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MANUSCRIPT REQUIREMENTS
SPIROMETRIC ASSESSMENT IN A LOT OF PATIENTS WITH CYSTIC FIBROSIS, FOLLOWING IMPLEMENTATION OF A PROGRAM FOR INCREASING OUTPATIENT USUAL PHYSICAL ACTIVITY LEVEL

Janine Lazăr¹, Roxana Popescu², Luminiţa Lazăr³

Abstract

Objectives. Cystic fibrosis (CF) is the most common autosomal recessive genetic disease of the caucasian race, with progressive and potentially fatal evolution. The objective of this study was to present the evolution of spirometry index in a group of patients with CF, a year after the implementation of a sustained program of outpatient physical activity. Material and method. The study design was prospective and included a group of 52 children, adolescents and young adults diagnosed with CF, 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 Rusescu” (IOMC), both from Bucharest. Spirometry records (VC, FEV1, FEF25-75 and FEV1/VC) were performed at two different times: before and after implementation of sustained physical activity at home for one year. By age, patients were divided into two groups: 6-12 years and more than 13 years. For statistical processing we used the Student test. Results. Although all spirometric values increased after implementation of the physical activity program in both age groups, the difference was statistically significant only for FEV1, in the age group 6-12 years (p = 0.016). Also, the lower age group, we observed a decrease in the number of patients with altered lung volumes and flows. Conclusions. Increased level of the usual physical activity in patients with CF has led to slow decline in lung function and spirometry indices showed a slight improvement or remained stable throughout the study. Increase in mucociliary clearance, with significant decrease bronchial obstruction (assessed by the value of FEV1) in patients lower age suggest the need to implement such a program as early as possible to prevent or at least slow the progression of lung disease, for longer period of time, and reduce complications. Key words: Cystic fibrosis, spirometry, physical activity

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive genetic disease of the caucasian race, with progressive and potentially fatal evolution. It is characterized by generalized dysfunction of exocrine glands, mucous and serous (sweat glands in this case), primary anomaly being CF gene (5, 14, 27).

Although, clinical and evolutionary context is highly polymorphic, translated by numerous phenotypic aspects, a single gene is responsible for this disease.

Defective gene, described in 1989, is located in the long arm of chromosome seventh (2, 16). The consequence of genetic abnormality is blocking or malfunction of chloride channels at the cellular level, and thus the sodium chloride and water. As a result, the secretions from the majority of organs and systems will be content, poor water, viscous, adherent to canaliculelor excretory epithelia, difficult to eliminate outward. The accumulation of these causes in time impaired organs and their destruction (lung, pancreas, liver, gall bladder, gastro-intestinal tract, reproductive organs). Sweat secretion from the skin has a very high concentration of salt. As a result, the clinical picture is highly polymorphic but major clinical signs are suffering chronic respiratory (chronic obstructive pneumopathy), chronic diarrhea or steatorrhea, and stationary or weight loss despite a good appetite and adequate nutritional intake (1, 27).

Although CF is a complex and multisystem disease, respiratory distress is the main element in terms of patient outcome; 85% of patients with CF die of the pulmonary disease (3, 14, 26).

The goal of therapy for respiratory distress is to limit the extension of the pulmonary lesions and to rarely exacerbations (13). In the past, the main purpose of pulmonary rehabilitation therapy in CF was eliminating excessive secretions, and thus reduce symptoms. Modern rehabilitation treatment is used today with a more comprehensive purpose. It is a pro-active treatment to prevent or at least trying to slow the progression of the pulmonary disease (4, 9).

Exercise and physical activity are an essential part of treatment of respiratory distress for all patients with CF, along with aerosol therapy and airway clearance techniques (ACTs) (9, 13, 15).

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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 wellbeing of these children as a result of sustained physical activity programs in outpatient (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 Rusescu” (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 which 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 these 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).
Methodological indications that I gave patients were general. Patients have total freedom in choosing the methods of training and technique work itself, thus increase compliance, as recommended in the literature (18, 19). I insisted on the necessity of making physical activity at least 3 - 4 times a week, lasting at least 30 minutes, in conditions of unpolluted air, pleasant landscape, not excessive meteorological conditions. I explained to the patient and their family that walks slowly, like shopping and light housework are not useful for achieving goals. To prevent any adverse effects, patients and their families have been trained on safety measures to be taken into account during physical activity.

- Additional therapy to exercise: proper nutrition program, the use of bronchodilators (for patients with bronchospasm due to effort), additional oxygen intake (for patients who have hypoxia during exercise).
- Adequate hydration with liquids with a safe level of electrolytes, for best absorption of ions and fluid in the blood (similar to the fluids consumed by athletes of performance), when their physical activity in hot weather conditions or excessive moisture.
- Appropriate clothing and footwear: reflective vest (if the exercise is executed at night, on the road), protective helmet (cycling), etc.
- Stop the physical activity event: the appearance or increase in dyspnea, a discomfort, appearance or increase in noisy breathing, the wheezing, tachypnea installation (over 30 breaths per minute), heart rate above 110-120 beats per minute or appearance of arrhythmias, the occurrence of constrictive chest pain or precordial pressure.

To analyze the results the 52 enrolled patients were divided into two age groups: 6 to 12 years and older than 12 years (≥13 years).

Date collected in the two time points were recorded in a database made in Microsoft Access. Results were expressed as number of cases (percentage) and mean ± SD (standard deviation). For the statistical analysis we used the Student test. Statistical significance was set at p < 0.05 for significant difference and p < 0.001 for highly significant differences.

Results

The lot included 52 patients, 23 (44.23%) female and 29 (55.77%) male. The average age of patients was 12.2 ± 4.7 years (range 6-29 years). Of the 52 patients, 26 were diagnosed with CF before the age of 2 years (51.92%), 14 patients between 2 and 6 years (26.92%), to 8 patients (15.38%) diagnosis was established between 6 and 12 years and to 3 patients (5.76%), CF diagnosis was made during adolescence. The average age at established diagnosis of CF was 3.5 ± 4.3 years (Table 1).

Of the 23 female patients, 12 belonged to 6-12 years group and 11 patients ≥13 years group. Male patients were divided into two groups according to age, as follows: 16 in 6-12 years group and 13 in the group ≥13 years (Figure 1).

Table 1 – General characteristics of patients with cystic fibrosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male), n</td>
<td>23/29</td>
</tr>
<tr>
<td>Age (years), mean±SD</td>
<td>12.2±4.7 (range: 6 – 29)</td>
</tr>
<tr>
<td>Diagnostic age (years), mean±SD</td>
<td>3.5 ± 4.3 (range: one month – 16 years)</td>
</tr>
<tr>
<td>BMI (Z score), mean±SD</td>
<td>-1.8±1.4</td>
</tr>
<tr>
<td>Weight (Z score), mean±SD</td>
<td>-1.9±1.1</td>
</tr>
<tr>
<td>Height (Z score), mean±SD</td>
<td>-1.3±0.9</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of the group depending on age and gender.
Table 2 shows the average of spirometry index (VC, FEV1, FEF25-75 and FEV1/VC) before and one year after the implementation of the physical activity program at home, in the age group 6-12 years. Although after one year of treatment was an average increase of all spirometry index, the increase was statistically significant only for FEV1 (p = 0.016) at this age.

I obtained similar results for girls group 6-12 years old: average spirometry indices increased to a year of treatment but the difference was significant only for FEV1 (p = 0.011) (Table 3).

For male patients of age group 6-12 years, we have achieved a significant increase in VC (p = 0.008) and highly significant for FEV1 (p = 0.00001), FEF25-75 (p = 0.0002) and airway permeability index (p = 0.0001), a year after the implementation of physical activity program at home (Table 4).

Regarding patients older than 12 years, the results are presented in Table 5. Although differences in flow and lung volumes values are not significant for two moments of time when records were made (p> 0.05), there is still a growth of averages spirometry indeces and airway permeability index (FEV1/VC) at one year after the start of outpatient physical activity program.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>69.84±19.33</td>
<td>76.21±18.02</td>
<td>0.2075</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>55.60±23.74</td>
<td>70.36±20.55</td>
<td>0.0160</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>50.31±30.04</td>
<td>59.91±25.59</td>
<td>0.2036</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.71±0.12</td>
<td>0.74±0.11</td>
<td>0.3393</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>68.22±20.13</td>
<td>70.68±19.67</td>
<td>0.06126</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>49.41±23.26</td>
<td>60.45±19.54</td>
<td>0.01116</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>42.52±27.50</td>
<td>48.90±22.00</td>
<td>0.14107</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.67±0.13</td>
<td>0.68±0.11</td>
<td>0.28361</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>70.98±18.80</td>
<td>80.24±15.69</td>
<td>0.00833</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>60.11±21.54</td>
<td>78.11±16.28</td>
<td>0.00001</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>53.31±29.92</td>
<td>66.66±23.98</td>
<td>0.00023</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.73±0.10</td>
<td>0.77±0.09</td>
<td>0.00011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>59.41±25.04</td>
<td>62.54±23.83</td>
<td>0.6595</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>51.85±25.48</td>
<td>56.61±25.98</td>
<td>0.5249</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>38.42±25.65</td>
<td>44.59±28.20</td>
<td>0.4319</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.65±0.14</td>
<td>0.66±0.14</td>
<td>0.9342</td>
</tr>
</tbody>
</table>
Analyzing the evolution of respiratory parameters by gender, in age group $\geq 13$ years, to one year of treatment, there is no significant difference between the two moments of assessment, both for female patients and male patients ($p > 0.05$) (Table 6 & Table 7).

Regarding the number of patients with changes in pulmonary function tests for the group 6-12 years, we obtained a decrease in the number of patients with changes in VC, FEV1 and the FEV1/VC report. Number of patients with changes in FEF25-75 remained the same, to a year of treatment for this age group. For the age group $\geq 13$ years, we have obtained only low numbers of patients with changes in FEF25-75, for other indices spirometry (VC, FEV1 and FEV1/VC) the number of patients with altered functional tests increased with a patient, to one year after starting the program (Table 8).

Table 6. Spirometry indices at one year after implementation of sustained physical activity at home, for female patients of the age group $\geq 13$ years.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>52.62±20.54</td>
<td>52.37±21.11</td>
<td>0.91510</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>50.23±28.62</td>
<td>48.68±24.76</td>
<td>0.68367</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>33.95±22.20</td>
<td>37.47±24.35</td>
<td>0.48410</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.64±0.17</td>
<td>0.62±0.15</td>
<td>0.42476</td>
</tr>
</tbody>
</table>

Table 7. Spirometry indices at one year after implementation of sustained physical activity at home, for male patients of the age group $\geq 13$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value (mean±SD)</th>
<th>Final value (mean±SD)</th>
<th>Student test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (percent of predicted value)</td>
<td>62.78±29.80</td>
<td>68.00±25.22</td>
<td>0.27856</td>
</tr>
<tr>
<td>FEV1 (percent of predicted value)</td>
<td>52.24±27.30</td>
<td>59.10±28.99</td>
<td>0.07738</td>
</tr>
<tr>
<td>FEF25-75 (percent of predicted value)</td>
<td>43.55±31.67</td>
<td>48.84±34.51</td>
<td>0.07725</td>
</tr>
<tr>
<td>VC/FEV1</td>
<td>0.66±0.14</td>
<td>0.68±0.15</td>
<td>0.18455</td>
</tr>
</tbody>
</table>

Table 8. Distribution of patients with impaired lung function, depending on age, in both times of assessment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>The age group 6-12 years -initially-</th>
<th>The age group 6-12 years -to one year of treatment-</th>
<th>The age group $\geq 13$ years -initially-</th>
<th>The age group $\geq 13$ years -to one year of treatment-</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC&lt;80% of predicted value</td>
<td>13 (46.42)</td>
<td>11 (39.28)</td>
<td>18 (75.00)</td>
<td>19 (79.16)</td>
</tr>
<tr>
<td>FEV1&lt;80% of predicted value</td>
<td>22 (78.57)</td>
<td>20 (71.42)</td>
<td>19 (79.16)</td>
<td>20 (83.33)</td>
</tr>
<tr>
<td>FEF25-75&lt;80% of predicted value</td>
<td>13 (46.42)</td>
<td>13 (46.42)</td>
<td>22 (91.66)</td>
<td>21 (87.50)</td>
</tr>
<tr>
<td>FEV1/VC&lt;0.75</td>
<td>19 (67.85)</td>
<td>18 (64.28)</td>
<td>18 (75.00)</td>
<td>19 (79.16)</td>
</tr>
</tbody>
</table>

Values are expressed as number of cases, n (%)

Discussions
There is many evidence of the benefits of daily physical activity, on the lung function. Zach M et al argue in this and adds that these benefits are lost very quickly when physical activity program is discontinued, it is not done regularly (25). Other studies show improvement in lung function after outpatient physical activity program. Thus, Schneiderman-Walker J et al, researchers randomized-controlled study on a group of 72 children and adolescents with CF, who have consistently performed an outpatient exercise program for three years, showed that this program, which increased to normal physical activity level was accompanied by a slower decline in VC and FEV1 and improved the wellbeing of these children (20). Wilkes DL et al they also get arguments in support of the recommendation to increase regular physical activity levels at patients with CF (23).

Although most patients of this study (52%) had early onset of symptoms and were diagnosed with CF in good time before the age of two years, and despite the small sample size, we chose to divide the group of 52 patients in two age groups because progression of the disease varies according by age. More, it is known that the health of these patients is less impaired in young ages, when are less extensive lung lesions (21).

In the group 6-12 years, the number of patients with changes in lung volumes and flows decreased and respectively remained the same for air flow indicates narrowing of small airways (FEF25-75). In addition, there was a significant increase in FEV1 after treatment applied,
while the average for other spirometry indices (VC, FEF25-75 and FEV1/VC) increased but not significant for female patients of this category age. Better results were obtained on lung function in male patients of this age category. For them, the increase of usual physical activity level has led to significant improvement in VC and highly significant improvement for pulmonary flows recorded and airway permeability index. According with other studies (11), we showed that as a result of treatment applied correctly, lung function and lung development can be improved until the age of 12 years. Knowing that FEV1 is a prognostic and follow up analytic factor (8, 24), its significantly improvement, thanks to the increase in common physical activity level, will lead consequently to improved prognosis for both girls and boys of 6-12 years age group. Furthermore, this study shows that the beneficial effects of the outpatient program of physical activity on lung function depend on gender, being more important for boys than girls. This is in line with some studies which showed a better survival rate in males; the favorable causes are still speculative (7).

In the group ≥13 years, values of lung volumes and flows and airway permeability index presented not significant variations for both girls and boys. This suggests that program to improve of usual physical activity level although not leading to a significant improvement in lung function in patients ≥13, regardless of gender, however helped to preserve the lung function for the entire the study period.

The study has two important limitations.

- The sample size was small.
- Because of the small number of patients with CF are under monitoring (FC isn’t a very common medical condition, on the one hand, and on the other hand it is still less diagnosed in our country, many patients dying with other diagnoses), I could form a control group to be excluded from the program to improve of regular physical activity level at home.

Conclusions

Increasing regular physical activity level had beneficial results on the lung function, whose value depends of age and gender. Male younger patients (6-12 years) had significant increases in all respiratory parameters studied, at one year of treatment.

Decreased number of patients with changes in lung volumes and flows, and significant improvement in FEV1 and consequently of prognosis, for all patients regardless of gender, observed in the group 6-12 years, suggests that any change is not permanent which is an additional incentive for continuous improvement therapeutic management of these patients.

In older patients, this program to increase outpatient usual physical activity level has helped to stability of the lung function.

This study provides evidence to recommend as early as possible exercise and physical activity as an educational measure of lifestyle for patients with CF, to prevent, improve or at least slow the progression of lung disease for a longer period of time, and thus reducing the complications.

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UP-TO-DATE STANDARDS OF PERMANENT TOOTH ERUPTION IN ROMANIAN CHILDREN

Ana Emilia Ogodescu¹, Anca Tudor³, Kinga Szabo², Camelia Daescu⁴, Elisabeta Bratu¹, Alexandru Ogodescu¹

Abstract

Standards of tooth development are important for medical fields, biology and anthropology. The last surveys in order to determine permanent tooth eruption standards in Romanian population were undertaken more than 30 years ago. The aim of this study was to present new data on the timing and sequence of permanent tooth emergence, using three different methods and to determine the correlations with age and other somatic growth parameters. Cross-sectional and longitudinal data on permanent tooth eruption were collected by examining 382 children (189 girls and 193 boys). The total number of recordings acquired between 2009 and 2011 was 646. Each present permanent tooth was scored: 0, 0.25, 0.5 or 1. The recordings were introduced in a database and statistical analysis was performed. The number of teeth was determined for each age interval of one year. It was significantly higher for girls in two age intervals: 9.5-10.4 and 11.5-12.4. The first permanent tooth that erupts is the lower first permanent molar, followed by first permanent upper molar or lower central incisor. The age of eruption of lower lateral incisor is much closer to the upper central incisor and it can sometimes precede or erupt simultaneously. The lower canines erupt after the upper and lower first premolars, around 10.5 years. The upper canines erupt around 11.5 years, after the eruption of both lower second premolars and much closer to the eruption of lower second molar. The last tooth to erupt is the upper second molar, after the age of 12 years. Photographs or study casts represented good proofs and we could verify the assessed data. The correlations were determined. The correlation with weight and height could be taken in account, but not the correlation with body mass index (BMI). The number of permanent teeth erupted, does not depend on the presence or absence of menstruation at the date of assessment, for our girls sample.

Keywords: permanent teeth, timing of tooth emergence, tooth eruption sequence, sex differences, height, weight, body mass index, menstruation, sequential intraoral photography, and sequential study casts

Introduction

The exfoliation of primary teeth and the subsequent eruption of permanent teeth is a developmental phenomenon that forms part of the body’s continual process of growth. It is a physiological phenomenon having characteristics not seen in any other body organ [1].

Development of the occlusion, in other words, eruption of the teeth and formation of the interrelationship between the teeth of the upper and lower jaws, is a genetically and environmentally regulated process [2].

The term “tooth eruption” generally refers to the appearance of some part of a tooth above the surface of the gingiva. However, eruption actually includes the entire embryological process from the formation of the tooth germs, in the mandible and maxilla, to calcification, crown formation and root formation. The root is only about one-third formed when the crown begins to erupt into the oral cavity. Not only is the embryological process part of eruption, but so is the long process of occlusal development. Thus, the emergence of the teeth into the oral cavity is only one part of the total eruption process [3].

Eruption of the teeth can be divided into different stages: preemergent eruption when the developing tooth moves inside the alveolar bone; emergence, the moment when a cusp or an incisal edge of a tooth first penetrates the gingiva; postemergent eruption follows and a tooth erupts until it reaches the occlusal level. Eruption speed is faster during this stage and therefore the stage term postemergent spurt is sometimes used. When a mesiolingual cusp of the lower first permanent molar has emerged, two months later the occlusal surface can be seen [2].

The mixed dentition period can be theoretically divided in three sub periods: between 6 and 8 years- the eruption of front teeth; between 8 and 10 years-intermediate period; between 10 and 12 years-the eruption of the teeth that belong to lateral segments [4,5]. In general teeth erupt earlier in girls than in boys [2] and the intermediate period is a little shorter in girls then in boys [4,5]. There is a great individual variation in the eruption timing of permanent teeth. Delay or acceleration of 12 months from the average eruption timetable is still within the normal range [2, 6].
Adequate knowledge of timing and pattern of tooth eruption are important for the diagnosis and treatment planning when working with children in pediatric dentistry and orthodontics [1]. From a dentist’s point of view it is necessary to reconsider tooth eruption times occasionally. Over the years, changes in sequence and time of tooth eruption are possible [7]. It is also useful in the field of surgery and for determination of age in forensic science [1]. Age estimation for humans plays an important role in mass disasters and unaccompanied or asylum-seeking minors in the absence of proper documents. It also contributes to anthropology [8]. Variation more than one year in timing of tooth development could be the indicator of one disease in pediatric medicine and pediatric endocrinology [6].

Dental age is determined from three characteristics. The first is which teeth have erupted. The second and third, which are closely related, are the amount of resorption of the roots of primary teeth and the amount of development of permanent teeth [9].

Many authors have reported differences in the permanent tooth eruption between ethnic groups and genders [1, 7, and 8]. These studies showed that variation exists in the eruption times of permanent teeth and this may be attributed to numerous racial differences [10]. Because a variety of factors relate to emergence, standards for emergence of the permanent teeth are most useful when they derive from the population to which they are applied [11].

The endogen factors (genetically or hormone derived) have the greatest influence on tooth eruption [12]. Socioeconomic and nutritional factors, caries conditions and the secular trend have also been found to have some effect on the eruption of permanent teeth [11,13].

Females generally precede males in the eruption timing by an average of 5 months [14]. The reason for the differences of tooth eruption in male and females are still poorly understood. It is assumed that the earlier onset of the permanent dentition is part of the different sexual maturity of both sexes at a given age [15, 16].

Children who are below average weight and height showed a later eruption time than those children who are within standard range [11, 17].

Recent studies reveal that teeth emerged at similar times on right and left sides, the mandibular teeth tended to emerge earlier than their maxillary counterparts and that girls tended to be advanced compared with boys [1, 10, 11, 15, 18].

Most of the studies concerning tooth emergence are cross-sectional, although a few longitudinal studies exist [3, 11, 19]. The prospective longitudinal studies provide most actual results.

When we take in account the short period of research time that we have, when we investigate such a dynamic, complex and long biological process we come to conclusion that we have to do our research as a cross-sectional survey or we have to investigate the most dynamic periods when doing mixed longitudinal studies. Another possibility is to create a good database; which can be used by future researchers in a longitudinal study [20].

Clinical findings are not enough in order to have the possibility to control the assessed data, to verify the inclusion criteria, to have good research proofs and database for future research [21].

Sequential intraoral photographs and sequential study casts, taken in the most dynamic stages, are tools needed to accompany clinical findings in each eruption research (Fig.1, Fig.2).

Fig.1 Sequential intraoral photographs of a boy at 6.8 (6 years 10 months), 7.3 (7 years 4 months), 7.8 (7 years 10 months), 8.3 (8 years 4 months) and 8.6 years (8 years 7 months).

Fig.2 Sequential study casts of a boy at 7.3 (7 years 4 months), 7.9 (7 years 11 months) and 9.3 (9 years 4 months).
Although the most accurate method for studying eruption order (and positions) of permanent teeth is to trace the dental history of the same individual, many researchers, in consideration of the many years and the various difficulties involved in this method, have opted to study this order in terms of average eruption times (average age at time of eruption) [3].

Purpose

Our clinical day by day observations proved that there are differences between the clinical findings regarding the age and sequence of eruption of some teeth and the mean ages that were determined more than 30 years ago on Romanian population. The objectives of this study were: to determine the mean age and the sequence of eruption of permanent teeth, the differences between three different methods, the number of teeth erupted at different ages and the sex differences, to find out the correlations between age, height, weight, body mass index, the presence of menstruation and the number permanent teeth erupted.

Material and methods

The data used for this study were collected from 382 children (189 girls and 193 boys), aged between 3.5 and 15.5 years. The children were from 3 different schools (one from Timisoara and two schools from two villages closed to Timisoara), one nursery school or were patients at the Clinic of Paedodontics-Orthodontics and one dental practice from Timisoara. Some of the children have only one recording and some of them have from two to five recordings at different age intervals. The total number of recordings acquired between 2009 and 2011 was 646 (331 recordings for girls and 315 recordings for boys). We divided the sample in groups, considering an age interval of one year. Our survey was prospective cross-sectional, but included longitudinal data as well (Fig. 3).

The inclusion criteria were: healthy children, free from any known disorder affecting growth, mental disease or congenital anomalies. The majority of the children were most likely to be of Romanian ancestry based on their names. No selection was made concerning caries, primary tooth premature extractions, differences in physical development, social status, religion, ethnicity or whether the patient was born in Timisoara or not. The children with known or suspected anodontia and children wearing fixed orthodontic appliances were excluded from our study.

The data were collected by two examiners: one who did the examination and second who registered the information on a dental chart, at the same time. Most of the registrations were accompanied by photographs or study casts. Date of birth and sex were taken from school register. The date of assessment was also registered. The age was calculated in years and months from each child’s date of birth to the date of examination.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>f</td>
<td>m</td>
</tr>
<tr>
<td>3.5-4.4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>4.5-5.4</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>5.5-6.4</td>
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<td>22</td>
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<td>6.5-7.4</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>7.5-8.4</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>8.5-9.4</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>9.5-10.4</td>
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<td>10.5-11.4</td>
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<td>11.5-12.4</td>
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<td>44</td>
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<tr>
<td>12.5-13.4</td>
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<td>36</td>
</tr>
<tr>
<td>13.5-14.4</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>14.5-15.4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>331</td>
<td>315</td>
</tr>
</tbody>
</table>

Fig.3 The distribution of cases by age group and gender represented by a table (left) and by a histogram (right).

Height and weight and the date of the first menstruation (at girls) were assessed in the same time.

Each present permanent tooth was scored: value 0 - the moment of tooth eruption (the tooth penetrates the gingiva with one part or all the incisal edge, for the incisors or with one or two cusps, for other teeth); value 0.25- if a quarter of the height of the tooth is erupted; value 0.5- if a half of the height of the tooth is erupted; and score 1 if the tooth has more then half until the whole clinical crown erupted. If the tooth was absent it was not scored (Fig. 4). Primary teeth were also scored and occlusion assessed because this study is part of a more extended survey: a dentofacial growth and development study.
All the determined data were included in a large database in order to be analyzed with statistical methods in the Department of Medical Informatics and Biostatistics from Timisoara (Fig. 5). The program used was SPSS v. 17. The following data were introduced in our database: the identity number and assessment number of each patient, date of birth, primary and permanent molar occlusion, date of first menstruation and if it is present/absent, date of assessment, age interval to which it belongs, age in years, age in months and years, height, weight, the body mass index calculated according to formula, the number of permanent teeth counted by computer, the values for each tooth from 1.7 to 2.7 and from 3.7 to 4.7, followed by primary teeth scores and the number of primary teeth present and absent.

Results

The age of each child and the number of permanent teeth was counted by the computer. We included each child in the corresponding one year age group. The mean number of present permanent teeth (all the values were counted, only blank cells were excluded) was determined for boys and girls and t-test was applied in order to compare the two groups. The differences between boys and girls were significant for 9.5-10.4 years (girls have mean number of 17.82 teeth, comparing to 15.23 which is the mean number
of teeth for boys, \( p=0.007 \) and 11.5-12.4 years (the mean number of teeth is 25.45 for girls and 23.00 for boys, \( p=0.004 \)). At these age groups, girls from our sample have significant more permanent teeth erupted than boys (Fig.6).

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Number of girls</th>
<th>Mean number of teeth for girls</th>
<th>SD</th>
<th>Number of boys</th>
<th>Mean number of teeth for boys</th>
<th>SD</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5-4.4</td>
<td>5</td>
<td>0.00</td>
<td>0.000</td>
<td>4</td>
<td>0.00</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>4.5-5.4</td>
<td>11</td>
<td>0.45</td>
<td>1.508</td>
<td>10</td>
<td>0.70</td>
<td>1.889</td>
<td>0.74</td>
</tr>
<tr>
<td>5.5-6.4</td>
<td>18</td>
<td>3.44</td>
<td>3.034</td>
<td>22</td>
<td>3.59</td>
<td>3.127</td>
<td>0.87</td>
</tr>
<tr>
<td>6.5-7.4</td>
<td>14</td>
<td>7.71</td>
<td>3.268</td>
<td>29</td>
<td>6.93</td>
<td>3.494</td>
<td>0.487</td>
</tr>
<tr>
<td>7.5-8.4</td>
<td>32</td>
<td>11.13</td>
<td>2.311</td>
<td>29</td>
<td>10.21</td>
<td>2.883</td>
<td>0.172</td>
</tr>
<tr>
<td>8.5-9.4</td>
<td>41</td>
<td>13.44</td>
<td>2.899</td>
<td>46</td>
<td>12.52</td>
<td>2.510</td>
<td>0.11</td>
</tr>
<tr>
<td>9.5-10.4</td>
<td>49</td>
<td>17.82</td>
<td>4.044</td>
<td>39</td>
<td>15.23</td>
<td>4.151</td>
<td>0.007</td>
</tr>
<tr>
<td>10.5-11.4</td>
<td>57</td>
<td>20.89</td>
<td>4.894</td>
<td>37</td>
<td>20.38</td>
<td>4.172</td>
<td>0.608</td>
</tr>
<tr>
<td>11.5-12.4</td>
<td>47</td>
<td>25.45</td>
<td>2.819</td>
<td>44</td>
<td>23.00</td>
<td>4.956</td>
<td>0.004</td>
</tr>
<tr>
<td>12.5-13.4</td>
<td>33</td>
<td>26.52</td>
<td>1.623</td>
<td>36</td>
<td>25.58</td>
<td>3.434</td>
<td>0.157</td>
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<td>13.5-14.4</td>
<td>21</td>
<td>27.52</td>
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<td>12</td>
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<td>0.905</td>
<td>0.956</td>
</tr>
<tr>
<td>14.5-15.4</td>
<td>3</td>
<td>26.67</td>
<td>2.309</td>
<td>7</td>
<td>28.00</td>
<td>0.000</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Fig.6 The number of permanent teeth erupted for boys and girls of our sample.

We determined the timing of tooth eruption in three different ways: for 0 values (the moment of tooth eruption, when the tooth penetrates the gingiva), which is the most accurate for large samples; for 0 and 0.25 values (we take in account both values, the moment of tooth eruption and the moment when a quarter of the height of the tooth is erupted), which is not so accurate but it has the advantage that the number of teeth that we take in our determination is larger than before; for 0 and 0.25 values (we take in account both values, like before, but we apply a correction that should improve our last results). The sequence of tooth eruption is not determined by tracing the dental history of the same individual, like in longitudinal studies, but taking in account the mean age of eruption of each homolog tooth pairs (Fig.7).

When taking in account the whole sample, the correlation between the number of teeth and age is almost perfect \( (r=0.914, p<0.001) \), with height and weight is strong and direct \( (r=0.86, p=0.001) \) for both correlations but low with body mass index (BMI) \( (r=0.34, p<0.001) \) (Fig.8). The number of permanent teeth erupted, for 124 girls, does not depend on the presence or absence of menstruation at the date of assessment.

Fig.7 The mean age and the sequence of eruption of permanent teeth.
Correlation between the number of teeth and age
Correlation between the number of teeth and height
Correlation between the number of teeth and weight
Correlation between the number of teeth and body mass index

Discussions and Conclusions

The correction for 0.25 was taken from the atlas [3], because we could not examine enough children at such age intervals. Each of the three methods applied in our study had advantages and disadvantages. That is why we try to analyze the results in three different ways, being conscious that small errors are part of each one. For the first method the number of teeth included is not enough. The sample of teeth enlarges when we use the second method, but the mean ages determined are higher, because in many situations a quarter of the tooth is already erupted. We needed a correction and the third method was developed. The disadvantage was that the correction was not original, but determined on Japanese sample 20 years ago. There is a demand for a future study in order to determine tooth eruption speed on Romanian children.

Girls have usually more teeth erupted, but significantly more at two age intervals. This could suggest that sexual differences are implied.

The lower canine erupts at 10.5. It is different comparing to national standards, determined long time ago [6, 12], but quite similar to European and American (of Caucasian origin) actual standards. In many cases it erupts after the first premolars and sometimes after the second premolars.

The upper canine erupts at 11.5 and the second lower molar erupts immediately after.

We know that inter individual variation is larger where SD is higher (more than 1). The standard deviation related to premolars is higher, because it depends on caries and the premature lost of the primary molars.

Lower first molars are always the first, but the related SD is always high. We have quite large inter individual variation regarding the mean age of eruption of the first permanent tooth.

The differences in sequence between the three methods occur between upper first molars and lower central incisors and between lower lateral incisors and upper central incisors. Our clinical observations are according to these results (Fig.7, Fig.9)

Because the eruption data were collected in the past two years and verified with photographs and study casts, the tables that we developed could be used as standards and clinically tested until a new survey, more organized and including more children, will be undertaken.

Fig. 8 Correlations between the number of teeth and other parameters.

Fig. 9 The different order of eruption between lower lateral incisors and upper central incisors.

References

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THE DIAGNOSIS AND PROPHYLAXIS OF THE IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN BABIES AND SMALL CHILDREN

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Abstract
The work refers to the diagnosis and prophylaxis of the iron deficiency and iron deficiency anemia in babies (naturally or artificially fed) and the children younger than 3 years. The recent studies show that iron deficiency anemia and iron deficiency without iron deficiency can have long term effects on neurological development. We hereby present the adequate iron addition and the screening of iron deficiency anemia.

Key words: iron deficiency, iron deficiency anemia, baby, small child, iron addition

Introduction
The iron deficiency and iron deficiency anemia continue to be a world health issue in the developing nations and even in the industrialized ones (2,23,28). Nevertheless, even more important than anemia is the iron deficiency without anemia which can have long term effects on the neurological development and behavior, some of them irreversible. This work refers to the diagnosis and prophylaxis of iron deficiency anemia.

Definition, prevalence and necessary iron
Anemia is defined as the drop in concentration of the hemoglobin under 11g/dL in children aged between 12 and 36 months. In certain populations (such as the ones leaving at high altitudes) the value adjustment must be done.

The normal iron concentration is the situation in which there is enough iron to maintain the physiological functions within normal limits. The iron deficiency is the situation in which there is not enough iron to maintain the physiological functions within normal limits. The iron deficiency is the result of the inadequate absorption of iron reported to the needs or of the negative balance of iron on long term. Each of these situations leads to the decrease in the iron deposits measured in serum ferritin or in the iron concentration in the bone marrow. The iron deficiency may or may not be accompanied by iron deficiency anemia. The iron deficiency anemia is the anemia resulting from the iron deficiency (2,16,18).

The iron overload is the excessive accumulation of iron in the tissues. The iron overload is usually the result of the genetic predisposition to excessively absorb and store iron (e.g. hereditary hemochromatosis). The iron overload may also be a complication in other hematologic diseases that need repeated blood transfusions, repeated iron injections or excessive iron ingestion.

The recommended iron diet is the average of the daily iron needs that is enough for almost all individuals, based on age and gender. The adequate iron need is the term used when there is not enough information to establish the recommended diet for certain population segments (newborns, babies younger than 6 months).

80% if the iron quantity of the new born at birth is formed during the last pregnancy trimester. The premature newborn “skips” this period and has an iron deficiency. Certain diseases of the mother, such as anemia, sugar diabetes, arterial hypertension with in-uterus growth deficiency, can lead to low iron deposits in the newborns born on time, as well as the premature ones. The iron deficiency in premature babies increases with the decrease of the gestational age and is worsened by the frequent phlebotomies without adequate blood replacement. On the other hand the premature babies who receive multiple blood transfusions run the risk of iron overload. The varying status in blood in premature babies, with the risk of iron deficiency or toxicity, makes the determination of the exact needs impossible, which is estimated at 2-4 mg/day if administered orally (1,12,28).

IOM (Institute of Medicine), taking into account the average iron content of the human milk, has determined the adequate intake at 0.27 mg/day in full term newborns since birth until 6 months of age (16).

The average of the iron content of the human milk if 0.37 mg/L and the average of the milk needs of the exclusively fed baby is estimated at 0.78 L/day. From these valued the necessary amount has been determined at 0.27 mg/day for the full term newborn until 6 months of age. IOM has considered that there must be a direct connection between the age of the baby and the milk ingestion; thus there must not be any correlation based on weight. Nevertheless, there is a large variation in the iron concentration in human milk and there is no guarantee that it will cover the needs of the baby. For the babies between 6 and 12 months the recommended diet for iron (according to IOM) is of 11 mg/day (16).

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The amount of iron losses – the epithelial exfoliation of the skin, the urinary and digestive tracts – was added to the amount of the iron needs for the increase of the blood volume with the growth of tissue mass and to the iron deposits of that period. It is mentioned that the necessary iron in babies does not pass directly from 0.27 mg/day to 11 mg/day at the age of 6 months. It is obvious that the full term healthy newborns need very little iron in the first 6 months as compared to the needs after 6 months (16,25).

Using the same reasoning, IOM considers that that recommended necessary iron for the child aged 1-3 is of 7 mg/day.

There is no national statistic on the prevalence of iron deficiency and iron deficiency anemia in babies. The general prevalence in the USA of iron deficiency anemia has dropped in babies and small children since the 1970s, with the use of iron-enriched milk formulae and with the drop of the use of cow milk in babies (2). Related the iron deficiency anemia is the issue of the interaction between iron and led. If the studies made on animals and humans it has been noticed that the iron deficiency anemia increases the intestinal absorption of led. Thus, iron deficiency anemia decreases the efficiency of lead chelators and the iron supplements correct this issue (7,38).

Many studies have shown the connection between iron deficiency anemia and later cognitive deficiencies. Lozoff et colab. (2006) have shown the cognitive deficiencies in the 1-2 decades after iron deficiency during the baby stage (18). Nevertheless, it is difficult to determine a causality connection. It is known that iron is essential in neurological development. The iron deficiency affects the neuronal metabolism, the neurotransmitter metabolism, the mielinisation and memory (6,11,30). These observations could explain the behavioral problems in children with iron deficiency.

**Paraclinical diagnosis**

We follow certain parameters: the hemoglobin concentration, the reticulocytes, erythrocytary indexes, the total iron assimilation, the transferrine saturation, protoporphyrine, ferritine and sTfr (transferrine receptor). The last parameter, the soluble form of the transferrine receptor that freely travels into the plasma, is an important indicator of the status of iron in the organism.

In this table we show the changed in the main parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Iron deficiency without anemia</th>
<th>Iron deficiency anemia</th>
<th>Iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritine</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Transferrine saturation</td>
<td>↓</td>
<td>↓</td>
<td>↑↑↑↓</td>
</tr>
<tr>
<td>Transferrine receptor (sTfr)</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Reticulocitary hemoglobin</td>
<td>↓</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>VEM</td>
<td>normal</td>
<td>↓</td>
<td>normal</td>
</tr>
</tbody>
</table>

↓ low value, ↑ high value

The iron status in children is not determined by a simple determination of hemoglobin concentration. The decrease in hemoglobin can have a variety of causes, of which we mention the hemolitical anemia, the chronic disease anemia, the B12 or folic acid deficiency anemia, the genetic disease anemia. But once put the iron deficiency diagnosis, the supervision of the hemoglobin concentration is a good response measure to the treatment.

Any set of analysis will include the hemoglobin concentration to determine whether or not there is anemia. The three parameters giving selective data about the status of the iron are: ferritine, reticulocitary hemoglobin and the transferrine receptor.

Ferritine is a sensitive parameter for the assessment of the iron deposits in healthy subjects (1 µg/L of ferritine corresponds to 8-10 mg of available iron). In children the value showing the depletion of the iron deposits is of 10 µg/L (in adults 12 µg/L) (9,17). Because the serum ferritine is a short phase reactant, its concentration can be increased in the presence of chronic inflammations, infections, malignancies, hepatic diseases. A simultaneous determination of protein C reactive is needed to exclude the inflammation.

Even though serum ferritine has a lower accuracy that reticulocitary hemoglobin or the transferrine receptor, the combination of ferritine and protein C reactive is more accessible and a more reliable test as long as the protein C reactive is not high (9,17,34).

The reticulocitary hemoglobin and the transferrine receptor are not influenced by the inflammation, malignancy, infections, chronic diseases and are preferable for the diagnosis. The reticulocitary hemoglobin has been validated, standardized in children and actually available. This parameter provides a measurement of the available iron in the cells recently released by the bone marrow (5). The reticulocitary hemoglobin can be measured by citometric flow and the low concentration is the most important in predicting iron deficiency in children.

The transferrine receptor (sTfr) is a measure of the iron status which finds the iron deficiency on a cellular level (32,37). It is found on the cell membrane and allows the transfer of iron in the cell. When the iron is insufficient, there is an imbalance of the transferrine receptor’s permission for the cell to have a more efficient iron composition and later its circular form has a serum increase. An increase in serum in the transferrine receptor can be
found in the patients with iron deficiency or iron deficiency anemia, even though the serum doesn’t increase until the iron deposits are depleted in the adults. The assessment of the transferrine receptor is not usually available and the standard value for children has not yet been established.

For putting the diagnosis of iron deficiency anemia (when a hemoglobin value smaller than 11g/dl is associated), nowadays the following tests can be used: ferritine + protein C reactive or reticulocitary hemoglobin. For the iron deficiency diagnosis without anemia the same parameters are measured.

Another approach in the diagnosis of iron deficiency anemia in mild anemia children (Hb 10-11g/dL) is the monitoring of the response to iron supplements, especially if the history of the nutrition involves an iron-poor diet. An increase in hemoglobin of 1 g/dL after 1 months of treatment is used as positive for iron deficiency anemia. This approach imposes an adequate iron treatment, the compliance of the patient and an adequate absorption.

**Correcting the iron deficiency and iron deficiency anemia.**

*Premature babies.* The naturally-fed premature babies (below 37 weeks of gestational age) will receive elementary iron supplements of 2 mg/kg/day beginning with 1 month of age until 12 months. The iron can be provided through medication or through an iron-rich diet. The premature babies who are fed with formulae for premature babies (14.6 mg iron/L) or ordinary formulae (12 mg iron/L) will receive approximately 1.8-2.2 mg/kg/day assuming a milk consumption of 150 ml/kg/day (12,29).

Despite the iron-enriched formulae, 14% of premature babies have an iron deficiency between 4 and 8 months of age. Thus the enriched formulae need an iron supplement addition. The exception for these iron supplements are the premature babies who received multiple transfusions during the hospitalization period, who might not need iron supplements.

*Naturally fed full term babies.* The full term baby has a higher hemoglobin concentration and a higher blood volume as compared to body weight. They go through a physiological decrease in hemoglobin and blood volume during the first four months of life. Usually the iron deposits are enough for the first 4-6 months. The iron content of human milk is enough for the newborns who are exclusively naturally fed.

The exclusively natural diet is recommended for 6 months. The exclusively natural diet for the newborns after 6 months is connected to a higher risk of iron deficiency anemia at the age of 9 months. The recommendation for an exclusively natural diet does not take into account the babies born with low iron deposits (the newborns with a low weight at birth, the babies whose mothers have diabetes), a situation which also determines a low iron concentration at the age of 9 months.

It is recommended that the full term babies who are exclusively naturally fed receive an iron supplement of 1 mg/kg/day starting with the age of 4 months until the introduction of the iron-rich foods (10,25).

For the mixed-fed babies, the proportion of the breastfeeding as opposed to the formulae is uncertain. Thus, after 4 months the babies who do not receive an iron-rich diet will get 1 mg/kgc/day supplemental iron.

**Artificially fed full term babies.** The American Pediatric Association has concluded that the milk formulae containing 12 mg elemental iron /L are safe (26,27,31). There is not enough data to relate the formulae with 12 mg/L to the gastro-intestinal symptoms (3,12,31).

Small children (1-3 years). The necessary iron in small children is of 7 mg/day. Ideally, the necessary iron must be provided through food naturally rich in iron and vitamin C which stimulates the iron absorption. In the developing countries, the necessary iron is covered by the iron strengthening of certain foods such as corn flour, soy sauce, rice, cereal. Nevertheless, there are barriers to providing an optimal iron intake: the lack of education of the parents, the low compliance to any digestive adverse effects, the price of enriched products, the federal nutrition programs which do not provide iron supplements. In the US, the iron-enriching of formulae and cereals for the babies has lead to the decrease of iron deficiency anemia (2).

As an alternative for those who do not take enough iron from the diet, there are also the iron supplements which are available as a component of the multivitamin syrup or chewable tablets (4,13,14).

**Screening for iron deficiency and iron deficiency anemia.**

The universal screening must assess the risk factors associated to the iron deficiency/iron deficiency anemia: a history of premature birth or small weight at birth, exposure to led, an exclusively natural diet over 4 months without iron supplements, an integral milk diet, a diet of non-iron enriched cereal or of low-iron foods. The additional risk factors include nutrition problems, an inadequate diet, a stationary weight curve.

In the US 60% of the anemia cases are not due to the iron deficiency and most of the iron deficiency children do not have anemia.

Selective screening tests can be done at any age when the risk factors for iron deficiency and iron deficiency anemia are found.

After determining the hemoglobin concentration, in children with hemoglobin below 11 mg/dL or with a high risk of iron deficiency the ferritine + protein C reactive and reticulocitary hemoglobin are determined. The determination of the transferrine receptor will enter the screening tests once the value in children is determined.

**Conclusions**

It is important that we eliminate the iron deficiency and iron deficiency anemia in babies and young children, considering their impact on cognitive and behavioral development(22,24,30). There are controversies regarding the time and methods of screening and on the use of iron supplements.

The present data support the following recommendations:
• Healthy newborns born on time have enough iron for at least the first four months of life. The exclusively natural feeding after the first four months without iron supplements leads to an iron deficiency. The naturally fed babies must receive 1 mg/kg/day starting with the age of 4 months until the iron-rich foods (including cereal) are introduced in the diet.
• For the mixed-fed babies, the proportion of mother milk vs. formula is uncertain. Consequently, starting with the age of 4 months the mixed-fed babies who do not receive iron-rich foods must receive 1 mg elemental iron/kg/day.
• For the formulae-fed babies, the necessary iron can be covered by standard milk formulae (iron content 10-12 mg/L) and the introduction of foods containing iron after 4-6 months of age, including cereal. The integral milk must not be used before 1 year of age.
• The iron addition between 6 and 12 months must be of 11 mg/day. When the food becomes more varied, the vegetables and red meat with a high iron content are introduced. If the food does not cover the necessary, the liquid iron supplements will be introduced.
• The small child (1-3 years) has a necessary of iron of 7 mg/day which will be provided by the red meat, iron-enriched cereal, iron-rich vegetables, fruit with vitamin C which increases the iron absorption (35,36). In the case of the children who do not receive the appropriate iron-rich food, iron supplements are recommended as syrup or chewing tablets.
• Premature babies must receive an iron addition of at least 2 mg/kg/day until 12 months old, including the supplementary iron in the milk formulae. Naturally fed premature babies must receive iron supplements of 2 mg/kg/day after 1 month of age until the diversifying with iron-rich foods (29). The exception consists of the premature babies who have received iron through blood transfusions and erythrocytic mass transfusions.
• The universal anemia screening must be done at approximately 12 months with the determination of the hemoglobin concentration and the assessment of the risk factors related to the iron deficiency/iron deficiency anemia. These risk factors include precarious socio-economic status, a history of premature birth or small weight at birth, exposure to lead, exclusively natural nutrition until 4 months of age without iron supplements, iron-rich foods and iron-enriched cereal. Additional risk factors are the eating disorders, inadequate weight gain, inadequate nutrition. In the case of babies and small children, the screening must be done whenever the risk factors are involved.
• If the hemoglobin level is less than 11 mg/dL at 12 months the cause of the anemia will be investigated. If there are risk factors of iron deficiency the status of the iron will be investigated. The ferritin + reactive protein C and reticulocitary hemoglobin will be determined. Afterwards the correct treatment will be applied.
• If a child has mild anemia (Hb 10-11 mg/dL) and can be closely monitored, an alternative diagnosis method will be the increase by 1g/dl of the hemoglobin concentration after a month of iron therapy.
• The use of the transferrin receptor (sTfs) as screening for the iron deficiency is promising and the establishing of the standard value is expected for the use on babies and small children.

References


THE ANSWER TO THE TREATMENT OF
THE CHILDREN WITH GH DEFICIENCY

Carmen Dragomirescu¹, I Vasile², Oana Pavel², Iulia Bistriceanu¹

Abstract
The aim: the evaluation of the results of the treatment
with growth hormone, obtained by genetic recombination
(rhGH) to a group of 47 children with pituitary dwarfism.
The method: the patients have used for a year a treatment of
growing advance with 0,2mg/kg/a week rhGH,( Zomacton)
taken every day. We have followed: the change of the
anthropometric parameters under therapy; the relation
between the different parameters and the answer to the
treatment. The results: during the treatment we noticed a
significant improvement of the growing speed, from 1,73
cm/year to 9,50 cm/year. As well as, the growing deficit has
improved from -3,07 SD to -2,33 SD. To the studied group
we found relations between the growing speed under
treatment and the following parameters: the chronological
age and the bone age at the beginning of the treatment; the
delay of the bone age with more than 3 years. Conclusions:
the obtained results show the fact that the treatment with
rhGH to the children with pituitary dwarfism is an
important ally regarding the improvement of the
consequences caused by the hormone deficiency, its main
purpose being the improvement of the height during the
childhood and the obtaining of a final, normal height.
Key words: GH, GH deficiency, rhGH

Introduction
The pituitary dwarfism is a debilitating disease,
regarding not only the social status of the short person, but
also because of the effects of the hormone deficiency in the
body, during the childhood and the adult period. This aspect
motivates the early diagnostic of GHD deficiency, using
very clear criteria in order to begin the replacement therapy.

The patients with such problems can be treated with GH
obtained through genetic recombination (rhGH) as soon as
possible after the diagnosis. The main objective of the
therapy is represented by the obtaining the normal height
during the childhood and also as an adult.

The growing as an answer to the exogenous GH varies
on many parameters: the frequency of the treatment, the
dosage, the age of the patient at the beginning of the
treatment, the weight, genetic factors, the serum level of
GHBP and, if possible, the season (1-4). This thing
motivates the study of the relations between different
parameters and the answer to the treatment in order to obtain
the best results.

Generally speaking, a daily treatment of rhGH with the
prescribed dosages, the children with GHD have a growing
speed from 3-4 cm/year in pretreatment to 10-12 cm/year in
the first year of therapy and to 7-9 cm/year in the second and
the third year of therapy.

The age at the beginning of the treatment inversely
correlates with the answer on growing and it is very
important that the rhGH substitution therapy should be
installed before the puberty start, because it is a fact that the
estrogens fasten the maturity of the bones (5, 6).

The genetic factors which influence the growing as an
answer to the rhGH therapy, remain mostly unknown. Up to
now there were information only about the gene of the GH
(GHPR) receiver. Polymorphisms of this gene have been
reported to the general population and they were described
in the exons 3, 6 and 10. Two of the most-known isoforms
of human GHR gene are generated by the presence or the
absence of the exon 3: GHR-fl (full-length GHR) and
GHRd3 (exon 3 deleted GHR). In the last years there have
been studies on children with growth hormone deficiency
and on children with a short stature, but without GH
deficiency. The problem of the dependence of the answer of
the rhGH substitution therapy to the genotype of the gene
receiver of the growing hormone still remains a
controversial subject, due to the fact there are pro and
against data (4, 7-9).

The possible role of the composition of the body in the
answer to rhGH therapy at the children with GHD require
more investigations (2).

The Aim
The study has as a goal the evaluation of the results of
the treatment of the growing promotion in the case of
weakness stature due to the growth hormone deficiency.

The material and the method
We included in our group 47 of children with growing
hormone deficiency, who were selected from the children
that came to the Endocrinology Clinic and Ambulatory of
the Emergency County Hospital from Craiova, between
2005-2010.

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In order to establish the diagnostic of GH deficiency we used the clinical criteria (history, objective examination) and paraclinical criteria.

**Clinic criteria of including the patients in the study:**
- The delay in the height of two or more standard deviations (SD) related to the average of age and sex.
- The growing speed is slow in the last year.
- The normal stature of the parents.
- Suggestive clinic features for the GH deficiency (acromicrie, pigmantation “in butterfly” of the facial skin, facies infanto-senescent, extreme body build, thin voice, upholstered adiposity, micropenis).
- Morfotip harmonic (the pituitary dwarfism is a harmonic one).
- Anamnesis for the exclusion of a psycho-social dwarfism.
- Late bone age < than the chronological age (a delay of, at least, two years).
- At two stimulation tests the value of GH <10 mUI/1.
- A small basic value of GH (or in the normal range, but correlated with post-stimulated values < 10 mUI/1).

Exclusion criteria: GH deficiency with an organic cause (tumor cause), head injury with hypothalamic-pituitary damage, GH deficiency secondary to the radiotherapy, weakness stature due to some chronic problems, Turner syndrome, a short stature in the family.

For analysis the delay of growing against the average of age and sex, the Z score of the stature was calculated after the formula:

\[
Z = \frac{\text{real stature} - \text{mean stature for age and sex}}{\text{SD for age and sex}}
\]

The Results of the Study

The distribution on the sex type of the 47 patients was made in this way:
- 15 girls → 31.91%
- 32 boys → 68.09%

As regarding the age, 7 girls were in the prepuberty period (3-9 years) -14.89% and 8 were of pubertal (≥ 10 years) – 17.02%. 19 boys (40.43%) were in the prepubertal age (3-11 years) and 13 boys (27.66%) were 12 years or older than this age (fig.1).

Out of the 47 children under treatment for a year, 46 had showed isolated GH deficiency, 8 of them also having increased values of TSH, and a patient had a pituitary dwarfism pluritrop (GH, FSH, LH, ACTH) and increased TSH. At the 9 children with increased TSH, the FT4 and FT3 values are normal, so the diagnosis established was subclinical hypothyroidism. At these patients, the TSH value was normalized by substitution with Levothyroxine (Euthyrox), before introducing the rhGH treatment.

One of our patients presented an increased value of insulin, a small basic value of GH (or in the normal range, but correlated with post-stimulated values < 10 mUI/1).

The imaging investigations: the skull radiography profile for the Turkic saddle, the radiography of the carpal bones of the non-dominant hand, for evaluating the age of the bones, CT/RM exams of the skull for establishing the etiologic diagnoses to the patients who have supposed to present changes at the skull radiography profile.

To the patients from our group who have presented modified values of TSH and ATPO, we have made ultrasound of the thyroid gland.

All the 47 children of our group have followed for a year a treatment with rhGH 0,2 mg/kg/a week, given every day. We used Zomacton, of rhGH preparations, because it has the advantage that is administered subcutaneously, through “no needle” jet injection, thus increasing patient compliance. Because of how easy administration, Zomacton not cause pain, not cause local skin irritation or lipodystrophy.

We analyzed the following issues:
A. The change of the anthropometric parameters under the therapy.
B. The relationship between different parameters and the answer to the treatment, evaluated in the number of cm gained in a year of GH administration (the growth speed).

**The change of the anthropometric parameters under the therapy.**

The anthropometric marks of the 47 patients at the beginning of the therapy are presented in the table nr.1.
Table nr.1 - Anthropometric Marks of the Patients at the Beginning of the Treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nr.</th>
<th>Media</th>
<th>Standard deviation</th>
<th>C.V. (% Ds/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Chronological Age (years) (Chr A)</td>
<td>47</td>
<td>10.29</td>
<td>3.23</td>
<td>31.37</td>
</tr>
<tr>
<td>The Bone Age (years) (BA)</td>
<td>47</td>
<td>7.33</td>
<td>3.02</td>
<td>41.23</td>
</tr>
<tr>
<td>The Height Age (years) (HA)</td>
<td>47</td>
<td>7.11</td>
<td>2.67</td>
<td>37.54</td>
</tr>
<tr>
<td>BA - HA</td>
<td>47</td>
<td>0.21</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>BA Delay (Chr A - BA)</td>
<td>47</td>
<td>2.99</td>
<td>0.61</td>
<td>20.40</td>
</tr>
<tr>
<td>The Growth speed prior to the treatment (cm/years)</td>
<td>47</td>
<td>1.73</td>
<td>0.62</td>
<td>36.04</td>
</tr>
<tr>
<td>The Z Height Score (SD)</td>
<td>47</td>
<td>-3.07</td>
<td>0.84</td>
<td>-27.23</td>
</tr>
<tr>
<td>The Index of the Body Mass (BMI)</td>
<td>47</td>
<td>16.14</td>
<td>2.17</td>
<td>13.42</td>
</tr>
<tr>
<td>The Medium Height of the Parents (MPH)</td>
<td>47</td>
<td>169.98</td>
<td>6.61</td>
<td>3.89</td>
</tr>
<tr>
<td>Peak GH Insuline Test</td>
<td>41</td>
<td>3.79</td>
<td>2.19</td>
<td>57.84</td>
</tr>
<tr>
<td>Peak GH Arginine Test</td>
<td>18</td>
<td>5.23</td>
<td>3.4</td>
<td>64.9</td>
</tr>
<tr>
<td>Peak GH Clonidine Test</td>
<td>10</td>
<td>3.5</td>
<td>2.17</td>
<td>62</td>
</tr>
</tbody>
</table>

The 47 children received treatment as it follows:
- 37 patients with isolated GH deficiency received recombinant growth hormone (ZOMACTON) 0,2mg/kg/week, subcutaneously given daily;
- 8 patients with GH deficiency and subclinical hypothyroidism received Euthyrox in doses (3-5 µg/kg/day) until the normalization of the TSH value, then we added the growth hormone;
- the patient with GH deficiency and chronic autoimmune thyroiditis received Euthyrox 25 µg/day (1,44 µg/kg/day) plus Zomacton 0,2 mg/kg/week;
- the patient with pluritrop deficiency received Zomacton associated with Euthyrox 50 µg/day and Prednison 7,5mg/day.

After a year of treatment we calculated:
- the growth speed under treatment (cm/year), given by the difference between the height measured at the end of the treatment and the height measured at the beginning of the treatment;
- the Z score of the height after a year of treatment (in SD);
- the difference between the Z score of the height after a year of treatment and the Z score of the height at the beginning of the treatment.

The comparison between the values of these parameters from the beginning and from the end of the treatment are presented in the tables 2 and 3.
Table nr. 2 - Anthropometric marks of the patients at the beginning and the end of the treatment.

<table>
<thead>
<tr>
<th>The parameter</th>
<th>Nr.</th>
<th>Media</th>
<th>Standard deviation</th>
<th>C.V. (% Ds/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The growth speed prior to the treatment (cm/year)</td>
<td>47</td>
<td>1.73</td>
<td>0.62</td>
<td>36.04</td>
</tr>
<tr>
<td>The growth speed during the treatment (cm/year)</td>
<td>47</td>
<td>9.50</td>
<td>2.30</td>
<td>24.17</td>
</tr>
<tr>
<td>The Z score of the height prior to the treatment (SD)</td>
<td>47</td>
<td>-3.07</td>
<td>0.84</td>
<td>-27.23</td>
</tr>
<tr>
<td>The Z score of the height after the treatment (SD)</td>
<td>47</td>
<td>-2.33</td>
<td>0.91</td>
<td>-38.96</td>
</tr>
<tr>
<td>The difference of the Z score (SD)</td>
<td>47</td>
<td>0.74</td>
<td>0.54</td>
<td>72.49</td>
</tr>
</tbody>
</table>

Table nr. 3 - The distribution on the sex of the anthropometric marks after a year of treatment.

<table>
<thead>
<tr>
<th>The parameter</th>
<th>GIRL</th>
<th>BOYS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr. patients</td>
<td>Media</td>
</tr>
<tr>
<td>The Z score of the height</td>
<td>15</td>
<td>-2.58</td>
</tr>
<tr>
<td>The growth speed (cm/year)</td>
<td>15</td>
<td>9.53</td>
</tr>
</tbody>
</table>

B. THE CORELLATION BETWEEN THE DIFFERENT PARAMETERS AND THE ANSWER TO THE TREATMENT

Regarding the basic marks we have and the answer to the treatment of our group of patients, we tried to find parameters which correlate well with the growth speed under the treatment.

Analyzing the nature of the relationship between the growth speed of the 47 patients, treated for a year, and different parameters, using Pearson’s correlation coefficient, we have found the following results, presented in the table nr. 4.

The coefficients of Pearson’s r correlation between the growth speed under treatment and the chronological age, namely the bone age has the values -0.271 and -0.288, that indicates a statistic significant inverse correlation (p<0.05), that means the bigger the BA delay, the smaller is the growth.

The coefficient of the Pearson’s r correlation between the growth speed under the treatment and the delay of the bone age bigger than 3 years had a value of -0.355, that means a significant statistic inverse correlation (p<0.05), that signifies the bigger the delay, the smaller is the growth (fig.2).

The analysis of the relationship between the growth speed under the treatment and the other parameters from table nr.4 does not show any correlation between these parameters.

The coefficient of Pearson’s r correlation between the growth speed under treatment and the maximum peak of GH at the stimulation test with arginine is -0.161, that shows a weak inverse correlation, statistic insignificant because of the small number of the tested patients, that means the bigger the peak, the smaller is the growth.

Table nr. 4 - The Correlation between the growth speed and different parameters.

<table>
<thead>
<tr>
<th>The parameter</th>
<th>The correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chronological age</td>
<td>-0.271</td>
</tr>
<tr>
<td>The bone age (BA)</td>
<td>-0.288</td>
</tr>
<tr>
<td>The BA delay (&gt;3 years)</td>
<td>-0.355</td>
</tr>
<tr>
<td>The Z score prior to the treatment</td>
<td>-0.091</td>
</tr>
<tr>
<td>The Z score after the treatment</td>
<td>0.419</td>
</tr>
<tr>
<td>The difference of the Z score</td>
<td>0.846</td>
</tr>
<tr>
<td>The growth speed before the treatment</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.265</td>
</tr>
<tr>
<td>MPH</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximum peak GH insulin test</td>
<td>-0.056</td>
</tr>
<tr>
<td>Maximum peak GH arginine test</td>
<td>-0.161</td>
</tr>
<tr>
<td>Maximum peak GH clonidine test</td>
<td>0.166</td>
</tr>
</tbody>
</table>
Discussions

The treatment to promote of the growth with genetic recombinant hormone was given for a year to all the 47 patients with pituitary dwarfism. 26 children were at the prepubertal age and 21 were at the pubertal age.

The growth speed under treatment is the mean indicator of the therapeutic effect. After a year of treatment we noticed, at our patients, a significant improvement of the growth speed, comparatively to the year prior to the introduction of the therapy, and we also noticed an amelioration of the stature deficiency with 0.74 SD (Table 2). The growth speed under treatment and the Z score of the height had comparable values at boys and also at girls (9.48 cm/year vs. 9.53 cm/year; -2.21 SD vs. -2.58 SD) (Table 3).

At our patients we tried to find correlations between the growth speed under treatment and different parameters: the chronological age, the bone age, the delay of the bone age more than 3 years, the Z score of the height before and after the treatment, the difference of Z score, IMC, MPH, the maximum peak of the GH at the stimulation tests.

In our analyze we showed that the growth speed under treatment is correlated with the chronological age at the beginning of the treatment (Table 4): the older the chronological age at the beginning of the treatment, the smaller is the growth increase. It seems that the sensitivity of the growth cartilage for the growth factors decreases as the children get older. So the delay of the beginning of the therapy specific to promote the growth could overcome the moment of maximum bone reception to the growth factors.

The fact that the age at the beginning of the treatment is inverse correlated to the answer on growth was confirmed by the studies made on groups of children with rhGH, treated at young ages, even before they are 12 months old. At these baby patients the benefit was bigger even if the doses were small and less frequent. Although, at these children we noticed a decreased sensitivity to the endogen GH, which adds complexity at the interpretation of the information (10, 11).

In our group we found inverse correlations between the growth speed under treatment with rhGH and the following parameters: the bone age at the beginning of the treatment, the delay of the bone age with more than 3 years. An inverse correlation was established between the growth speed and the maximum peak of the GH at the anginine test, but statistic insignificant because of the small number of the patients that made this test.

At our group we did not find correlations between the growth speed and the maximum peak of GH at the insuline and clonidine tests.

Many studies appreciated different variables that can influence the final height, obtained after treatment with rhGH at children with GHD: the duration of the treatment, the delay of the height appreciated in SD (standard deviations) at the beginning of the treatment, the delay of the bone age (BA), the height at the beginning of puberty, the medium height of the parents (MPH) and the growth speed in the first year of treatment (GV - growth velocity).

All these variables positively correlate with the obtained height, while the age at the beginning of the treatment and the maximum peak of the GH at the stimulation tests are correlated negatively (4, 12). These factors explain only partial the individual variability to the answer at the treatment of rhGH substitution at children with pituitary dwarfism.

It seems that only the patients with severe GH deficiency (GH peak <5ng/ml post-stimulation) or those
GHD due to the congenital abnormalities of hypothalamic – pituitary (eg. interrupted pituitary stem syndrome - PSIS), the maximum peak of the GH is correlated negatively with the answer to the treatment with rhGH in the first year of therapy (13-15). There are some authors who deny this thing, who have demonstrated that the small values of GH at the stimulation tests are weak predictors of the growth (16).

Out of our group of 47 children with pituitary dwarfism, 9 of them associated subclinical hypothyroidism, and one of them was diagnosed with chronic autoimmune thyroiditis. In the case of these patients, the treatment with thyroid hormones in moderate doses should be associated with growth hormone, known being the fact that T4 multiplies the receivers for GH.

The natural course of the chronic autoimmune thyroiditis at children and teenagers presents a high variability regarding the dimensions of the thyroid and the hormonal status (17-20). The treatment with Euthyzrox at these patients is controversial and, up to now, it was recommended only to the patients with goiter and hypothyroidism (21).

There are a few studies about the children with Hashimoto thyroiditis for evaluating the dimension of the thyroid under treatment with Euthyzrox and most of them did not use the ultrasound as a means for measurement (17, 22, 23). In the last years it was shown that using Euthyzrox is efficient in decreasing the thyroid volume (ultrasound evaluated) not only at the children with goiter and hypothyroidism, but also at those with or without goiter and normal thyroid function (22,23).

Conclusions

1. The treatment with the growth hormone at the children with GHD is an important ally regarding the amelioration of the consequences due to the hormone deficiency, its main aim being the improvement of the height during the childhood and the obtaining of a final normal height.

2. After a year of treatment with rhGH (Zomacton), at our patients, we noticed a significant improvement of the growing speed, comparatively with the year prior to the beginning of the therapy, and we also saw an amelioration of the deficiency of the stature with 0,74 SD. The growth speed under treatment the Z score of the height had comparable values at the boys and at the girls.

3. It was shown there are different variables that correlate, in a negative or in a positive way, with the answer to the therapy with rhGH at the children with GHD. These factors only partially explain the individual variability in the case of the substitution therapy at the children with pituitary dwarfism.

4. Our results show inverse correlation between the growth speed during the treatment and the following parameters: the chronological age at the beginning of the treatment, the bone age, the delay of the bone age more than 3 years.

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ASSESSMENT OF THE PRESCHOOL AND SCHOOL OBESE AND OVERWEIGHT CHILDREN

Simona Coșoveanu¹, D Bulucea¹

Abstract

In the last decades, obesity became one of the most frequent nutritional diseases in the world, resembling a pandemy and being considered the 21st century disease. Obesity is characterized by an excess in weight, which represents more than 20% of the ideal weight and it occurs due to an increased food intake in the people with a particular constitutional predisposition. BMI is an indirect measure of body fatness. BMI does not measure body fat directly, but research has shown that BMI correlates to direct measures of body fat, such as underwater weighing and dual energy x-ray absorptiometry.

Keywords: obesity, evaluation, BMI, child

Introduction

In the last decades, obesity became one of the most frequent nutritional diseases in the world, resembling a pandemy and being considered the 21st century disease. Obesity is a plurifactorial disease, its occurrence supposing multiple interactions among genetic, social, behavioral, metabolic, cellular and molecular factors that lead to changes of the energetic balance [1]. The specialty literature defines obesity as an excess of body fat or adipose tissue quantity as compared to the “lean” tissue mass (National Research Council, Diet and Health, 1989). Obesity is characterized by an excess in weight, which represents more than 20% of the ideal weight and it occurs due to an increased food intake in the people with a particular constitutional predisposition. [2]

According to a study carried out in 79 countries, World Health Organization (WHO) estimates that there are 250 million obese people in the world, among which approximately 22 million are children aged less than 5 years. The study stresses upon the fact that 50% of the obese children will become obese adults. [3] The IOTF (International Obesity Taskforce) Report showed that 1 in 10 children is overweight, leading to a total of 155 million, among which 30 to 45 million are regarded as obese. [4] NCHS/WHO Source: National Nutrition Surveillance Programme, 1993-2002. Bucharest, "Alfred Rusescu" Institute for Mother and Child Care, shows a prevalence of overweight in the children aged 0-4 years of 6.4% in girls and 5.5 % in boys. [5] A study carried out between 2005 and 2006 in children aged 11 to 15 years (published in a report of The International Association for the Study of Obesity, London, 2009), showed that, in Romania, the overweight prevalence is 14.7% in girls and 8.7% in boys, the highest prevalence being registered in Malta (31% in boys and 28% in girls) and the lowest in Lithuania (10.3% in boys and 4.7% in girls).

Most researchers stress up on the idea that obesity which occurs in childhood and maintained when adult is more difficult to treat than the obesity occurred when an adult. Children obesity in the 21st century inevitably leads to a decrease of life expectancy. [6]

ASSESSMENT OF OBESITY IN CHILDREN

The assessment of obesity in children implies several stages (fig. 1).

![Fig. 1 Assessment of obesity in children.](image)

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1. ANAMNESIS
- Obesity onset age: more frequent in the first year of life, between 5 and 6 years of age and during adolescence;
- Food inquiry: an excess in food intake, particularly in sweets and fats, fast-food; the meal program is not observed;
- Physical activity inquiry: sedentarism, performed physical activity, sports, time spent in front of the computer and TV;
- Trigger factors: infectious episodes, drugs, psychological factors, overfeeding;
- Events which had a serious psychological impact and which can represent the moment of hyperphagia; family conflicts, parents divorce, accidents).

Identifying the obesity risk children:
- Relation weight at birth – obesity,
- Pre- and postnatal development, age stages development,
- Overfeeding when infant,
- Obesity onset age,
- Relation between food intake/physical activity and obesity; food intake – physical activity.

2. CLINICAL FINDINGS
Infant obesity, in both sexes, develops, as a rule, a uniform clinical picture, characterized by truncal fat deposits, partly avoiding the face and extremities. The distribution of the adipose panicle is generalized and symmetric and it varies according to sex and age. In preschool children it is diffuse, leading to uniform, harmonious obesity while in school children, the weight excess is associated with a distribution of the weight at the level of the abdominal wall, hips, thighs, buttocks, the pectoral region and the subscapular area. The height of children is normal or even increased as compared to the age average. At pre-puberty age, one can notice that obese children are taller as compared to children with normal weight and same age, the height of the obese being over percentile 97, until puberty. [1]

Fighting against obesity starts ever since childhood; in girls, the early obesity leads to a stop of the growth cartilages, reducing the height, while obese boys will have a defictitary sexual development. One can notice whitish, sometimes reddish, stretch marks on the abdomen flanks, on hips and thighs, and facial erythrosis. Because of the excessive adipose tissue deposits, the cutaneous folds are getting more and more profound, leading to friction, hyper-sweating – the teguments have a drier aspect and the acne is more frequently met.

Morphology of genital organs. Because of the adipose deposits in the lower abdominal and pubian regions, the genital organs are almost hidden. In boys, the pubian and perineal fat makes the penis to be engrossed in it, the scrotum flat and the testicles difficult to palpate; a false adiposogenital diagnosis (Babinski-Frohlich), genital infantilism, and adiposity in the mammal region (thorax-abdominal adiposity) lead to the appearance of gynecomastia which can produce complexes.

Psychological problems: inferiority complex and rejection from the same age children, frustration, depression; sometimes poor results at school, antisocial behavior, sedentarism, normal intellectual development.

There occurs a low tolerance in effort: tiredness, dyspnea, polipnea, tachycardia which lead to avoiding effort and consecutively to decreasing the energy consumption and aggravating obesity.

The overcharge of the osteoarticular apparatus has several consequences: genu valgum, flat foot, edema of the lower limbs in orthostatism, articular pains, gonarthrosis, femoral head aseptic necrosis, hyperlordosis.

Unspecific symptomatology: cephalea, asthenia, flatulence, bloating, period dysfunctions, constipation, normal or increased BP values.

OBESITY PHENOTYPES
- Androgynous type (upper truncular, abdominal, central, upper, “apple” type) – the distribution of the fat is mainly in the abdominal region; it is frequently associated with the increase of the visceral and intra-abdominal tissue deposits, and it correlates with high morbidity and mortality due to cardio-vascular diseases, especially in boys.
- Ginoid type (pelvis, lower, peripheral, “pear” type), distribution of the adipose tissue mainly on buttocks and thighs, especially in girls.
- VAT (visceral adipose tissue) can be noticed by means of imagistic techniques (ECHO, CT, MRI): particular cardiovascular and diabetes risk, frequently associated with insulin resistance and hyperinsulinism

1. ANTHROPOMETRIC MEASUREMENTS
The normal growth is defined as the progression in weight and height in accordance with the established standards for age, sex and the genetic potential of the individual. The growth process is monitored by comparing the weight and the height of the child with the standard references offered by the growth maps (nomograms). These maps are a set of curves which indicate the normal progression of an anthropometric parameter according to age and sex. The location on that map of an anthropometric parameter registered for a certain subject indicates where that parameter is situated, as compared to the reference population of the same age and sex. By mapping the different measurements, a child with a normal growth groups the values, which were registered on the occasion of different assessments, between two curves of the map, marking his/her own growth band [7]. The growth maps are more useful than the anthropometric indicators, since they report the evolution of the child’s growth to the average values for the age group (percentile 50) and they allow the calculus of the anthropometric indicators when one does not know the weight or the height at birth. Harmonious growth and development mean that the values of different measurements of the child at a certain age will be found approximately on the same curve, percentile.

Nomograms (CDC 2000) for the 0-36 months and 2-20 years categories of age [8]:
- Weight for age/ sex
- Height for age/ sex – the deficit in height means a slow development of the skeleton and it is due to a
chronic cause which acted in time; the recovery is going to be a long one

- **Weight for length/sex** – the deficit in weight for a certain length reflects an acute cause of the nutritional state which can be easily recovered
- **Up to the age of 2 years: Ponderal Index = Weight present / Weight ideal**

The ideal weight is assessed by means of some nomograms (which have a regional specificity or are calculated according to some formulas).

- **BMI for age/sex** – after 2 years of age.

BMI is an anthropometric index of weight and height that is defined as body weight in kilograms divided by height in square meters; and calculated with EXCEL BMI Calculator English Version – www.cdc.gov/healthyweight/BMI.

BMI = Weight (kg) / Height (m)²

The growth charts show the weight status categories used with children and teens (underweight, healthy weight, overweight, and obese).

- **Underweight:** BMI < percentile 5/sex/age
- **Health weight:** 5 ≤ BMI < 85 percentile/sex/age
- **Overweight:** 85 ≤ BMI < percentile 95/sex/age
- **Obese:** BMI ≥ percentile 95 (+2DS)/sex/age

BMI is an indirect measure of body fat. Recent research has shown that the age when the “adiposity” rebound occurs may be a critical period in childhood for the development of obesity as an adult. An early "adiposity" rebound, occurring before ages 4-6, is associated with obesity in adulthood.

BMI is a reliable indicator of body fatness for most children and teens. BMI does not measure body fat directly, but research has shown that BMI correlates to direct measures of body fat, such as underwater weighing and dual energy X-ray absorptiometry (DXA). BMI can be considered an alternative for direct measures of body fat. Additionally, BMI is an inexpensive and easy-to-perform method of screening for weight categories that may lead to health problems.

After BMI is calculated for children and teens, the BMI number is plotted on the CDC BMI-for-age growth charts (for either girls or boys) to obtain a percentile ranking. Percentiles are the most commonly used indicator to assess the size and growth patterns of individual children. The IOTF Report recommended using age and gender specific BMI cut-off points which equate to an adult BMI of 25 and 30. This approach defines overweight as the childhood equivalent of having a BMI of 25 or above (age and gender adjusted) and obese as the childhood equivalent of having a BMI of 30 and above (age and gender adjusted) [4].

The best definition of obesity in children is given by the content of the body fat mass calculated through bioelectric impedance. Up to 16 years, the child is considered obese if the fat mass is more than 20% of the reference value for age and sex, while for the age of plus 16 years, the diagnosis implies a fat mass more than 25% of the weight in boys and more than 32% in girls.

**Classification according to the excess weight:**

- **Overweight:** increased values, more than 10-20 % Wideal
- **Light obesity:** increased values, between 20 and 30 % Wideal
- **Medium obesity:** increased values, between 30 and 50 % Wideal
- **Severe obesity:** increased values, more than 50 % Wideal

Other parameters can only be obtained through imagistic methods (ECHO, CT, MRI):
- Total Body Fat Mass – TFM;
- Body Fat – BF;
- Visceral Adipose Tissue – VAT.

Abdominal ECHO: measurement of the thickness of the intra-abdominal adipose tissue layer by determining the fat located between the anterior abdominal muscles and the aorta.

- An accurate estimation of the adipose tissue quantity with OMNRON BF 302.
- There is a correlation among BMI, TFM, the thickness of the tricipital skinfold, the level of insulin, and BP
- Thickness of the tricipital cutaneous skinfold > percentile 95 for age/sex
- Waist circumference has attracted much recent attention as an indicator of fatness and health risks in children and adults.

**Metabolic profile:**
- Glucidic (glucose tolerance test, glycemia);
- Lipidic (cholesterol, HDL, LDL, TG, lipemia).

**Enzymatic:** serum leptin (the serum levels are influenced by the food intake, the glycemia level, the adipose tissue mass, sleep-watch rhythm and they vary according to age, sex)

**Complementary tests**

**OBESITY CLASSIFICATION**

I. **Primary obesity (ordinary, idiopathic, essential)** 95-98%

1. **familial:** (with an abusive feeding behavior, sedentarism or both)

2. **non-familial:** it occurs in several family generations, the onset is at the infancy age, children are normally developed from the psychic point of view, adiposity is located in the ½ lower part of the trunk and at the level of the lower limbs (cylindrical aspect).

- **Ordinary type:** the onset is between 4 and 6 years, but the specific aspect is to be noticed at puberty, familial feature (70% have at least one obese parent)

- **“Cushing”** type: 2%, onset usually at 5 or 6 years of age, “full moon” face, thick, “bull-like” neck, fat in the ½ upper part of the trunk, hyperpilosity.

- **Familial plethoric obesity:** 5%, onset when an infant, rather tall, well-developed muscular mass, excessive fat prevails in the ½ lower part of the trunk and at the level of the lower limbs.

II. **Secondary obesity (symptomatic, endogenous, unknown cause)** 10%

1. **endocrine:** Cushing syndrome, insulinoma, polycystic ovary Stein-Leventhal syndrome), hypothyroidism
2. hypothalamic: central obesity of tumor cause, inflammatory, post-traumatic, vascular obesity, Babinski-Frohlich syndrome

3. deposit diseases: glycogenosis type I, Mauriac syndrome

4. genetic diseases:
   - pleiotropic obesity syndrome (obesity “symptom”)
     - with dominant autosomal transmission: acondroplasia, Albright hereditary osteodystrophy, Prader-Willi syndrome
   - with recessive transmission: Bardet-Biedl syndrome
   - with X linked transmission: Turner syndrome

5. diseases with particular deposits of adipose tissue: paralipodystrophy, lipomatosis

6. drugs: treatment with HIN or corticoids.

7. lack of physical activity: in the severe motor defects due to infantile cerebral paralyses, invalidant sequels of poliomyelitis, myopathy.

Conclusions
A child up to 16 years of age is considered obese if the body fat is more than 20% of the reference value for age and sex. BMI does not measure body fat directly, but research has shown that BMI correlates to direct measures of body fat, such as underwater weighing and dual energy x-ray absorptiometry. The best definition of obesity in children is given by the body fat content which is measured through bioelectric impedance. Excessive food intake obviously represents the main exogenous factor with a role in the obesity genesis and perpetuation. The prevention of obesity is a public health issue which imposes a careful supervision of the children with a tendency in gaining weight.

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CASE PRESENTATION – DILATED CARDIOMYOPATHY MAY BE SECONDARY TO SCAR POSTABLATION FOR PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Ramona Olariu1, A Lăcătușu1

Abstract
Adolescent known with paroxysmal supraventricular tachycardia (SVPT) of approximately 5 years (electrophysiological study benefits from a slow track ablation), converted to sinus rhythm and variable antiarrhythmic treatment, is hospitalized with signs and symptoms significant for severe congestive heart failure. ECG on admission shows SVPT, transthoracic echocardiography shows severely depressed contractile function, dilatation of both ventricles, chest radiography shows a global increase of the heart mostly due to the left ventricle increase. The patient is diagnosed with arrhythmic dilated cardiomyopathy - ADCM (possibly by reentry mechanism) and severe congestive heart failure, it was frequently investigated, currently under treatment with Amiodarona, reserved for long-term prognosis.
Keywords: cardiomyopathy, supraventricular tachycardia, heart failure.

Introduction
Any type of rhythm disorder SVPT with high frequencies and long action causes impaired myocardial contractile function and installing of DCM. Recovery capacity of the myocardium is directly proportional to the period of action of arrhythmia, if arrhythmic pathology is resolved early can lead to restitutio ad integrum of myocardial function, whereas the prolongation of action will lead invariably to irreversible DCM, even through arrhythmic pathology will be treated. In this combination SVPT plus DCM, causality is hard to establish, which disease generated the other one. Some DCM (e.g., toxic, hereditary) are easily diagnosed and excluded, remains in question the association between viral myocarditis and DCM.

Case report
IR, 13.6 years, male admitted to emergency presenting extreme fatigue, palpitations, nausea/vomiting - occurred during the examination, moderate dyspnea, jugular turgidity - pulse jugular, hepatic-splenomegaly, pulse and weight substernal/abdominal pain, stetacustic gallop rhythm, with the presence zg 3 and 4, systolic gr III/VI murmur - irradiated in axilla and substernal, biological samples - normal. Family history is non significant for the underlying disease.

At age 8 the patient was diagnosed with SVPT (tachycardia type intranodal cleave to slow-fast) and frequency of 200-240 bpm, with hemodynamic deterioration and acute heart failure. Electrophysiological study was performed and radiofrequency ablation of the slow pathway, the patient is subsequently converted to sinus rhythm and put under home observation in good clinical condition. Postablation the patient followed antiarrhythmic therapy with amiodarone, propafenone, beta-blocker in variable dose. The last treatment was Rythmonorm, 3x 75 mg (propafenona cp 150 mg).

ECG on admission revealed sinus rhythm, regular, AV=180 bpm, QRS complex thin normal driving routes, supraventricular tachycardia (fig 1).

Fig. 1

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Chest X-ray background of asthenic chest, relatively normal lung, moderate congestive and increased overall heart dimensiones, ICT=0.7, in contrast with narrow vascular pedicle, cardiomegaly is global, but is predominantly due to left ventricular increase. (fig2)

Fig. 2

Trasthoracic echocardiography on admission revealed severely depressed contractile function aspect, marked dilatation of both ventricles; DTDvd=79mm, DTDvd=56mm, EF=35%, hipocontractility, septal akinesia. Cord arrhythmic pulse wave, aortic flow and pulmonary flow with small aspect, the blocking period, the contraction following the pause will slightly increase the flow extrasystole, Ao=29mm to the ring, Ap=27mm to the ring, I/II degree tricuspid insufficiency (E=0.72m/s, A=0.44m/s), I degree aortic insufficiency (Vmax=0.77m/s, Pmax=2.40mmHg), III degree tricuspid insufficiency (E=0.74m/s, A=0.58m/s), wall motion - global hypokinesia (fig 3).

Fig. 3
Emergency clinical diagnosis: paroxysmal supraventricular tachycardia- possible reentry mecanism trough re-scaring on radio frequency ablation and severe congestive heart failure NYHA III/IV.

The recommended initial regimen was Rithmonorm 3x75mg/day with Carvedilol 12.5mg- then 18.75mg/day. Following the introduction beta-blocker decreased heart rate (160-140-90bpm)(fig. 4), then converting to sinus rhythm temporarily (fig.5).

Following specialist consultans at arrhythmology departement, Rithmonorm discontinue (because the negative inotropic effect) and introduce treatement with Cordarone (antiarrhythmic drugs with the lowest negative inotropic effect) in 15mg/kg/day (loading dose). After changing various antiarrhythmic drugs the patient has varaible arrhythmias: jonctional extrasystole (fig 6), 2 degree Mobitz 2 AV block, jonctional trigeminism, and good clinical condition.

![Fig. 4](image1.jpg)

![Fig. 5](image2.jpg)

![Fig. 6](image3.jpg)

![Fig. 7](image4.jpg)
The dose of Cordarone 3x1cp/day → AV= 45bpm (fig 7), it was decided to reduce the 2x1cp antiarrhythmic drugs Cordarone/day (Cordarone 1cp=200mg). The patient is currently treated with Cordarone 2x1/2cp/day and Carvedilol 2x1/4cp/day, is in sinus rhythm, AV=70-80bpm, with AV jonctional bigemism, clinical status improved. Echocardiographic parameters improved, contractile function reversed, diastolic function improved, DTDvs decreased from 70mm to 59mm, EF increased from 35% to 55%, mitral regurgitation decreased.

In this case the differential diagnosis involved other arrhythmias for TPSV and other DCM for ADCM. TPSV with other arrhythmias: atrial ectopic tachycardia, multifocal atrial tachycardia, junctional ectopic tachycardia, atrial reentrant tachycardia, atrial fibrillation/atrial flutter, WPV, reentrant NAV tachycardia, reentrant accessory fascicle tachycardia, supraventricular ondromic tachycardia, supraventricular antidromic tachycardia, permanent junctional tachycardia. The final diagnosis (which differentiates between different types of tachycardia) is made using the ECG and electrophysiological study. ADCM with other DCM: toxic DCM (chemotherapeutic agents, alcohol), viral infection DCM (CMV, HIV, richetioze), metabolic abnormalities DCM (selenium deficiency, thiamin deficiency, carnitine deficiency, hypothyroidism, thyrototoxicosis, diabetes, Cushing disease, hypocalcemia, hypophosphatemia), parasitic infections DCM (toxoplasmosis, trichinosis), inflammatory disease DCM – collagen disease, muscular diseases with DCM.

Evolution/ Aims

In this acute stage electrophysiological study was not indicated because of the fragility of the patient. The purpose of antiarrhythmic therapy in this situation is to improve hemodynamic performance before electrophysiological study is possible.

The electrophysiological study will identify the mechanism and will perform the ablation.

ADCM has an unpredictable evolution depending on the antiarrhythmic and cardiac insufficiency treatment, possibly evolving towards gradual deterioration of contractile function and the need for cardiac transplantation.

The treatment of arrhythmia (in the electrophysiological study) consists in the removal of scar tissue and the ablation of arrhythmia generating pathways. If, as a complication of extensive ablation, the patient develops a total heart block, he will need permanent electrostimulation. If the myocardium has been compromised over time, with the installation of global heart failure, the patient may benefit resynchronisation therapy and electrophysiological study.

Drug treatment is long term, Cordarone is provisionally due to numerous side effects. After an electrophysiological study and ablation therapy is performed, it is considered a prophylactic antiarrhythmic therapy, the most likely drug used being Propafenona.

Prognosis reserved due to: the age on onset, the frequent TPSV, expansion and remodeling of the heart, postablation arrhythmia relapse, ADCM complications, congestive heart failure, mitral, tricuspid and aortic insufficiency.

Along with other conditions that generate DCM, acute or chronic arrhythmias may cause compromised contractile function of the heart, leading to congestive heart failure, with progressive loss of contractile function and possible indication of cardiac transplantation.

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NEPHROTOXICITIES OF ANTI-RETROVIRAL TREATMENT

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Abstract

Human immunodeficiency virus (HIV) infection is a global pandemic, with cases reported virtually from every country. HIV/AIDS being one of the world’s recent most devastating diseases, nearly 25 million people have died world over due to HIV infection since June 1981, when it was first diagnosed. According to the WHO, 33 million people worldwide are living with HIV. To provide access to highly active antiretroviral therapy (HAART), to the whole HIV-suffering population remains a major goal to accomplish. Several studies have suggested that HAART improves renal function and prognosis for patients with HIV. Many individuals diagnosed are already with advanced renal disease and then due to lack of renal replacement therapies the mortality rate rises. HIV associated nephropathy (HIVAN) outcomes correlate with the clinical stage of the disease suggesting that early detection improves patient survival. On the other hand, with significant reductions in mortality and risk of progression to AIDS in the era of HAART, complications of long standing HIV infection and treatment should be dwelt with extreme importance. Most common nephrotoxic effects of antiretroviral include crystal-induced obstruction secondary to the use of protease inhibitors (indinavir and atanavir) and proximal tubule damage related to nucleoside reverse transcriptase inhibitors tenofovir. Acute kidney injury (AKI) can occur following tenofovir induced tubular dysfunction or because of mitochondrial dysfunction and lactic acidosis induced by nucleoside reverse transcriptase inhibitors. However looking to the benefits of HAART, fear of nephrotoxic effects can never be a valid reason for physicians to withhold antiretroviral therapy. Hence, identification of patients with pre-existing chronic kidney disease, who are at increased risk of renal damage, enables appropriate dose modifications, close monitoring and avoiding potential nephrotoxic drugs. Putting into practice some of the guidelines can further help save the renal complications.

Key words: HIV, HAART, Kidney, Nephrotoxic

Introduction

Kidney proves to be the major excretory pathway for many drugs and their metabolites. Proximal tubule plays an important role due to its high rate of blood flow and the high level of toxins it has to process and hence this part of the kidney is always vulnerable to develop drug related damage. With the introduction of HAART, which has led to a dramatic decline in the mortality and morbidity of HIV infection, varieties of adverse renal effects have come up. Furthermore, improved survival among patients with HIV is anticipated to result in an increase in the risk of chronic HAART-associated metabolic complications, such as diabetes and dyslipidemia, which in turn can contribute to vascular damage and decreased renal function. Understanding the pathogenesis of HIV/AIDS, the HIV replication cycle and the mechanisms of HAART-related kidney disease is essential to adapt to future preventive measures such as dose adjustments, avoiding nephrotoxic drugs in patients at risk of developing kidney disease or having underlying renal diseases.

Anti-retroviral for the treatment of HIV/AIDS

Anti-retroviral drugs acting against the HIV are divided into 4 classes, which have received FDA approval: protease inhibitors (PIs), fusion inhibitors, non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) and nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs) (Table I). Of the 25 ARVs that have been approved, 3 are no longer being manufactured, either because of the development of improved formulations (i.e., amprenavir* replaced by fosamprenavir*) or because of limited use (i.e., delavirdine and zalcitabine). Currently, there are 22 antiretroviral agents available for clinical use. Several others are in various stages of basic and clinical development. As of February 2009, 17 of these have an approved pediatric treatment indication (noted with * below), and 16 are available as a pediatric formulation or capsule size.

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These agents are the CCR5 antagonist (maraviroc) and fusion inhibitor (enfuvirtide*), which prevent viral entry; the nucleoside/nucleotide reverse transcriptase inhibitors (abacavir*, didanosine*, emtricitabine*, lamivudine*, stavudine*, tenofovir, zalcitabine, and zidovudine*) and non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz*, etravirine, and nevirapine*), which act at the early stage of replication, prior to viral integration into the host genome; one inhibitor of viral genome integration into host genetic material (raltegravir); and the protease inhibitors (amprenavir*, atazanavir*, darunavir*, fosamprenavir*, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, saquinavir, and tipranavir*), which exert their effects when the integrated HIV genome is subsequently expressed, by interfering with cleavage of HIV proteins by the viral protease. New classes of antiretroviral agents, such as maturation inhibitors, are currently under investigation. Understanding how these drugs work, what their potential adverse effects are, and how they interact with each other as well as with other concomitantly administered drugs, play a critical role to achieve successful treatment outcome (1).

<p>| Table I. Anti-retroviral drugs acting against the HIV. |</p>
<table>
<thead>
<tr>
<th>DRUG GROUP</th>
<th>NAME OF DRUG</th>
</tr>
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<tbody>
<tr>
<td>Protease Inhibitor (PIs)</td>
<td>• Atazanavir (ATZ)</td>
</tr>
<tr>
<td></td>
<td>• Darunavir (DRV)</td>
</tr>
<tr>
<td></td>
<td>• Fosamprenavir (FPV)</td>
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<td>Fusion/ Entry inhibitors</td>
<td>• gp41 {Enfuvirtide (T20) }</td>
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<td>• CCR5 (Maraviroc, Vicriviroc, PRO 140)</td>
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<td>Reverse transcriptase inhibitors</td>
<td>Non-Nucleoside (NNRTI)</td>
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<td>• Abacavir (ABC)</td>
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<td>Nucleotide analogues/ NtRTIs:</td>
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**Protease inhibitors**

HIV-1 protease is responsible for the cleavage of the large viral precursor polypeptide chains into smaller, functional proteins, thus allowing maturation of the HIV virion (2). There are 10 PIs currently approved for clinical use.

Crystal nephropathy- 30 cases of atazanavir-associated nephro lithiasis were recorded in the adverse Event Reporting System database (3). Few case reports have been observed (4).

Indinavir can cause dysuria, flank pain, renal colic, hematuria, crystalluria, nephrolithiasis, AKI, and papillary necrosis at a dose of 800mg twice daily. Nevertheless, currently indicated dose of 400mg twice daily proved to have no more renal adverse effects and hence is now considered safe (5).

Renal involvement- several cases of AK, some requiring dialysis were reported in association with full-dose (400mg twice daily) ritonavir therapy. But the etiology of renal damage is unknown (6). Long term therapy with indinavir could cause CKD and renal atrophy associated with severe hypertension.(7, 8) Protease inhibitors have shown to be contributing to a 10mmHg rise in blood pressure and are involved in development of diabetic nephropathy(8, 9, 10).

**Fusion Inhibitors**

Enfuvirtide (also known as T-20) is the first, and thus far the only, fusion inhibitor to be approved by the FDA. It is a linear 36-amino acid peptide homologous to a segment of the HR2 region of gp41. It binds to the HR1 region of gp41 and blocks the formation of the 6-helix bundle necessary for fusion. Enfuvirtide is indicated for the treatment of HIV-1 infection. It is not active against HIV-2. Possible side effects were found in some case report showing Membranoproliferative glomerulonephritis. But studies still to be conducted further for more precise proofing.

**Non-nucleoside reverse transcriptase inhibitors**

Non-nucleoside reverse transcriptase inhibitors bind directly and noncompetitively to the enzyme reverse transcriptase (11, 12). Although these drugs differ structurally from each other, they all share the same mechanism of action, binding to a site on the reverse transcriptase enzyme that is distinct from the substrate (dNTP) binding site and blocking DNA polymerase activity by causing a conformational change and disrupting the catalytic site of the enzyme (13). Unlike nucleoside analogs, NNRTIs do not require phosphorylation to become active and are not incorporated into viral DNA. They also have no activity against HIV-2 (14). There are 3 NNRTIs approved for the treatment of HIV at the present time: nevirapine, delavirdine, and efavirenz.

As small number of cases of crystalluria or obstructive uropathy associated with the use of NNRTI agent efavirenz are reported (15). **Nucleoside/nucleotide analog reverse transcriptase inhibitors**

Nucleoside analog reverse transcriptase inhibitors are the first antiretroviral drugs to be approved for the treatment of HIV. The NRTIs are potent inhibitors of the HIV reverse transcriptase (RT) enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs prior to integration of viral DNA into the chromosomes of the host cell. The antiviral activity of NRTIs depends upon intracellular serial phosphorylation by host cellular kinases to the active triphosphate drug (16). The phosphorylated drug competitively inhibits viral reverse transcriptase and, following incorporation of the drug into the growing DNA chain, terminates further elongation of viral DNA. Because these drugs act at a pre-integration step in the viral life cycle, they have little to no effect on chronically infected cells, in which proviral DNA has already been integrated into cellular chromosomes.

Like the NRTIs, nucleotide reverse transcriptase inhibitors (NtRTIs) also competitively inhibit the viral reverse transcriptase, but because the nucleotide drugs already possess a phosphate molecule (the NRTIs do not), the nucleotide drugs bypass the rate-limiting initial phosphorylation step required for activation of NRTIs. Although resistance to these agents eventually develops during the course of long-term single-drug therapy, combination therapy with these drugs may prevent, delay, or reverse the development of resistance (17). Notable exceptions are lamivudine (3TC) and emtricitabine (FTC), with which a single point mutation can confer resistance in as little as 4 to 8 weeks when given as monotherapy or in combination with an antiretroviral regimen that does not fully suppress viral replication (e.g., dual NRTI therapy with zidovudine [ZDV] /3TC).

The prototype drug in this class, zidovudine, was approved in 1987. The designation nucleoside analog refers to the structural similarity of these drugs to the building blocks of nucleic acids (RNA, DNA) from which they differ by the replacement of the hydroxy (-OH) group in the 3' position by another group that is unable to form the 5' to 3' phosphodiester linkage essential for DNA elongation. Thus, NRTIs interfere with reverse transcriptase activity by competing with the natural substrates and incorporating into viral DNA to act as chain terminators in the synthesis of proviral DNA. To exert their antiviral activity, NRTIs must first be intracellularly phosphorylated to their active 5' triphosphate forms by cellular kinases. Because Tenofovir already contains a phosphate molecule in its structure, it only requires phosphorylation by cellular enzymes to its diphosphate form for its antiviral activity.
Currently, there are 8 individual NRTIs and 5 co-formulated products approved for the treatment of HIV. The production of one of the earlier NRTIs, zalcitabine, has been discontinued; it is no longer used in clinical practice because of its weak antiviral activity and unfavorable pharmacokinetic and toxicity profile. Kidneys are the primary route for elimination of all NRTIs. Thus, dose adjustment is required in renal insufficiency for all NRTIs with the exception of abacavir. One notable class wide adverse effect is mitochondrial toxicity, which is responsible for the clinical syndromes of lactic acidosis with hepatic steatosis, peripheral neuropathy, and lipoatrophy. Although this toxicity is a class wide toxicity, stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) are the drugs most frequently associated with it. Lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC) are the NNRTIs with low mitochondrial toxicity potential.

**Didanosine** is eliminated by glomerular filtration and active tubular secretion (18). The renal clearance of didanosine is significantly greater than the glomerular filtration rate, indicating that renal tubular secretion of didanosine occurs. Compared with patients who have normal renal function, in patients with chronic renal failure, there are significant increases in the half-life and significant decreases in the total body clearance of didanosine. Didanosine is taken up by hOAT1 at the proximal tubules, and it is possible that competition between tenofovir and didanosine for the hOAT1 transporter produces an increase in the didanosine concentration, leading to an increased risk of mitochondrial damage and nephropathy. Co-administration of tenofovir with didanosine has resulted in a significant increase (28%) in maximum serum concentrations of didanosine, leading to an increased risk of didanosine toxicity (19). Hence, a reduction in the dosage of didanosine is recommended when it is coadministered with tenofovir (32).

**Tubular dysfunction-** NRTIs (for eg- didanosine and abacavir) (20, 21, 22) have been occasionally associated with Fanconi syndrome and nephrotoxic diabetes insipidus. Hence serum levels of potassium and magnesium ions should be monitored in patients with HIV receiving NRTIs.

**AKI** can develop with lactic acidosis secondary to NRTI-related mitochondrial cytopathy. Risk factors for lactic acidosis include extended duration of treatment, old age, female gender, pregnancy, hyper triglycerideries, obesity, hepatitis C infection, impaired kidney function, treatment with ribavirin and alcohol use. Rabdomyolysis should be considered in patients with HIV who have AKI, particularly if they are being treated with Zidovudine or Didanosine (23, 24, 25, 26).

**Nucleoside/nucleotide analog reverse transcriptase inhibitors and the kidney**

Patients with HIV infection are at increased risk of drug-induced renal toxicity, most commonly associated with trimethoprim-sulfamethoxazole (TMP-SMZ), pentamidine, or acyclovir treatment. Nephrotoxicity is dose-limiting toxicity associated with the clinical use of nucleotide analogue reverse transcriptase inhibitors.

Evidence suggests that polymerase gamma, the DNA polymerase present in mitochondria, is inhibited by NRTIs/NtRTIs (27, 28, 29). It is thought that this leads to depletion of mitochondrial DNA (mtDNA) through inhibition of mtDNA synthesis. This depletion may contribute to toxicity associated with NRTIs/NtRTIs. Unusual, but significant, serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy, peripheral neuropathy, and rapidly ascending muscular weakness. Interestingly, although some toxicity (e.g., lactic acidosis) may occur with all NRTI drugs, other toxicities (such as peripheral neuropathy) may predominantly occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the NRTIs/NtRTIs in inhibiting polymerase gamma in vitro is highest for zalcitabine (ddC); followed by didanosine (ddI), stavudine (d4T), and ZDV; with the lowest potency for 3TC, abacavir (ABC), and tenofovir disoproxil fumarate (TDF) (14, 30). The prevalence of mitochondrial-associated adverse effects in children is unknown. A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC. Before using ABC, patients must be cautioned about the risk of a serious hypersensitivity reaction and how to recognize symptoms. A genetic predisposition to this syndrome has been identified (HLA-B*5701) and patients with this HLA type should not be treated with ABC.

**Tenofovir** (Viread; Gilead) - represents the first of a new class of antiretroviral drugs, the nucleotide reverse-transcriptase inhibitors. It is the best studied culprit of kidney damage in HIV. Two similar acyclic nucleoside phosphonate antiviral derivatives, adefovir and cidofovir, have been associated with dose-limiting, renal tubular cell toxicity in patients with infectious hepatitis or cytomegalovirus infection who have been treated with these agents (31, 32, 33). In 2007 report, the cumulative tenofovir exposure was estimated to be 455,392 persons per year in Europe and North America (34). Tenofovir related kidney disease occurs generally in patients with predisposing renal illnesses or co morbidities such as diabetes (35). Proposed mechanisms for this Tenofovir drug-induced proximal tubular toxicity include epithelial cell mitochondrial DNA depletion (16, 17) and/or direct tubular cytotoxicity (36). No direct association with mitochondrial toxicity has been found for tenofovir (37). Multiple drug interactions with tenofovir and other HIV drugs lead to renal tubular toxicity and tenofovir associated ARF (38). Tenofovir predominately accumulates in proximal renal
tubular cells and is eliminated by active tubular secretion and glomerular filtration. The renal clearance of tenofovir is significantly greater than the glomerular filtration rate, indicating that renal tubular secretion of tenofovir occurs. Active uptake of nucleotides from blood into proximal tubular cells occurs via hOAT1, which is located in the baso-lateral membrane of proximal tubules (19). Once accumulated, the nucleotides are secreted into the urine via the multidrug-resistance protein (MRP2) on the apical side of the proximal tubular cell. The package insert states that the dose of tenofovir should be adjusted for patients with a creatinine clearance rate of 50 mL/min. If the dose is not adjusted, the increased tenofovir concentrations could increase the possibility of developing tenofovir-associated ARF. Administration of ritonavir alone or with lopinavir has been shown to increase the maximum serum concentrations of tenofovir by 130% (39). Ritonavir is not an inhibitor of hOAT1 but is a potent inhibitor of MRP2-mediated transport, which transports anionic compounds, including tenofovir (40). It is also an inhibitor of P-glycoprotein, an efflux pump for organic cations. We believe that it is likely that ritonavir increased proximal tubular concentrations of tenofovir by decreasing urinary secretion through this pathway.

According to in-vitro studies, atazanavir has been shown to be an inhibitor and inducer of P-glycoprotein and an inhibitor of cytochrome P450 3A activity (41). Co-administration of tenofovir with atazanavir resulted in increases in the following tenofovir pharmacokinetic parameters. Patients who are receiving both ritonavir and atazanavir should be carefully monitored for an increase in tenofovir-associated adverse effects (21). The safety profile of tenofovir has been reported to be safe and is similar to that of placebo (42). However, several recent case reports of drug-induced renal tubular dysfunction and Fanconi syndrome involving patients who had been taking tenofovir for up to 26 months have been published (43, 44, 45, 46). Verhelst et al. (29) and Karras et al. (27) reported cases of tenofovir-induced tubular injury with Fanconi syndrome in HIV-infected patients who had normal renal function. These patients developed tubular injury 1 to 126 months after initiating tenofovir treatment. Another case of renal tubular dysfunction was reported to have occurred in a patient with stable chronic renal disease (26) Schaaf et al. (28) described a patient who presented with proximal tubular necrosis without Fanconi syndrome after only 8 weeks of tenofovir therapy. Holiday trials can be used to test for drug induced renal pathology or primary renal disease. Clinicians should be aware of possible drug interactions, because increased tenofovir exposure due to co-administration of lopinavir-ritonavir could have contributed to toxicity. Pharmacological studies should evaluate the interaction that other ritonavir-containing antiretroviral therapies have on tenofovir levels. Monitoring of creatinine levels should be performed in patients taking tenofovir during at least the first 2 months of treatment, especially when drug combinations known to increase tenofovir exposure are used. 5 out of 19 patients in one study had experienced an AKI episode while being treated with tenofovir, having elevated serum creatinine level at a 24 month follow up after inception of tenofovir therapy (47). Irrespective of the low (0.5%-1.5%) incidence of potentially reversible tenofovir-related AKI, early detection of proximal tubule injury (as indicated by normoglycemic glucosuria, leukocyturia, proteinuria and low serum phosphate level) is critical to prevent irreversible chronic tubulointerstitial fibrosis (48, 49).

**Adefovir- Fanconi's syndrome** is characterized by proximal renal tubular dysfunction and is associated with hyperaminoaciduria, glucosuria, and phosphaturia. Although serum glucose is typically within normal limits, other laboratory abnormalities are hypophosphatemia and hypouricemia. Fanconi's syndrome can be related to inherited or acquired conditions; iatrogenic causes are ifosfamide, cisplatin, tetracycline, aminoglycosides, valproic acid, and the acyclic nucleotide analogs cidofovir and adefovir.

**Combination Therapy / HAART**

The purpose of combination is to prevent viral replication in more than one mechanism to minimize the potential for viral mutations to escape inhibition. The choice of the combination should be one that provides a complementary viral inhibition, is convenient and is well tolerated. Highly Active Anti-Retroviral Therapy (HAART) consists of 3 or more highly potent anti-HIV drugs, commonly reverse transcriptase inhibitors and protease inhibitors. The principle that lies behind HAART is that a single drug therapy may be successful for a while, but because HIV changes to avoid detection, drug-resistant strains will often arise in the patient. The chances of a HIV genome mutating such that it can resist three separate drug treatments at once, however, is so small that the pressure of this therapy prevents the emergence of resistant strains.

**HAART and antihypertensive drugs**

No antihypertensive agents are currently contraindicated in patients receiving HAART. Nonetheless, Calcium channel blockers should be avoided. Protease inhibitors can increase serum concentration of calcium channel blockers below therapeutic levels and thereby leading to hypotension and bradycardia. While NNRTIs reduce serum concentration of calcium channel blockers below therapeutic levels. In addition, serum levels are increased by atazanavir, and the effects of metoprolol might be enhanced.

**Conclusions**

Every good thing in this world comes with its own side effects; hence even though ARV's are life saving drugs for HIV/AIDS population, they are at times proved to have harmful effects. HAART itself can cause renal toxic effects directly by inducing acute interstitial nephritis, crystal nephropathy and renal tubular dysfunction. Hence, it is important to remember that many patients may present with muscle wasting while they are receiving HAART. Renal abnormalities tend to develop in the setting of multiple
patients who are receiving tenofovir concomitantly with the first 2 months of treatment, then monthly thereafter, for magnesium levels) should be monitored every 2 weeks for serum creatinine, electrolytes, calcium, phosphorus, and function (including determination of blood urea nitrogen, any tenofovir recipient. We strongly recommend that renal care professionals to the potential of renal insufficiency in either 0.5 mg/dL or an increase of 50% should alert health recommended that any change in serum creatinine level of insufficiency with normal serum creatinine levels. It is filtration rate, and patients could have significant renal level is an insensitive measurement of the glomerular drug. Renal function should be monitored on a regular basis treatments and cannot be always attributed to a specific drug. Renal function should be monitored on a regular basis in patients receiving antiretroviral drugs. Serum creatinine level is an insensitive measurement of the glomerular filtration rate, and patients could have significant renal insufficiency with normal serum creatinine levels. It is recommended that any change in serum creatinine level of either 0.5 mg/dL or an increase of 50% should alert health care professionals to the potential of renal insufficiency in any tenofovir recipient. We strongly recommend that renal function (including determination of blood urea nitrogen, serum creatinine, electrolytes, calcium, phosphorus, and magnesium levels) should be monitored every 2 weeks for the first 2 months of treatment, then monthly thereafter, for patients who are receiving tenofovir concomitantly with ritonavir or lopinavir-ritonavir, ritonavir plus didanosine, or ritonavir plus atazanavir. A significant increase in the serum creatinine level or new-onset renal tubular dysfunction during tenofovir therapy with ritonavir, lopinavir-ritonavir, ritonavir plus didanosine should lead one to immediately discontinue tenofovir treatment and to perform more-detailed assessments of renal function. Earlier recognition of tenofovir-associated acute changes in renal function can benefit on a large scale. Hence either avoidance to use of Tenofovir or if used under special precautions can decrease its renal toxicity effects. Fear of possible nephrotoxic effects is not a valid reason to withhold life saving antiretroviral therapy in HIV infected patients. Periodic evaluation can prove to lower advancing of renal damage.

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WHEEZING AND CYSTIC FIBROSIS CHILDREN

Ioana Ciucă¹, L Pop¹, Zagorca Popa², B Almajan-Guta³, I Popa¹

Abstract
Cystic fibrosis is the most frequent monogenic disease in population with Caucasian origin, potentially lethal, with marked clinical variability. Wheezing is a common symptom in cystic fibrosis, asthma, allergic bronchopulmonary aspergillosis, even in tuberculosis. Sometimes these pathological conditions are difficult if not impossible to be differentiated. The aim of the paper was to evaluate the frequency of co morbidities like asthma, ABPA or TB in children with CF. Methods: One hundred and twenty-four children with CF were evaluated. For the retrospective analysis on the frequency of associated TB, asthma, ABPA, we used data records from our CF Centre. Results: A small percent of these children 7.25% were diagnosed with associated asthma. Thirteen children (10.4%) were diagnosed with sensitization to ABPA, 3 of them had aspergilosis, with rapid decline of lung function. Regarding the tuberculosis, only one patient (<1%) with CF had criteria for TB diagnosis. Interestingly, before being diagnosed with CF, almost 13% of patients were considered and treated as TB cases, most of them with predominant respiratory symptoms. Conclusion: ABPA is significant co morbidity in CF patients, while asthma occurs rarely. Although TB is a quit common condition in our area, CF children seemed to be protected against it. Further studies need to be done to evaluate this hypothesis.

Key words: wheezing, cystic fibrosis, children

Methods
One hundred and twenty-four children with CF, aged between 5-21 years, with median age at diagnosis = 11.34 years were evaluated. Study design: observational, retrospective for ten years period. For the retrospective analysis on the frequency of associated TB, asthma, ABPA, we used data records of CF Centre. Diagnosis criteria for ABPA used IN the study were according European Cystic Fibrosis Society: Two of three criteria: Immediate skin reactivity to Af antigen, Precipitating antibodies to Af antigen, Total serum IgE . 1,000 IU/mL and at least two of the following: Bronchoconstriction, Peripheral blood eosinophils. 1,000/mL, History of pulmonary infiltrates, Elevated serum IgE/IgG specific to Af, Af in sputum by smear or culture Af, Response to steroids. The diagnosis of asthma was suggested by the following: episodes of acute airway obstruction reversed by bronchodilators (especially if seasonal), a strong family history of asthma and/or evidence of atopy, or laboratory evidence of allergy such as eosinophilia or elevated IgE; This definition is reasonable although the use of serum IgE and eosinophilia is only of value if allergic bronchopulmonary aspergillosis (ABPA) has been excluded. Briefly, diagnosis of asthma require: history of atopy+FEV1 variation >20% +positive bronchodilation test +/-increase IgE and eosinophilia; positive skin prick test or IgE specific For diagnosis of tuberculosis, positive Mantoux test, BAAR positive smear and bacteriological confirmation, additional to clinical and radiological signs were considered. As investigation, spirometry tests, radiography or CT scan were used when necessary.

Results
A small percent of these children 7.25% were diagnosed with associated asthma. Thirteen children (10.4%) were diagnosed with sensitization to ABPA, 3 of them had aspergilosis (fig. 1), with rapid decline of lung function. (ABPA) is a lung disease caused by an immunologic response to the mold Aspergillus spp.

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Regarding the tuberculosis, only one patient (<1%) with CF had criteria for TB diagnosis (fig. 2). Interestingly, before being diagnosed with CF, almost 13% of patients were considered and treated as TB cases, most of them with predominant respiratory symptoms.

Estimates and descriptions of the prevalence of ABPA and of sensitization to A. fumigatus based only on classic criteria, even in developed countries, may be underestimated, since the difficulties in diagnosing ABPA in CF are universal. Thirteen children (10.4%) were diagnosed with sensitization to ABPA, 3 of them had aspergillosis.

Regarding the tuberculosis, only one patient (<1%) with CF had criteria for TB diagnosis. A small percent of these children 7.25% (9 pts) were diagnosed with associated asthma.

Only one patient had active TB, bacteriological confirmed, genotype del F508 homozygous, Pseudomonas positive, although 16 patients (12.9%) were considered having tuberculosis, before being diagnosed with cystic fibrosis. Multiple common features present in both diseases, especially bronchiectasis, could be responsible for this.

**Conclusion**

ABPA is significant co morbidity in CF patients, with increasing prevalence. Although TB is a quit common condition in our country, CF children seemed to be protected against it. Further studies need to be done in order to evaluate the interrelation of cystic fibrosis with other wheezing conditions. Uniform diagnosis criteria may be useful for proper diagnosis and subsequent management.
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THERAPEUTICALLY ASPECTS IN ESOPHAGEAL ATRESIA

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Abstract

Introduction. The esophageal atresia (E.A.) treatment still represents a challenge, concerning both the maintaining of the native esophagus and the neonatal intensive care efficiency.

Purpose. The aim of this paper is to present a single team experience in E.A. treatment in the last five years.

Materials and Methods. 28 consecutive cases, treated in the last five years (between 2005 and 2009) were retrospectively analyzed. We studied the type of the malformation, associated diseases, results regarding the saving of the native esophagus, and also the value of colon esophagoplasty.

Results. In our series 24 patients (85.6%) had E.A. with distal tracheo-esophageal fistula (TEF), one case (3.6%) – EA with both proximal and distal TEF, one case (3.6%) – isolated TEF, and in 2 cases (7.2%) – isolated EA. 6 patients were initially treated in other surgical units (gastrostomy, TEF ligation and cervical esophagostomy), one of them subsequently suffering multiple failed interventions, in which it was attempted the saving of the native esophagus, by the traction of the esophageal ends. We noted different associated anomalies in 9 patients (cardiac malformations, duodenal atresia, imperforate anus, tracheomalacia, skeletal deformities, paraesophageal hernia and pyloric stenosis).

Among the 22 patients treated from the beginning in our unit, in 20 cases we performed primary repair of the EA. In one case – isolated TEF ligation and in one case we renounced at the native esophagus after a failed traction procedure. 2 patients developing esophageal anastomotic tight stricture and 2 patients with significant anastomotic leak required the revision of the anastomosis, which was performed successfully. In one case a recurrent fistula occurred. All the 6 patients, initially having gastrostomy, TEF ligation and cervical esophagostomy, suffered colon esophagoplasty.

We encountered 4 deaths (14.3%), 3 of them weighting less than 1.500 g. at birth.

Conclusions. The developing of the neonatal intensive care allows us to increase the percentage of cases with preserving the native esophagus. In long gap cases, the esophageal traction may represent a good instrument for primary anastomosis achievement. However, the reconversion of the EA patients initially having esophagostomy and cervical esophagostomy, in order to elongate and save the native esophagus leads to a serious morbidity. Colon esophagoplasty in failed esophageal repair is a safe and functional alternative.

Key words: esophageal atresia

Background/Purpose.

Since the first successfully primary repair of EA with a TEF (Cameron Haight, March 15, 1941) (1), a spectacular improvement in the knowledge and treatment of EA has been encountered. According to Spitz (1,2), the survival rate of the AE patients having a birth weight less than 1500 g and associated major congenital heart disease is now more than 20%, which means a huge progress. Nevertheless, in the developing countries consistent steps are needed in order to achieve similar results. The aim of the study was to evaluate a single team experience in E.A. treatment in the last five years.

Materials and Methods.

From 2004 to 2009, 28 AE patients were treated by a single surgical team. The medical records of these patients were retrospectively analyzed, regarding the type of the malformation, associated diseases, surgical treatment, complications and survival rate.

Results.

Among these 28 consecutive EA patients treated by our team, 24 patients (85.6%) had type C, one case (3.6%) – EA with both proximal and distal TEF, one case (3.6%) – isolated TEF, and in 2 cases (7.2%) – isolated EA. 6 patients were initially treated in other surgical units (gastrostomy, TEF ligation and cervical esophagostomy), 9 patients (32.15%) had different associated anomalies - cardiac malformations (atrial septal defect, 5), duodenal atresia (2), imperforate anus (1), tracheomalacia (1), skeletal deformities (radius agenesis, 1 case), para esophageal hernia (1) and hypertrophic pyloric stenosis (1).

• 22 patients were treated from the beginning in our unit. In this group, in 20 cases we performed primary repair of the EA. In 5 of them (25%) we used intraoperative esophageal elongation as it was described by Foker (6,7). The mean distance between the esophageal ends in these 5 cases was 2.5 cm. (between 1.5 and 3.5 cm). In 3 cases (15%) mild esophageal stenosis occurred, successfully treated by dilatations. 2 patients (10%) developed undilatable esophageal anastomotic tight stricture (fig. 1, 2). In both cases the esophageal gap was about 3.5 cm.
One month after the primary repair open gastrostomy together with a Nissen antireflux procedure was performed. After several failed attempted antegrade bougienage procedures the stenotic segment was removed, followed by reanastomosis.

2 patients (10%) developed significant anastomotic leak, requiring the revision of the anastomosis, which was performed successfully. In one of them (fig.3), having associated cardiac dextroposition, we started with right thoracotomy. We found and dissect the proximal esophagus, but the distal esophagus was absent in the right mediastinum. We performed a left thoracotomy, finding and ligating the TEF and performing the esophageal primary repair. 3 days postop a significant leak occurred, requiring prompt reintervention and anastomosis repair. The final result was satisfactory.
The patient with EA and both proximal and distal TEF was operated on, ligating the fistulas and performing an esophageal end-to-end anastomosis. A major disruption of the esophageal anastomosis occurred 48 hours after the initial repair. We performed a gastrostomy, putting the distal esophageal end on internal traction and the proximal end on external traction through a cervical subcutaneous tunnel. 3 days postoperatory a perforation occurred at the proximal esophageal level, requiring the renouncing of the lengthening procedure and cervical esophagostomy. One year later he was reoperated in another country, suffering a gastric pull-up procedure.

In one case, weighting 900 g, a recurrent undetected fistula occurred, finally leading to uncontrolled sepsis and subsequent death.

In one case we performed a successfully isolated TEF ligation, at the age of 3 years (fig.4).

One patient of our series, weighting 1580 g, had EA with distal TEF, duodenal atresia and perineal fistula. We performed TEF ligation and primary esophageal repair, diamond-shaped duodenal anastomosis and “V” anoplasty.
The patient was discharged one month postop., weighting 2000 g, with good functional results. 4 patients (14.3% from all our cases), 3 of them weighting less than 1.500 g, at birth, had an unfavorable evolution finally leading to death, due to septic complications.

6 patients were initially treated in other units having gastrostomy, TEF ligation and cervical esophagostomy. One of them was admitted in our department after he suffered several failed lengthening procedures suffered in other country. In all these patients we performed colon esophagoplasty. We used transverse colon irrigated by the left colic a. We preferred to pull-up the graft through a retrosternal route in an isoperistaltic manner. The postoperatory results were very good in all cases (fig 6), with no significant complication at all.

**Discussion**

The developing of the neonatal intensive care, a more surgical aggressive attitude in complicated cases, together with a higher accuracy in esophageal dissection allows us to increase the percentage of cases with preserving the native esophagus. In long gap cases the esophageal intraoperatory traction as it was described by Focker (4,5,6) represent a good instrument in order to achieve primary anastomosis. However, the reconversion of the EA patients initially having esophagostomy and cervical esophagostomy (6,7), in order to elongate and save the native esophagus leads to a serious morbidity. Colon esophagoplasty in failed esophageal repair is a safe and functional alternative.

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INFARCTION OF A MESOCOLIC LIPOMA ASSOCIATED WITH CATARRHAL APPENDICITIS IN A 12 YEARS OLD GIRL A CASE REPORT

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Abstract:
Lipoma is called the universal tumour. It can occur anywhere in the body. Mesenteric lipomas are considered rare probably because they are often asymptomatic or only mildly symptomatic, however they can cause significant pain, melena or diarrhoea or more serious conditions like intussusception and intestinal obstruction. Solid lipomas, in the paediatric abdomen are very rare. We present such a case, that of an 12-year-old girl who was admitted with abdominal pain, nausea and mild pyrexia. The pre-operative diagnosis of acute appendicitis was suggested by ultrasound (US). The diagnosis of infarctised lipoma arising in the ascendent mesocolon, without immature cells, was made microscopically after the operation.

Key words: lipoma, appendicitis, mesenteric tumors

Introduction:
Lipoma is a benign soft-tissue tumor and one of the most common types of mesenchymal neoplasms in adults. It can be single or multiple (lipomatosis) and superficially or deeply localized. In children, lipomas occasionally develop superficially or in the trunk.(1,2). Deep lipomas can be localized in the thorax, mediastinum, thoracic wall, pleura, pelvis, retroperitoneum, and paratesticular area, but they rarely originate in the intestinal mesentery in children.(1,3–5) There have been sporadic reports of mesenteric lipomas causing intermittent abdominal pain, distension, and intestinal volvulus.(3–5). Herein, we report a case of a small infarctised mesocolic lipoma associated with catarrhal appendicitis in a 12-year-old girl.

Case report:
A 12 years old girl was admitted with a two-day history of generalised abdominal pain, settling on the right side. She was anorexic and nauseated. Examination revealed a low grade pyrexia of 38.1 °C. Full blood count showed mild leucocytosis with white blood cell count of 12500 with high neutrophil percentage (81,5%). Blood urea, creatinine and electrolytes were within normal limits. An US was done revealing a distended appendix measuring about 11mm in the proximal portion associated with mild thickened wall, with no significant fat stranding in the peri-appendicular region.

After treating the patient conservatively for suspected appendicular reaction, the next day we found tenderness with rigidity and rebound in the right iliac fossa while examining the patient. No significant modifications were found repeating the US and blood tests. Given the worsening symptoms we decided to perform surgery for acute appendicitis. Intraoperatively the appendix was found slightly hyperaemic and a 1,5/1 cm encapsulated and yellowish mass with a black contour surrounding it, originating from ascending mesocolon was found near the caecum.

Discussion:
Lipomas are benign tumors with a low potential for malignant degeneration. They are most often found in adults between 40 and 60 years of age and rarely occur in the first decade of life. Lipomas are the most common soft-tissue tumors and their incidence is far higher than reported. Most lipomas are ignored if they do not cause esthetic problems or any symptoms of their anatomical localization.(1,2) The etiology is not well known, although obesity, diabetes mellitus, trauma, radiation, and certain chromosomal translocations and rearrangements have been reported as etiological factors, none of which were applicable to this case.(1)

Lipomas are composed of mature fat and are common mesenchymal tumors, however very little is known about their pathogenesis (6). They may occur in any part of the body but lipoma of the mesentery is a rare finding, mostly described in case reports while the precise incidence is unknown (6). Most of the described intraperitoneal lipomas had an asymptomatic course and were discovered by accident (1,7) and only a few cases presented with acute abdomen (2).

Macroscopically, lipomas are soft, well-capsulated, oval, and yellow. Deep lipomas are usually only diagnosed when the tumor grows very big or becomes symptomatic of its anatomical localization. Microscopically, they are uniform and have a centrally located single lipid vacuole with peripheral cytoplasm and nucleus (1,2). The tumor from our patient was oval, soft, yellow with a black contour (probably caused by the thrombosis of blood supplying vessels) well encapsulated (Fig. 1).

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The intestinal mesentery is an extremely rare site for a deep lipoma. Lipomas generally form a slow-growing, nonlobulated, soft, and mobile mass, which does not penetrate into the surrounding organs (1,2,4). Occasionally they may cause acute or intermittent abdominal pain, distension, small bowel volvulus, and constipation (3–5).

Primary mesenteric tumors, often hard to detect, are usually diagnosed upon laparotomy or necroscopy because of their slow growth and infrequent complications such as bowel obstruction, torsion with necrosis, invasion of adjoining organs or bowel perforation with peritonitis (3).

Benign cystic tumors occur more frequently than solid tumors. A benign mesenteric cyst was first reported in 1507 by Beniviene upon necroscopy (7,8). Histologically, lipomas arise from mature adipose tissue and may be malignant (7,8). They have been reported in children of all ages with no specific predilection (1, 3). Preoperative diagnosis can be difficult if there are no symptoms or if the tumor is small sized as in our case, but computed tomography and ultrasound (US) may be helpful in patients with larger tumors (3,4). The US findings prevented us to further investigate the cause of the abdominal pain, leading us to an incomplete diagnosis. In our opinion, only both the appendix obstruction and the infarction of the lipoma could cause such a severe abdominal pain.

Despite the benign nature of the tumor and the non life threatening complication, emergency surgical resection of the tumor is necessary. In addition, mesenteric lipomas may undergo malignant degeneration and may grow in very large sizes, therefore resection is the treatment of choice (8).

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PRELIMINARY RESULTS OF AN ACUTE OSTEOMYELITIS OF THE FEMUR WITH STAPHYLOCOCCUS AUREUS INFECTION IN A NEWBORN

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Abstract
Osteomyelitis refers to bony inflammation that is almost always due to infection typically bacterial. This article primarily deals with pyogenic osteomyelitis. Drainage of superiosteal abscess at the upper end of the femur (upper ½). Pus found under considerable pressure (subperiosteal abscess) was drained, 1 drill hole down the medulla, bone biopsy, 2 drainage tubes were placed. One for flushing initially with antiseptic solution (Betadine) dissolved in 500 ml of distilled water. Flushing was stop on 14th postoperative day. Pus was taken for culture and antibiotic sensitivity during surgery.

Key words: osteomyelitis, epiphysis, metaphysic, femur, hip, newborn, abscess, biopsy.

Background
Osteomyelitis is inflammation of the bone caused by an infecting organism (3). Although bone is normally resistant to bacterial colonization, events such as trauma, surgery, presence of foreign bodies, or prostheses may disrupt bony integrity and lead to the onset of bone infection. Osteomyelitis can also result from hematogenous spread after bacteremia. Early and specific treatment is important in osteomyelitis, and identification of the causative microorganisms is essential for antibiotic therapy (6,7). The major cause of bone infections is Staphylococcus aureus (5).

Osteomyelitis is often diagnosed clinically with nonspecific symptoms such as fever, chills, fatigue, lethargy, or irritability. The classic signs of inflammation, including local pain, swelling, or redness, may also occur and normally disappear within 5-7 days.

On physical examination, scars or local disturbance of wound healing may be noted along with the cardinal signs of inflammation. Range of motion, deformity, and local signs of impaired vascularity are also sought in the involved extremity. If periosteal tissues are involved, point tenderness may be present.

In children, the clinical presentation of osteomyelitis can be challenging for physicians because it can present with only nonspecific signs and symptoms, and the clinical findings are extremely variable. Children may present with decreased movement and pain in the affected limb and adjacent joint, as well as edema and erythema over the involved area. In addition, children may also present with fever, malaise, and irritability. Newborns with osteomyelitis may demonstrate decreased movement of a limb without any other signs or symptoms.

Approximately 20% of adult cases of osteomyelitis are hematogenous, which is more common in males for unknown reasons (9).

The incidence of spinal osteomyelitis, as depicted in the image below, was estimated to be 1 in 450,000 in 2001. Surgery is indicated when the patient has not responded to specific antimicrobial treatment, if there is evidence of a persistent soft tissue abscess or subperiosteal collection, or if concomitant joint infection is suspected. Debridement of necrotic tissues, removal of foreign materials, and sometimes skin closure of chronic unhealed wounds are necessary in some cases (1,2,4,8).

Case presentation
C.R., a male 30 days old baby was admitted late evening at the county hospital Arad through the ER, with no known history of trauma, according to mum baby was discharged 10 days earlier after receiving treatment at the pediatric department for upper respiratory tract infection on admission mum complained that baby had difficulty sleeping with frequent cries, swelling and redness of the thigh and right hip joint, pain fever and asymmetric movement of the extremities.

Mum observed the swelling 5 days ago, she saw the primary care physician but was told that it is probably an insect bite and given antihistaminic and paracetamol. Babies condition worsened and was sent to us by the primary care physician.

Physical examination:
General clinical signs: low grade fever, pallor, anemia, weight loss, omblital hernia, no chest rales, no urine infection.

Local clinical signs: painful focal swelling with cardinal signs of inflammation of the right thigh, right leg extremity edema, right thigh and focal join redness, no draining pus, bone deformity (twice enlarged right thigh), restricted movement of right joint, cellulities, no sign of fracture.

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Laboratory studies:
- X-ray of the affected leg and hip joint shows: focus of infection of the upper end (epiphysis and metaphysis) of the right femur, subperiosteal abscess, periosteal reaction including Codman’s triangle, peripheral regions of osteolysis and osteosclerosis, no septic joint (fig. 1).
- WBC was elevated
- C-reactive protein was elevated
- Erythrocyte sedimentation rate (ESR) was elevated.

In view of clinical findings baby was admitted and scheduled for surgery the next day. Patient was placed on i.v. fluids, i.v. antibiotics, antithermic and vitamins.

Operation:
- Cut down of upper ½ of the right femur (epiphysis, metaphysis and diaphysis) through the soft tissues. Periosteum was detached from bone. Pus was found under considerable tension posteriorly. Culture sample was taking, wound washed thoroughly and drained with 2 drainage tubes one placed superiorly through the greater trochanter and the other placed inferiorly at the diaphysis (fig. 2). The upper tube was use for flushing while the low tube was used for drainage.

Patient was monitored at ICU, i.v. fluid administration continued with i.v. antibiotics (cefort) and gentamycine, antithermic and vitamins for the first 2 days while awaiting the result of culture and sensitivity. Flushing of wound with antiseptic (betadine) solution 10 ml dissolved in 500 ml sterile water, 24 h, for the first 2 days.

Patient post operation remained afebrile, stable, feeding well. Clear chest X-ray, but received blood transfusion because of severe secondary anemia. Negative blood culture, but pus culture was positive for staphylococcus aureus:
- sensitive for the following antibiotics clindamycin, linezolid, ofloxacin, teicoplanin;
- intermediate sensitivity – tobramicin;
- resistant for: meticillin, gentamycin, eritromycyn, cefoxitin.

Patient was immediately switched to i.v. linezolid (zyvoxid) 50 mg at 8 h interval systemic antibiotics (gentamycin) was immediately stopped.

Patient right leg was immobilized in a back slab for easy wound access.

Evolution:
- Despite baby’s good clinical status lab test continued to show elevated WBC, C-reactive protein and Erythrocyte sedimentation rate. On 14th postoperative day Linezolid (zyvoxid) was changed to clindamycin, despite patient being stable, afebrile, feeding well, and clear chest. Change of antibiotics was based on elevated WBC, C-reactive protein and erythrocyte sedimentation rate. Blood work (WBC, C-reactive protein, Erythrocyte sedimentation rate) normalised after 7 days of clindamycin treatment. We waited 4 more days and repeated tests, patient continued to maintain normal WBC, C-reactive protein and Erythrocyte sedimentation rate. Patient was then placed in a plaster of paris (hip abduction position) Lorenz and sent home and asked to continue oral antibiotics. Checkup in a month time. On checkup patient was admitted for blood work, x-ray and cast was removed. X-ray showed no hip dislocation and an intact growth plate and satisfactory bone regeneration (fig. 3). Normal WBC, C reactive protein and Erythrocyte sedimentation rate. Hip abduction orthosis was then recommended and patient is to be seen again in 2 months time.
Conclusion

The absence of trauma leaves us to believe that osteomyelitis is hematogenous. Even though it is difficult to say when exactly this child fell sick the clinical signs of disease were clear upon admission, we moved fast with the right treatment and at the end everyone is happy. The future looks bright and we will continue to follow our patient. Primary care physicians should be better trained and well informed about this disease and a child with history of trauma or no trauma, fever irritability, swollen reddish extremity should always be considered for osteomyelitis until proven otherwise. Let us also underline the fact that our patient response well to linezolid when through sensitivity test showed that it should we had to change to clindamycin. Antibiotics should be continued for at least 6-8 weeks. Clinicians should keep in mind to also cover gram negative organisms during antibiotics selection.

Elevated WBC, C-reactive protein and ESR along with x-ray or ultrasonographic changes seen in bone and soft tissues are the most valuable supportive investigations, It was observed that early decompression of the /soft tissue under cover of combinations of antibiotics led to resolution of disease.

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EARLY DIAGNOSIS OF INTESTINAL INTUSSUSCEPTION IN THE NEW-BORN BABIES AND INFANTS

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Abstract

Intestinal intussusception can be regarded today as a classical problem, although largely solved. All the experts were concerned to know this disorder, so that they can establish an early diagnosis and start an appropriate treatment. Intussusception can be seen in all ages, but more often in small children and especially infants between 4-10 months. Infants are, usually, eutrofical. Intussusception occurs when the child's condition seems perfectly alright, but a properly examined medical history will show the existence of a coryza or diarrhea.

In explaining the production of intestinal intussusception, the following determinant and contributing factors are considered responsible:

Favouring factors:
- Abnormal growth of ECSC-colic region;
- ECSC-delay in setting of the colon;
- Change of diet;
- Seasonal diarrhea that causes mesenteric adenopathies generating vasomotor disturbances.

Determinant factors:
The intestinal peristalsis explained by Reilly by allergising the mesenteric lymphs with bacterial or viral toxins. This allergic reaction can cause a tumoral ulcerative-necrotic mesenteric adenopathy, and vascular disorders with transudate in the peritoneal cavity.

In establishing the early diagnosis an important role is played by clinical examination and laboratory examinations that include: ultrasound, Doppler ultrasound, x-ray, with contrast barium enema, computed tomography.

Key words: intussusception, early diagnosis, laboratory examination, mesenteric lymph nodes.

Introduction

Intestinal intussusception is one of the most common causes of acute surgical abdomen in infants and small children, with an incidence of 1.5 to 4 per 1000 children. Intussusception is produced by “telescoping an intestinal segment in the underlying segment” by two known mechanisms - prolapse or inversion. It occurs most frequently between 6th and 24th months of life, in this age group being considered idiopathic and favored by an "increased intestinal peristalsis". In the case of older children it usually reveals the existence of a mechanical cause, which is the starting point for intussusception. The vast majority of cases of intussusception are ECSC-ileo-colic, although it can have any location, produced by “telescoping the colon and ileum”.

The progress of imagistic methods has made this condition easily recognizable, even though, in the past it was difficult to diagnose and was associated with morbidity and mortality. Early diagnosis and appropriate treatment have considerably improved the prognosis of this disease, “mortality from intestinal intussusception being less than 2%.” However, there is a large percentage of cases in which the diagnosis is established late, requiring a difficult surgery, extensive bowel resection, these cases involving high morbidity and sometimes evolving unfavorably towards exitus.

The aim of the paper

The paper intends to clarify the idea that intestinal intussusception is a surgical emergency that should be known by many doctors and, in particular by the GP, for he/she is the first to see the sick child and the prognosis of this condition depends on his/her early diagnosis.

The best possible training and knowledge of the disease correlated with a close collaboration improves the surgical prognosis of the disease.

It’s important for most pediatricians to know all the signs of the disease, so that it can be recognized on time, and the child sent to the surgeon; after a diagnosis of certainty and investigations, the proper treatment is applied.

Treatment of intestinal intussusception is not a problem today, and the children, who are sent immediately to surgery, after the onset of the disease, are treated with good results.

Material and method

The author carried out a retrospective study on a group of 30 patients hospitalized between January 2000 and December 2010 with the diagnosis of intestinal intussusception. It examines the clinical symptoms, their duration, the existence of underlying diseases, diagnostic methods, conservative or surgical treatment and evolution of these patients, in order to emphasize the importance of early diagnosis and highlight the difficulties in recognizing the disease. Diagnostic methods used were clinical history, physical examination and paraclinical diagnosis - supported by abdominal ultrasound, native abdominal X-ray and enema with contrast substances.

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Results

The study group consists of 8 girls (23%) and 22 boys (77%), (Fig.No.1) high prevalence of disease is observed in males. Their origin environment was: 12 patients (44.66%) in urban and 18 patients (55.33%) in rural areas. This difference is not statistically significant, except that all cases were presented early in the service of pediatric surgery (7 cases in the first 12 hours), came from urban areas, due to a greater accessibility to medical services. (fig.No.2)

The age of the patients from the study group varied between 7 weeks and 1 year, with a higher frequency for the infants, especially after the first 6 months of life.

Clinical symptoms were varied. Although classically described in the literature, the classic symptomatic triad (“colicky abdominal pain, bloody stools, palpable abdominal tumor”) (4,6), the combination of pain-bloody stools has been described in a relatively small number of patients (15 - 50%) and intussusception tumor was palpable in one patient. The symptoms were the following: (fig.No.3)

- abdominal pain in 15 cases (50%);
- bloody stools in 14 cases (46,66%);
- diarrhea in 3 cases (10%);
- food/bilious vomiting 24 cases (80,66%);
- altered general condition in 18 cases (60,66%);
- refusal to eat in 10 cases (34,66%);
- lack of transit for faeces 3 cases (10%);
- haematemesis 1 case (3,33%);
- palpable abdominal tumor case in 1 case (3,33%);
- seizures in 1 case (3,33%).
The onset was nonspecific through symptoms of gastrointestinal origin, predominantly vomiting and bowel disorders (stools with bloody streaks, diarrhea, and lack of transit or even normal transit). The difficulty of analysing a clinical history at this age, plus the difficulties caused by parents, whose misleading stories confuse the medical staff, cause that in about 50% of cases the initial clinical presentation to be misinterpreted as another disease, and, therefore, delay the diagnosis of intussusception. The most important event described by parents is “impaired general condition of the child” (1,2), sometimes associated with seizures, a situation interpreted as a digestive distress (acute nasopharyngitis, gastro-enteritis).

Patients are hospitalized in other services (pediatrics, infectious diseases) until symptoms such as bloody stools and abdominal bloating, occur; those are alarming symptoms, that require surgical examination.

The time interval, from the appearance of the first clinical symptoms and admission to our clinic ranged from several hours to less than 4 days, most patients being admitted within 24-48 hours.

We notice the degree of subjectivity of the parents related to the description of symptoms and the range of occurrence. Patients have come to our surgery department directly (7 cases - 23.66%), in a state of emergency, sent from other medical services, where they were initially hospitalized and treated for other diseases (18 patients - 59.33%) and sent to our clinic on suspicion of intestinal intussusception or other surgical diseases (5-15%).

Addressability to our clinic was as follows: (Fig.No.4)
- direct 7 cases;
- 8 cases admitted to other clinics for: acute nasopharyngitis 8 cases and 10 cases of acute gastro-enteritis;
- 5 cases were sent to the clinic on suspicion of: intestinal intussusception 4 cases and acute abdomen 1 case.

We note that more than half of the cases were hospitalized for other conditions in various medical services (pediatrics, infectious). The question is whether these cases are diagnostic errors or the intestinal intussusception appeared secondary to other conditions that increase peristalsis (mechanism known to produce intestinal intussusception in infants - gastroenteritis, respiratory infections). To this, we add the fact that some patients were polio vaccinated (4 cases - 10%) and the intraoperative evidence of significant mesenteric lymphadenitis (4 cases - 10%)

Laboratory methods used for diagnostic were the ultrasound, empty abdominal radiography and enema with contrast substances (gastrografin). In the early presented cases, the “enema with contrast substances has both a diagnostic and a therapeutic role”.(7,8,9)

Abdominal ultrasound revealed a cockade image in 21 cases (69.66%), “peritoneal collection in Douglas and Morrison space”(9,10), in 1 case. In five cases, ultrasound was not very revealing because of the abdominal distension, and in 8 cases, no ultrasound was performed. (Fig.No.5)

Abdominal radiography showed “hydroaeric levels” in 15 cases (9,10), (50%), abdominal opacity in 4 cases, 4 cases showed the normal picture, and in 7 cases it was not performed.(Fig.No.6)

Gastrografin enema was performed in 12 cases, all with early presentation up to 12-36 hours. Cases considered obsolete (over 36 hours), have not benefited from conservative treatment and because intestinal perforation might occur, it was decided to abandon this examination. All cases of enema with contrast substances revealed a stop of the contrast. In 8 of the cases disintussusception by enema occurred with contrast substances, and in 5 cases the procedure didn’t succeed. In the study group there were two dead patients, both in patients who were hospitalized after 48-72 hours from the onset and had loop necrosis, needing a right hemicolectomy. Both cases had postoperative complications, generalized peritonitis with anastomotic dehiscence, which required surgical reinterventions.
Other laboratory examinations to be taken into consideration in case of failure can be described: Doppler examination should be performed in case of emergency and” provides information regarding vascularization loops involved in intussusception and, thus, regarding the viability of loops handlers”(9,10). It can detect changes in the invaginated loop: “arterial stenosis until the disappearance of the arterial signal with increasing velocity at the site of vascular stenosis and poststenotic decreased speed and the corresponding change of the spectral appearance.”(9) “The vassel circulation in the loop is quite abundant; the veins seem dilated with low velocities compared to other loops.”(10)

Ultrasoundography controls and views the therapeutic attempts successfully by “instillation of fluid under retrograded dosed pressure” (9). Also, there is a margin of error and intussusception cases where the tumor is not seen by ultrasounds: interposed loops, artifacts, echoes. For the ultrasound examination of abdominal loops the “ultrasound transducer”(10) is used according to the patient’s age and position of the explored segment. The digestive surface structures in ECSC-appendicular region are further examined with high-frequency linear transducer 5 to 7.5 MHz, allowing a detailed structural assessment. In the case of children,” convex or linear transducers are used, with a frequency of 5 MHz.”(9)

The non-contrast abdominal radiography is non-specific as indicative value, and the aspect varies from a normal exam "opaque abdomen" to the classic picture of mechanical obstruction and possibly with hidroaeric levels and delayed pneumoperitoneum. After birth, swallowed air is distributed throughout the intestinal tract, physiological aeroentery, but, starting with the food diversification after the age of 3 months and a half, gas distribution starts to resemble that of adults. “Aeroentery and marked distention of the colon”(8) are the signs detected in the first hours. On a background of gaseous distension or independently of this, there is the accumulation of fluid in loops creating hidroaeric images. Their appearance varies by location: the "organ pipe image (large longitudinal diameter, centrally located, disposed on levels) for the enteral ones, or large with peripheral location, the colic ones. Intestinal perforation is illustrated by the presence of pneumoperitoneum, semilunar image with diaphragmatic domes standing under or between the side of the liver and abdominal wall for the patient with the left lateral decubitus patient or in the anterior abdominal wall for the patient in supine horizontal radius. “It is recommended to avoid administration of barium sulphate per bone; the examination
was possible only with Gastrografin or Gastromiro non-ionic water-soluble contrast agents.”(8)

Because CT is especially radiant to young children, it remains a solution when the other methods have been irrelevant, “bringing additional information on associated pathology, may specify the place, and the related extrinsic or intrinsic pathology”(9): adhesions, strangulation, intraperitoneal hernias, extrinsic masses, benign and malignant tumors, Crohn disease, tuberculosis, radiation enteritis or colitis, intramural hemorrhage, intussusception, malrotatations.

Conclusions

1. Early diagnosis of intestinal intussusception is made by associating the clinical history with the clinical examination and the laboratory examination.

2. Intestinal intussusception appears when the patient is healthy with violent abdominal pain accompanied by restlessness, interrupted by periods of calm of variable duration.

3. Correct diagnosis based on abdominal examination, rectal examination, ultrasound and barium enema should be established before the onset of gastrointestinal bleeding.

4. Clinical examinations in the early diagnosis of intestinal intussusception include:
   - Intermittent abdominal crisis associated with vomiting and with the presence of intussusception tumor = intestinal intussusception.
   - Abdominal pain and intermittent crises, finding blood on rectal examination = intestinal intussusception.

5. In infants, the underdeveloped subcortical brain area produces disorder of the excitation and inhibition processes, favoring the excitation, and lack of inhibition and difusability of excitation influences subcortical centers producing important circulatory and respiratory disorders, trophic state of shock that damage the child’s condition.

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CHEMICAL SYNOVECTOMY OF THE KNEE IN RABBITS – OXYTETRACYCLINE VERSUS AETOXYSKLEROL – A EXPERIMENTAL STUDY

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Abstract

Introduction. Recurrent haemarthroses will inevitably lead to significant hypertrophic synovitis in patients with haemophilia (PwH), progressive joint cartilage degradation, ultimately resulting in haemophilic arthropathy with significant functional impairment of the affected joints. The degree of haemophilia synovitis is directly related to an increase in bleeding frequency in the affected joint. Synoviorthesis or non-surgical synovectomy is a therapeutic method which consists in injection of a substance into the joint, which acts on the synovial membrane by means of a fibrosis that constricts the subsynovial plexus and thus prevents future bleeding. There are two groups of preparations: chemical and radioactive isotopes. Material and methods. Twenty two albino New Zealand White specific pathogen free rabbits were used for the study. From one of them synovial membrane was harvested from both knees and send for anatomopathological examination. The remaining rabbits were injected into both knees once a week for 4 weeks with autologous blood (2 ml) harvested from the safenous vein, mimicking the pattern of repeated hemarthroses that the patients with haemophilia experience. After this synovial membrane and articular cartilage were harvested from both knees from a second rabbit and send for anatomopathological examination to observe intraarticular damage. The remaining rabbits were divided in two groups and oxytetracycline (200 mg/ml) and aetoxysklerol 1% (20 mg/ml) were injected into their left knee, while the right knee was injected with saline solution in each group of rabbits once a week for a period of 4 weeks. After that all rabbits were euthanized and synovial membrane and joint cartilage were harvested. Theanatomopathological specimens were stained with hematoxylin-eosin and examined under optic microscopy. Results and discussions. No problems related to the procedures were encountered, except for discrete ambulatory problems after injection of blood into the knee joints. The general status of all rabbits was good during the whole period of the experiment. Repeated hemarthroses into the knee resulted in proliferation of the synoviocits with inflammatory signs resembling acute synovitis and higher magnification levels in optical microscopy revealed presence of hemosiderin and inflammatory cells. This proliferation of the synovium and neovascularization of the subsynovial layer results in an inflamed, villous, friable and highly vascular synovial tissue. The specimens from the rabbits injected with oxytetracycline and aetoxysklerol showed fibrosis, regeneration of the synovial tissue and controlled reparation, with slide enlargement of synovial tissue, less irrigated, and less prone to rebleed in 100% of cases. Conclusions. Synoviorthesis should be the first choice of treatment for persistent synovitis of the joints in patients with haemophilia. It is a simple procedure, which eliminates the risks associated with surgery and is also cost-efficient. Preliminary experimental data show a good efficiency of both oxytetracycline and aetoxysklerol as materials used for chemical synovectomy in rabbits with acute synovitis of the knees. There is still need for further experimental data gathering and dosage adjusting before optimal use of these substances in the treatment of haemophiliacs.

Key words: hemophilia, rabbit, chronic synovitis, synoviorthesis, aetoxysklerol, oxytetracycline

Introduction

Recurrent haemarthroses will inevitably lead to significant hypertrophic synovitis in patients with haemophilia (PwH), progressive joint cartilage degradation, ultimately resulting in haemophilic arthropathy with significant functional impairment of the affected joints. The degree of haemophilia synovitis is directly related to an increase in bleeding frequency in the affected joint(1). There are two basic types of procedures for synovial control: medical synovectomy (or synoviorthesis) and surgical synovectomy (open or arthroscopic.) It is commonly accepted today that synoviorthesis is the procedure of choice, and that surgical synovectomy should be performed only if a number of consecutive synoviortheses fail to stop or diminish the frequency of recurrent haemarthrosis(2,3).

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A synoviorthesis consists of the intra-articular injection of a certain material with the aim of ‘stabilizing’ (orthesis) the synovial membrane of a joint (synoviorthesis) by means of a fibrosis that constricts the subsynovial plexus and thus prevents future bleeding. There are two groups of preparations: chemical and radioactive isotopes. Thus, the main indication for a synoviorthesis in a haemophilic joint is hypertrophic synovitis and recurrent bleeding. Synoviorthesis has been utilized for more than 25 years (4-7).

Aim of the present study
The aim of the present study is to test the efficiency of new chemical substances for synoviorthesis and introduce them to clinical practice. Oxytetracycline has been used on an experimental basis before (8-11), aetoxysklerol was chosen because of very good fibrotic properties in the treatment of pediatric hemangiomas (personal experience). The rabbit was chosen for this experiment because of the histological similarity of the animal synovium with the human one (12-18).

Material and methods
Twenty two albino New Zealand White specific pathogen free rabbits were used for the study. All surgical interventions were conducted under general anesthesia with ketamine associated with xylazine. The rabbits were prepared for surgery and all rules of asepsia and antisepsia were respected. From one of the rabbits synovial membrane was harvested from both knees and send for anatomopathological examination (Fig.1-3). The remaining rabbits were injected into both knees once a week for 4 weeks with autologous blood (2 ml) harvested from the safenous vein, mimicking the pattern of repeated hemarthroses that the patients with haemophilia experience. After this synovial membrane and articular cartilage were harvested from both knees from a second rabbit and send for anatomopathological examination to observe intraarticular damage. Intraoperative findings were: amber color, brown staining (hemosiderin) and thickening of the synovium at the level of both knees, the presence of numerous envelopes, secondary hyperaemia, increased vascularization of the synovium with subsequent tendency towards bleeding (Fig. 4). The synovium appeared thickened, inflamed and hypervascular (Fig. 5, 6). These findings together with the anatomopathological ones correspond to the ones observed in patients with haemophilia after repeated intraarticular bleedings and in experiments done by other authors (8-11, 19-25).

The remaining rabbits were divided in two groups and oxytetracycline (50 mg / kg body weight) and aetoxysklerol 1% (1 mg / kg body weight) were injected into their left knee, while the right knee was injected with saline solution in each group of rabbits (1 ml), once a week, for a period of 4 weeks. After that all rabbits were euthanized by injection of Euthanyl (100 mg / kg body weight) and synovial membrane and articular cartilage were harvested in 30 minutes after death. Macroscopic intraoperative findings were a shrinking of the synovium in the joints injected with aetoxysklerol and oxytetraccline and fibrosing aspect in all rabbits with reduction of vascularization (Fig. 7). The anatomopathological specimens were stained hematoxylin-eosin, Perls, Tricrome Gömöri, Tricrome Masson and examined under optic microscopy (Fig. 8-11).
Fig. 3 Hematoxylin-eosin staining, magnification 400X: loose connective tissue rich in fundamental substance, small capillary-type vessels.

Fig. 4. Intraoperative aspect of the synovium after repeated injections of autologous blood.

Fig. 5 Hematoxylin-eosin stain, magnification 400X: Proliferated synoviocytes across layers associated with hemosiderin loaded histiocyte macrophages.

Fig. 6 Hematoxylin-eosin stain, magnification 400X: Intensely proliferated synoviocytes, subjacent histiocyte macrophages loaded with hemosiderin.

Fig. 7. Macroscopic aspect of the joint injected with aetoxysklerol.

Fig. 8. Hematoxylin-eosin stain, magnification 200X: Proliferation of synoviocytes, marked fibrosis and reduction of vessels.
Fig. 9., Fig.10., Hematoxylin-eosin stain, magnification 400X (detail): Proliferation of synoviocytes, marked fibrosis and reduction of vessels (slide enlargement of synovium with appearance of tissue less irrigated and thus less prone to rebleed).

Fig. 11. Tricrome Masson stain, magnification 200 X: Marked fibrosis of the synovium.

**Results and discussions**

Repeated hemorrhages into the knee resulted in proliferation of the synoviocytes with inflammatory signs resembling acute synovitis and higher magnification levels in optical microscopy revealed presence of hemosiderin and inflammatory cells. This proliferation of the synovium and neovascularization of the subsynovial layer results in an inflamed, villous, friable and highly vascular synovial tissue.

The specimens from the rabbits injected with oxytetracycline and aetoxysklerol, examined under optic microscopy, showed fibrosis, regeneration of the synovial tissue and controlled repair, with slide enlargement of synovial tissue, less irrigated, and less prone to rebleed in 100% of cases (Fig. 8-11). This demonstrates the efficiency of chemical synoviorthesis with these two substances in the animal subject. Aetoxysklerol appeared to be more efficient than oxytetracycline, with a more pronounced fibrosis in the examined samples.

There were absolutely no local complications in the studied lot of rabbits and as a systemic complication we noted only pain which responded well to analgesic treatment over a short period of time (usually 24-48 hours). The general status of all rabbits was good during the whole period of the experiment.

Other authors have used osmic acid, rifampicine and oxytetracycline for chemical synovectomies in the treatment of patients with hemophilia.

The most commonly used chemicals have been osmic acid and rifampicine. In fact, they have been utilized as an alternative to radioactive agents because of lack of availability or fear of radiation as a potential source of malignancy.

In 1973, Menkes et al. (19) reported their experience with the use of intra-articular osmic acid. Their results were
mixed and this procedure never achieved wide popularity. Caruso, in the 1980’s was one of the first to use rifampicin as a chemical agent for the treatment of synovitis associated with rheumatoid arthritis (20). Rifampicin was chosen for its proteolytic and fibrinolytic properties. Despite encouraging early results there was, however, a high failure rate.

Salis et al.(21) retrospectively reviewed their experience with non-surgical synovectomy in the treatment of recurrent haemarthrosis with arthropathy in patients with von Willebrand's disease, which is the most common inherited bleeding disorder, with an overall prevalence in the general population of 0.8-1.3%. Haemarthrosis occurs mainly in the most severe forms of the disease (type 3), with a frequency of 3.5-11%, and can cause severe arthropathy similar to that seen in haemophilia. Four of six patients had type 3 disease and the remaining two had type 2 disease. The age range was 13-63 years. The frequency of haemarthrosis prior to synovectomy was 1-4 per month. One (n = 2) or both (n = 1) knees were treated in four cases, one (n = 1) or both (n = 1) ankles in three cases and an elbow in one case. $^{18}$Y was used in a dose of 5millicuries (mCi) (or185 mega becquerels (MBq)) for one knee, $^{180}$Re in a dose of 2 mCi (or 74 MBq) for two ankles and the elbow andosmic acid for two knees and one ankle. Clinical and radiological results were evaluated 6 months aftersynovectomy using the World Federation of Haemophilia score. Radiological lesions remained stable and clinical manifestations improved in every case (P < 0.05). Five patients achieved a complete remission. Safety was satisfactory and there were no complications. The clinical efficacy of synovectomy, using radiocolloids or osmic acid in arthropathy caused by von Willebrand's disease, seems similar to that in haemophilia.

Caviglia et al.(22,23) reported that, for many years, rifampicin has been used empirically for the treatment of chronic haemophilicsynovitis with encouraging results. A clinical study was performed on 48 haemophilic patients (48 joints). Seventeen elbows, eight knees and 23 ankles were treated. The mean age of the patients was 6 years (range 4-23 years) and the mean follow-up was 29 months (range 24-53 months). Overall, 40 excellent and eight good results were obtained. The average number of weekly injections of rifampicin was 3.06 (range 1-10 injections). Eight patients experienced pain on the first injection, which subsided gradually with the subsequent procedures.

Synoviorthesis with rifampicin seems to be a good method for the treatment of haemophilicsynovitis, especially in small joints (elbows and ankles) and in younger children.

Fernandez-Palazzi et al. (24) also assessed the effectiveness of intra-articular rifampicin in haemophilic patients. Two hundred and fifty milligrams of rifampicin was injected into the elbow and ankle joints and 500 mg was injected into knee joints with 3-10 ml of lidocaine, depending on the joint size. The injections were repeated once a week for 7 weeks. This paper reports on the results of 38 patients with 39 joints with more than 3 years followup (mean 1.8 years). There were 22 knees, nine elbows and eight ankles. Subjectively, there were excellent results in 21 joints (11 knees, six elbows and four ankles), good results in 15 joints (eight knees, three elbows and four ankles), fair results in two knees and a poor result in one knee. Objectively, results obtained were excellent in 20 joints (11 knees, six elbows and three ankles); good in 17 (nine knees, three elbows and five ankles); fair in one knee and poor in one knee.

Radossi et al.(25) have used intra-articular injections of rifamycin. Among a large cohort of nearly 500 patients, they treated 28 patients during a 2-year period. The patients followed an on-demand replacement therapy programme and developed single or multiple joint chronic synovitis. The indications for synoviorthesis were symptoms of chronic synovitis referred by patients reported in a questionnaire.

In Radossi’s series there were five patients with inhibitors to factor VIII. Their average age was 34 years. Rifamycin (250 mg) was diluted in 10 ml of saline solution and 1–5 ml was then injected into the joint. The follow-up ranged from 6 to 24 months. Thirty-five joints were treated with 169 infiltrations in total. Rifamycin was injected once a week for 5 weeks, that is the patient had to come to hospital at weekly intervals. Twenty-four procedures were considered effective in 19 patients according to the evaluation scale, while six treatments were considered fair to poor. Five patients (six joints) with anti-factor VIII inhibitors were treated. In four joints the results were good, while in the two remaining joints the results were poor.

Oxytetracycline is a broad-spectrum antibiotic, active in both Gram-positive and Gram-negative bacteria, especially filarias and rickettsias. In intravenous injections it was noted that phlebitis developed because of its irritative property. This antibiotic was withdrawn from human use as a result of this irritating action when injected intravenously, and is now only used for veterinarian purposes. This irritating action is what we were searching for, in order to produce fibrosis of the synovial membrane.

Oxytetracycline has been used before on a experimental basis and later during clinical trials by Fernandez-Palazzi et al.(8-11). The authors had excellent results in 32 joints, good in 16 joints, fair in two joints and poor in four (two underwent surgical intervention). In spite of these being early results, they were very satisfactory in the opinion of these authors, especially in relation to pain, diminution of joint diameter and increase of ROM. Patient satisfaction, despite some failures, was above 90%.

Aetoxysklerol has never been used for chemical synovectomy but was chosen because of very good fibrotic properties in the treatment of pediatric hemangiomias and lymphangiomias (personal experience).

Synoviorthesis can be performed at any age in haemophilia patients. Performing an intra-articular injection in a very young child does pose the problem of patient cooperation which may require conscious sedation or even generalanaesthesia. It is possible to perform multiple synoviorthesis in a single session. The other non-invasive alternative to chemical synovectomy would be radiosynovectomy.

There is always a concern about the use of radiosynovectomy, the effects on joint cartilage and the incidence of cancer after this kind of treatment. Jahangier et
al. (26) have found that radiation synovectomy with 90Y for persisting arthritides has harmful effects in vitro on human cartilage that cannot be prevented by co-administration of glucocorticoids. These results urge for a more detailed in vivo evaluation of cartilage changes after radiosynovectomy. Dunn et al. (27) reported about two patients which developed acute lymphocytic leukemia (ALL), one T-cell ALL and one precursor B-cell ALL, within one year of radioactive synovectomy with 32P. There are also new radiocolloids tested. Calegaro et al. (28) reported of the results in the treatment of chronic haemophilic arthropathy with 153-samarium hydroxyapatite (153Sm-HA) in 31 patients with haemophilia.

**Conclusions**

Synoviorthesis should be the first choice of treatment for persistent synovitis of the joints in patients with haemophilia. It is a simple procedure, which eliminates the risks associated with surgery and is also cost-efficient. Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage, which, based on many studies, is irreversible. It can also be used in patients with inhibitors with minimal risk of complications. On average, synoviorthesis has a 75-80% satisfactory outcome in the long term. From the clinical standpoint, such efficacy can be measured by the decrease in the number of haemarthroses, with complete cessation for several years in some cases. Synoviorthesis of any kind is a highly cost-effective method compared to open or arthroscopic synovectomy. One should bear in mind that in 20-25% of cases, synoviorthesis fails to control haemarthroses. In such cases, it can be repeated.

Based on the animal experiment we propose the introduction of chemical synovectomy with oxytetracycline and aetoxysklerol in clinical practices (29). For oxytetracycline we propose injections depending on the affected joint:
- for knees: 250 mg associated with 5 ml anaesthetic
- for elbows: 100 mg associated with 2 ml anaesthetic
- for ankles: 50 mg associated with 1 ml anaesthetic

The dosis may vary depending on the age and body weight of the patient. In small aged patients we also recommend the use of general anesthesia.

The maximum daily dosis of aetoxysklerol we recommend is 2 mg/kg body weight. Due to the fact that aetoxysklerol is also a local anaesthetic we do not recommend the associated use of lidocaine, to prevent secondary reactions. A initial quantity of 1-2 ml of aetoxysklerol 2% can be injected at the level of small joints and 3-4 ml of aetoxysklerol 2% can be injected at the level of large joints. The dosis can be increased to the maximum daily dosis if no secondary reactions appear. Multiple joints can be treated in the same therapeutic session.

Preliminary experimental data show a good efficiency of both oxytetracycline and aetoxysklerol as materials used for chemical synovectomy in rabbits with synovitis of the knees. There are also other advantages of this therapeutic method such as low cost, easy technique, immediate therapeutic effects, short period of treatment and low consumption level of coagulation factor. There is still need for further experimental data gathering and dosage adjusting before optimal use of these substances in the treatment of patients with haemophilia.

**References**


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MESENTERIC INFARCTION AT A TEENAGER
RARE CASE OF ACUTE SURGICAL ABDOMEN IN
PEDIATRIC PATHOLOGY

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Abstract
The mesenteric infarction, named also intestinal infarction, stays one of the world’s severe dramas of acute surgical abdomen. It represents one of the main objectives in the field of clinical and therapeutic investigations due to the dramatic clinical phenomena of the disease and adds a high mortality rate, between 80 and 100. Although the symptoms are known, several elements, including the etiology are difficult to determine both clinical and intra-operative, physio-pathology mechanisms are incompletely elucidated, as events that are common with other abdominal diseases, are major difficulties in establishing a diagnosis of certainty, often delaying proper therapeutic attitude. Intense abdominal pain can be accompanied by collapse, where lean peristaltic contractions, may suggest either a hemorrhagic pancreatitis and other diseases of an acute surgical abdomen. The notion of mesenteric infarction is related to total and sudden interruption of blood flow through the superior mesenteric artery or vein. The mesenteric infarction is a maximum emergency of an acute surgical abdomen due to high diagnostic difficulties that often arises later. Rarely, intestinal-mesenteric infarction may occur in very young subjects which do not suffer from heart or vascular diseases.

Clinic study: As I said the condition is extremely rare in a child or teenager. However I intervened surgically to a girl of 16 years, initially hospitalized in pediatric clinic of the hospital. After hospitalization, the patient had diffuse abdominal pain, mainly in the epigastrium (pain which initially has been like a epigastrium distress, the primary cause being the our-days eating habits), vomiting, malaise. Key words: mesenteric infarction, teenager

Introduction
Mesenteric infarction or intestinal infarction remains one of the world serious dramas of the acute surgical abdomen. Although the symptoms are well known, a series of elements, including the etiology, are hard to predict both clinic and intra-operative; the physiopathology is still not completely elucidated, as well as the clinical manifestations which are a lot like others abdominal diseases; gives a hard time in diagnostic decision making, most of the times delaying the right therapeutic procedure. The very intense abdominal pain which can be accompanied by collapse; muscular contraction without peristaltic wave, can suggest an acute hemorrhagic pancreatitis, volvulus, intestinal occlusion, but also other diseases if an acute surgical abdomen. [1]H. Mondor (1960) stated that “The mesenteric infraction represents one of the hardest diseases to be diagnosed”. [2]The notion of mesenteric infraction is related to the total and suddenly interruption of the blood flow through the superior mesenteric artery or vein. [3] Classic, the mesenteric infraction, the way it is known in the specific literature, presents, intra-operative, a blood infiltration of the intestinal wall, causing a red-violet or a cyanotic coloration of a portion of bowel related area where blood supply has been stopped. [4] Microscopic, in the affected intestinal wall necrosis and hematic infarction are found, lesions that lead to an implacable evolution towards gangrene, perforation and peritonitis. [5]

Short anatomical considerations
Mesentery support certain portions of the small intestine from the abdomen also serves to movement and nutrition of small intestine, [6] inserted of the posterior wall of the abdomen; its root begins at the level of the flexion of the jejuna-duodenum, at the lateral edge of the lumbar spine at the level of L1-L2 vertebrae and ends in the right iliac fossae corresponding to the sacroiliac joint. [7] It divides the lower abdominal floor in two regions: the right mesenteric-colic space (Right colic niche) and left mesenteric-colic space (Left colic niche). The superior pole of the mesentery is situated at the origin of the superior mesentery artery la the level of the flexion of the jejuna-duodenum, and the inferior pole corresponding to the place where the ileocaecal valve will be situated (Fig. 1).

The obstruction of the superior mesentery artery or some branches that detach from it stands first place for mesenteric infarction. [8] It’s the fourth artery that originate from the abdominal aorta, as size (after the inferior diaphragmatic artery, medium supra-renal artery and the celiac trunk). It irrigates the jejuno-ileum, the caecum, the appendix, the descendant and transversal colon, physiologically corresponding to the intestinal segment which main function is to absorb. The superior mesentery artery comes from the abdominal aorta in front of the L1 vertebra and ends in the mesentery latch loop, in the place of implantation of the Meckel diverticulum. At the ending place, in full bowel, It divides into two arteries: a left branch, most voluminous and a right branch.
The physiopathology of mesenteric infraction

The mesenteric infraction is a major emergency of the acute surgical abdomen and due to difficulties the diagnosis is most of the times lately right. Extremely rare, the intestinal mesenteric infraction can appear to young subjects who do not suffer from heart or vascular diseases. [9] There have been cases of thrombocytopenic purpura which have had died through mesenteric infraction. [10] The mesenteric infraction at a child can also appear in some local diseases. [11] There have been such cases in strangled hernia (inguinal or hiatal), abdominal trauma, volvulus, intussusceptions easy to reduce [12] and generally diseases that needed or have exerted alone the trauma of the intestine. [13] It mostly appears to sick people in their second or third age. [14]

The most frequent causes which facilitate mesenteric infraction at an adult can be:

- sufferings of phlebitis or the phlebitis of the inferior vena cava; [15]
- a significant decrease of the arterial pressure, after a complex surgical intervention, when hypovolemia has occurred; [16]
- the Buerger disease; [17]
- in periarteritis nodosa; [18]
- cardiac patients, with arterial fibrillation. [19]

Although it’s not well determined, the intestinal infraction can also occurred due to “visceral apoplexy” [20] (which cannot be ignored) like the vascular spasm and other mechanical factors, [21] eaven though the patient show any vascular lesions. [22] Mainly, the obstruction of intestinal arteries, veins or only capillaries represent the main cause to the occurrence of mesentery infraction. The sickness slowly determines necrosis of one intestinal segment or more intestinal loops, depending on the irrigated segment of the obstructed bowl.

The gravity, spread and evolution of the infraction differs from the ways of the obstructed bowl (artery or vein) and, specially, of its size.

Not all infractions evolve from the begging with gangrene, perforation and peritonitis; there are also clinical forms of evolution through stages, the process unfolding in more than a few days, time in which there can be put a firm diagnosis, therapy being efficient, and survival assured. The disease can be structured in 3 stages:

1. The apoplexy stage – when the dilatation of the capillary begins and shows an interstitial plasmatic exudate, and the affected intestinal loop red, cyanotic, edematiate, the leisure being in this stage irreversible. [23]
2. The true heart – with the loop of the color violet, black, not viable. [24]
3. The gangrene stage – in which the alterations are deep and irreversible, due to parietal vessel thrombosis. [25]

The most frequent mesentery infractions are the ones of arterial origin, in proportion of about 60%, while the vein origin of the disease stands around 35-40% of cases. [26] Judging on the length of the affected intestine, there can be distinguished two forms: the segmentary infraction – the most frequent form, [27] in which the leisure can have a length between a few centimeters to the maximum of 40-50 centimeters. In this form the affected most part is the ileum, also some part of the jejunum and the upward colon and the total or subtotal infraction [28] – which affects all of the irrigated portion of the superior mesenteric artery.

In terms of clinical symptoms, the intestinal infarction caused by the veins is installed less brutal than the one caused by the arteries, only that the differential diagnose between the two forms cannot be made clinical, because both start with a period of digestive discomfort, followed by anorexia, moderate abdominal aches, sometimes vomiting which do not ease the pain. From the moment when the intestinal leisures become irreversible, the symptoms are very noisy.

Clinical, the mesenteric infarction is characterized through the following events:
- abdominal pain of high intensity, generalized, persistent, frequently in the mesogastrium;
- state of shock with tendency of collapse;
- stop of intestinal transit for faeces or gas;
- vomiting.

The X-ray examination, shows the distension of the small intestine which has three specific characterizations:
equal bubbles of gas, 
- air in jejunum, 
- lack of peristaltic, 
at the opening of the peritoneum we can find a infarcted loop very relaxed, whith thick walls, opaque. In the intestinal lumen we can find modified blood and in the peritoneum we can find flowed fluid.

Clinic study

As I have stated the disease is extremely rare in a child or teenager but there are situations with undetermined etiology that lead to the appearance of this disease.

At a such case I stepped in surgically, the patient being 16 years old. She was initially hospitalized in the pediatric clinic. In the description the patient had diffused abdominal pain, found predominant in the epigastrium (which at the beginning have been like a epigastrium distress, the primary cause being the eating in our days), vomiting, malaise.

With approximately 6 months before, the child had another hospitalization for a stomach pain, being labeled now as a new spurt in the same disease as “antroduodenal dyskinesia”.

After hospitalization there have been made minimum paraclinic and laboratory investigations and there has been established a treatment for electrolyte rebalance and pain removal. The results of the investigation were in normal parameters, only a leukocytosis of 17700/mm and a erythrocyte sedimentation rate of 20/hour. The general state of the patient continued to get worse, the pains from the epigastrium have increased in intensity and have slowly placed themselves in the periumbilical area, vomiting became more frequent, and the intestinal transit for gas and faeces was interrupted. The following day after hospitalization the recomandation was a abdominal X-Ray while standing, which showed a important intestinal distention, without seeing the hydroaeric levels. The abdominal ultrasound also showed a significant dilatation of the intestine, visible intestinal plies, absence of peristaltic, and at the bottom of the Douglas bag and the Morrison space, a huge quantity of fluid.

The ultrasound diagnose was a recent intestinal occlusion, with transudate liquid in the peritoneum cavity. At the Gynecological Exam there were discovered clots and menstrual blood inside the vagina, utter and impalpable annexes, put together in a enormous tumor mass. In these conditions, a surgical advice was asked for, from which it was determined that it was a teenager, with asthenic constitution, longilina physical constitution , underweight, with a suffering look, ringed, pale, with the nose wing-beats, placed in a antalgesic antalgic position. On palpation, was observed an abdomen with both spontaneous pain and especially stylus, located in hypogastrum and periombilical, with generalized muscle contracture. Digital rectal exam showed a sficter sphincter with normal tonicity, additional rectal wall, rectal ampoule blank, Douglas bag bulging bottom, painfully. On bimanual palpation was felt a tumor in hypogastric region who occupy the small pelvis, very sensitive. The examination of skins didn't show scarlet elements or petechiae that could prove that it is a thrombocytopenic purpura. For this reason, and beacause of palpation of the hypogastrum of that formations, has been a suspected ovarian cyst torsion, whose symptoms are similar, but also took the discussion a bowel obstruction (the radiography didn't revealed the hidroaeric levels), a nefretica colic, one pancreatitis (pain ought to be in the bar) or a ruptured ectopic pregnancy ((negative gynecological examination).

It was decided, after all examinations, emergency surgery.

It entered on a xifopubiana incision, and on opening the peritoneum poured a significant amount of sero-bloody fluid. In the small pelvis was discovered a cluster of bowel loops, black, non viable, with walls edematiate edema filled with blood clots "heavy" because of the content, and the display of necrotic bowel was found that is the chance that the small intestine which corresponded to a necrotic mezou mesentery , in up, based at the mezostenica mesostenic edge of the bowel and the top by the root of mesentery (Fig. 2).

Necrotic bowel ends were clearly demarcated areas of viable. Necrotic area began in the terminal portion of the jejunum and continues with the ileum to about 20-30 cm by the ileocaecal valve, meaning a segmental bowel infarction. With regard to intestinal necrosis that required resection of non-viable portion was approximately 0.80 to 1 m.
Resection was done in the area viable, above the necrotic portion and even under of the necrotic portion in healthy intestinal. After resection was done anastomosia termino-terminal in a layer, and bowel resection was sent to the pathological examination (Fig.3).

Fig. 3 Snare resection.

Postoperatively, the teenager received electrolyte rebalancing treatment, vitamin-antibiotic therapy, to sustain the general state, diet and protection of the anastomosis. Intestinal gas transit has been resumed at 5 days postoperatively, and the faeces after 7 days. At 11 days postoperatively, the patient was discharged with diet and life tips. On the first postoperative control, patient’s general condition was normal, appetite returned, bowel present. I considered this as a quick adaptation to the small size of the jejuno-ileum, even if the absorption area had decreased.

At about 10 days after discharge, the child readmission, with identical symptoms (vomiting, abdominal pain, intestinal transit stop for gas and faeces), only, at the simple abdominal radiograph, made in standing, is worked out hydroaeric levels, radiographic characteristic of intestinal obstruction. There was surgery and has been found an intestinal obstruction by a bracket, located above the anastomosis which led to suffering. Postoperatively, the evolution was normal and the child was able to be discharged after 14 days. Reviewed periodically for 2 years (first three months every year and next year every 6 months, then she disappeared from the records), the patient didn’t showed "short bowel", its development being normal.

Conclusions
I presented this case rare for pediatricians (surgeons or internists), because is an uncharacteristic affection disease for a child and the specialty literature (pediatric surgery) doesn’t mention it. Just the pediatric books mentioned it as a possible complication of thrombocytopenic purpura. Researching the hospital archive I found only one case of a sick girl of 16 years, known with purpura trombocitopenica thrombocytopenic purpura but it all ended in exitus, diagnosis of mesenteric infarction was made when was made the necropsy.

Particularity of the case is that it appeared at a teenager of 16 years age, which may have contributed to and its constitution (asthenic), and perhaps, and last but not least predisposing land.

This diagnosis should be considered in the differential diagnosis when pediatric surgeon or internist is also facing a serious pain.

References

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COMPLICATED COURSE OF A CROHN’S DISEASE CASE, PRESENTING WITH ABDOMINAL PAIN AND DIAGNOSED WITH ILEAL FISTULA AND ABSCESS

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Abstract
About one fifth of cases with Crohn’s disease (CD) are diagnosed in people less than 18 years. Although most of pediatric patients present with inflammatory behaviour, penetrating CD is increasingly seen. We report a case of an adolescent female, whose main complain was abdominal pain and who was diagnosed with ileal fistula and abscess. Even if surgery was initially planned, she has been treated with steroids and Sulphasalazine. She developed peritonitis and underwent ileo-cecal resection. Shortly after, an ileal fistula developed, requiring the second surgery. After the operation, she was given Sulphasalazine. In our service, she was found with active disease in the remnant ileum. She was switched to Mesalazine and Azathioprine. Currently, 13 months after starting the new therapy, she is in clinical and endoscopic remission. We emphasize the current concepts in managing fistulizing disease and preventing the post-surgical recurrence.

Key words: Crohn’s disease, fistula, surgery, post-surgical recurrence, children

Case report
A 14-year 5-month-old girl, without any significant personal medical history, presented at our hospital in March 2010, with pain, mainly in the epigastrum, rarely also in the right iliac fossa, heartburn, nausea, and poor appetite, for about 5 months. During this period, she has lost approximately 2 kg, mainly due to the appetite loss. Three months before, she had been treated with Omeprazole for 10 days, without any effect. The parents mentioned that she has always been slim. Her mother and grand-father were treated for gastro-duodenal ulcer, in their childhood.

At admission, the physical examination revealed pathologically an adolescent female with cachexia (weight 33 kg, height 152 cm, BMI 13.8 kg/m\(^2\) < p5), pallor and slight tenderness at the abdominal palpation in the epigastric area, without any sign of acute surgical abdomen. She was switched to Mesalazine and Azathioprine. Currently, 13 months after starting the new therapy, she is in clinical and endoscopic remission. We emphasize the current concepts in managing fistulizing disease and preventing the post-surgical recurrence.

Introduction
Crohn’s disease (CD) is diagnosed in about 20% of patients before the age of 18 years\(^1\). Its phenotype is more complicated than in adult-onset CD patients\(^2\) and requires a more aggressive therapy, including surgery\(^3\). Although the inflammatory behaviour (B1) predominates at the onset (68%), the penetrating (B3 – 18%) and strictureing (B2 – 11%) disease is also described in children\(^5\). The cumulative incidence of fistula formation in patients with Crohn’s disease is 17–50% in population-based studies\(^6,8\). We present a case of an adolescent female, whose main complain was abdominal pain and who was diagnosed with ileal fistula and abscess at the disease onset. Since the course of the disease was more complicated during and after the therapy, we emphasize the current concepts in managing fistulizing disease and preventing the post-surgical recurrence.

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Abdominal Doppler hydrosonography showed pathologically: inhomogeneous thickness of the ascendant colonic wall (5.5 cm), with hypervascularisation and a terminal ileum with thickened wall and stenosis on the last 4 cm, (wall thickness of 7 mm), loss of stratification and hypervascularisation. On the ileal area, 3.5 cm from the ileocecal valve, a fistula was identified, which continued with a small hypoechochogenic collection, 1.5 cm in diameter (possible abscess). Lateral from the collection, the appendix was normal. Numerous lymph nodes were identified within this area, up to 14 mm in diameter. A marked suspicion of complicated ileo-colonic Crohn’s disease was raised, but other diagnoses had to be ruled out (intestinal tuberculosis, yersiniosis, anisakiasis). Lower endoscopy was contraindicated. Immunologic panel (including antinuclear antibodies, antiDNA, serum immunoglobulins, pANCA, cANCA, ASCA) was normal. HIV and cytomegalovirus Ig M antibodies were negative. Hemocult test was only slightly positive, without any pathologic infectious agents or dysbiosis in the stool. Tuberculin intradermoreaction was negative, as was the chest X-ray.

A discussion with the adult-patients surgeon concluded on the necessity of surgery. Until the transfer, the girl was given intravenously Ceftazidime, Ciprofloxacine and Metronidazole (the last one not tolerated), associated with probiotics and partial parenteral nutrition. After a slight improvement over the first 2 days, her condition worsened, with insupportable abdominal pain, without any answer to analgesics, total loss of appetite, nausea and vomiting. Transferred to the adult surgery department after 1 week, it was considered that she did not need surgery anymore; the abscess was questioned since she did not experience fever or leukocytosis. She was treated with Prednisone 0.75 mg/kg/day and Sulphasalazine, in the medical section of the adult hospital and after 1 week she was dismissed. Nine days later, she presented to the adult clinic with paroxysmal abdominal pain, nausea, vomiting and marked weight loss (3 kg). Abdominal sonography showed perihepatic fluid collection, liquid collection in Douglas and between the loops, bilateral pleural effusion. An emergency surgery was performed, while the patient’s weight was 27 kg. An inflammatory abscessed lump comprising the terminal ileum, the caecum and the proximal ascendant colon was found. The affected segments were resected (Fig 1) with latero-lateral anastomosis. The pathology report concluded that the microscopic features were consistent with Crohn’s disease.

The post-surgical course of the disease was eventful, with fever and leukocytosis. Ultrasound showed new ileal fistula and right subphrenic abscess, and another surgery was required. After surgery, the abdominal incision became dehiscet 3 times, requiring repeated sutures. To prevent the recurring disease, the girl was treated with Mesalazine for 2 weeks and after, switched to Sulphasalazine. Two months after, in July, she was asymptomatic but returned to our clinic, because of cachexia (weight 34 kg, BMI 13.8 kg/m² << pc 5) and pallor. Laboratory analyses showed only a slight leukopenia (L 3500/mm3), probably as result of Sulphsalazine. Ultrasonography detected a slight inhomogeneous thickness of the terminal ileum, above the anastomosis. We raised the hypothesis of a recurrence or of an incomplete resection of the previously affected area. We decided to use Modulen, in addition to the normal food, as she did not accept exclusive enteral nutrition. Also, we switched the medication to Mesalazine and Imuran (2 mg/kg/day), closely monitoring the hematologic, liver, renal and pancreatic functions. Five months later, the ileal aspect was normal at ultrasonography.

Last follow-up in July 2011 (15 months after the surgery) showed no symptoms, weight of 43 kg, height of 156 cm, with a BMI of 17.7 kg/m² (pc 5-10), normal results of the blood tests, normal hydrosonography and endoscopy with biopsies. She did not develop any severe infection and no side effects related to the therapy.

**Discussions**

Given the complicated presentation and the course of the CD in this child, we consider important to discuss the following points: the optimal management in patients presenting with fistula and abscess, the best post-surgical approach in order to prevent the recurrence and the gold Fig. 1. Macroscopical aspect of the resected area.
standard methods for detecting the relapse.

The current approach in the management of complicated CD states that surgery should be considered for fistulas, abscess and stenosis; an abscess must be drained. Close collaboration between gastroenterologists and a surgeon experienced in pediatric inflammatory bowel disease (IBD) is essential, as stated in the literature. In our region, given the relatively recent emergence of the childhood-IBD, pediatric surgical experience is rather limited. This is the reason why we usually resolve our cases with adult-patient surgeons. Maybe fever and leukocytosis are required to diagnose an abscess in adults; however, in children its signs may be rather atypical. Not considering that this child had an abscess ended up in treating her with steroids. According to the current guidelines, glucocorticoids are not an effective treatment for fistulas in patients with CD. Moreover, studies showed that patients with CD who received prednisolone for the treatment of fistulas had a more deleterious outcome than patients not receiving steroids. It is possible that, in our case, steroid treatment and the absence of the abscess drainage favored the peritonitis. Giving the poor nutritional state of this patient, a fistula developed after the first surgery and the wound healing was problematic as well.

Approximately 75% of patients with CD will eventually undergo surgery. Unfortunately, surgery for CD is not curative. Recurrence of disease following a primary resection for CD is a common phenomenon. Approximately 30% of patients who require surgery for CD will experience symptomatic recurrence within 3 years, and as high as 60%, within 10 years, in the absence of prophylactic therapy. Endoscopic recurrence is more common than symptomatic relapse, approaching 90% one year after surgery. Early recurrence of symptoms is particularly undesirable in adolescents, as prolonged disease activity in this patient group can lead to significant morbidity and permanent stunting (education, socialization and particularly growth). Currently, there are reports of pediatric surgery for ileocecal resection performed for fistula and abscess and/or stenosis, either classically, by laparotomy, or by laparoscopy, with the latter having the best outcomes (reducing complications from adhesions). Some retrospective data in adults suggests that laparoscopic techniques may reduce the need for further surgery to < 10% in patients having a laparoscopic ileo-cecal resection. There are still only very limited reports of laparoscopic resections in children with CD. A very recent study on 30 children has shown that laparoscopic ileocectomy, both single-incision laparoscopic approach and standard laparoscopy, is safe and effective.

How to prevent the recurrence? There are no formal guidelines for the prevention of postoperative CD. A recent Cochrane review (until February 2009) has shown that probiotics, corticosteroids (systemic and rapidly metabolized steroids - like Budesonide) are probably of little benefit in preventing postoperative recurrence. Budesonide could have been efficacious to heal the active ileal inflammation, but not in this patient with cachexia and wound healing troubles. A systematic review and meta-analysis of all randomized controlled trials conducted until April 2010 in adults with luminal CD in remission after a surgical resection showed that Sulphasalazine was of no benefit in preventing relapse in 448 patients. Mesalazine compounds are of modest benefit, but they are widely used, given their safety profile, as it was proved in a recent meta-analysis. The agents of choice, according to the ECCO Consensus, are currently the thiopurines, even if they are not ideal in preventing the relapse and have important side effects. A recent meta-analysis found puromycin analogs to be more effective than either placebo or mesalazine in preventing 1-year clinical recurrence and severe endoscopic recurrence, although the numbers needed to treat were 13 and 7, respectively. In a recent Cochrane review (until February 2009), the use of nitroimidazole antibiotics appeared to reduce the risk of clinical and endoscopic recurrence relative to placebo. However, these agents were associated with higher risk of serious adverse events. We could not use Metronidazole in our patient, since it was not tolerated. The experience with Infliximab (IFX) is very limited; however excellent results have recently been published. The endoscopic recurrence with IFX 1-year after surgery was 9% vs 84.6% with placebo. In another study, a dose of 3 mg/kg of IFX, every 8 weeks, was sufficient to avoid disease recurrence, determined by endoscopy, in all patients at 1 year.

Which patients require therapy? According to the recent ECCO Consensus, there are predictors of early postoperative recurrence after ileocolonic resection: smoking, prior intestinal surgery, penetrating disease behavior (as in our patient), perianal location and extensive small bowel resection. Other risk factors have also been associated: early age at initial surgery, short duration of disease prior to initial surgery, both ileal and colonic disease distribution, use of corticosteroids prior to surgery, all being found in our patient. Moreover, Swoger et al classified the risk of recurrence according to the risk factors. A very low risk of recurrence is considered in those with a longstanding history of CD (> 10 years) who come to their first surgery for a short stricture (< 10 cm). No maintenance medication may be necessary in these patients. A low-to-moderate risk of disease recurrence appears in those naive to immunomodulators with less than 10 years of disease duration, a long stricture (>10 cm), or significant inflammation. In this category of patients, the authors suggest thiopurines, with or without a 3-month course of Metronidazole. The high risk for recurrence include penetrating disease (e.g., abscess, perforation or internal fistula), smokers, patients with a prior surgery for Crohn’s disease, and those who progressed to surgery despite treatment with an immuno-modulator. In these patients, an anti-TNF agent within 2–4 weeks of surgery should be started. With all these data, our choice was to use Mesalazine in association with Azathioprine. However, in our patient we had to do more than prevent the recurrence of the disease, since the disease was already active in the terminal ileum, whatever it was - early recurrence or incomplete resection. We had first to induce the remission and after to maintain it. Our main concern was the
impossibility of dosing the thiopurine methyltransferase activity or the levels of the metabolites 6-thioguanine and 6-methylmercaptopurine, in order to ensure maximal benefit, with minimal toxicity. However, considering the results of the new studies and our patient having a high risk of recurrence, it is possible that IFX therapy could be required.

How to assess the recurrence? The relapse of the disease should not be assessed by clinical signs or biological markers. According to the recent ECCO consensus,[10] ileocolonoscopy is the gold standard in the diagnosis of post-operative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course (by the Rutgeerts’s score[13]). Ileocolonoscopy is recommended within the first year after surgery, where treatment decisions may be affected. Trans-abdominal ultrasound, magnetic resonance enterography, small bowel capsule endoscopy are less invasive diagnostic methods, emerging as alternative tools for identifying post-operative recurrence[16]. Endoscopic findings that indicate recurrence include small aphthous ulcers, deep linear ulcers, mucosal inflammation, fistulae, and strictures. These varying degrees of endoscopic disease activity may be seen within 3 months of surgery in more than 70% of patients. The most common site of recurrence is the surgical anastomosis, especially the proximal side of the anastomosis[14]. In low- and moderate-risk-factor patients, if there is no endoscopic recurrence, some authors do not modify the previous regimen, and repeat a colonoscopy 1–3 years later[6]. If there is evidence of early endoscopic recurrence, they recommend an immunomodulator or anti-TNF agent. In high-risk patients, if there is significant endoscopic recurrence, they check anti-TNF antibodies and serum trough levels and escalate anti-TNF dosing when appropriate and/or add an immunomodulator. In our patient, whatever caused the active inflammation in the remnant ileum (incomplete resection or recurrence), the absence of relapse was demonstrated by abdominal ultrasound and endoscopies with biopsies.

In conclusion, we have presented a CD case, with a severe complicated onset, contrasting with the paucity of symptoms and blood tests results. The course of the disease was also complicated during the medical and surgical therapy. The presence of poor prognostic factors requires a close follow-up of this patient, given the impossibility of a post-surgical optimum therapy and monitoring. We emphasize the necessity of knowing the current management of CD, before taking major therapeutic decisions and also the importance of a close collaboration between the gastroenterologists and surgeons specialized in IBD.

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