especially those located near the pituitary gland), brain hemorrhage, convulsions;

f) prolonged, major surgeries can temporarily increase glucose levels;

g) certain forms of severe stress and physical trauma can increase levels for a brief time as well, yet rarely exceeds 6,6 mmol/l (> 120 mg/dl).

An unusual differential diagnosis of hyperglycemia is a psychiatric disorder. In recent years somatoform disorders gained increasing significance in all medical specialties, although in child psychiatry, publications on this topic are rare.

Case report

We present the case of an adolescent girl, aged 15 years, who was admitted to the Pediatric Clinic, presenting pseudoneurological symptoms (weakness, trembling, sweating, dizziness, headaches) and abnormal capillary blood glucose levels, higher than 11,1 mmol/l (> 200 mg/dl) – random determinations. The patient was checking her glucose level 7 - 8 times a day, using test strips.

She is the first borne of a young, healthy couple, out of an uncomplicated pregnancy, birth age: 38 weeks, normal birth in cranial presentation, birth weight: 3350 grams, birth length: 51 cm, physiologic jaundice, breastfeed untill 4 months old, rickets prophylaxis and complete immunization scheme. Menarche at 13 years, regular menses.

She has a healthy younger sister, aged 5 years, and a recently deceased grandfather who had Type 2 Diabetes mellitus.

Personal medical history reveals two other hospital admissions for: impaired glucose tolerance, overweight and loss of consciousness. The first admission was 3 years ago for: loss of consciousness accompanied with trembling, sweating and one episode of emesis without nausea.

1II nd Clinic of Pediatrics, Timisoara County Clinical Emergency Hospital.
2University of Medicine and Pharmacy “Victor Babes” Timisoara.
3Pediatric neuropsychiatry – Children’s Hospital “Louis Turcanu” Timisoara.
E-mail: mire_med02@yahoo.com, ivelea56@yahoo.com, dumitriusimona@yahoo.com, paulcorina@yahoo.com, georgetanoditi@yahoo.com

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The biological tests performed then were relatively normal except the Oral Glucose Tolerance Test (OGTT) which showed an Impaired glucose tolerance (fasting blood glucose level was 5.3 mmol/l (96 mg/dl) and at 120 minutes the glucose level was 7.05 mmol/l (127 mg/dl). The glycemic profile was in normal range. After 3 years, she was again admitted, in another hospital for: dizziness, weakness, headaches, abdominal pain. Laboratory tests were normal and the OGTT is presented in Table 1 (The 1st test column). Her medical history is remarkable for repeated episodes of neurological symptoms accompanied with pathological glucose blood levels, episodes that cannot be proved with medical records. Also she described one episode, a few days prior admission, when she had the same symptomatology. Then she was taken with an ambulance from school to an Emergency Room, where she did some laboratory tests and was treated with insulin for hyperglycemia (blood glucose value higher than 22.2 mmol/l (400 mg/dl). In the same afternoon she was released from hospital. These affirmations were later infirmed by the Emergency Room doctors.

Physical examination at admission: weight = 73 kg, height = 174 cm, BMI = 24.17 kg/m² s.c. (> 85% CDC 2000 Growth Charts). Waist circumference = 96 cm. Pale skin with latero-abdominal white striae. Excessive adipose tissue with android disposition. The blood pressure and the rest of the clinical examination were normal for her age.

Laboratory test: fasting glycemia (capillary blood) = 10,2 mmol/l (185 mg/dl), urine = negative ketonuria, absent glycosuria. Cortisol (8.00 a.m) = 14.7 µg/dl (N = 6.2 – 19.4 µg/dl).

Table 1 – Oral Glucose Tolerance Test (75 g anhydrous Glucose) – the test was performed after an overnight fast of 8 hours, from capillary blood, using strip test and the patient’s own needle

<table>
<thead>
<tr>
<th>1st test</th>
<th>2nd test</th>
<th>Normal</th>
<th>IGT</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glycemia</td>
<td>5.38 mmol/l</td>
<td>5.33 mmol/l</td>
<td>&lt; 5.7 mmol/l</td>
<td>&lt;6,1 mmol/l</td>
</tr>
<tr>
<td>At 30 min.</td>
<td>11.05 mmol/l</td>
<td>29.7 mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 60 min.</td>
<td>7.5 mmol/l</td>
<td>13.6 mmol/l</td>
<td></td>
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</tr>
<tr>
<td>At 120 min.</td>
<td>7.38 mmol/l</td>
<td>9.8 mmol/l</td>
<td>&lt; 7.8 mmol/l</td>
<td>≥ 7.8 mmol/l</td>
</tr>
<tr>
<td>At 180 min.</td>
<td>5.77 mmol/l</td>
<td>16.6 mmol/l</td>
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</table>

IGT – Impaired Glucose Tolerance
DM – Diabetes Mellitus

ECG and cardiac ultrasound evaluation: normal. Abdominal ultrasound evaluation: normal. Sella turcica radiography: normal. Neuropsychological evaluation: normal. Diagnosis: Lipothyemia. Recommendations: No medical treatment. The patient began a normocaloric diet, divided into six meals, with strict adherence to mealtimes and we were monitoring the glucose blood levels (preprandial, 1 hour postprandial and 2 hour postprandial glycemia – Table 2). We have to mention that since she has been admitted the patient hasn’t experienced any symptoms in spite of the high glycemic levels.

Table 2: Pre and postprandial glycemia

<table>
<thead>
<tr>
<th>Hour</th>
<th>Day</th>
<th>6.30</th>
<th>7.30</th>
<th>8.30</th>
<th>13.30</th>
<th>14.30</th>
<th>15.30</th>
<th>18.00</th>
<th>19.00</th>
<th>20.00</th>
<th>0.00</th>
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<tbody>
<tr>
<td>1</td>
<td>Glycemia (mmol/l)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.66</td>
<td>8.88</td>
<td>7.16</td>
<td>6.66</td>
<td>9.05</td>
<td>10.66</td>
<td>6.22</td>
<td>5.72</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10.2</td>
<td>14.6</td>
<td>19.3</td>
<td>334</td>
<td>18.5</td>
<td>16.6</td>
<td>13.6</td>
<td>7.6</td>
<td>7.3</td>
<td>5.83</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Considering the high glucose blood levels during the day, in spite of the normal glycemic levels during the night when the patient was asleep, we decided to determine the value of: HbA1c, C Peptide, Islet Cell Antibody (ICA) and Glutamic acid decarboxylase autoantibodies (GAD Ab). All these determinations were normal: HbA1c = 5%, (N < 6%); C Peptide = 3.4 ng/ml, (N = 1.1 - 4.4 ng/ml); ICA = negative, GAD Ab = negative. Then we repeated the OGTT, but only this time from venous blood and under strict supervision, the results were: fasting blood glucose = 3.6 mmol/l (66 mg/dl), at 30 min = 7.2 mmol/l (131 mg/dl), at 60 min = 6.1 mmol/l (111 mg/dl), at 120 min = 5.4 mmol/l (98 mg/dl), at 180 min = 4.9 mmol/l (89 mg/dl). Given the medical history, physical examination and the new laboratory tests results, we decided to ask for another neuropsychological evaluation.

The examination, performed by another neuropsychiatrist, reveals: "Cheerful affective disposition, increased interest in describing the symptoms without associating any concern indicators, group integration difficulties, adaptation problems. Separation anxiety regarding her father, mild social anxiety. Poor ability to resolve problems and low emotional self-regulation. Impulsivity, egocentrism, without any prosexic and memory difficulties, no perception deficit. Mild global executive functions deficit. Conclusion: Somatoform disorder."
Tendency to develop disharmonic personality - emotional unstable personality structure

Discussions
Children and adolescents suspected of having somatisation disorders present a challenge to pediatricians. Somatoform disorders present with somatic complaints and/or dysfunctions that are not under conscious control and for which physical findings are absent or insufficient to explain all complaints. These disorders include body dysmorphic disorder, conversion disorder, hypochondriasis, somatisation disorder, and somatoform pain disorder (3).

Differential diagnosis of pediatric somatisation is made with: 1) Unrecognized physical disease (e.g. multiple sclerosis, endometriosis etc); 2) Unrecognized psychiatric disorder (depression, anxiety); 3) Factitious disorder / Munchausen by proxy syndrome; 4) Psychological factors influencing a medical condition (11). Distinguishing somatoform disorders from factitious disorders can be difficult: in the former, symptoms are associated with unconscious conflict, whereas in the latter the unconscious need to be cared for motivates the falsification of symptoms. However, in clinical practice, the boundaries between factitious disorder, somatisation and malingering are often unclear and there is also a strong association with personality disorder.

Treatment of these patients, who repeatedly succeed in subjecting themselves to invasive and sophisticated procedures is difficult because of minimal compliance. Unless the underlying psychopathology is recognized by the treating physician, chronic somatisation may result in high cost to the health care system due to frequent use and unnecessary biochemical and radiographic evaluation.

With appropriate intervention, the prognosis for most somatisation disorders in children and adolescents is very good. Sometimes, somatisation is the „tip of the iceberg”, that calls attention to a psychiatric disorder necessitating mental health consultation and treatment. Unfortunately many untreated children risk continuous somatisation as adults.

Conclusions
1. Although the psychiatric pathology is an unusual pediatric differential diagnosis we have to think of it every time we have a patient with medically unexplained symptoms.
2. The interdisciplinary pediatric teams are needed in every hospital. Routine neuropsychological evaluation is a very important part in the overall evaluation.
3. Even the strip tests are easy to use, the OGTT test should be done using venous blood as Global IDF / ISPAD Guideline for diabetes recommends.

References

Correspondance to:
Mogoi Mirela
Str. E.Celebi, nr. 1-3,
Timisoara,
România,
E-mail: mire_med02@yahoo.com
A STUDY REGARDING MECHANICAL VENTILATION AMONG 153 PREMATURE NEWBORN BORN AT A GESTATIONAL AGE LESS THAN 32 WEEKS

Ramona Dorobanțu¹, C Ilie², Valeria Filip³, Bianca Chirea¹, C Dorobanțu⁴

Abstract
The hyaline membrane disease is a typical disease of prematurity and it is caused by surfactant deficiency. The incidence of hyaline membrane disease is inversely related to gestational age, but it is not influenced by the birth weight. The therapy involves: prophylactic therapy, supportive therapy, mechanical ventilation, surfactant replacement. Objective. To set up a guideline for the respiratory therapy of premature newborns with respiratory distress syndrome, in order to rise survival, decreasing complications and sequelae, lower hospitalization’s duration. Method. There were 153 premature newborns included in study, all born before 32 weeks of gestational age, born in Oradea Maternity Hospital or transferred here from level II units, between 01.01.2010- 31.08.2011. Results and conclusions: These times, the neonatal intensive care is improving day after day, the respiratory care is a necessity for premature newborns’ survival. For the premature under 29 weeks of gestation, exogenous surfactant instillation immediately after birth and CPAP respiratory support improves lung ventilation, lower oxygen requirements, lowers the incidence of immediate complications (air leak, infection, intraventricular hemorrhage) and of long term complications (bronchopulmonary dysplasia). INSURE therapy and CPAP were effective in promoting an adequate ventilation and had low complication rate in newborns > 29 weeks of gestation with severe/medium RDS. In the future, it will be a necessity to use other ventilation mode, currently unavailable for our clinical practice (NO, liquid ventilation, ECMO)

Key words: premature newborn, ventilation, survival

Introduction
The hyaline membrane disease is a typical disease of prematurity and it is caused by surfactant deficiency. The incidence of hyaline membrane disease is inversely related to gestational age, but it is not influenced by the birth weight. The clinical course of the disease starts in the first 10 hours of life with symptoms of respiratory distress of various severity and it worsens for the next 24-72 hours of life. After that, the disease may have a favorable course or it may worsen and may result in complications, sequelae or death.

The therapy involves: prophylactic therapy, supportive therapy, mechanical ventilation, surfactant replacement. The ventilation modes and strategies used in clinical practice are

1.1 Continuous Positive Airway Pressure (noninvasive respiratory care). The continuous positive airway pressure may be achieved by mask, by nasal prongs or by endotracheal intubation or nasopharyngeal intubation. Nasal CPAP is considered the most gentle kind of respiratory support, having less adverse outcomes. The many forms of CPAP ventilation include bubble CPAP and variable flow CPAP।

1.2 Positive pressure ventilation, time-control, limited pressure, conventional rate (Intermitent Positive Pressure Ventilation- IPPV) is conventional ventilation and it is the most used mode of ventilation in the neonate. In IPPV mode are used ventilator rates between 30-120/min (with a lower rate the ventilation mode is called IMV- Intermittent Mandatory Ventilation) the inspire/expire fraction is inversed (there is an inversion when the inspire is longer than the expire), positive end expiratory pressure of 0-12 cm H₂O (the most used are the pressures between 3-6 cm H₂O).²

1.3 Volume-control mechanical ventilation (VCV). In this ventilation mode a preset volume of air is delivered to the neonate. The efficiency of this mode of ventilation was compared to IPPV in many trials and meta-analyses which showed that VCV was linked to lower ventilation time and air leak rate, but there weren’t differences in chronic lung disease and mortality rates.³

¹Clinical Emergency County Hospital of Oradea
²University of Medicine and Pharmacy of Timisoara
³Faculty of Medicine and Pharmacy of Oradea
E-mail: dorobanturamona@yahoo.com, constantinilie@umft.ro, valeriafilip@yahoo.com, biancamch@yahoo.com, dorojar@yahoo.com
Increasing regular physical activity is accompanied by slowing the pulmonary function decline and constant participation in various physical activities may increase the compliance in the long term (12, 23). Short-term studies have shown an improvement in lung function and well-being of these children as a result of sustained physical activity programs in outpatients (20).

This study provides evidence for the earliest possible implementation of a sustained program of usual physical activity at home, as part of therapy in patients with CF. The study presents spirometry indices: vital capacity (VC), forced expiratory volume in one second (FEV1), forced expiratory flow between 25 and 75% of forced vital capacity (FEF25-75) and airway permeability index (FEV1/VC report), in a group of patients with CF, after implementing an outpatient program to increase the level of physical activity for one year.

Material and method

The study design was prospective, multicenter, and included a group of 52 children (older than 6 years), adolescents and young adults diagnosed with CF, which are found in the records of the 2nd Pediatric Clinic of Emergency Hospital from Craiova, Children’s Emergency Hospital “Maria Sklodowska Curie” and the Institute for Maternal and Child, “Alfred Ruseascu” (IOMC), both from Bucharest. We included patients with definite diagnosis of CF, based on characteristic anamnestic - clinical criteria and confirmed by two positive sweat tests and in some patients by the genetic test (1, 9, 13, 27), without acute respiratory failure, chronic pulmonary heart (CPC) or the coexistence of decompensated heart disease, independent of respiratory disease but exacerbated by it. Any patient in the study had no contraindications to perform airway clearance techniques (ACTs). Were included only patients who did regular treatment and were able to perform spirometry tests. General characteristics of patients, weight (W), size (S) and body mass index (BMI) were recorded in case report forms and those values (expressed in kg, m and kg / m²) were converted into number of standard deviations (SD) compared with mean values correlated with the age and gender (Z score).

Spirometry tests were conducted in laboratories functional exploration of the three medical units who studied for the treatment of CF. Has been recorded vital capacity (VC), forced expiratory volume in one second (FEV1) and forced expiratory flow between 25 and 75% of forced vital capacity (FEF25-75) and the report FEV1/VC (airway permeability index). During spirometry test was performed three forced expiration maneuvers were recorded the best results. All values were expressed in liters and percentage of predicted for age, height and sex. Spirometry records were analyzed in two different moments of time: before (the beginning of 2009) and one year after implementation of an outpatient program to increase physical activity level (end 2009). We considered the lower limit of normal the 80% of predicted for VC, FEV1 and FEF25-75 and 0.75 for the ratio FEV1/VC (6, 26).

All enrolled patients received a comprehensive treatment, according to management guidelines in CF (1, 9, 13, 27): dietary and hygiene measures, drug treatment (by systemic antibiotic, anti-inflammatory and antifungal therapy) and aerosol therapy (antibiotics, mucolytics, corticosteroids and bronchodilators), depending on the specifics of each case. In terms of respiratory physiotherapy, airway clearance techniques (ACTs) were given daily, two sessions per day, morning, before a meal and evening, two hours after eating, before going to bed, each session lasting 30 minutes. All patients performed active cycle of breathing techniques (ACBT): controlled breathing (CB), thoracic expansion exercises (TEE) and forced expiratory technique (FET), performed in different postural drainage positions (depending on the lobe or lung segment drained), which alternated with percussion, vibration and assisted cough. Number of postural drainage positions was limited to three for each session. Once a patient with CF was placed in a postural drainage positions, the person assisting him performed chest wall percussion, for a period of 3-5 minutes for each position, followed by vibration on the same segment, for approximately 15 seconds (or during the five exhalations). Then, the patient was encouraged to cough or perform huff for elimination of excess mucus. Modified postural drainage positions were indicated in patients with gastroesophageal reflux (GOR).

Since 2009, all the 52 patients have been included in an outpatient exercise program to increase the usual physical activity level. Although a correct prescription for such a program would have to start from the results of the exercise testing (17), this test could not be performed due to lack of adequate equipment, including blood gas analysis, lack of compliance for patients or carers in some cases, the absence of a full medical team to allow safe testing conditions.

According to the literature, practice has shown that the vast majority of patients with respiratory disease do not need an exercise testing to be prescribed them a program of physical activity (18, 19). Medical history of the different types (respectively degree) of physical effort that these patients are made daily in the normal activity, and on aspects of how the patient supports this efforts, provided us sufficient data to recommend complete safety an outpatient exercise program for patients from this study. Thus, depending of the intensity of exercise supported by the patient and of the patient age, we recommended the following types of physical activity, according to specialized studies (22, 28):

- moderate physical activities: walking briskly - about 3 ½ miles (5.6 km) per hour, hiking, gardening/yard work, dancing, golf (walking and carrying clubs), bicycling - less than 10 miles (16 km) per hour, weight training (general light workout);
- vigorous physical activities: running/jogging - 5 miles (8 km) per hour, bicycling - more than 10 miles (16 km) per hour, swimming (freestyle laps), aerobics, walking very fast - 4 ½ miles (7.2 km) per hour, heavy yard work, such as chopping wood (for teens and adults), weight lifting (vigorous effort), basketball (competitive).
1.4 Patient-triggered ventilation. Through the last 2 decades this mode of ventilation was used in neonatal respiratory care as control-assisted ventilation (ventilation is triggered by spontaneous breaths which exceed the trigger’s threshold) and as synchronized intermittent mechanical ventilation (SIMV)(the rate is preset and it isn’t related to spontaneous breaths’ rate but inflation is synchronized to spontaneous breaths). The trigger modes- PSV- Pressure Support ventilation, VG- Volume Guarantee ventilation, PAV- Proportionally Assisted ventilation, are not usually available.

1.5 High frequency ventilation is a mode of ventilation that uses respiratory rates which are much higher than normal respiratory rates. There are 3 modes of HFV:
- 1.5.1. High Frequency Positive Pressure Ventilation (HPPV, rates 60-150/min)
- 1.5.2. High Frequency Jet Ventilation (HFJV, rates 100-600/min)
- 1.5.3. High Frequency Oscillator Ventilation (HFOV, rates 300-3000/min)

High Frequency Ventilation indications: conventional ventilation failure, prevention of pulmonary injury, neonatal chronic pulmonary disease, air leak syndromes, diaphragmatic hernia, meconium aspiration syndrome.

1.6 Liquid Ventilation (LV) is a technique of mechanical ventilation in which the lungs are insufflated with an oxygenated perfluorocarbon (PFC) liquid. The perfluorocarbon is comparable to water and it has low superficial tensions and a high solubility for respiratory gases.

1.7 Extracorporeal membrane oxygenation (ECMO) is the use of an artificial lung (membrane) located outside the body (extracorporeal), that puts oxygen into the blood and then carries this blood to the body tissues (oxygenation). The CO₂ and the water are eliminated and the blood is rewarmed before reintroducing it into the body. Ecmo is generally used in those neonates with intractable but reversible respiratory disease which failed other therapies.

1.8 Nitric oxide therapy. Nitric Oxide is inhaled into the lungs and acts as a pulmonary selective vasodilator used for hypoxemic respiratory distress linked to pulmonary hypertension. The trials showed that NO ventilation lowers the necessity for ECMO and mortality in premature and term newborns.

Objective
To set up a guideline for the respiratory therapy of premature newborns with respiratory distress syndrome, in order to rise survival, decreasing complications and sequelae, lower hospitalization’s duration.

Method
There were 153 premature newborns included in study, all born before 32 weeks of gestational age, born in Oradea Maternity Hospital or transferred here from level II units, between 01.01.2010- 31.08.2011.

Results
1. The incidence of Prematurity in Maternity Hospital of Oradea between 01.01.2010- 31.08.2011: from a total 7277 newborns, 153 where premature newborns (GA under 32 weks) with prematurity rate (GA under 32 weeks): 2.1%

2. Totality of premature newborns treated in Neonatal Intensive Care Unit between 01.01.2010- 31.08.2011
- Neonates born in Maternity Hospital of Oradea - 131 cases (86%)
- Neonates transferred from other hospitals - 19 cases (12%)
- Neonates born at home - 3 cases (2%)

3. Gender distribution: 87 cases where female and 66 cases where male.

4. Birth weight distribution:
- <799 g - 18 Newborns
- 800-999 g - 24 Newborns
- 1000-1249 g - 38 Newborns
- 1250-1499 g - 43 Newborns
- >1500 g - 30 Newborns

5. Apgar Score Distribution:
- Apgar Score 1-3 / 56 Newborns
- Apgar Score 4-5 / 49 Newborns
- Apgar Score 6-7 / 38 Newborns
- Apgar Score 8-10 / 7 Newborns

6. Neonatal deaths - 21 cases
Cause of death: Intra-ventricular haemorrhage 10 cases, hydrocephaly 1 case, infection 4 cases, pneumothorax 2 bronchopulmonary dysplasia 1 case, congenital malformations 2 cases.

7. Strategies of neonatal ventilation
- Neonates with severe respiratory distress syndrome (radiological ground-glass image) - 32 cases,
- Surfactant (prophylaxis or curative) treated newborns - 52 cases,
- Neonates treated with CPAP without surfactant therapy - 23 cases,
- Surfactant and CPAP treated newborns - 49 cases,
- Neonates treated only by oxygen flow - 49 cases,
- SIMV ventilated newborns - 12 cases,
- HFOV ventilated newborns - 3 cases,
- IPPV ventilated newborns - 3 cases,
- INSURE therapy - 14 cases.

8. The respiratory care groups were compared regarding:
- Blood gases in the first 10 days of life
- FiO2 used
- radiologic al findings
- oxygen therapy total duration
- enteral feeding tolerance
- hospitalisation time
- complications
- sequelae
3.9. Newborns treated with CPAP without surfactant therapy

**Neonates GA >29 weeks - 20**
- FiO\textsubscript{2} used: 25-45%
- Radiological image improved in 4-5 days
- CPAP treated for 7-8 days and oxygen therapy until 2 weeks of age
- Enteral feedings well tolerated within 14 days
- Complication: gastric air distention, bronchopulmonary dysplasia - 3 cases
- Hospital staying: for 2 months (average)

**Neonates GA <29 weeks - 4**
- FiO\textsubscript{2} used: 40-70%
- PEEP >5cm H\textsubscript{2}O
- Radiological image improved after 10 days in one case
- CPAP treated for 20 days and oxygen therapy beyond 25 days of age
- Enteral feedings well tolerated within 21 days
- Complication: gastric air distention, bronchopulmonary dysplasia, pneumothorax - 2 cases, infection
- Hospital staying: for 3 months (average)

10. Surfactant+CPAP treated newborns - 49

**Neonates <29 weeks of GA and neonates >29 weeks of GA with severe respiratory distress syndrome**
- FiO\textsubscript{2} used of 21-35% after surfactant treatment
- PEEP of 2 to 4 cm H\textsubscript{2}O
- Radiological improvement within 2 days
- CPAP treated for 7-10 days and oxygen therapy for 12-15 days
- Enteral feedings tolerated within 14 days
- Complication: gastric air distention
- Hospital staying: for 6-8 weeks (average)

**Neonates <32 weeks of GA with severe respiratory distress syndrome or no spontaneous breathing or CPAP therapy failure:**
- FiO\textsubscript{2} of 40-70% before surfactant treatment and 30-40% after surfactant instillation
- Radiologic improvement in 4-5 days
- SIMV ventilated for 6 days (maximum), CPAP treated after extubation for 7-10 days and oxygen therapy within 15-25 days of life
- Enteral feedings tolerated within 14 days (maximum)
- Complications: bronchopulmonary dysplasia, infections, intraventricular hemorrhage
- Hospital staying: 8 weeks (average)

**11. SIMV ventilated newborns - 12 cases.**
- FiO\textsubscript{2} used after surfactant instillation: 21-35%
- Radiological improvement within 2 days

**12. HFOV ventilated Newborns - 3 cases.**
- FiO\textsubscript{2} used: 21-35%
- Radiological improvement within 2 days

13. IPPV ventilated newborns - 3 cases.
- FiO\textsubscript{2} used after surfactant instillation: 21-35%
- Radiological improvement within 2 days

Conclusions
- These times, the neonatal intensive care is improving day after day, the respiratory care is a necessity for premature newborns' survival.
- For the prematures under 29 weeks of gestation, exogenous surfactant instillation immediately after birth and CPAP respiratory support improves lung ventilation, lower oxygen requirements, lowers the incidence of immediate complications (air leak, infection, intraventricular hemorrhage) and of long term complications (bronchopulmonary dysplasia).
- Bronchopulmonary dysplasia occurred in very premature newborns which also had early-onset sepsis.
- Pneumothorax occurred in premature newborns with severe RDS and without surfactant treatment and a PEEP > 4 cm H\textsubscript{2}O. PEEP>4 cm H\textsubscript{2}O set up immediately after birth in lung pathology newborns was linked to increased incidence of pneumothorax.
- Intraventricular hemorrhage occurred in severely asphyxiated newborns, in twins (second twin) and in newborns born by vaginal delivery rather than cesarean section.
- INSURE therapy and CPAP were effective in promoting an adequate ventilation and had low complication rate in newborns > 29 weeks of gestation with severe/medium RDS.
- HFOV did not have superior results compared to conventional ventilation in RDS but it was highly effective in air leak treatment.
- In the future, it will be a necessity to use other ventilation mode, currently unavailable for our clinical practice (NO, liquid ventilation, ECMO).
- This study has to continue with comparisons of different ventilator settings and oxygenation effect in order to achieve an effective and less invasive respiratory care and the maximal benefit for the patient.
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Correspondance to:
Ramona Dorobanțu,
Graurilor Street, No. 29,
Oradea,
România,
Telephone: 0740208484
E-mail: dorobanturamona@yahoo.com
Abstract

Multiple hereditary exostoses (MHE) or Multiple osteochondromas is a rare autosomal dominant condition characterized by bony outgrowths (benign tumors) covered by a cartilaginous cap on the outer surface of bone. The prevalence is estimated at 1: 50,000. The syndrome is caused by mutations in members of the EXT gene family, EXT1 or EXT2. The disease is characterized by bone pain, bony deformity and restricted joint motion. We report two cases of skeletally immature patients who presented with multiple exostoses, bone deformation without bone pain; and growth and pubertal retardation. The cases need adequate counseling, long-term follow-up, and measures to improve the quality of life of patients with multiple hereditary exostoses. Multiple hereditary exostoses are rare conditions, and expertise in management of MHE is equally scarce.

Key words: Multiple osteochondromas, exostoses, bony deformity

Introduction

Multiple hereditary exostoses (MHE) or Multiple Osteochondromas is a rare autosomal dominant condition characterized by bony outgrowths (benign tumors) covered by a cartilaginous cap on the outer surface of bone. This tumor develops during childhood or adolescence around the growth plates and it also may develop as a single tumor (osteocartilaginous exostosis). The prevalence is estimated at 1: 50,000, and it seems to be higher in males (male-to-female ratio 1.5:1) (1). In almost 90% of MHE patients germline mutations in the tumor suppressor genes EXT1 or EXT2 are found. However, the increased sensitivity of mutation detection and the use of new techniques screening for larger deletions, such as MLPA, have dramatically decreased the proportion of MO patients without an EXT1 or EXT2 mutation to <15% (2,3). The EXT genes encode glycosyltransferases, catalyzing heparan sulphate polymerization. The pathogenesis of osteochondromas still needs to be elucidated. Osteochondromas develop and increase in size in the first decade of life, ceasing to grow when the growth plates close at puberty (4). The majority are asymptomatic and located in bones that develop from cartilage, especially the long bones of the extremities, predominantly around the knee (5). The facial bones are not affected. Osteochondromas may be associated with a reduction in skeletal growth, bony deformity, restricted joint motion, shortened stature, premature osteoarthrosis, and compression of peripheral nerves (4,5). The risk for malignant degeneration to osteochondrosarcoma increases with age, although the lifetime risk of malignant degeneration is low: 0.57% to 5%, but is rare at children. Being benign lesions and not affecting life expectancy, in most cases, treatment consists of careful observation over time with regular x-rays to keep track of any changes in the tumors but osteochondromas can be surgically removed for cosmetic or functional reasons (6).

Case report

We report 2 children from nonconsanguineous young parents (under 30 years at the moment of conception). The children were placed in management for basic medical care with the general practitioner. B.A., a 11 years old girl and B.G., a 15 years old boy, were first presented to a geneticists at this age, at the recommendation of the orthopedist. They both presented multiple exostoses starting with the age of 5 years and short stature. However, the sole complaints of patients regarding these tumors were aesthetics and a slight difficulty in walking for the girl.

The mother has a height of 168 cm - 75th percentile for height and she is overweight BMI=28.3kg/m². She presents multiple osteochondromas with different locations: curved right second finger, exostose on the distal 1/3 of right radius and on the proximal 1/3 of the left tibia (figure 1).

The father is healthy, with a height of 165cm- the 15th percentile for height.

The children's expected height is at 45th percentile for age and gender. Expected height for BA at age 11 is 139 cm, while for BG at age 15 years is 165 cm.
The genetic pedigree of the family is presented in figure 2, showing strong family determination, several affected individuals occurring in each generation (7). Six males and seven females are affected.

The girl, B.A. at the age of 11, has a height of 134 cm-10th percentile for height, weight of 25 kg, BMI=13.96 kg/m² – 10th percentile. She presents cartilage capped bony outgrowths (osteochondromas) on the distal half of the right forearm, on the proximal finger I and distal finger IV metatarsals, on the proximal left finger II phalanx, finger III with a “mallet finger” aspect, slight varus angulation of the left ankle (figure 3). She presents a slight difficulty in walking. No bone pain was mentioned. Pubertal Tanner stage II. The clinical exam was otherwise normal. She has a normal intelligence and is well integrated in school. The girl is engaged in sports activity in school.

The boy, B.G. at the age of 15 has a height of 157 cm-3rd percentile for height, weight of 42 kg, BMI=17.07kg/m² – 10th percentile. He presents multiple osteochondromas on the distal half of the ulna and on the proximal half of the radius, curved left forearm, multiples bony growths on the proximal 1/3 of calves, bilateral (figure 4). Pubertal Tanner stage III. No bone pain was mentioned. The clinical exam was otherwise normal. He has a normal intelligence and is well integrated in school. The child is engaged in sports activity in school.
Blood work
The usual laboratory investigations (complete blood count, liver and renal function tests, and electrolytes) investigations were unremarkable, with the exception of low serum calcium level. Bone Alkaline Phosphatase and Intact Parathyroid Hormone were in normal range.

Imagistics
Abdominal ultrasound revealed normal aspect.

Bone radiographs are illustrated in figures 5 and 6 for B.A. and in figures 7 and 8, for B.G. Head and chest radiographs have normal aspect (not presented), no skull or thorax deformities were observed in both children. The conclusion of the radiologist was: suspected osteogenic hereditary disease.

Figure 3. B.A. – female, age 11 years - deformities in hands and right forearm.

Figure 4. B.G. male, age 15 years - Bone deformities in left arm.

Figure 5. B.A. Antero-posterior and profile forearm radiographs: Scoliosis in the right forearm bones with profoundly modified radial head by enlarged bulging structure, with growths in the distal half of forearm bones. Changes in the elbow joint axis.

Figure 6. B.A. Antero-posterior left leg: changes in bone structure with bony growths in proximal metatarsals in the finger I and distal finger IV, proximal phalanx left finger II. Fingers III and IV have a “hammer” appearance; proximal phalanges of finger V have a widening shaft.
We investigated the health-related quality of life (HRQL) in both patients and parents (table 1). There is clearly no impact on the quality of life in children. Overall, the family is not influenced by the existence of this pathology and no difference exists between the perspectives of the affected parent compared to the healthy one, regarding the functioning of their children. Moreover, due to the fact that they have many relatives with the same condition, they understand the prognosis of the syndrome very well.

Table 1. HRQL in patients and parents perspective.

<table>
<thead>
<tr>
<th>HRQL</th>
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<tr>
<td>Physical Functioning Scale</td>
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<td>90 no impact</td>
</tr>
<tr>
<td>Physisocial Health Summary Score</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>Father’s perspective Physical Functioning Scale</td>
<td>90.6 no impact</td>
<td>87 no impact</td>
</tr>
<tr>
<td>Father’s perspective Physisocial Health Summary Score</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Mother’s perspective Physical Functioning Scale</td>
<td>87 no impact</td>
<td>85 no impact</td>
</tr>
<tr>
<td>Mother’s perspective Physisocial Health Summary Score</td>
<td>80</td>
<td>79</td>
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<tr>
<td>Family Functioning Father’s perspective</td>
<td>98</td>
<td>94</td>
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<tr>
<td>Family Functioning Mother’s perspective</td>
<td>93</td>
<td>94</td>
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</tbody>
</table>

The diagnosis was made on patient history and family history, clinical aspect, lab work and radiological documentation. Screening for germline mutations in EXT1 or EXT2 was not performed due to limited resources.

Management: The children receive calcium and vitamin D supplements. Surgical intervention was not considered to be appropriate at this stage. As all tumours were identified, the patients were instructed to seek earlier medical attention if their condition changes, for instance if there is pain or growth of a known lesion. Also, they will remain in regular follow-up to discover potential malignant transformation at an early stage and thus, to enable adequate treatment.

Genetic counseling: MHE is an autosomal dominant disorder. Affected individuals have 50% risk of transmitting the disorder to their offspring. MHE has nearly 100% penetrance. If the exact mutation is known antenatal diagnosis is technically possible.

Discussions
Both children present growth retardation together with pubertal retardation. This is not uncommon in patients with...
MHE, especially before puberty (8,9). Clement at al reported that MHE is associated with a diminished stature. Adults with MHE were significantly shorter when compared with a control group (P<0.001); preadolescents, however, were significantly taller than predicted (P=0.01). This was reflected by their height centile; 58% of the adults were under the 25th centile, whereas 53% of the preadolescence group were above the 75th centile. Stature was more severely affected in patients with an EXT1 mutation (P=0.008). This study illustrates a novel age-related growth pattern associated with MHE, which is also affected by genotype (8).

Even though the diagnosis in our cases was clinical, in the case of a positive family history in which MHE is clearly established in relatives, the diagnosis can be clinically made and mutation analysis is not essential (4). Differential diagnosis should be made with Dysplasia Epiphysealis Hemimelica (Trevor's disease, tarso-epiphysial aclasis) and metachondromatosis are considered in the differential diagnosis of solitary and hereditary osteochondromas. Despite their similarities, they were shown to be separate entities and the EXT downstream pathway is not involved (10). Moreover, MHE should be distinguished from enchondromatosis (Ollier disease and Maffucci syndrome), in which multiple cartilage tumours are found in the medulla of bone, with a predilection for the short tubular bones and a unilateral predominance (11).

The children presented above did not report bone pain, only small inconvenience at palpation of exostosis, however it does not influence their quality of life. Nevertheless, in literature, the study by Goud et al. showed that approximately 60% of the children had pain (usually associated with a more negative perception of their disease), problems at school, and a greater number of surgical procedures (12). Darilek et al. showed in their cross-sectional study that the prevalence of pain (diffuse, not necessarily over an exostosis) in children and adults with multiple hereditary exostoses reached approximately 80%.

Also, approximately 80% of the patients in their study needed surgical treatment. Over 70% of the study cohort used some pain medication (13).

Surgical management of forearm deformities remains controversial. In a retrospective series 23 MHE patients corrective osteotomy and/or lengthening of forearm bones was not beneficial (14). Moreover, one should consider the possible recurrence of ulnar shortening within 1.5 years when operating skeletally immature patients (14,15). The most beneficial procedure was excision of the osteochondromas. The simple removal of an osteochondroma can improve forearm rotation and correct deformity, especially if there is an isolated tumour of the distal part of the ulna.

Regular follow-up to discover potential malignant transformation at an early stage is very important. The risk of malignant transformation of osteochondroma towards secondary peripheral chondrosarcoma is estimated at 1–5% (16). It is important to realise that no new osteochondromas develop after puberty (4). After skeletal maturation a baseline bone scan is recommended. If lesions change over time, further examination, using magnetic resonance imaging including contrast enhanced magnetic resonance sequences, is indicated.

Consent: Children’s legal guardians gave their informed consent to participate in this study.

Conclusion

Multiple hereditary exostoses are rare conditions, and thus, expertise in management of MHE is equally scarce. While multiple hereditary exostoses may be seen as a disease of the growing skeleton, it is evident that the burden of this condition extends beyond childhood and adolescence, and this burden may actually worsen throughout life. The cases need adequate counseling, long-term follow-up, and measures to improve the quality of life of patients with multiple hereditary exostoses.

References

10. Glick R, Khaldi L, Ptaszynski K, Steiner GC. Dysplasia epiphysealis hemimelica (Trevor disease): a rare


Correspondance to:
Chirita Emandi Adela,
University of Medicine and Pharmacy
“Victor Babes” Timisoara
Pta Eftimie Murgu nr 2,
cod 300041,
Timisoara
România,
Telephone: 0040724369599
E-mail: adela.chirita@yahoo.com
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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.

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