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CONTENTS

A 10-YEAR FOLLOW-UP OF ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS IN A REGIONAL PEDIATRIC HEMATOLOGY CENTER FROM ROMANIA

A Horvath[1], Maria Despina Baghiu[1], Z Pavai[2], Mihaela Chincesan[1], Alina Grama[1]

Abstract

Introduction: Childhood ALL is not a single disease, but a group of diseases with a variety of genetic and molecular abnormalities in the leukemic cells leading to a wide range of clinical presentations and outcomes. Histochemistry, immunophenotyping, cytogenetics and molecular biology of the blast cells are able to identify different types of ALL. The aim of the paper is to present the improvements made in the diagnosis and risk stratification of the patients as well as the analysis of survival correlated to a number of risk factors.

Material and methods: We studied 59 ALL patients diagnosed between 2001 January – 2010 December, treated in the Haematology Department of the Pediatric Clinic nr. 1 from Targu-Mures. We studied age, gender, white blood cell (WBC) count at diagnosis, absolute lymphoblast count (AlyC) on the 8th day of treatment, blast immunophenotype, BCR-ABL gene expression with qRT-PCR analysis, early treatment response, CNS involvement, relapses and survival. Descriptive analysis, chi-square test, Kaplan- Meier survival curves were performed.

Results: Out of the 59 ALL patients, four were diagnosed before 2 years of age (7%), 34 were between 2-6 years (58%) and 21 were older than 6 years (35%). 36 patients were boys and 23 girls (ratio 1,6:1). WBC count at diagnosis varied between 1.300-770.000/mm^3. Fifteen patients (25%) presented CNS involvement at diagnosis. Pre-B lymphoblasts were noticed in 35 patients, T cell in 9 and mature B cell in 2 patients. Early corticosteroid therapy failure was noticed in 11 children and 3 patients had M2 type BM on day 33. BCR-ABL gene expression was searched in 29 BM samples with 3 positive results. Overall survival after a mean of 41 months was 75%. Survival was strongly influenced by blast immunophenotype (mean survival of 84 months in pre-B ALL, 67 months in T cell ALL and 2 months in mature B cell ALL), early induction failure, CNS involvement at diagnosis (47 versus 104 months) and relapses (29% versus 81%).

Conclusions: 1.During 2001-2010 we diagnosed and treated 59 children with ALL, the overall survival at a medium of 41 months was 75%. 2. We performed blast immunophenotyping in 46 patients and BCR-ABL gene expression assessment with qRT-PCR method in 29 patients with 3 positive results. 3. Statistically significant unfavourable prognostic factors were the mature B immunophenotype, early induction failure, CNS involvement at diagnosis and relapses.

Key words: children, leukemia, risk factors, survival

Introduction

Acute lymphoblastic leukemia (ALL) is a clonal expansion and maturation arrest of lymphoid hematopoiesis, which accounts for 25-30% of childhood cancers. The hallmark of diagnosis in ALL is the lymphoblast in the BM. Histochemistry, immunophenotyping, cytogenetics and molecular biology of the blast cells are able to identify different types of ALL. Age, gender, white blood cell (WBC) count, cytogenetics, immunophenotype and molecular characteristics of the blast cells, central nervous system (CNS) disease, early response to corticosteroid therapy, bone marrow (BM) response to chemotherapy on the 15th and 33rd days, are the basic prognostic factors in ALL. The presence of two specific genetic translocations, the t(9;22) (q34;q11) and the t(4;11) (q21;q23) or their corresponding molecular alterations, the BCR-ABL and MLL-AF4 gene rearrangements indicate a very high malignity.

The aim of the paper is to present the improvements made in the diagnosis and risk stratification of the patients as well as the analysis of survival correlated to a number of risk factors.

Material and methods

We studied 59 ALL patients diagnosed between 2001 January – 2010 December, treated in the Haematology Department of the Pediatric Clinic nr. 1 from Targu-Mures with the ALL-BFM 95 protocol. The studied criteria were the date of onset, age, gender, white blood cell (WBC) count at diagnosis, absolute lymphoblast count (AlyC) on the 8th day of treatment, immunophenotype of lymphoblasts, minor and major BCR-ABL gene expression from bone marrow (BM), the improvement of BM on the 15th and 33th days of treatment, CNS involvement at diagnosis, relapses and survival.

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The real-time PCR method for BCR-ABL gene rearrangement detection was introduced in 2010. BM samples were obtained from the anterior or posterior iliac crista, after previous sedation with 0,1 mg/kg intravenous midazolam and local anaesthesia with 1% lidocain. We collected 2 x 2 ml bone marrow in EDTA tubes for molecular testing and immunophenotyping, and 6-8 smears for morphology. Quantitative RT-PCR analysis was performed in the Molecular Biology Laboratory of our university: RNA extraction was performed using QIAmp RNA Blood Mini Kit 50 (QIAGEN cat.no. 52304) and cDNA transcription with High Capacity cDNA Reverse Transcription Kit (Applied Biosystems cat.no 4374966) according to the supplier's instructions. We studied the b3-a2 and b2-a2 BCR/ABL fusion gene using the primers and protocols recommended by the Europe Against Cancer Program[1]. The RQ-PCR reaction was performed on an ABI 7500 Real Time PCR instrument (Applied Biosystem), using 5 µlcDNA and TaqMan ® Universal PCR Master Mix (Applied Biosystem) in 25 µl end volum. All reactions were made in triplicate. The ABL gene was used as endogenous control and also were used known positive and negative control samples. We performed relative quantification. Data were statistically processed with descriptive analysis, chi-square, Log Rank test and Kaplan- Meier survival curves.

Results

Among the 59 ALL patients diagnosed between January 2001- December 2010, four patients were diagnosed before 2 years of age (7%), 34 were between 2-6 years (58%) and 21 were older than 6 years (35%). We assessed a male predominance: 36 patients were boys and 23 girls (ratio 1,6:1). WBC count at diagnosis varied between 1.300-770.000/mm^3, with an average of 61.140/mm^3 and median of 40.480/mm^3. Twenty nine patients had an initial WBC count below 20.000/mm^3 and 30 above this number. Fifteen patients (25%) presented CNS involvement at diagnosis. After 7 days of corticosteroid therapy, the absolute peripheral lymphoblast count exceeded 1000/mm^3 in 11 patients. Immunophenotyping of marrow lymphoblasts revealed pre-B type in 35 patients, T cell in 9 and mature B cell in 2 patients. On day 15 of chemotherapy, 27 patients had an M1 type marrow (under 5% blasts), 18 had M2 type BM (5-25% blasts) and 9 patients had M3 type BM with more than 25% lymphoblasts. On day 33 of treatment 51 patients had M1 type (86%) and 3 patients M2 type of BM (5%), 5 cases (9%) were missing because of early death. Major and minor BCR-ABL gene expressions were assessed with quantitative real-time PCR method from BM and peripheral blood in 29 patients, out of which 3 results were positive. Based on these criteria, 63% of patients were included in medium malignity and 37% in high risk group. Overall survival after a follow-up of 0-122 months (mean 41,08 months) was 75,9%. (table 1. Figure 1.)

The median survival time was 102 months. The outcome of the 3 patients with BCR-ABL gene expression differed grossly according to treatment options: one patient who was treated with intensive chemotherapy and continuous tyrosine kinase inhibitor is being in first complete remission now for 6 years, the second patient underwent allogeneic stem cell tranplantation in first remission but died after 7 months from the transplantation in systemic herpes infection and the third patient died in early infectious complication.

Table 1. Outcome of childhood ALL (2001-2010).

	Males	Females	Total
Alive	25	19	44
Deceased	10 (28,6%)	4 (17,4%)	14
Total	35	23	58
Missing		1	59

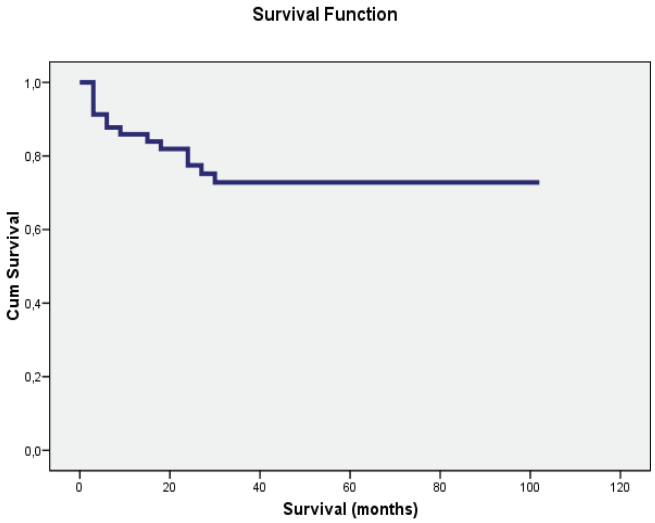

Figure 1. Overall survival in ALL patients during 2001-2010

We lost 14 patients (24,1% mortality) after a mean of 10,4 months and median of 6,5 months of treatment, the longest survival in this goup was 28 months. The causes of deaths were relapses in 6 cases, abandon of treatment in 2 patients, infections (3 patients), tumor lysis syndrome (2 patients) and cerebral inclavation in one patient. Ten boys died out of 35 and 4 girls out of 17. The mean survival in males was 86,7 months and in females 87,4 months, the difference is not significant (p=0,369). Survival correlated to risk groups showed significant difference (Log rank test: p< 0,001): in MR ALL survival was 108 months, while in HR ALL survival was significantly shorter, 55,6 months, as shown in Figure 3. Immunophenotype of the lymphoblast was a strong predictor for survival, in common B ALL the mean survival was 84 months, in T cell ALL 67 months and in mature B cell ALL 2 months (Figure 4). If only pre-B and T cell ALL are compared in respect for survival, the difference is not significant (Figure 5).CNS involvement at diagnosis halved the estimated survival (47 versus 104 months). (Figure 6). BM status at day 15 of treatment was a strong predictor of survival, however, the result was not significant because of the small number of cases in the M3 group. (Figure 7).

Patients with M1 type BM on day 33 had an average survival of 100 months, compared to patients with M2 type BM whose survival was 4-fold lower (25 months). (Figure 8). In the M2 group there were 3 patients, two of them died after 2 years.

Patients who relapsed had a significantly lower survival (Log Rank p=0,011). (Figure 9).

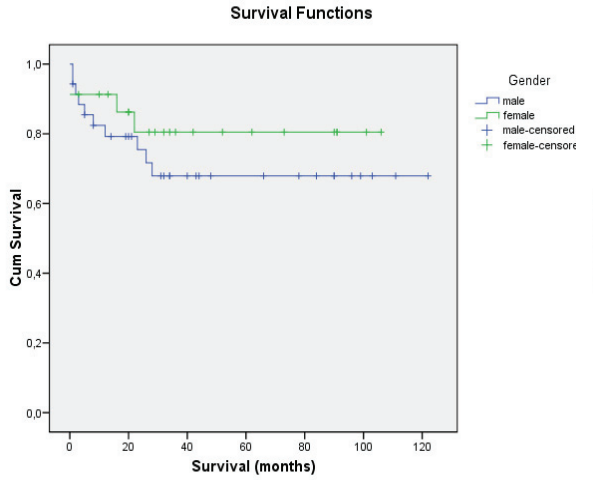

Figure 2. Mean survival according to gender (p=0,369)

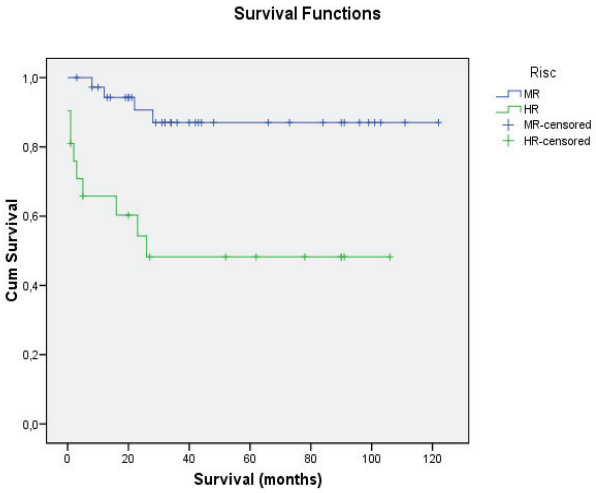

Figure 3. Survival correlated with risk groups (p< 0,001)

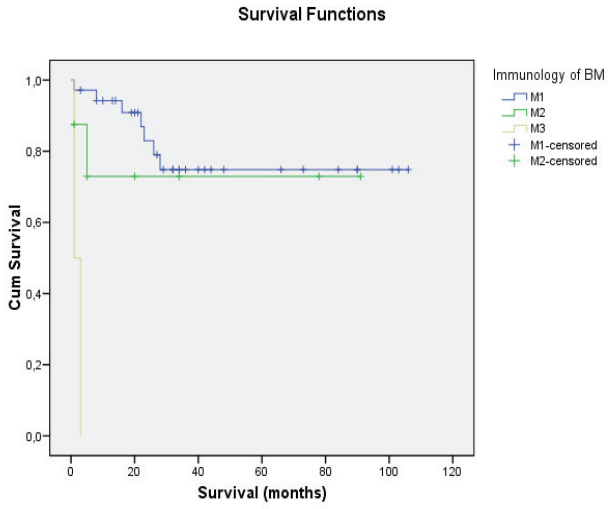

Figure 4. Survival according to blast immunophenotype (M1=pre-B, M2=Tcell, M3=mature B cell)

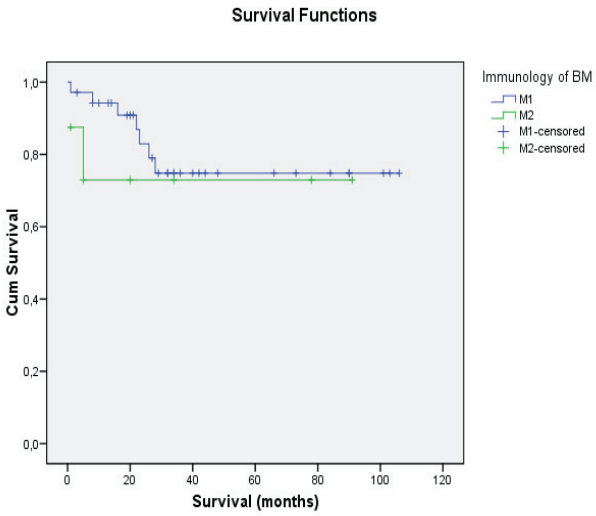

Figure 5. Survival in pre-B and T cell ALL (M1=pre-B, M2=T cell ALL)

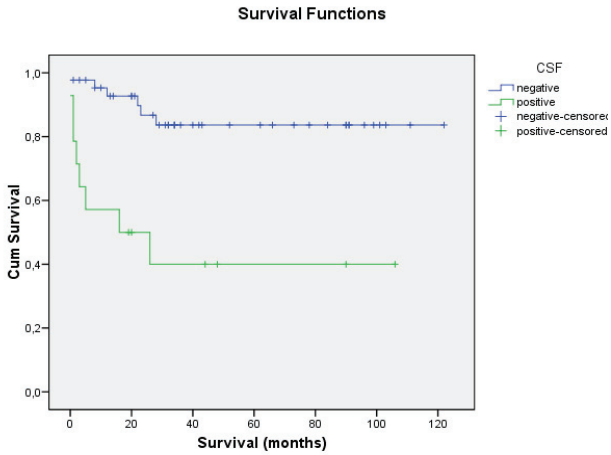

Figure 6. Survival according to CNS involvement.

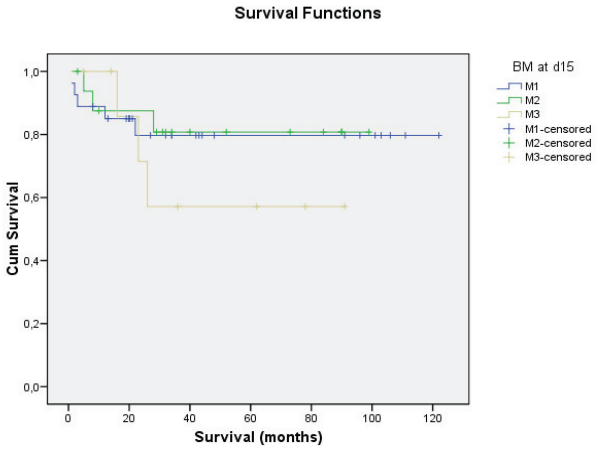

Figure 7. Survival according to bone marrow status on day 15.

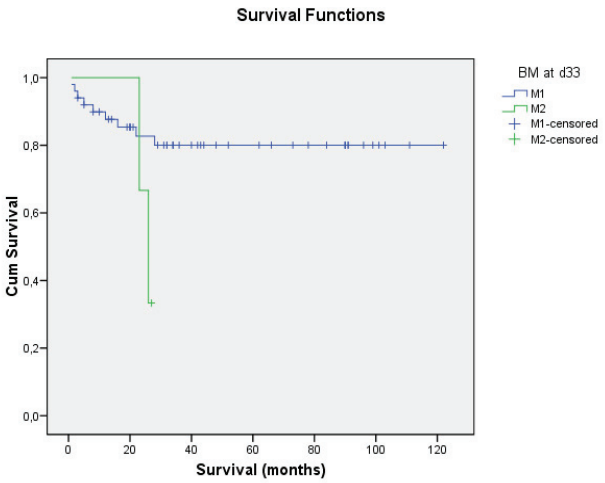

Figure 8. Survival according to bone marrow status on day 33.

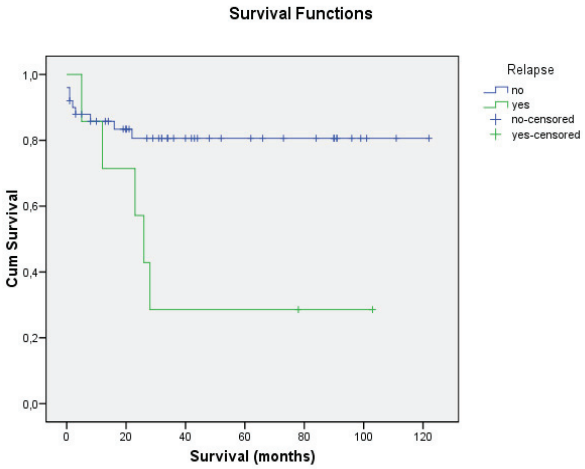

Figure 9. Survival according to relapse (p=0,011).

Discussion

Recently long term survival in childhood ALL is achieved in 80-85% of the patients but the remaining 15-20% can not be cured with current therapies. That is the reason why research is conducted towards identification of more precise risk factors and individualized, targeted therapies [2]. In a large study conducted between 1991-1995 in Japan, the estimated 7-year overall survival rate (OS) and event free survival (EFS) in ALL was 76% and 61,4% respectively [3]. In our study, the OS at 41 months was 75%.

Age younger than 1 and older than 10 years and male gender are unfavourable prognostic factors in childhood leukemia [4].

High WBC count at presentation, usually over 50.000/mm^3 and especially when associated with pre-B immunophenotype, predicts a poor outcome [4].

Blast immunology is an important prognostic feature. Approximately 80-85% of ALL in children are of B lineage and 10-15% of T cell lineage, in 15-30% of cases they coexpress myeloid markers. B cell lineage diagnosed by CD19, CD22, CD79a positivity, is stratified into 4 subgroups: pro-B with no expansion of other B-lineage antigen, common ALL with CD10 positivity, pre-B which has intracytoplasmatic IgM and mature-B which contains cytoplasmatic or surface kappa or lambda. A poor prognostic impact is seen in T-cell ALL, which is less sensitive to methotrexate treatment, caused by its modified metabolism. The mature B cell lymphoblast has a very high rate of proliferation and dismal prognosis. Mixed lineage

leukemias are difficult to diagnose, scoring systems have been developed for better assessment [5,6].

Genetic abnormalities like translocation t(12;21) corresponding to TEL-AML1 fusion gene or hyperdiploidy with 51-65 chromosomes and DNA index above 1,16 are signs for good prognosis. These features are ferquently associated with age between 1-10 years, low presenting WBC count and good response to treatment. Other abnormalities like hypodiploidy (less than 44 chromosomes), MLL gene rearrangements on chromosome 11q23 [(especially t(4;11)], the Philadelphia chromosome [translocation t(9;22)], are associated with poor prognosis, when intensive chemotherapy, allogeneic bone marrow transplantation in the first remission, tyrosine kinase inhibitors may ameliorate the outcome. [4]. In our study we had the possibility to check BCR-ABL gene expression by qRT-PCR in 29 patients with 3 positive results, but could not determine the MLL-AF4 gene expressions because of financial reasons, however the marrow DNA samples are preserved for future examinations.

Early good response to treatment, defined as absolute lymphoblast count in the peripheral blood below 1000/mm^3 after 7 days of corticotherapy, reducing the lymphoblast count below 5% in the bone marrow on day 15 and 33 of treatment, indicates good prognosis. In the french FRALLE-93 study (1993-1999), 3,8% of all ALL patients failed to achieve remission after induction therapy, which greatly affected the 5-year OS of this group, hardly reaching 30% compared to 90% in the group with complete remission. [7]. In our study, early good response to treatment, age, leukemic cell burden at diagnosis and immunophenotyping were used in risk stratification. Similar to the results obtained by the french study, however on a much smaller number of patients, we found a statistically significant difference in survival according to risk groups: in MR group median survival was 108 months (90%) and in the HR group 55 months (45,83%). A nationwide finnish study performed two decades earlier (1989-91), noticed an OS of 76% in SR group and 64% in the merged MR and HR group. [5]. In the same finnish study, 5-year EFS was 78% in the group of patients who achieved M1 bone marrow on day 15 of treatment and only 62% in the group with M2 or M3 BM type. BM status on day 15 and 33 were also significant prognostic factors in our patients, M2 type BM on day 33 lowered fourfold the OS.

Survival rate in cases with relapses was significantly lower compared to patients who did not experience relapses (29% versus 81%).

CNS involvement at diagnosis, as well as traumatic lumbar puncture raises the probability of CNS relapse and lowers the chance of survival (3). This relationship was relevant in our patients, we noticed a reduction of survival to 40% in patients with CNS involvement, compared to OS above 80% in cases when CNS was free from leukemic infiltrates.

Submicroscopic levels of the disease or minimal residual disease (MRD) can be detected by PCR analysis, targeting lymphoblast-specific immunoglobulin or T-cell receptor gene rearrangements or chromosomal translocations in the range of 1/100.000 cells. End-induction MRD is an independent, important predictor of outcome in children with ALL [8].

Conclusions

1. During 2001-2010 we diagnosed and treated 59 children with ALL, the overall survival at a medium of 41 months was 75%.
2. Our diagnostic tools have developed so that we can perform blast immunophenotyping for every patient and minor and major BCR-ABL gene expression assessment with quantitative real-time PCR technique from bone marrow from 2010 on. MLL-AF4 determination has not yet been introduced. Molecular analysis is highly important for accurate risk stratification.
3. Statistically significant unfavourable prognostic factors were blast mature B immunophenotype, early induction failure, CNS involvement at diagnosis and relapses.
4. We did not find significant difference in survival between the pre-B and T cell immunophenotype groups.

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CASE OF SEVERE SEPSIS OF BILIOUS ORIGIN

Laura Marinău[1], Polixenia Stancu[1], Ileana Petrescu[1], Carmen Niculescu[1]

Summary

In most cases, sepsis in children appears as a complication of a respiratory infection, especially viral and bacterial pneumonia. It can occur in setting of other infections: endocarditis, osteomyelitis, appendicitis, artrtitis, celulitis. Sepsis is exceptionally of biliary etiology, as a complication of lithiasis; gallstones are rarely described in children.

Severe sepsis was defined as sepsis associated with at least one acute organ dysfunction. The authors report the case of a patient 14 years and 8 months age, diagnosed with gallstones and sepsis with acute cholecystitis starting point. Medical history noted a family predisposition to gallstones and obesity, and improper diet. Onset of disease was through food and bilious vomiting, severe dehydration, fever, colicky abdominal pain, especially right upper quadrant. Laboratory analysis showed leukocytosis, increased ALT and AST levels four times of normal, and ultrasound revealed the presence of numerous gallstones. After hydric reballancing and treatment with antibiotics, the medical healing of cholecystitis, followed by removal of the gallbladder surgical cure, accomplished with success.

Conclusion: It was a severe sepsis score 4, which required medical treatment and surgery. After 2 years and 4 months after the intervention, teenage feels great, has not accused any epigastric pain.

Key-words: sepsis, gallstones.

Introduction

Severe sepsis was defined as sepsis associated with at least one acute organ dysfunction.

Diagnosis of infectious SIRS (sepsis) is put on record the condition of infection and the following criteria (1;2; 3) of which is sufficient presence of at least two:

- Fever: rectal temperature of at least 38.4 Celsius or hypotermia under 36,4 degrees C.
- Tachypnea: an amount twice the average age of the child, when it was measured, a value Pco2 <32 mmHg was considered objective evidence of tachypnea (33). Type gasping breath, the need intubation and mechanical ventilation is also a criterion for SIRS (4).
- Tachycardia: value > 2SD from the average age, in the absence of MCC, chronic heart failure or sympathomimetic medications (4).
- Leukocytosis > 12000/mmc or an increase of over 10% of young forms in LF or leukopenia <4000/mmc (5).

Since tachycardia and tachypnea are common symptoms of many pediatric diseases, the main difference in the diagnosis of SIRS in children compared to adults is mandatory changes in temperature and / or leukocytes. In pediatric, SIRS can not only diagnose on the heart rate and breathing (6, 7).

Case report

Introducing BC girl patient, aged 14 years and 8 months, was admitted to the Pediatric Clinic from 11 to 19 December 2008 (the no: 64509).

Grounds admission: food and bilious vomiting incoercible, colicky abdominal pain and fever. The family history-collateral remember that girl's father has suffered of diabetes mellitus type II, and her mother was without gallbladder from the age of 37 years. Maternal grandmother died from pancreatic head cancer.

The patient has a healthy sister and two brothers.

History remembers from the patient's eating habits, propensity to consume animal fat in fried food and soft drinks like Pepsi-Cola, as a personal history of pathological mind a hospitalization at the age of 2 years and 4 months for erythema nodosum.

On physical examination at admission, noted: Height = 161 cm, Weight = 65 kg, malaise, ringed face; drowsiness, pale skin with reduced elasticity; dry mucous membranes; tongue aloin, "adherenced" of spatula; panicle fat surplus; normal respiratory relations; HR = 118 b/ min, sinus rhythm; congested oropharynx with hypertrophic tonsils; intense abdominal pain in epigastrium at palpation of the deep "in the bar" and in right upper quadrant; the liver with the lower limit at one cm below last coast; mictions rare, small quantity of urine, intense coloured; state of marked weakness. Patient had presented the first day of hospitalization, one green bilious vomiting, respectively yellow heavy, the second; continued to accuse colicky abdominal pain. From the second until the seventh day of hospitalization, he presented twice fever 38 to 38 and four degrees Celsius, nausea, loss of appetite. Laboratory investigations (findings):

On the first day of hospitalization, surgical consultation had the result: "Current is not acute surgical abdomen. Ulcerous dyspepsia".

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ECHO abdominal and pelvic in 15 XII 2008:
"Liver with left lobe = 6 cm, right lobe = 11, 5 cm, homogeneous structure. Hyperechougenous gallbladder shows multiple images of 3-4 mm, latch located rear and left obscurity - suggestive of gallstones. Hyperechougenous gallbladder walls, thickness of four mm, main bilious channel = 3 mm, 11 mm PV, VS = 5 mm. hyperechougenous. Pancreas diffuse, homogeneous, 1.8 cm mediumsize of the body and 1 cm diameter of head. Left kidney = 11.2 cm, PI = 25 mm, expansion, without stones, right kidney = 17 cm long axis, net shape and regular PI = 22 mm, dilatation without stones. Spleen: 9 / 3/ 7 cm homogeneous, without dilated veins. Uterus intermediate position 5, 6 / 3, 3 / 4 cm homogeneous structure. Both normal-sized ovaries, without cystic formations; peritoneal cavity drained".

The second echo in 19 XII 2008 confirmed gallstones:
"Liver with homogeneous structure LL = 55 mm. Additional gallbladder wall, has got deposits of microstones (3-4 mm). PBC, VP of normal diameter. Pancreas increased: 26 mm AP, hypoechougenous body, contours deleted. Kidneys are normal. Normal uterus, no ovarie's cystic formations. There is fluid in the peritoneal cavity".

Abdominal X-ray in 11-XII- 2008: "Without airhydrous levels.

H-L + LF: first count of leukocytes in emergency:
- 11 XII: WBC = 17000/mmc, Hb = 80%;
- 15 XII: WBC= 15000/mmc, PMN = 66%, Hb = 12.52 g / dl, Platelets = 160000/mmc;
- 11 XII: ALT = 140 / l, AST = 149 / l, urea = 29 mg%, creatinine = 0.73 mg%.

Repeat the next day- in 12 XII: ALT= 84 u / l, AST = 30 U / l, BBt= 1.09 mg / dl, TQ = 100 sec;

Ex urine: acid pH, albumin fine traces, Ubg-normal; bile pigments = absent, ASO = 600UI/l, fibrinogen = 320 mg / dl.

Treatment

It was necessary to rebalance fluids by vein infusion the first two days, then treatment of gastritis and gallbladder infection. Were given antibiotics: Ampicillin four days, then Penicillin and Sulperazon 5 days. 4 days was given: Controloc, Helicid, Metoclopramide necessary, Algocalmin (Metamizolum natricum).

Evolution

Evolution was favorable, she has got no fever anymore, abdominal pain has finished. She was transferred to the surgical service where she suffered laparoscopic gallbladder extraction. It was performed successfully, with discharge after two days.

Disscution

In most cases, sepsis in children appears as a complication of a respiratory infection, especially viral and bacterial pneumonia.

It can occur in setting of other infections: endocarditis, osteomyelitis, appendicitis, artrtitis, celulitis. Sepsis is exceptionally of biliary etiology, as a complication of lithiasis.

Gallstone disease is not commonly encountered in children. Meets, however, the overweight adolescents (fig. 1), sedentary, with unhealthy diet, in part this risk group included the patient described. In addition, it also had a family history, being overweight father and mother with gallstones, surgically resolved. The diagnosis of sepsis could be established in the presence of fever and leukocytosis, acute cholecystitis as the initial infection.

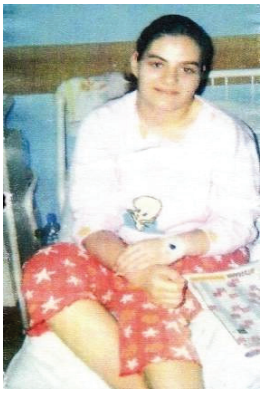

Fig. 1 The overweight adolescents with gallstone disease.

With the exception of certain pediatric-specific diagnostic criteria for sepsis introduced in the 2001 Consensus Conference report, little consensus exists in the literature for the definition of pediatric severe sepsis.

Complicated sepsis score was performed starting from Levy and all. (8), Angelescu N.(9), Munford R.(10) and others authors(11, 12, 13, 14, 15):

Clinical criteria-score

Coma I degree, vigilante: 1p.
Coma gr. II, average: 2 p.
Coma gr. III, deep: 3 p
Capillary refill time > 3s and/or "mottled", low BP <1h: 1 p.
Capillary refill time (CRT) > 3s and/or "mottled", low BP > 1h: 2 p.
Hepatosplenomegaly: 0.5 p.
Dynamic ileus: 1 p.
Hemorrhagic purpura: 1 p.
Laboratory Criteria -score
100000/mmc > Plt > 20000/mmc: 1 p.
Platelets <20000/mmc: 2 p.

80% <satO2 <85%: 1 p.
Oxygen saturation < 80%, pO2 < 49mmHg: 2 p.
Lactic acidosis, pH between 7.2 and 7.35 p.
Severe acidosis pH <7.2 2 p.
ALT> 2SD or/ Bbt> 4mg/dl: 1p.
CRP > 2SD: 1p.
moderated nitrogen retention =1p
marked nitrogen retention = 2p
Glucose > 120mg/dl, transient = 1p.
Hb <7.5 g / dl: 1p.

According this score, severe sepsis has been calculated from 4 points.

Passenger increased transaminases (4 times higher than normal values), calls for severe sepsis triggered by a gall infection, recommended, as liver ultrasound, the calculate of Bbt, excluded the diagnosis of acute or chronic hepatitis. Ultrasound suggested a pancreatic involvement, but was merely a reactive inflammation of this organ, probably triggered by the migration of a gall mycrostone. Amylasemia (harvested on December 18) was 32 units per liter. Given the family history (father ill of diabetes mellitus and grandmother died in pancreatic cancer), the patient may pose a pancreatic sensitivity but glucose were collected in the normal range. At one month after surgery, the patient was clinically healthy, just sometimes accusing postprandial gastric discomfort, but did not comply with recommended diet.

Conclusion

It was a severe sepsis gallbladder origin, with 4 points score, resolved after 14 days of antibiotics (in Surgery Clinic followed Sulperazon another 5 days) and surgical excluded of gallbladder. After surgical intervention, prognosis is excellent. Two years after disease, the teenager never accused anything, nor presented anymore gastrointestinal infection.

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LONGITUDINAL CHANGES OF DENTAL ARCHES IN GROWING CHILDREN

Ana Emilia Ogodescu[1], Anca Tudor[3], Kinga Szabo[2], Camelia Daescu[4], Elisabeta Bratu[1], Alexandru Ogodescu[1]

Abstract

Dental arch changes are important in the diagnosis, treatment planning and long term stability in dentistry. Our aim was to develop a specific methodology and to train in analyzing the changes on sequential dental casts, in order to initiate a Longitudinal Growth Study. The specific changes and the assessed distances that increased and decreased during different age stages in children that have not been orthodontically influenced demonstrate the tremendous potential of natural growth, development and tooth alignment. In most of the cases lower incisors erupt somewhat lingually and in a slightly irregular position, but have the tendency and start to align very soon. Anterior arch length and depth increases because of the more labial eruption position of the permanent incisors. Posterior arch length usually decreases because of the leeway space, except the eruption of upper permanent canines, when it slightly increases. Intercanine width increases during the eruption of permanent incisors, then can decrease at the beginning of canines eruption and increases later again. The dimensional difference between permanent and primary teeth and the measurement of spaces between primary teeth are important parameters in space analysis at different stages.

Keywords: dentoalveolar natural development, mixed dentition, study casts, mechanical and digital caliper measurements, individual variations

Introduction

Dentoalveolar development is a complex and continuous biological process [1, 2].

Orthodontic treatment represents a cultural influence on the growth and development of the dentition and face [3]. Arch dimensions change with growth; therefore it is necessary to distinguish changes induced by appliance therapy from those that occur as a result of natural growth. Naturally occurring changes in untreated persons should be used as the gold standard for evaluating dental arch changes produced by orthodontic treatment. [4]

The orthodontic records taken to document the patient's initial conditions and to supplement the information gathered from clinical examination, can be divided in three categories: study casts, photographs and radiographs. Study casts are the only non-invasive three-dimensional records that provide information which is important for orthodontic diagnosis, treatment planning and as medico-legal documents. [5].

The natural development of dental arches has to be considered in orthodontic treatment planning as well as in assessment of stability following orthodontic treatment [1].

Every dentist who provides care for children and adolescents should be able to properly assess and manage their developing occlusions [6]. In planning the management of these patients, the deficit of arch space must be predicted early and the indicated preventive or interceptive procedures instituted [7].

In the cast analysis, the actual value of the individual case is compared with the standard values of the "normal arch" [8].

Graber stated that a balanced, healthy, stable occlusion could be considered normal, even with small tooth rotations and small tooth size-arch length discrepancies [4, 9]. In persons with normal occlusion who have not previously undergone orthodontic treatment, an initial evaluation of adaptive longitudinal changes in the occlusion should be performed. These changes become especially important in growing patients [4]. Based on these initial observations, changes that might occur in the posttreatment period could be determined [4, 10].

Tooth buds lie lingual as well as apical to the primary incisors. The result is a tendency for the mandibular permanent incisors to erupt somewhat lingually and in the slightly irregular position, even in children who have normal dental arches and normal spacing within the arches. In the mandibular arch in both sexes, the amount of space for the mandibular incisors is negative for about 2 years after their eruption meaning that a small amount of crowding in the mandibular arch at this time is normal [11].

The growth process continues throughout life with a smaller rate. The results verified that continuous changes of the dental arches occur from the primary until the adult period, with individual variations, resulting in anterior crowding especially in the mandible and infraposition of the implant-supported crowns [1].

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For determining the variation that occurs in dental arches during development we should have longitudinal dates acquired during long periods of time, which requires a digital database that provide a safe storage [12]. It was verified that there are no major differences between the measurements carried on digital models and that done with a digital caliper on plaster models [12].

The recorded parameters of dental arches, which resulted from longitudinal studies, are presented in tables or graphically in order to illustrate as clear as possible the changes during the observation periods [1, 4, 10, and 14].

Studies that investigated secular changes suggest that average arch dimensions may be smaller in contemporary children than in past generations. The results indicated that arch lengths in both sexes were significantly shorter in the contemporary sample; all arch widths were significantly smaller in contemporary boys, but not in girls [15].

The recorded distances of the dental arches were constantly larger in males compared with those of females [1].

Purpose

The aim of our study is to "make the first steps" in producing actual "normal arch" standards for our population. This means: development of the specific methodology; training in analyzing the changes that occur during growth and development on sequential casts (taken at relatively short age intervals); improvement of own measurement and observation skills; creating an initial database of study casts of untreated children of different ages in order to measure the dimensions at this stages and to initiate a longitudinal study. We will try to keep our sample as large as possible and to take a study cast each year for every included child.

Final goal is a better understanding of growth and prevention of two frequently met aspects: more or less orthodontic treatment then needed at specific stages of dentoalveolar development.

Materials and methods

We started a longitudinal study on 70 children from one school from Timisoara, one nursery school near Timisoara and patients from Paedodontics-Orthodontics Department and one dental practice from Timisoara. The children were selected from those who expressed the acceptance for participating in our Growth and Development Study (including eruption, dentoalveolar and occlusal development and facial growth) and their parents gave us a written consent. Only children that have agreed with the impression were included in this part of the study.

The inclusion criteria were: healthy children with late primary dentition or mixed dentition stage that have never been orthodontically treated before. We tried to select the children with less severe visible malocclusion and less primary premature extractions, but we have not strictly respected the last criteria because the sample would be too small and some children that wanted to participate could have the feeling of discrimination. The group of casts of each child is individually measured and judged. The children were in late primary (from 5 to 6 years), transitional (from 6 to 8 years and from 10 to 12 years) or intermediate mixed dentition (from 8 to 10 years) stage. We wanted to assess dental arch changes during the intermediate stage as well and we considered that for all this children the second transitional stage will follow.

They were not selected and included at one moment of time, but during one year and a half. That is why some children have one study cast; some have two or three casts.

Cast measurements were made by two trained operators using a mechanic caliper and a digital caliper (Fig. 1).

The mechanic caliper had an accuracy of 0.1 mm and the digital caliper had an accuracy of 0.01mm. The mechanic caliper had an improved design which permitted a better positioning of the free ends at interdental spaces. The final accuracy considered in our study was of 0.1 mm.

We measured the following distances on each study cast: tooth width and arch length, width and depth. We measured *tooth width* by considering the greatest mesiodistal distance between the contact points of each tooth.

Arch length (perimeter) was determined by adding the length of the posterior arch segments from right and left sides and the length of the anterior arch segments. The *posterior arch length* was measured between the distal surface of the primary second molars or premolars and the mesial surface of primary or permanent canines on the right or left sides.

The *anterior length* represents the distance between the mesial surface of primary or permanent canine and the midline of the dental arch added from both sides.

Arch width was obtained by measuring the distance between the corresponding teeth of right and left sides at different levels: *intercanine width* was measured as the distance between the crown tips of the canines (Fig.1); *interpremolar width* as the distance between the lower most point of the transverse fissure of the first premolars in the *maxilla* and the distance between the facial contact point between first and second premolars in the *mandible*; *intermolar width* between primary molars was determined as the distance between the posterior groove of the transverse fissure of the first deciduous molars in the *maxilla* and between the distobuccal cusp tip of first deciduous molars in the *mandible*; intermolar with between the permanent first molars was measured as the distance between the central fossa of the first permanent molars in the *maxilla* and between the tip of the mesiobucal cusp of the lower first permanent molars in the *mandible.*

The depth of the dental arch was obtained at the midline at different levels by measuring the perpendicular distance from the buccal surface of the central incisors to the distal surface of the canine, to interpremolar width and to distal surface of the first permanent molars (Fig.1)

We compared the dimensions and assessed the changes for each dimension between the successive study casts. All the data were registered on a specific chart.

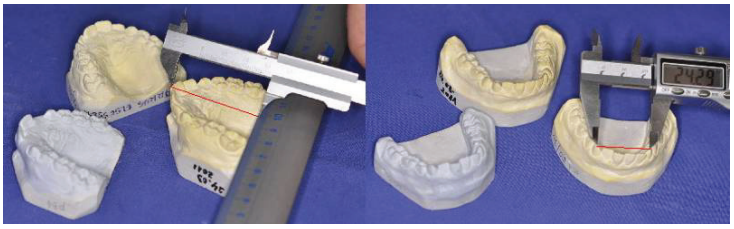

Fig.1 The measurements of arch depth with mechanical caliper (left) and arch width with digital caliper (right) on three sequential study casts at 7 years 4 months, 7 years 11 months and 9 years 4 months.

Results

Case report 1 We measured two study casts of a girl, taken at 6 years 1 month and 7 years 1 month of age (Fig. 2). Dimensions of the same teeth were the same on both measured casts. *Upper intercanine width* increased with 2.4 mm (from 31.3mm to 33.7mm), *upper intermolar width between the primary first molars* increased with 1.5mm (from 34mm to 35.5mm) and *intermolar width between the second primary molars* also increased with 0.5mm (from 37.6mm to 38.1mm). The *intermolar upper width between the permanent first molars* can be determined only on the second cast (43 mm). *The depth of the upper arch to canine level* decreased with 0.5 mm (because of the initial position of the permanent central incisors). *Lower intercanine width* increased 1mm (from 23.6mm to 24.6mm) and *intermolar width between the primary first molars*, *the primary second molars* and the *permanent first molars* remained unchanged. *The depth of the lower arch to canine level* increased with 1.2 mm (because of the more labial position of the lower incisors). The dimensional difference between an upper permanent central incisor (8.2mm) and an upper primary central incisor (6.5mm) is 1.7mm. The difference for both sides is 3.4mm. Measuring the spaces between primary upper frontal teeth we determined the amount of space (4.7 mm) that is available for the alignment of permanent central and lateral incisors. The primate spaces are of 1.2 and 1.6mm and the other three spaces 0.8mm, 0.5mm and 0.6 mm. At this stage, we have 1.3 mm space excess (the difference between 4.7mm and 3.4mm), that will be necessary when the upper second incisors will erupt.

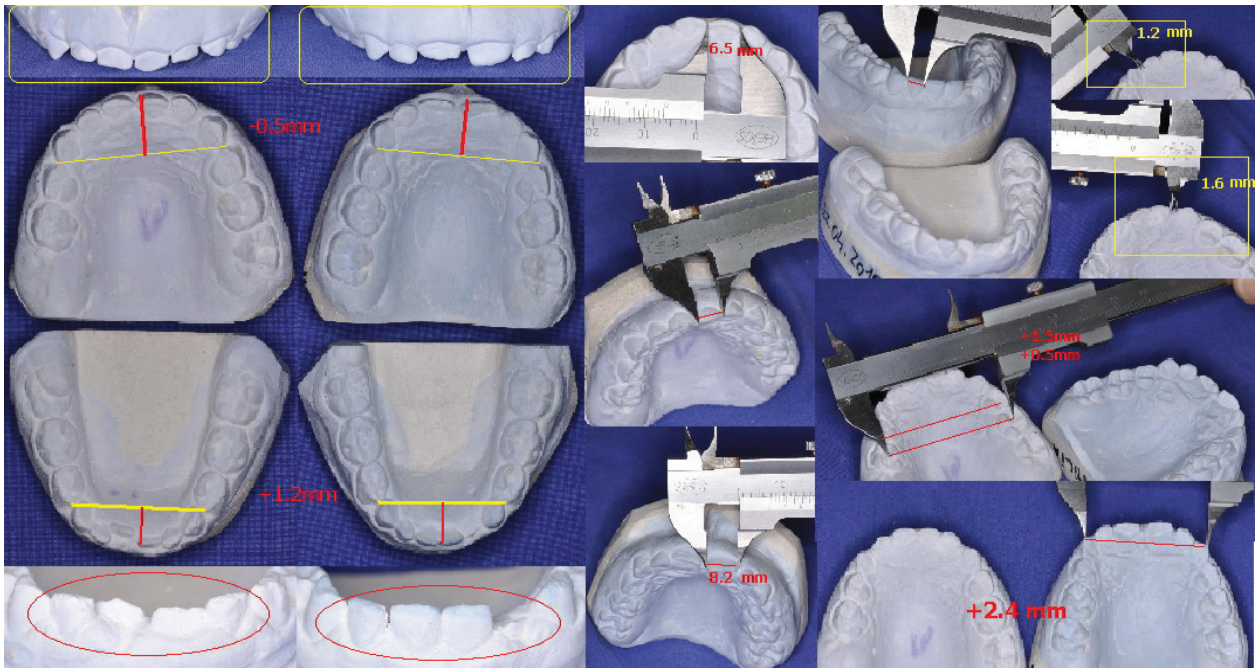

Fig.2 The changes that occur during dental arch development assessed on two study casts (at 6 years 1 month and 7 years 1 month) and the measurements made in order to determine the direction and amount of changes of different diameters

Case Report 2 The study casts of one boy, taken at 6 years 7 months, 7 years 2months and 8 years of age, were measured (Fig.3). *Upper intercanine width* increased with 1.5 mm (from 33.4mm to 34.4mm and then to 34.9), *intermolar width between the primary first molars* increased with 0.5mm (from 35.7mm to 36mm and then to 36.3mm) and *intermolar width between the second primary molars* also increased with 1mm (from 39.5mm to 40.1mm and then

to 40.5). The *intermolar upper width between the permanent first molars* remained unchanged. The dimensional difference between an upper permanent lateral incisor (7.5mm) and an upper primary lateral incisor (5 mm) is 2.5mm. The *upper arch depth to canine level* increased 2mm between the last two study casts. The *upper anterior arch length* increased 1.3mm between the second and third study cast (from 31.7mm to 33mm). The sum of the upper four incisors is 33mm (7.5mm the lateral incisors and 9mm the central incisors). The space was enough for the incisor alignment. *Lower intercanine width* increased 1mm (from 25.5mm on both first and second study casts, to 26.5mm on the last study cast) and *intermolar width between the primary first molars* increased 0.5mm, *the intermolar width between primary second molars* and *between the permanent first molars* remained unchanged. *The depth of the lower arch to canine level* increased with 1mm (0.5 mm between each of the study casts). The dimensional difference between a lower permanent central incisor (6.5mm) and an upper primary central incisor (5mm) is 1.5mm. The *lower anterior arch length* increased 1.5mm between the first and third study cast (from 23mm to 24mm and then to 24.5mm). The sum of the lower four incisors is 25mm (6.5mm the lateral incisors and 6mm the central incisors). We have a space deficit of 0.5mm. We have 1.3 mm space located posterior to primary lower canines.

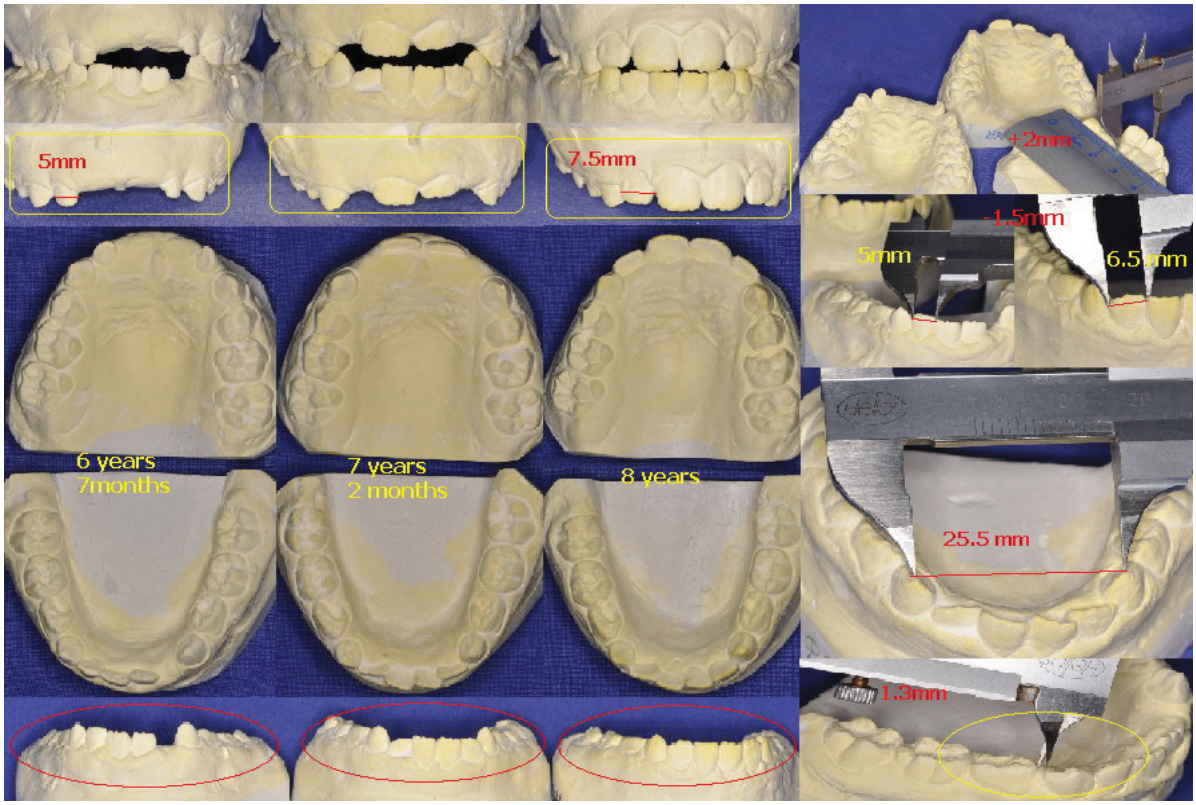

Fig.3 Sequential study casts of one boy at 6 years 7 months, 7 years 2 months and 8 years of age.

<u>*Case Report 3*</u> The study casts of a female patient, taken during a period of 2 years (at 10 years 6 months, 11 years 2 months, 11 years 8 months and 12 years 6 months), were analyzed (Fig.4). *Upper intercanine width* decreased in our case between the first two study casts with 2mm (the left canine was pushed palatal), then increased 2.5 mm (during the permanent canine eruption). *The interpremolar width between the first permanent premolars*, *interpremolar width between the second permanent premolars* and *the intermolar upper width between the permanent first molars* increased insignificantly. The upper posterior arch length slightly decreased when comparing the first casts and then slightly increased during the eruption of permanent canines (from 21.5mm to 21mm to 21mm to 21.5mm on the right side and from 20.5mm to 20.5mm to 20mm to 21mm on the left side). The *upper arch depth to canine level* and *the total arch depth* increased 1.5mm (central incisors are more overlapped and the left central incisor is more labially positioned). *Lower intercanine width* decreased between the first and second study cast with 3.6mm, then increased 1.3mm (during the permanent canine eruption). The changes in *lower interpremolar width* could not be assessed; the *lower intermolar width* remained stable. *The lower posterior arch length* constantly decreased on both right and left sides (from 23mm to 23mm to 22mm to 21.5mm on the right side and from 23.5mm to 23mm to 22.5mm to 22mm on the left

side). The total amount of decrease was 1.5mm on each side. *The lower arch depth* to canine level increased 1mm between the last two study casts and *the total arch depth* decreased with 1.5mm.

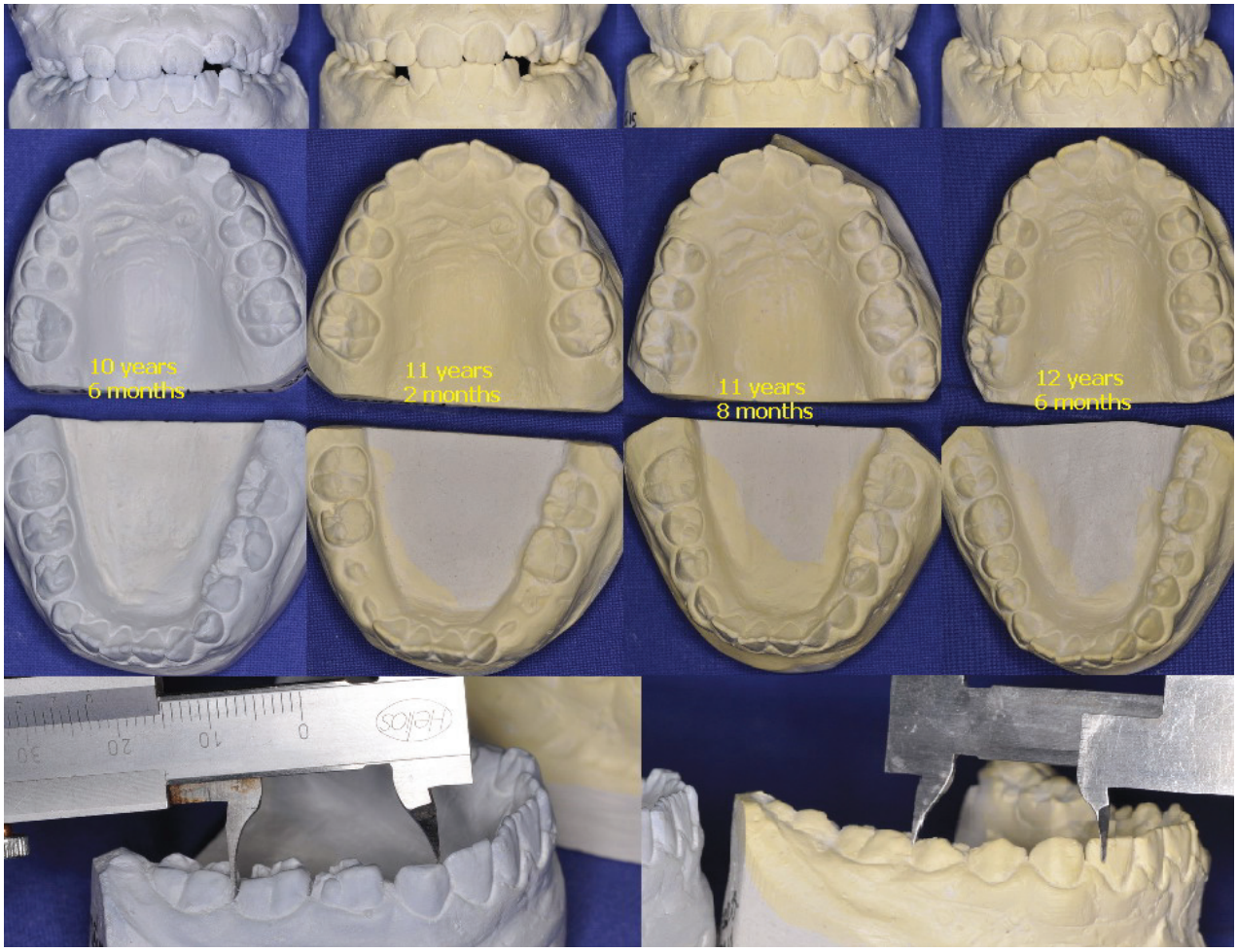

Fig.4 Sequential casts of arch development of one girl, between 10 years 6 months and 12 years 6 months of age.

Discussions and conclusions

Tooth dimensions of the same teeth were identical on all study casts of one patient that means that the dimensional differences between the casts (due to impression and cast manufacturing) were very small.

The upper intercanine width increases between 6 and 8 years, during the eruption of the incisors, because of sutural growth and pushing effect. The other transversal dimensions increase also, but with a slower rate. It can decrease when one canine is pushed palatal (in space discrepancy) and it increases again during permanent tooth eruption. Upper anterior arch length increases during the eruption of permanent central, lateral incisors and canines. Anterior arch depth can slightly decrease during the first eruption stage of permanent upper central incisors, but it will increase soon because of the labial position of the upper incisors. The arch length of the upper posterior segments slightly decreases during the eruption of the premolars, but it will increase during the eruption of the permanent canine. Dimensional primary and permanent tooth measurements and primate spaces and other spaces measurements are useful for crowding prediction.

The lower intercanine width increases during the incisor eruption (due to the pushing effect) then decreases during first stages of canine eruption. The other transversal dimensions are almost unchanged. Lower anterior arch length and arch depth to canine level increase during incisor eruption and then canine eruption. The lower posterior arch length decreases constantly on both sides during the exchange of primary molars with premolars. The lower permanent first molars will migrate more mesially, establishing the corresponding Angle class.

Crowding depends on the relationship between the size of the teeth and the length, width and depth of the jaws. Any change in dental arch dimension has an influence on this relationship.

The findings of the present study demonstrated significant and important changes in dental arches of contemporary children, over short but dynamic age intervals.

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CORRELATIONS OF FECAL CALPROTECTIN WITH CLINICAL AND ENDOSCOPIC SCORES IN INFLAMMATORY BOWEL DISEASES IN CHILDREN

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Abstract

Background: An accurate monitoring of mucosal inflammation is important for an effective management of children with inflammatory bowel disease (IBD). The aim of the study was to evaluate the efficacy of the fecal calprotectin as indicator of inflammatory activity in children with Crohn's disease (CD) and ulcerative colitis (UC) by correlating it with biological, clinical and endoscopic indices. Methods: A total of 22 children presenting IBD were evaluated (16CD/6UC). Fecal calprotectin, blood tests, Pediatric CD Activity Index (PCDAI), Pediatric UC Activity Index (PUCAI), CD Endoscopic Index of Severity (CDEIS) and Mayo Disease Activity Index (MDAI) were used for children evaluation at diagnosis and after 6 months of treatment. Results: In CD children, calprotectin showed a high correlation ($r = 0.775$) with the histologic grade of mucosal inflammation, showed by CDEIS and a medium correlation with CRP($r = 0.623$). lt didn't correlated with PCDAI ($r = 0.325$). In UC children, calprotectin correlated moderate (r=0.581) with CRP and it was strongly correlated with PUCAI (r = 0.752) and MDAI (r = 0.796). Calprotectin levels decreased significantly after 6 months of treatment in all IBD patients (p = 0.038). Conclusions: In CD children fecal calprotectin was more accurate in detection of active mucosal inflammation when compared to clinical score and serum marker CRP. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease. Fecal calprotectin correlated well with endoscopic indices both in CD and UC children. So, it can provide a reliable noninvasive marker for monitoring IBD activity.

Key words: Crohn's disease, ulcerative colitis, calprotectin, children

Introduction

Inflammatory Bowel Disease (IBD) includes Crohn's Disease (CD), Ulcerative Colitis (UC) and Indeterminate Colitis (IC), which is considered to be an intermediary condition that will progress to one of those two entities above, according to some authors. *(1)* These are chronic idiopathic disorders, characterized by recurrent episodes of inflammation of the gastrointestinal tract, interspersed with periods of remission*)*.

In order to monitor patient's clinical evolution and adjust the therapy, it is very important to determine the degree of inflammatory activity at the moment of diagnosis and in evolution. *(2*An accurate monitoring of mucosal inflammation is important for an effective management of patients with IBD. *(3)* Beside clinical and biological remission, the mucosal healing represents an important goal to be achieved by treatment. Several indexes are proposed for evaluation of disease activity, which differ from each other in terms of being more subjective (clinical), more objective (endoscopic-histological) or a combination of the two. *(4)* However, despite the different scores available, there is not any consensus in the literature as which is the most valid. *(5)* Laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum fibrinogen level and haematocrit, among others, are not specific for active IBD, so those can not be used routinely as markers of inflammatory activity in clinical practice. *(6)*

Many authors consider that colonoscopy with biopsy represents the best method for evaluating inflammation location, extent, and severity. *(7)* Beside from being an invasive method especially in children, this approach carries risks of complications. Various studies have described fecal markers as powerful biomarkers of inflammation of the intestinal mucosa in patients with IBD. Fecal markers selected and studied by different recent authors as indicators of inflammation include neutrophil granule proteins, lactoferrin and calprotectin. *(8)*

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Objectives of the study

Several studies have compared fecal calprotectin with activity indexes and/or endoscopic/histological evaluation to confirm intestinal inflammation in IBD adult patients. The results of these studies are promising, demonstrating that these markers are useful in detecting inflammation and differentiating it from other diseases as well as in predicting recurrence for periods of up to one year. *(9)* The objectives of this paper were to assess calprotectin in children as indicator of IBD activity and to determine if this marker correlates with other indexes of inflammatory activity including laboratory measures (CRP), two diseases activity scores (Paediatric Crohn's Disease Activity Index – PCDAI, Pediatric Ulcerative Colitis Activity Index – PUCAI) and endoscopic evaluation, at the moment of diagnosis and after 6 months of treatment.

Material and methods

We conducted a retrospective, descriptive study on a lot of 22 children diagnosed with IBD between February 2005 and December 2010. The lot of study included 16 children with CD and 6 children with UC. The patients were aged between 4 and 18 years.

The work-up diagnosis included at all children detailed clinical examination followed by biological assessment (blood cells count, CRP, ESR, fibrinogen, serum iron, glicemia, liver and renal function tests). Fecal calprotectin was measured in all cases and IBD diagnosis was certified by endoscopic assessment (colonoscopy± upper digestive endoscopy) and histological interpretation of the biopsy samples (from colon and/or ileum).

Fecal calprotectin was measured using a quantitative ELISA tests.

Calprotectin, also known as MRP-8/MRP-14 or S100A8/A9 heterocomplex, is formed out of the calcium-binding, migration inhibitory factor-related proteins MRP-8 (S100A8) and MRP-14 (S100A9). The expression of these proteins is largely confined to the cytosol of neutrophils and monocytes. The complex formation of these proteins is calcium-dependent. Calprotectin comprises 60% of the cytoplasmic protein fraction of circulating polymorphonuclear granulocytes and is also found in monocytes, macrophages and ileal tissue eosinophils. *(10)* It was suggested that measurement of faecal calprotectin would represent a surrogate marker of neutrophil influx into the bowel lumen and in turn act as a marker of intestinal inflammation. *(11)*

In our study, results interpretation for fecal calprotectin values is described in table I, according to manufacturing recommendations:

For all children with IBD, we calculated clinical and endoscopic indices of disease activity.

In 16 cases of children with CD we calculated the activity index PCDAI (table II) and in 6 cases of children with UC we calculated the activity index PUCAI (table III).

Conform to some authors, no single clinical or biochemical parameter consistently reflects activity of intestinal inflammation. Therefore, multi-attribute measures of disease activity have been developed for use in the clinical trial setting. Although other CD activity indices have been used, the Crohn's Disease Activity Index (CDAI) is generally accepted as the standard clinical outcome measure in adult CD trials. The Pediatric Crohn's Disease Activity Index has became the accepted disease activity measure in childhood CD. PCDAI, in contrast to the adult-derived CDAI, includes linear growth, recognizing that height velocity is an important marker of disease activity among children with CD. *(12)*

PCDAI values were considered negative for disease activity between 6.8 ± 6.6, mild inflammatory activity between18.7 ± 7.3, moderate between 38.5 ± 12.9 and severe between 54.2 ± 14.0 points *(13)*

In the context of a Pediatric IBD Clinical trials workshop, sponsored by the Crohn's and Colitis Foundation of America (CCFA) in 2004, a group of pediatric IBD experts was assembled to reach consensus concerning outcome assessment in pediatric IBD. Although recommendations for outcome assessment in CD made use of existing measures, the panel concluded that for UC, a novel instrument measuring disease activity in pediatric patients should be developed. *(14)* Clinical trials in adult patients with UC most commonly include post-treatment endoscopic examination as an endpoint, with or without clinical criteria, but follow-up colonoscopy is not routinely performed and would not be well accepted at pediatric institutions. The result was the development of the Pediatric UC Activity Index (PUCAI).

Table I

Fecal calprotectin values (µg/g)	Results interpretation
< 50	There is no inflammation of the gastrointestinal tract
50-150	Mild inflammation of the gastrointestinal tract; the inflammatory response can be due to an enteral infection, alimentary allergy or previous treatment with non-steroidian anti-inflammatory drugs.
>150	Important inflammation of the gastrointestinal tract, associated to IBD, infections, non-steroidian anti-inflammatory drugs, polyps, colonic cancer. Further investigations are needed for establishing the cause of inflammation.
> 250	Besides the previous comment, in case of known IBD patients, this result indicates an active period of disease. In case of IBD patients in remissions, this result confers a high risk of relapse within an year.

Table II: The PCDAI score

Abdominal pain	No abdominal pain	0
	Mild; no interference with Activities of Daily Living (ADL)	5
	Moderate/severe; daily, nocturnal, interferes with ADL	10
Stools/day	0-1 liquid, no blood	0
	≤ 2 Semi-formed + small blood or 2-5 liquid	5
	≥ 6 liquid stools, gross blood or nocturnal diarrhoea	10
General function	Well, no limitation of activities	0
	Occasional difficulty with activities	5
	Very poor, frequent limitation of activities	10
Weight	Weight gain (or voluntary stable, reduction)	0
	Weight loss < 10% (or involuntary stable)	5
	Weight los ≥ 10%	10
Height (at diagnosis)	< 1 channel decrease from previous percentile	0
	1 to < 2 channel decrease from previous percentile	5
	≥ 2 channel decrease from previous percentile	10
OR		
Height velocity	≤ -1 standard deviation from normal	0
	-1 to < -2 standard deviation from normal	5
	≥ -2 standard deviation from normal	10
Abdomen	No tenderness or mass	0
	Tenderness, or mass without tenderness	5
	Tenderness, involuntary guarding, definite mass	10
Peri-rectal disease	None, asymptomatic tags	0
	1-2 indolent fistula, scant drainage, non-tender	5
	Active fistula, drainage, tenderness, or abscess	10
Extra-intestinal	None	0
	1 manifestation	5
	≥ 2 manifestations	10
Haematocrit (%) M = male F = female	M/F 6-10 years ≥ 33	0
	M 11-14 years ≥ 35	
	F 11-19 years ≥ 34	
	M 15-19 years ≥ 37	
	M/F 6-10 years 28-32	2,5
	M 11-14 years 30-34	
	F 11-19 years 29-33	
	M 15-19 years 32-36	
	M/F 6-10 years < 28	5
	M 11-14 years < 30	
	F 11-19 years < 29	
	M 15-19 years < 32	
ESR (mm/hr)	< 20	0
	20-50	2,5
	> 50	5
Albumin (g/L)	≥ 35	0
	31-34	5
	≤ 30	10

Table III: The PUCAI score

ITEM	POINTS
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of cativity	5
Severe restricted activity	10

The PUCAI is able to detect change also in a short period of a few weeks and can perform well in both in and outpatient setup including patients with mild to severe disease activity. *(14)* The rigorously developed PUCAI is a non-invasive, valid, highly reliable and responsive index with which to assess disease activity in pediatric ulcerative colitis.

The values of PUCAI score varies between 0 and 85 points, reflecting absence or presence of disease activity of various degrees as following: 0-10 inactive disease, 10-34 mild disease activity, 35-64 moderate disease activity, 65-85 severe disease activity. *(14)*

Assessment of disease severity and extension of the lesions at children with CD was made by computing Crohn's Disease Endoscopic Index of Severity (CDEIS) and at children with UC we used the sub-endoscopic score Mayo Disease Activity Index (MDAI) (table IV).

CDEIS reflects endoscopists' global appraisals of lesions'severity. For calculating this index, the presence of nine preselected lesions was recorded in the following segments: (1) rectum, (2) sigmoid and left colon, (3) transverse colon, (4) right colon, and (5) ileum. The nine mucosal lesions recorded were: pseudopolyps, healed ulcerations, frank erythema, frankly swollen mucosa, aphthoid ulcerations, superficial or shallow ulcerations, deep ulcerations, non ulcerated stenosis, ulcerated stenosis. In addition the extent of the diseased and ulcerated areas were estimated in each segment. The percentage of the segmental surfaces involved by the disease (SSD) - taking into account these nine lesions – and the percentage of the segmental surfaces involved by ulcerations only (SSU) were recorded. For colonic segments only partially explored and for ileum, the 10 cm scale represented the area actually seen. *(15)*

The following calculations were carried out: (1) The average segmental surfaces involved by the disease (ASSD) was calculated by dividing the sum of SSD by the number of segments explored at endoscopy. An identical calculation was performed with SSU to obtain the average segmental surfaces involved by ulcerations only (ASSU). (2) For each mucosal lesion, two variables were derived: (a) the first (PRES) was either 0 if the lesion was not seen at all or 1 if it was seen at least once at a given endoscopy; (b) the second - the individual segmental recto-colonic frequency (ISRCF) - was calculated by dividing the number of segments in which a lesion was seen by the number of segments examined. Thus ISRCF could take a series of values from 0 (lesion not seen in any of the segments explored) to 1 (lesion seen in all segments explored). *(16)*

Table IV Components of Mayo Disease Activity Index

Stool Frequency
0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Mucosal appearance at endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

The final formula for CDEIS calculation is as follows:

CDEIS = 12 x ISRCF (deep ulcerations)
+ 6 x ISRCF (superficial ulcerations)
+ ASSD
+ ASSU
+ 3 x PRES (non ulcerated stenosis)
+ 3 x PRES (ulcerated stenosis)

*ISRCF: number of segments exhibiting the lesion divided by the number of explored segments.

PRES is taken to be 1 if the lesion is seen at least once at a given endoscopy and 0 otherwise.

ASSD: Average surface involved by the disease.

ASSU: Average surface involved by ulcerations only.

CDEIS varies from 0 to 30 points, reflecting the severity of mucosal injury. *(16)*

The Mayo Score and the nearly identical Disease Activity Index (DAI) described by Sutherland are two of the most commonly used activity indices in placebo-controlled clinical trials for ulcerative colitis. Each is composed of four categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0–3 that are summed to give a total score that ranges from 0–12. *(17)*

Statistic analyze was made using SPSS 16 soft (Statistical Package For Social Sciences for Windows, version 16).

Results and discussions

IBD is a lifelong disease with significant morbidity and requires endoscopy for diagnosis and disease monitoring. Identifying markers of IBD that allow noninvasive diagnosis and disease monitoring would be of great advantage, especially in children. This study examined if fecal calprotectin correlates with CRP serum level, clinical activity indexes and endoscopic indices in CD and UC paediatric patients.

Clinical parameters of patients are presented in Table V.

We tried to correlate the values of fecal calprotectin quantitative assessed with serum CRP, clinical activity scores: PCDAI, PUCAI and endoscopic score CDEIS for Crohn's disease and sub-endoscopic score MDAI in ulcerative colitis. We studied if there are significant differences between the inflammatory markers values and clinical/endoscopic indices before and after 6 months of treatment.

We studied among the 16 CD children if fecal calprotectin correlates with CRP level and disease activity showed by clinical score PUCAI and endoscopic score CDEIS.

Table V Summary of IBD patients' clinical data

Illness	**CD**	**UC**
Number of patients	16	6
Sex (male/female)	9/7	3/3
Median age (minimum-maximum years)	7,5 (4-18)	15,5 (14-17)
Family history of IBD (yes/no)	3/13	0/6
Extent of disease		
Terminal ileum	0	
Ileum and colon	13	
Pancolitis	1	5
Rectal + sigmoid + descending colon	2	1
Rectal	0	0
Surgery intended (Yes/no)	1/15	0/6
Treatment		
Aminosalicylate	2	4
Immunosuppressant	9	2
Anti-TNF	5	0

Fecal calprotectin values correlated positive with clinical indices of disease activity PUCAI at UC children (r=0,752). We obtained also a high direct correlation, statistically significant between calprotectin and sub-endoscopic index MDAI (r = 0,796) and a medium direct correlation between calprotectin and seric CRP (r =0,623) in UC lot.

An important tool to assess inflammation is the analysis of the infiltration of neutrophils in the intestinal mucosa and their transmigration to the lumen. When intestinal inflammation occurs, fecal calprotectin rises rapidly and correlates with endoscopic and histological alterations in patients with IBD, supporting the idea that it is a sensitive and specific means to identity inflammatory activity in these patients. *(17)*

Many authors have claimed that calprotectin levels correlate closely with histological evaluation than macroscopic findings, suggesting that this biological marker is more sensible than endoscopy in evaluating IBDs activity. Furthermore fecal calprotectin concentrations predicted the severity of colorectal inflammation, with advanced histological grades of colorectal inflammation. *(18)*

This study showed that more intense levels of inflammation are associated with elevated calprotectin values, demonstrating a significant correlation between calprotectin and the severity of inflammation.

Calprotectin determination appears to better reflect disease activity in UC than CD. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease, which is known to occur rather frequently in CD.

It has been suggested that CD patients' stratification based on phenotypical pattern (inflammatory, stricturing or fistulizing) could improve calprotectin's predictive capacity for this disease. As calprotectin is an inflammation marker, its predictive role will probably produce best results in the inflammatory pattern of the disease. In summary, the exact strength of any correlation of fecal calprotectin levels with disease activity clinical indicators is therefore not well established at present. *(19)*

In our study, calprotectine correlated very well with endoscopic index CDEIS in children. Similar resuls were reported in literature. Sipponen found that both fecal calprotectin and lactoferrin correlated significantly with CDEIS but in adults patients (Spearman's r 0,729, $p < 0,001$). With a cut-off level of 200 microg/g for a raised fecal calprotectin concentration, sensitivity was 70%, specificity 92% in predicting endoscopically active disease. *(16)*

In children with ulcerative colitis, it was observed that all patients with clinical and endoscopic signs of inflammation (as determined by the PUCAI and MDAI) had high values of calprotectin presents in their stool and these parameters were significantly correlated.

High values of calprotectin were present in the majority of samples from children with elevated CRP, these two inflammatory markers correlated moderate in both groups of children, with CD and UC.

We compared the medium values calculated separately in CD group and UC group respectively, for fecal calprotectin, CRP, clinical scores PCDAI/PUCAI and endoscopic indices CDEIS/MDAI at diagnosis and after 6 months of treatment. The results are presented in table VI. There were no significant differences between calprotectin medium values at CD and UC lot before treatment ($p>0,05$). We found a higher medium value of CRP at CD group compared to UC lot before treatment ($p=0.05$). After 6 months of treatment, we obtained a significant decreasing of calprotectin and CRP medim values in both lots with CD and UC ($p<0.05$). We found a direct significant correlation between calprotectin levels and endoscopic indices CDEI and MDAI after 6 months of treatment.

Table VI: Medium values for calprotectin, CRP, clinical and endoscopic sores in both CD and UC groups before and after 6 months of treatment

	Parameter	Medium value before treatment	Medium value after 6 months of treatment
Crohn's disease lot	Calprotectin (μg/g)	266.5±12.5	50.2±9.5 *p<0.05*
	CRP (g/l)	107.9±10.3 *p=0.05*	6.5±1.3
	PCDAI	39.5±6.5	11.5±3.5
	CDEIS	23.3±6.4	8.6±2.4 *r=0.75*
Ulcerative colitis lot	Calprotectin(μg/g)	236.4±13.6 *p>0.05*	48.2±9.3 *p<0.05*
	CRP (g/l)	86.5±7.2	6.2±1.5
	PUCAI	62.5±8.3	17.2±6.5
	MDAI	8.6±2.4	4.3±1.5 *r=0.78*

Conclusions

Fecal calprotectin represents a sensitive and specific marker for the detection of intestinal inflammation in IBD children. Calprotectin levels are directly proportional to the degree of inflammation in the intestinal mucosa, but did not correlated with clinical activity score in Crohn's disease children, only in the group with ulcerative colitis. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease. Instead, it strongly correlated with both endoscopic indices, CDEIS and MDAI in CD and respectively UC children. These results suggest that fecal calprotectin may be valuable not only for screening children suspected of having IBD but also for monitoring disease activity and reducing the need for colonoscopy in disease follow-up.

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NEONATAL JAUNDICE - ETIOLOGY AND INCIDENCE

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Abstract

Jaundice usually appears in newborns approximately 24 hours after birth, as a result of the imbalance between bilirubin production and excretion. Normally the jaundice disappears or its intensity decreases spontaneously in one or two weeks, with no treatment and living no sequels. Children having dangerously high levels of blood bilirubin need treatment, as it causes cerebral lesions, situation referred to as nuclear jaundice.

The aim of this paper was to perform a clinical and statistical study of the neonatal jaundice and to establish the extent to which the treatment and care of newborns influences neonatal jaundice evolution.

Key words: jaundice, newborn, cerebral lesions

Introduction

Jaundice appears as a result of the imbalance between bilirubin production and excretion (4). This is eliminated from the human organism by urine and faeces. During pregnancy, mother's body discards foetus's bilirubin through the placenta. After birth, the newborn has to discard blood bilirubin by itself. The bilirubin may have elevated values in newborns, up to concentrations causing the yellow coloration of skin and mucosae, because of organs immaturity unable to cope with the rhythm needed for the bilirubin to be excreted from the organism. Dehydration occurs easily in infants and leads to the slowing of urine and faeces formation, which results in the increase of bilirubin excretion time (7). Bilirubin metabolism is also influenced by some substances in breast milk. Hyperbilirubinemia may rarely be caused by other conditions or diseases, such as digestive system diseases, infections or blood groups incompatibilities (6).

Jaundice usually appears in newborns approximately 24 hours after birth. In case of healthy breast fed newborns, a certain degree of yellow skin coloration appears approximately 2-4 days after birth. Jaundice disappears or its intensity decreases spontaneously in one or two weeks, with no treatment and living no sequels (2).

In case of breast fed newborns, mild jaundice may remain 10-14 days after birth or may reoccur during breast feeding period. As long as the infant receives enough milk and is correctly and frequently fed (8 to10 or more times within 24 hours), the jaundice is not o problem. Even tough, the baby must be monitored. Very large amounts of bilirubin are rarely accumulating in the blood and cause cerebral lesions, situation known as nuclear jaundice. These lesions may be followed by hearing loss, mental retardation and behavioural disorders.

No treatment of jaundice (hyperbilirubinemia) in newborns is required in most cases. However, follow-up of babies is required to monitor the possible changes in skin colour and behaviour. Infants with high levels of blood bilirubin need treatment (1,3,5).

Aim of the paper

The aim of this paper was to a clinical and statistical study of the neonatal jaundice and to establish the extent to which the treatment and care of newborns influences neonatal jaundice evolution.

Material and method

This study was conducted on a group of 35 newborns out of the 2035 births in the years 2008 and 2009 within neonatology department of Louis Turcanu Children Clinical Emergency Hospital in Timisoara.

The study has been performed by statistical analysis and graphic illustration of the cases depending on the reference of the study group to the total of births between 2009-2009, newborn's gestational age, gender, origin, age, type of jaundice, treatment, mortality index and clinical case presentations.

Study protocol included:

• detailed anamnesis intended to acquire as much data as possible

• complete clinical examination on a daily basis monitoring the clinical signs specific to the newborns and each case's evolution

• paraclinical investigation and establishment of diagnostic value on the studied group

• application of therapeutic conduct and assessment of the treatment on newborns studied group

• anatomopathologic examination of all the deceased newborns, in which anatomical samples harvesting and bacteriological inseminations from organs.

Results and discussions

Out of the 2035 births (100%) in the years 2008-2009, a group of 35 cases was studied (1.71%) with neonatal jaundice.

According on the gestational age, it was concluded that 25 newborns (71.42%) were full-term and 10 newborns (28.57%) were premature (Fig 1).

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Out of the 35 cases studied, depending on newborn's gender, it was concluded that 20 newborns were girls and 15 newborns were boys. Prevalence of female newborns was determined at 57.14%.

Depending on the newborn's origin, it was established that 12 newborns came from rural areas and 23 newborns originated in urban environment. Overweight of newborns from urban area was ascertained: 65.71%

Out of the 35 cases studied, depending on newborn's age, it was concluded that 5 newborns (14.28%) had 24 hours, 5 newborns (14.28%) had 48 hours, 10 newborns (28.57%) had between 60 hours and 7 days and 15 newborns (48.85%) had between 7 and 28 days. Prevalence of newborns aged between 7 and 28 days was seen: 48.85%. (Fig. 2)

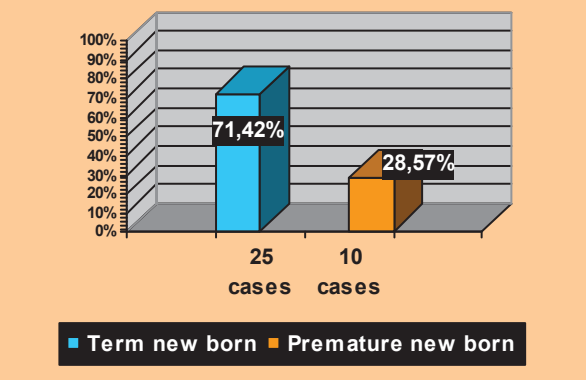

Fig. 1. Case distribution according to gestational age.

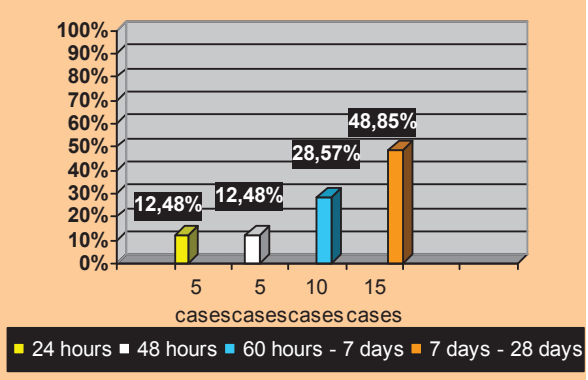

Fig. 2. Distribution of cases according to age newborn.

Out of the 35 cases studied, depending on the newborn's type of jaundice, it was concluded that 25 newborns had physiological jaundice and 10 newborns had pathological jaundice. Preponderance of newborns with physiological jaundice was established at 71.42%. (Fig. 3)

Depending on the treatment, it was determined that 20 newborns (57.14%) underwent phototherapy, 5 newborns (14.28%) required exchange transfusion, while in 10 newborns (28.57%) treatment of hepatic disease or other causes was performed. Overweight of phototherapy was seen: 57.14%. (Fig. 4)

Out of the 35 cases studied (100%), depending on mortality, it was concluded that 0 deaths (0%) occurred.

It was established that the treatment and the techniques of newborns' care reduced to 0% the deaths.

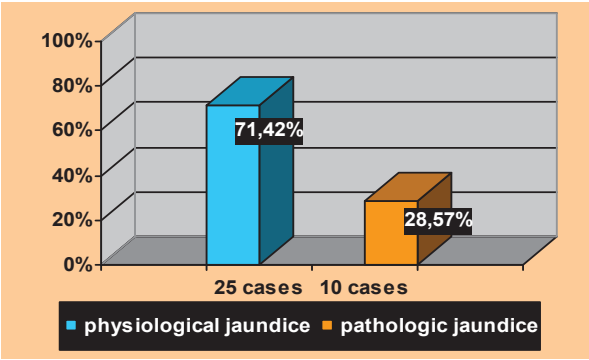

Fig. 3. Distribution of cases according to the type of jaundice.

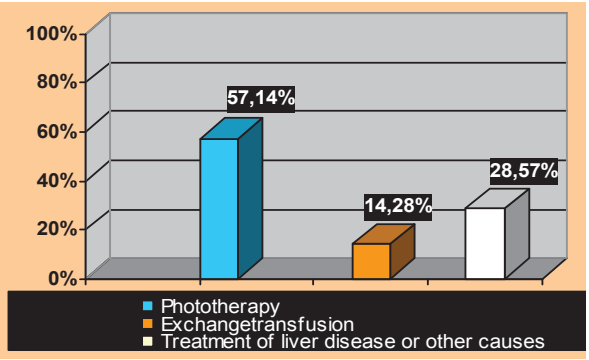

Fig. 4. Distribution of cases according to established treatment.

Conclusions

1. Physiological jaundice: benign and transient, appears in newborns after an interval of 2-3 days; clinical signs of alert lack (hepatosplenomegaly), traces are obvious, hepatic functional tests are normal, Bi values are 70-100 umol/l. It last up to 14-21 days. Bilirubin values rarely exceed 250 umol/l, when there are different associated factors: prolonged labour, hypoxia, shortage of antioxidants (E vitamin). Usually they require no treatment.

2. Pathological jaundice: it starts earlier than 36 hours or in the second week of life, persistent clinical jaundice over 8-10 days in full-term newborns and over 21 days in premature newborns, hepatosplenomegaly, bilirubin serum concentration increases more than 8.5 umol/l hour or 85

umol/day and may exceed 320 umol/l. Associated clinical signs: lethargy, feeding disturbances, neurological disturbances of variable intensity (skin and mucosae jaundice increases), the dynamic of bilirubin increase is higher than 171 umol/l in the second day, maximum values of indirect bilirubin in the next days exceed 205-222 umol/l, maximum level of bilirubin diglucuronide – higher than 25 umol/l.

3. Doctor's care and follow-up will focus on:
- ensuring environmental conditions
- general clinical surveillance of the newborn
- measurement of vital and vegetative functions
- care of newborn's skin
- assuring the hygiene of newborn's clothes
- newborn's feeding
- recognition of transient physiological changes
- tracking of pathological signs and symptoms
- application of treatment

4. Out of total births - 2035 newborns (100%) between 2008-2009 a group of 35 cases (1.71%) with neonatal jaundice was studies.

5. Depending on gestational age, it was concluded that 25 newborns (71.42%) were full-term and 10 newborns (28.57%) were premature. Prevalence of full-term newborns was ascertained: 71.42%.

6. Depending on the newborn's type of jaundice, it was concluded that 25 newborns (71.42%) had physiological jaundice and 10 newborns (28.57%) had pathological jaundice. Preponderance of newborns with physiological jaundice was established: 71.42%.

7. Depending on the treatment, it was determined that 20 newborns (57.14%) underwent phototherapy, 5 newborns (14.28%) required exchange transfusion, while in 10 newborns (28.57%) treatment of hepatic disease or other causes was performed. Overweight of phototherapy was seen: 57.14%.

8. Depending on mortality, out of the 35 cases studied (100%), it was concluded that 0 deaths occurred.

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ASPECTS OF THE LUNG FUNCTION DETERIORATION IN A GROUP OF PATIENTS DIAGNOSED WITH CYSTIC FIBROSIS

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Abstract

Objectives. To assess the types of respiratory dysfunction and their relationship with functional severity, maximal expiratory flows at low lung volumes and prognosis, in patients with cystic fibrosis (CF).

Material and methods. We studied a group of 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 of Bucharest. All patients performed spirometry tests. They were classified as having normal respiratory function (N), obstructive lung disease (OLD), presumptive restrictive lung disease (RLD) and mixed obstructive and restrictive lung disease (MORLD). Maximal expiratory flows at low lung volumes were assessed using FEF25-75. The prognosis was assessed using a simplified cystic fibrosis scoring system (SCS), described by Cooperman. We also included 52 subjects without respiratory disease, as control group, tested spirometry.

Results. The group included 52 patients studied, 11 (21.15%) with normal respiratory function, 15 (28.84%) with OLD, 2 (3.84%) with presumptive RLD and 24 (46.15%) with MORLD. The FEV1 and the Cooperman Score (SCS) were significantly lower in the MORLD group then in the other groups ($p<0.0001$). In the group with normal respiratory function, FEF25-75 showed a decrease of up to 60% of predicted value, in 5 patients.

Conclusions. The respiratory types was impaired in 78.83% of the patients with CF. The most common type of respiratory dysfunction was MORLD. The degree of functional damage was significantly higher and the prognosis more reserved in the MORLD group then in the other groups. Even some patients, regarded as having normal respiratory function, showed a slight deterioration of FEF25-75.

Keywords: cystic fibrosis, respiratory patterns, spirometric tests, early diagnosis, prognosis.

Introduction

Cystic fibrosis (CF) or mucoviscidosis is the most common monogenic disease in people of caucasian origin, autosomal recessive, multisystemic disease, with chronic progressive evolution, potentially fatal, translating it in terms of pathophysiology by altering the transport of chloride in the serous and mucous glands, the primary abnormality is represented by CF gene (3, 8, 11). Because CF is characterized by wide phenotypic variability, there are significant clinical differences between patients in terms of severity and complications. A major clinical repercussion is given of the pulmonary and respiratory symptoms that are responsible for 90% of cases of morbidity and mortality, infection and chronic inflammation leading invariably to progressive respiratory failure (1, 11, 13). In the lung, the mechanisms to increase the rate of absorption of sodium and chloride excretion decreased, leading to a liquid periciliar thick, dehydrated, sticky and consequently to a decrease in mucociliary clearance (11) and the excretory ducts obstruction leading to atrophy, fibrosis, destruction (12). Studies conducted in the second trimester of pregnancy showed the accumulation of mucin in the glands tracheobronchitis. The histopathological aspects can be drawn from the first days of life, even before infection: the submucosal glands hypertrophy, secretory ducts obstruction and the mucous cells hyperplasia of the trachea and major bronchi (12). The retention of the thick mucus in bronchioles promotes the vicious cycle of inflammation, the bacterial infection, the destruction of architecture and the bronchiectasis (9, 15).

Due to improvements in the symptomatic therapies and the late decline in lung function, increased survival over the past 30 years (16, 17). Recent epidemiological data showed an average survival in Europe for over 22 years (11) and another study observed an average survival of 38.6 years in Germany, in 2006 (16). The regular assessment of the lung function in patients with CF and the early detection of alterations that occur in the airways, play an important role in treatment, helping to decrease the morbidity and mortality rate (17). Once the patient can cooperate, the pulmonary function tests are particularly useful for the evaluation of the bronchoalveolar performance and to assess the airways damage. The clinical studies recommended inspection every three months, and at times of exacerbation of the disease, providing the optimal therapy for clinically (11, 14, 18).

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Measuring and monitoring of the maximale expiratory flows at low lung volumes - FEF25-75 is particularly useful in the early diagnosis of the distal obstructive syndrome, because it reveals more sensitive than forced expiratory volume in one second (FEV1) and the ratio FEV1/VC, narrowing the small airways , allowing prevention of the major functional changes (5, 11). The objective of this study was to evaluate the spirometric types of the respiratory disorders and to determine their relationship with the functional severity, prognosis (assessed by Cooperman Score) and values of the end-expiratory air flow, in a group of patients diagnosed with CF.

Material and methods

The study design was a retrospective cross-sectional multicenter, conducted on a lot of 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 of Bucharest. The case histories of the 52 patients have been updated. We used data from the last hospitalization of the patients, in 2008-2009. We included patients with definite diagnosis of CF, based on characteristic anamnestic clinical criteria and confirmed by the sweat test, and in some patients by the genetic test. They received a comprehensive treatment according to the management guidelines FC (2, 7, 8, 10). We selected a control group of the healthy patients with normal lung function from the database of the functional exploration laboratories of the medical centers, where this study was conducted. The control subjects were matched with the study subjects in terms of the age and sex.

The general characteristics of patients, weight, height and body mass index (BMI) were recorded from the case report forms and these values (expressed in kg, m, kg/m2) were converted into numbers standard deviation (SD) from average values correlated with the age and gender (Z Score).The data from the case report forms allowed to evaluate the five dimensions of the Cooperman Score, a simplified cystic fibrosis scoring system (SCS): the genelal activity, the aspects of the chest radiography, the digital hipocratism degree, the growth and development, the complications, which was obtained by adding an overall score for each patient. Each dimension is valued at 0, 1 or 2, the total score is the sum of the 5 points A patient with an excellent health may be of a score of 10 points (4). Spirometry tests were performed in the laboratories of functional exploration of the three medical centers to treat CF. It was measured vital capacity (VC), forced expiratory volume in one second (FEV1), forced expiratory flow between 25 and 75% of forced VC (FEF25-75) and FEV1/VC report. During the spirometry test was performed three forced expiration maneuvers, and were recorded the best results. All values were expressed in liters and percentage of predicted for age, height and sex. Respiratory disorders were classified in accordance with the guidelines of the pulmonary function investigations (5). For the statistical analysis patients were classified according to two directions:

1. by the type of the respiratory disorders: normal respiratory function (N), obstructive lung disease (OLD), presumptive restrictive lung disease (RLD) and mixed obstructive and restrictive lung disease (MORLD);
2. by the severity of respiratory disorder: normal spirometry results (FEV1≥80% of predicted), mild respiratory disorder (FEV1≥60-80% of predicted), moderate respiratory disorder (FEV1≥40-60% of predicted) and severe respiratory disorder (FEV1<40% of predicted) .

Data were expressed as number of cases (percentage) and mean ± SD. Anova test was used to compare variables between three or more groups.The statistical significance was set at $p < 0.05$.

Results

Of the 52 patients, 23 were female and 29 male. The average age of patients was 12.2 ± 4.7 years (range 6-29 years). Patients had a mean weight (Z score) of -1.9 ± 1.1 SD, a mean height (Z score) of -1.3 ± 0.9 SD and an average BMI (Z score) of -1.8 ± 1.4. Averages of the VC, FEV1 and FEF25-75 were 69.9 ± 21.8, 64 ± 24, respectively 52.8 ± 27.7, percent of the predicted value. The average of the Cooperman Score (SCS), which was considered the prognosis, was 3.7 ± 2.6. The average days of hospitalization per year was 20.9 ± 21.3 (Table 1).

Table 1 – General characteristics of the patients with cystic fibrosis

Variable	n=52
Gender (female/male), n	23/29
Age (years), mean±SD	12.2±4.7 (6 – 29)
BMI (Z score), mean±SD	-1.8±1.4
Weight (Z score), mean±SD	-1.9±1.1
Height (Z score), mean±SD	-1.3±0.9
VC (%),mean±SD	69.9±21.8
FEV1(%),mean±SD	64±24
FEF25-75(%), mean±SD	52.8±27.7
FEV1/VC, mean±SD	0.7±0.1
Cooperman Score, mean±SD	3.7±2.6
Number of hospital days/year, mean±SD	20.9±21.3

BMI – body mass index; **VC** – vital capacity; FEV1 – forced expiratory volume in one second; FEF25-75 – forced expiratory flow between 25 and 75% of VC.

Table 2 compares the spirometric variables depending on the type of the respiratory disorder. In our sample, 11 patients (21.15%) were classified as having normal spirometry results (N), 15 (28.84%) with OLD, 2 (3.84%) with RLD and 24 (46.15%) as being MORLD. FEV1 values were significantly lower in the MORLD, than the other groups (p<0.0001). Of the 11 patients classified as having preserved respiratory function, FEF25-75 showed a decrease of up to 60% of predicted, in 5 patients.

Table 2 – Comparison of the spirometric variables by respiratory disorder.

Variable	N	OLD	RLD	MORLD	p
	n=11	n=15	n=2	n=24	
Age (years)	11.8±4.2	9.3±2.5	9±2.8	14.4±5.1	p=0.004
VC (% of predicted)	96.1±8	81.7±6.6	70.5±3.5	50.5±13.7	p<0.0001
FEV1 (% of predicted)	95.7±13	68.2±3.7	79.5±2.1	45.5±18	p<0.0001
FEF25-75 (% of predicted)	84.3±19.2	52.5±9	108.5±17.7	34±18.9	p<0.0001
FEV1/VC	0.9±0	0.7±0	0.9±0.1	0.6±0.1	p<0.0001

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease.

Figure 1 compares the values of FEV1/VC ratio (bronchial permeability index) in normal individuals and the patients with CF, grouped by the type of respiratory disorders. No statistically significant differences between the control group, the group with preserved respiratory function and the group with presumptive RLD, although these groups differ significantly from the OLD and MORLD groups, that did not differ among themselves (p<0.0001). Regarding the patients grouped according to severity of respiratory dysfunction, there are statistically significant differences of the bronchial permeability index, in the 4 classes of patients (p <0.0001), those with severe respiratory dysfunction were having lower value of this report (Table 3).

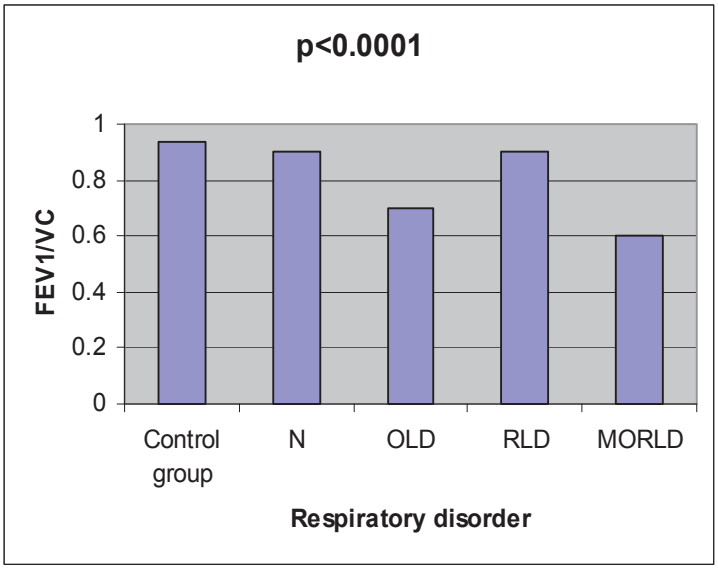

Figure 1 – Mean values of the airway permeability index (FEV1/VC) in the control group and in cystic fibrosis patients grouped by the type of respiratory disorder.

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease; VC – vital capacity; FEV1 – forced expiratory volume in one second.

Figure 2 compares patients with CF, grouped by the type of respiratory disorders, according to the value of the Cooperman Score (SCS), which considers the prognosis. The group with preserved respiratory function differs significantly from the other three groups in terms of prognosis, and the Cooperman Score in patients with MORLD is significantly lower than in groups with OLD and presumptive RLD (p<0.0001).

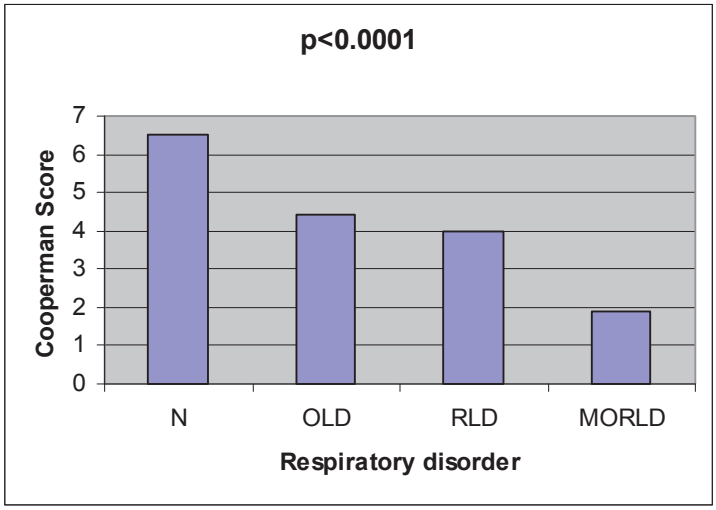

Figure 2 – Mean values of the Cooperman Score in the cystic fibrosis patients grouped by the type of respiratory disorder.

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease.

Table 3 and Figure 3 examine spirometry variables and the Cooperman Score, according to the functional severity (value of FEV1). Of the 52 patients, 12 (23.07%) had FEV1 ≥ 80%, for 21 (40.38%), FEV1 was between 60 and 80%, 9 (17.30%), FEV1 was between 40 and 60% and 10 patients (19.23%) had an FEV1 <40%. There are significant differences between the four groups of patients, by the value Cooperman Score (p <0.0001).

Table 3 – Comparision of the spirometric variables by functional severity (value of FEV1).

Variable	**FEV1≥80**	**FEV1≥60-80**	**FEV1≥40-60**	**FEV1<40**	**p**
	n=12	n=21	n=9	n=10	
VC (% of predicted)	94.2±9.7	76.1±11.1	57.8±9.5	38.6±8.5	p<0.0001
FEV1 (% of predicted)	94.5±12.5	68.8±4.3	53.8±4.3	26.5±5.4	p<0.0001
FEF25-75 (% of predicted)	87.4±20.2	56.2±13.4	38.1±9.5	17.5±7.3	p<0.0001
FEV1/VC	0.9±0.1	0.7±0.1	0.6±0	0.5±0	p<0.0001
Cooperman Score	6.4±2.5	3.9±1.9	2.3±1.5	1.2±1	p<0.0001

VC – vital capacity; FEV1 – forced expiratory volume in one second; FEF25-75 – forced expiratory flow between 25 and 75% of VC.

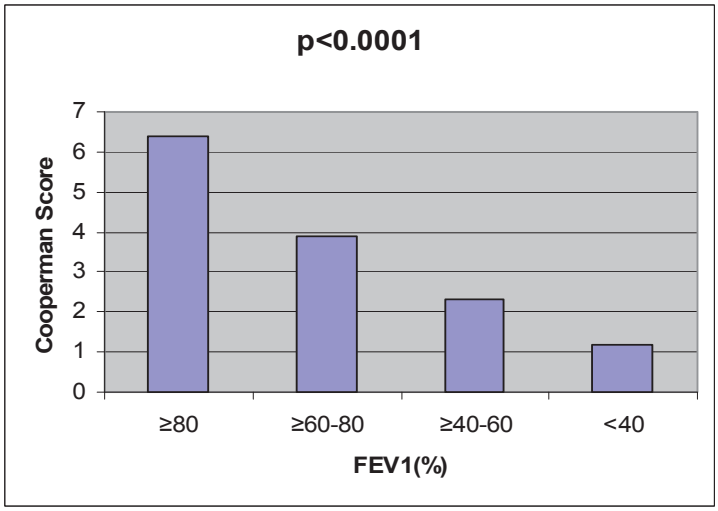

Figure 3 – Mean values of the the Cooperman Score in the cystic fibrosis patients grouped by the functional severity (value of FEV1).

FEV1 – forced expiratory volume in one second.

Discussion

In this retrospective cross-sectional study, we observed that out of 52 patients with CF, 41 (78.83%) showed deterioration in the respiratory function, as demonstrated by spirometry tests. The pulmonary function was preserved in 11 patients (21.15%). The most common type of the respiratory disorder was MORLD (46.15%), followed by OLD (28.84%). The average age of the MORLD group was significantly higher than other groups of patients, which shows the inherent progression of the disease and worsening lung function with age (p=0.004) (Table 2). If at first, inflammatory events, superimposed on obstruction, are reversible, their repetition leads to destruction of the lung parenchyma (12). The changes in the pulmonary function in patients with CF lung correlates with the severity of the structural changes and clinical manifestations. Our study showed a parallel trend in VC and FEV1 values (Table 3), which demonstrates the mixed character of the bronchoalveolar damage, at least in the stage where the endobronchial barrier is overcome. Thus, it becomes useful measure VC, as an indicator of the bronchoalveolar damage, to children who can not work for the determination of FEV1. The decline in the respiratory function is progressive, each exacerbation, representing another step toward the final moment (11).

There was a statistically significant association between the type of the ventilatory dysfunction, functional severity (FEV1 determination) and prognosis (Cooperman Score), MORLD patients had the highest degree of the functional deterioration and the more reserved prognosis. The average of the Cooperman Score for patients with MORLD was 1.9 ± 1.3 SD. Cooperman says in his article titled "A Simplified cystic fibrosis scoring system", that a score value of 4 or less has a serious prognosis (4). Although, CF is a multisystem disease, the prognosis is usually dependent on the degree of the respiratory impairment, some researchers agree that the pulmonary involvement is most responsible for morbidity and mortality (4). The evaluation of end-expiratory air flows, in patients with preserved lung function, showed a decrease in FEF25-75 to 60% of predicted value, in 5 patients. This shows narrowing of bronchial small pipes in a less advanced stage of disease, probably caused by the inflammatory process. Regarding the assessment of functional severity, as determination of FEV1, 40.38% of patients had mild pulmonary disease, 17.3% moderate damage and for 19.23% of the patients was severely impaired pulmonary function. 23.07% of patients had normal lung function. According to bibliographic data, it is considered that the value of FEV1 less than 30% mortality over the next two years is 50%, so the value of FEV1 may be useful in considering the optimal timing for heart-lung transplantation (6). In our study of 10 patients with severe pulmonary disease, 6 (11.53%) had a value of FEV1 below 30%. In agreement with the literature, this study highlights the value of marker stable of FEV1 in relation to prognosis (assessed by Cooperman Score), it is the more reserved (Cooperman Score lower value), as the value of FEV1 decreases. There were statistically significant differences Cooperman Score values in patients grouped according to severity of respiratory dysfunction (FEV1 value). Therefore, Cooperman Score is valuable for assessing pulmonary functional status (Figura 3).

Airway permeability index (FEV1/VC) was significantly lower in patients with OLD and MORLD, compared to other patients and its value decreased with the deterioration of the respiratory function (Figure 1 and Table 3). Particularly useful is monitoring the FEV1/VC ratio values, over time, for each patient. A study conducted in the Center of Mucoviscidosis from Timisoara showed that patients with clinical condition stabilized, despite the lower values of VC and FEV1, the values of the FEV1/VC report were acceptable. In contrast, in those that the FEV1/VC values curve became downward in parallel with decreased FEV1 and VC, the prognosis was infaust (11).

The main limit of this study was that respiratory tests did not include determining residual volume (RV) and total lung capacity (TLC), (TLC=VC+RV), which can not be assessed by spirometry. Thus, some patients diagnosed with MORLD, could have pure DVO, because of reduced VC (the restrictive component of MORLD) might be due to an excessive increase in RV. For these patients should be demonstrated decreased TLC, for the correct diagnosis of respiratory dysfunction (5).

Another limit of the present study was that it used a cross-sectional design, which does not provide sufficient evidence to establish a temporal link between the progression of disease severity and the patterns of alterations, as determineted by spirometry.

In **conclusion,** we observed that 78.83% of patients with CF taking the study had a lung function deterioration. MORLD has been the most common type of respiratory dysfunction due to the inherent disease progression with age. MORLD patients showed the greatest degree of severity funtion.

In CF, ventilatory exploration should include determination of RV and TLC, in addition to the usual tests, for correct diagnosis of respiratory dysfunction.

FEV1, VC and FEV1/VC report have demonstrated its important as prognostic factors. It is necessary to perform periodic spirometry for providing therapy to the clinical condition (including when necessary the heart-lung transplantation).

Analysis of end-expiratory flow parameters (FEF25-75) allowed the identification of respiratory disorders in some patients initially classified as having normal lung function, leading to early recognition of changes in peripheral airway levels.

The Cooperman Score is a simple tool which assesses both prognosis and effects of different drugs and treatments, used in the management of CF. The study highlighted the importance of this score for pulmonary functional status, responsible for the greatest morbidity and mortality in CF.

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HISTOLOGICAL MODIFICATIONS OF THE FETO - PLACENTAL INTERFACE IN PREGNANCY INDUCED HYPERTENSION

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Abstract

Objective. To present the main structural modifications of the feto-placental interface, in pregnancy induced hypertension (PIH).

Material and Method. We have studied the main microscopical modifications of 68 placentas obtained after delivery for two equal groups: one group (**N1**=34), representing mothers with PIH and another group (**N2** = 34) normotensive mothers. The samples obtained by sections were specificaly prepared for the study of 3 types of histological stains and 2 types of immunohistochemical stains. For the histological examination we used optical microscopy for observing mainly the lumen of spiral arteriole and changes in its tunica intima and media.

Results. We registered the following structural modifications in the pregnancies with PIH versus normal ones: changes in endothelium –76,47%, fibrinoid necrosis – 73,52%, the hypertrophy of tunica media – 67,64%, bridging syncytial knots –32,35%, avascular small terminal villi with hyaline fibrosis of the stroma–41,17% and the thrombosis of the spiral arterioles –26,47%.

Conclusions. A better understanding of the immunohistological damages demonstrated through our study, concerning the preeclamtic feto-maternal interface, will change in the future, our understanding about the role of this placental unit in PIH.

Key words: Pregnancy Induced Hypertension (PIH); Fetal Chronic Hypoxemia; Feto-maternal interface; Histological modifications.

Introduction

Preeclampsia is a major problem of modern obstetrics and various studies are mentioning PIH as a severe complication, one of the largest causes of maternal and perinatal morbidity and mortality of about 5 – 7% pregnancies throughout the world[1,2]. The gravity of the disease is a real emergency in obstetrical departments. The incontestable paradox is the fact that after the birth and the delivery of the placenta, the arterial hypertension disappears[3]. Because PIH is associated with the increase of the feto-placental vascular resistance[4], the disease represents one of the most important causes of: intrauterine growth limitation, premature birth, low birth weight, perinatal mortality.

Material and method

The study was performed with the written consent of the mothers between january 2008 and december 2010. We have studied the main microscopical modifications of the 64 placentas - obtained after delivery - from the two equal groups: one group (**N1**=34), representing mothers with (PIH) and another group (**N2** = 34), with normotensive mothers.

The main factor of differentiation was the value of the blood presure: For the group of normotensive pregnant women, the values of the systolic TA ranged between 100-135 mmHg, and of the diastolic TA, between 60-85 mmHg. The difference to the hypertensive pregnant women group was made only in the cases where the values of the systolic TA > 140mmHg and diastolic TA > 90 mmHg.

Significant differences in the rest of the clinical parameters between the two groups were registered also for the gestational age, birth weight, type of the birth and immediate neonatal adaptation.

For both groups, the following cases were not included: those with essential hypertension, multiple pregnancy, diabetes mellitus, chronic renal diseases, epilepsy and hematological disorders.

Specimens

Samples were obtained from the 64 placentas immediately after the birth.We have taken at least 2 samples of sections made from both - maternal and fetal - side of the placenta, for the study of 3 types of histological stains and 2 types of immunohistochemical stains.

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For the histological examination of the samples we used optical microscopy for observing mainly the lumen of spiral arteriole and changes in its tunica intima and media. They were in fixation in 4% buffered formalin, for 24-48 hours.

Hematoxylin–Eosin technique
- fixation in a 10% formalin solution
- dehydration in ethanol gradated series
- sedimentation in xylene
- sections
- paraffining
- deparaffining
- hydration and coloring with hematoxylene – eosine

Van Gieson's technique
- tissue sections to Ethyl Alcohol and stain with Weigert's iron hematoxylin for 15 minutes
- wash in running water for 15 minutes and rinse with distilled water
- Van Gieson's stain for 5 minutes and rinse in distilled water
- rinse rapidly in 70% Ethyl Alcohol
- dehydrate rapidly in Absolute Alcohol
- clear and mount in Neutral balsam

Masson's Trichrome technique
- deparaffinize and hydrate to distilled water
- slides in 40 ml of Bouin's solution contained in a plastic coplin jar and microwave
- mix solution with beral pipet
- incubate slides in heated Bouin's solution for 15 minutes in a fume hood
- wash slides in tap water until sections are clear
- stain in working Weigert's hematoxylin 5 minutes
- wash slides thoroughly in tap water
- 0.5% Hydrochloric acid alcohol for 5 seconds
- wash in running tap water for 30 seconds and rinse in two changes of distilled water
- stain in TRICHROME solution for 15 minutes and wash slides in tap water
- rinse in 0.5% Acetic acid 10 seconds and in distilled water
- dehydrate through graded alcohols
- mount with resinous mounting media

Immunohistochemistry

The IHC experiment was performed using the DAKO LSAB2 System method.

Samples sections were rehydrated, washed and then rinsed in PBS (pH 7.2). Antigen retrieval was achieved by using the HIER (Heat Induced Epitope Retrieval) method. IHC staining was performed upon 0.5 μm thick, on PolysineTM slides wich were incubated with 3% hydrogen peroxide solution for 5 minutes, then washed with PBS. Formalin-fixed, paraffin-embedded tissues were incubated so the slides could react with a labelled avidin-biotin complex, peroxidase-labelling detection system (Vector Universal Elite kit) and then treated with 3,3'-diaminobenzidine-peroxidase substrate solution, as chromogen (DAB Tablets, S3000-Dakopatts, Glostrup Denmark) until color was visualized. It was done using the method EmVision Dual Link-HRP. All reagents and supplies for the technique were from Dako, Denmark.

The primary antibodies were mouse monoclonal anti-Human Cytokeratin (code M 0821 Dako, 1:50) and monoclonal mouse anti-Human CD34 (Class II, clone QBEnd-10, DAKO, 1:50). Those were incubated for 30 minutes. The negative control reagent used for LSAB2 was Universal Negative Control, Rabbit (code N1699) and Dako Mouse IgG1 (code X0931) diluted to the same mouse IgG concentration as the primary antibody. Sections were washed twice in distilled water to stop the reaction, then counterstained in hematoxylin, washed, dehydrated, cleared in xylene, mounted with DPX, and glass cover-slipped.

Sections were examined with a ×100 objective on a AmScope microscope, and images were captured using a High speed 1.3 Megapixel USB 2.0 digital camera AmScope and a DN–100 digital imaging system.

Results

Histological aspects of the placentas comparing group N1 with group N2, we have registered the following modifications – Tabel 1:

- ***changes in endothelium*** were - enlargement, atrophy, disruption
- the considered pathognomonic lesion - the ***fibrinoid necrosis*** wich affects ***the wall of the spiral arteriole***
- the ***hypertrophy of the smooth muscles tunica media***
- ***avascular small villi*** meaning ***terminal villi*** showing the total loss of villous capillaries and bland ***hyaline fibrosis of the villous stroma***
- fibrin and/or bridging **syncytial knots** and **villous agglutination** is seen as clusters of adherent distal villi agglutinated
- the **thrombosis of the spiral arterioles**

In the group N2, by the microscopical examination, villous structures appeared almost normal, the connective tissues of each villous covered by trophoblastic cell layers and rich in fetal capillaries. The intervillous spaces were filled with maternal blood separated from each other. Figure 1.

In the group N1, microscopical changes of the placentas showed diffuse hypoxia histologically diagnosed based on the next main modification:
- heterogenous placental maturation – Figures 2 and 3,
- decreased chorionic villi by amount of the extracellular matrix,
- decreased density of the villous cytotrophoblastic cells and Hofbauer cells of the villous
branching of capillaries excessive,
- fetal capillaries have usually disappeared in most villi – Figure 4,
- syncytial knotting (smudgy and granular nuclear chromatin).

Tabel 1 – Histolological modifications of the placentas in the 2 study group.

Nr. crt	Structural modifications	P I H + (N1 group)		P I H – (N2group)	
		Nr.	%	Nr.	%
1.	Endothelium - enlarged, disrupted, atrophied	26	74,47	3	8,82
2.	Fibrinoid necrosis of the wall of the spiral arteriole	25	73,52	1	2,94
3.	Hypertrophy of the smooth muscles tunica	23	67,64	2	5,88
4.	Hyaline fibrosis of the villous stroma and avascular small terminal villi	9	26,47	0	0
5.	Bridging syncytial knots and fibrinous distal villous agglutination	11	32,35	0	0
6.	Thrombosis of the spiral arterioles	14	41,17	0	0

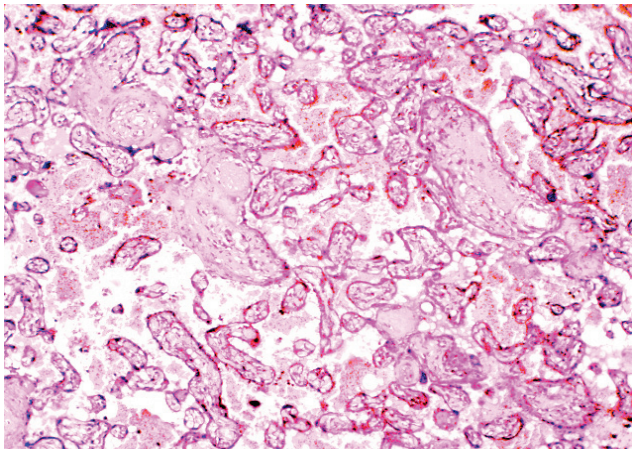

Figure 1 – Villous covered by trophoblastic cell layers and rich in fetal capillaries (H.E., x 40).

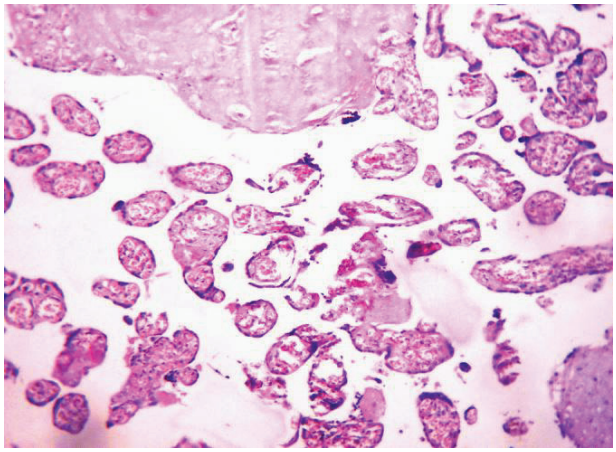

Figure 2 - Avascular terminal villi total loss of villous capillaries (H.E., x 40).

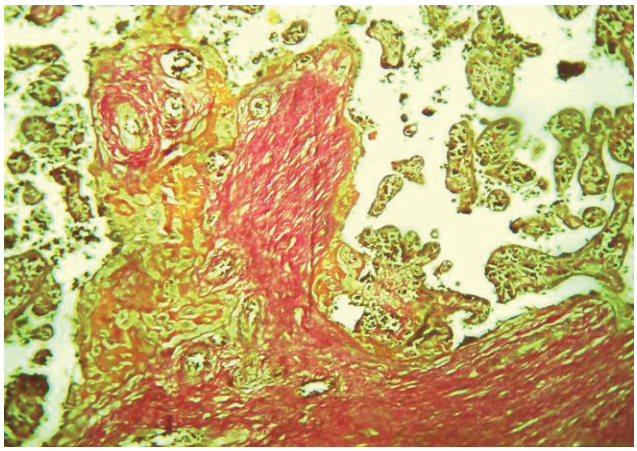

Figure 3 – Heterogenous villous maturation, hyaline stromal fibrosis (Van Gieson's x 40).

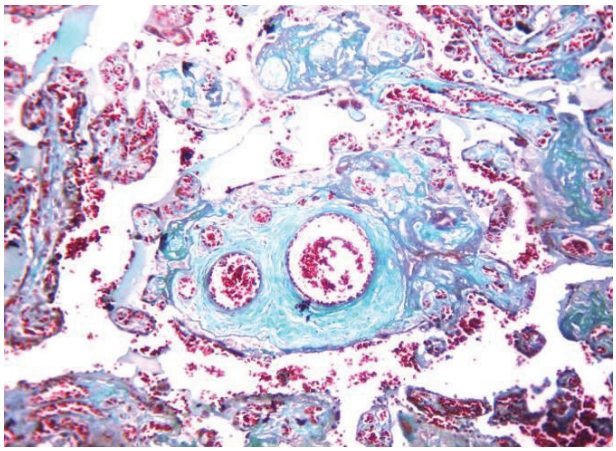

Figure 4 – Acute atherosis of the arterial smooth muscle (Masson's Trichrome, x 40).

The decidua presented some chorionic pseudocysts, laminar fibrinoid necrosis of the arterial smooth muscle with acute atherosis, which is characterized by and a lot of arterioles showed endothelial degeneration with progressive fibrosis and obliteration – Figures 5, 6 and 7.

The nuclei of the syncytiotrophoblasts had the tendency to develop clusters and sprouts protruding into the intervillous spaces – Figure 8.

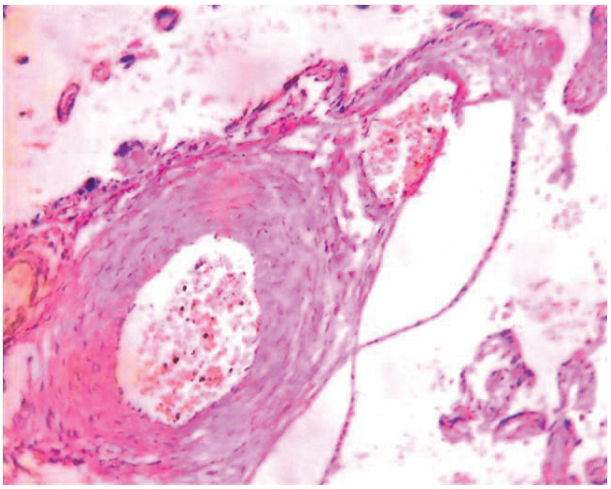

Figure 5 – Decidual chorionic pseudocysts, with laminar fibrinoid necrosis (H.E., x 100).

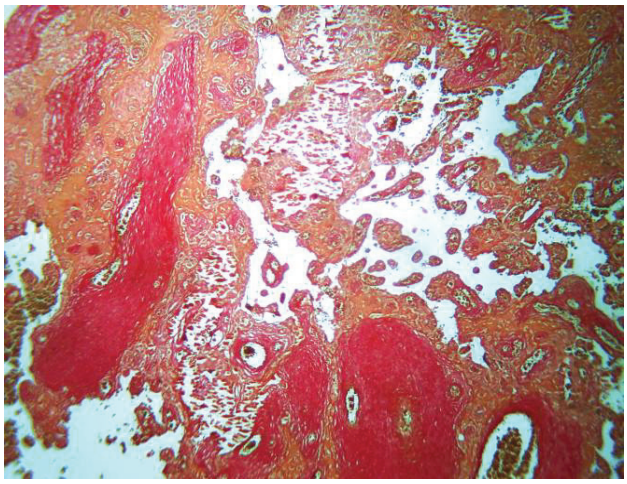

Figure 6 – Endothelial degeneration, fibrosis, obliteration of arterioles (Van Gieson's x 40).

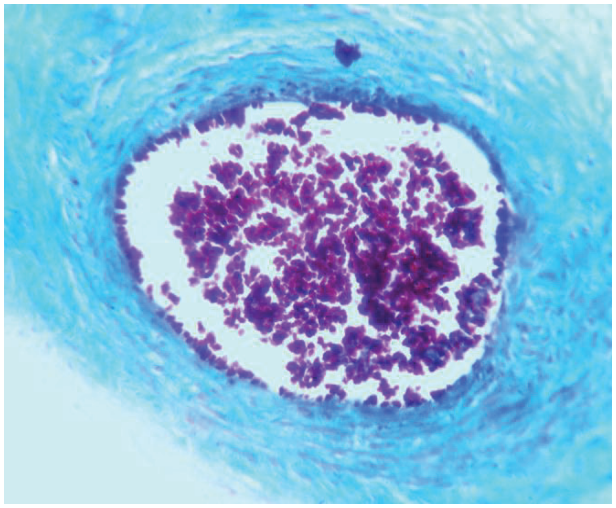

Figure 7 – Fibrinoid necrosis of the arterial smooth muscle (Masson's Trichrome, x 100).

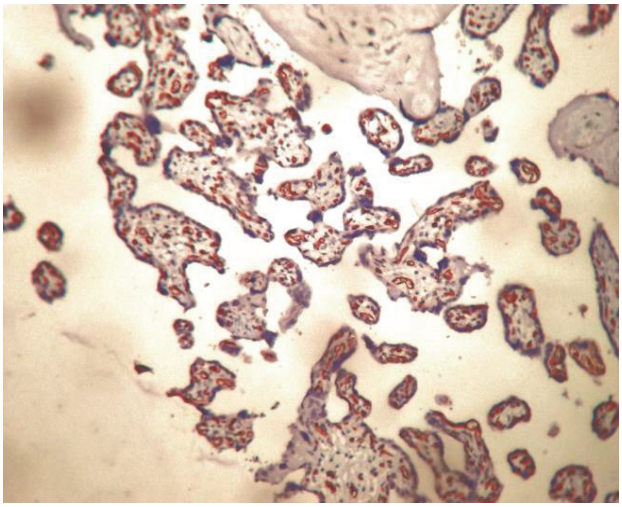

Figure 8 – Syncytial knots along the stem or distal villi with trophoblast cells invading the placental bed (IHC – CD34+, x 40).

We noticed the absence of any distal villous core and a lot of fibrous bridges who connected the intervillous spaces of one villus to another, giving a pseudolabyrinthine appearance to the villous tree – Figure 9.

In the lumina of the still preserved capillaries we recognised red blood corpuscles and the fibrous connective tissue proliferating and replacing the fetal blood sinusoids, in the terminal villi.The absence of the capillary wall structure, in the reduced number of villi exhibited some fetal nucleated red blood cells with the appearence to rise directly from the connective tissue stroma – Figure 10.

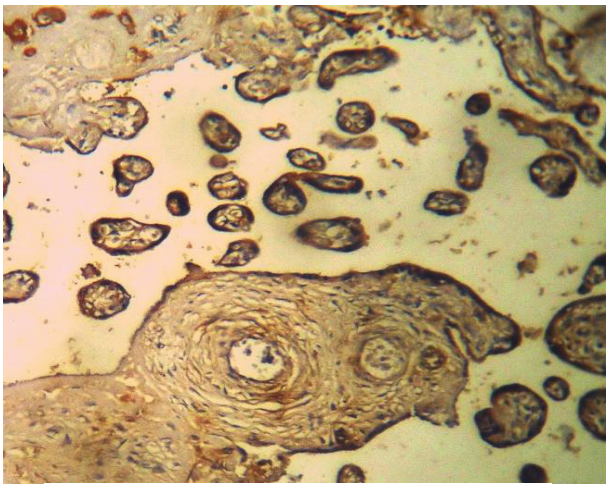

Figure 9 – Fibrin or bridging syncytial knots, pseudola- byrinthine appearance of the villous tree (IHC - Cytokeratin +, x 100).

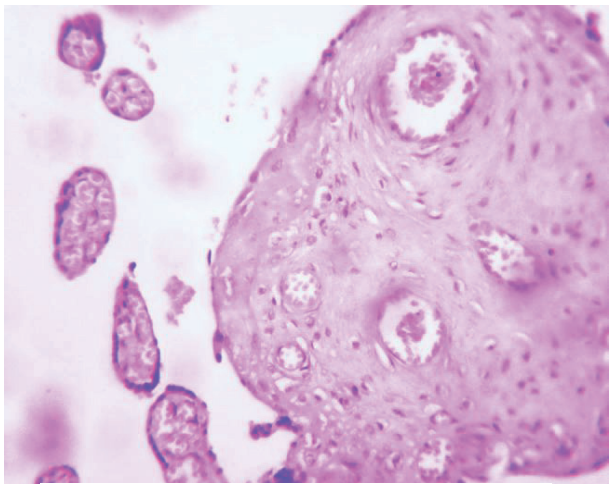

Figure 10 – Stromal vascular karyorrhexis with nuclear debris of fetal cells (H.E., x 200).

Discussions

PIH represents a real natural model of fetal malnutrition and hypoxia.The reduction of the vascular dimensions is constantly accompanied by significant structural disorders which have an impact upon the lumen of spiral arteriole[5] with changes in its tunica intima, media and fibrillary structures[6].These structural modifications are associated quasi-constantly with the PIH cases versus the normotensive cases, in which they are quite rare and isolated.

In our study the group N1 microscopical changes of the placentas showed diffuse hypoxia[7,8] histologically and modifications are suggestive for a predominantly hypoplastic mechanism. At a vascular level the first reaction to hypoxemia is the vasoconstriction. If the hypoxemia continues, it produces hypoplastic modifications, with immediate and late hemodynamic consequences[9]. The morphological modifications of the fetal vascular system may represent a main factor, for vascular affections of the future adult[10].

Conclusions

The morphological modifications of the feto-placental interface in the PIH represent a marker of important fetal and postnatal hemodynamic deficiencies. The hemodynamic status of the foetus and of the new-born baby by mothers suffering from PIH are characterized by hypoxia/ischemia with an immediate and late impact upon their cerebral development.

We consider that the above described lesions leed to many physiopathological consequences:

- important, and for long time, fetal blood stream reduction;
- a fetal oxygenation reduction with chronic hypoxemia, wich has a direct impact upon the cerebral development;
- fetal molecular signals by the mother with massive reaction from the pregnant woman body, leading to a bad evolution for both – fetus and mother.

A better understanding of the histological damages in preeclamtic feto-maternal interface, will change in the future, our medical assistance during the pregnancy.

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CONGENITAL RUBELLA SYNDROME – CASE REPORT

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Abstract

Congenital rubella syndrome is a group of physical abnormalities that have been developed in an infant as a result of maternal infection and subsequent fetal infection with rubella virus. Rubella is a common cause of maculopapular rash illness with fever. The disease has few complications unless it is contracted by a pregnant woman. Rubella infection in pregnancy can lead to miscarriage, stillbirth, or an infant born with congenital rubella infection. The paper presents the case of a patient who came into our service for the first time in 2004 with some severe symptoms and signs. The first diagnostic was diabetic ketoacidosis stage III (ketoacidosic coma), but after that, the child comes into the Hospital several times more along the following years for reevaluation, when other complications are revealed.

Key words: Congenital rubella syndrome, diabetes mellitus, cardiac malformations, delayed diagnose

Background

Congenital rubella syndrome is a consequence of rubella infection that can occur when the virus is transmitted in utero during maternal primary infection [1].

When infection occurs in the first 11 weeks of pregnancy, babies presents heart defects and deafness; between weeks 13 to 16 only deafness. When infection occurs after 16 weeks, newborns don't have any congenital defect [2]. So, fetal pathology is common when infection occurs in the first 16 weeks of pregnancy. Pathogenic mechanisms of teratogenic effect induced by rubella are not well known, the most common hypothesis is to suggest direct involvement of viral replication in cell clones during fetal organogenesis [3]. In classical acceptance, congenital rubella syndrome is the triad consists of: cataracts, deafness and heart defects. Cataracts and microphthalmia occur in 1/3 of cases [4]. Sensory or central deafness is the most common sequel, appears at a rate of 80% of infected children [5]. It is the only event that can come as isolated congenital rubella. In addition to congenital syndromes, maternal infection near term is commonly associated with fatal neonatal diseases, possibly due to fetal exposure to transplacental viremia in the absence of maternal protector antibodies. Passive immunization with immunoglobulins does not guarantee fetal safety [6].

Case presentation

First hospitalization:

Clinical examination revealed an 12 years old infant with the following parameters: weight = 36 kg, height = 140 cm, ideal waist for age = 149,32 ± 7,5 cm, ideal weight for current waist = 32,01 ± 6,6 kg, age current waist = 10,5 years (Fig. 1).

Family history of child comes from G II, P II, gestational age (GA) = 37 weeks, birth weight 2000 g, 49 cm, 1,69 ponderal index (P.I. = G/T3 x 100), intrauterine growth restriction, breastfed up to 1 year and 6 months.

Clinical examination on admission revealed: general condition deeply altered, obnubilation, pale, warm, dry, rough skin, subcutaneous tissues completely disappeared from the trunk and limbs, dry mucous, dry, friable hair and nails, muscular system - hypotonia, hypotrophy, hipokinetic, cardio-respiratory system- asthenic chest, respiratory rate = 22 breaths/min, pearly white linear scar on the midline from the sternal manubrium to the epigastric region after surgical procedure, pulse rate = 104 beats/min, systolic murmur II degree, closing click, digestive system – oral infection, carmine dry lips, splenomegaly.

Laboratory investigations revealed: total bilirubin - 5.62 mg / dl (N = 0.1 to 1.1), lipids – 3215mg/dl (N = 400-800 mg / dl) cholesterol – 603 mg/dl (n = 0 - 200 mg / dL), triglycerides - 1768mg/dl (N = 28-127 mg / dl), blood sugar – 817 mg% (N = 80-120 mg%), HbA1c - 16% (N = 4,5 - 7%) . Normal eye exam. EKG - sinusal rhythm, HR = 100 beats/min, electric axis deviated to the left, right bundle branch block.

Echocadiography: Bicuspid aortic valve without regurgitation, intact interatrial septum. In the left ventricle, it is highlighted a single posteroinferior pillar. Mitral valve regurgitation to the posterior wall of the left atrium, I/II degree. Without liquid in the pericardium. Conclusion: heart surgery, mitral regurgitation, I/II degree.

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Infantile neuropsychiatry examination: Babinski cutaneous-plantar reflex positive to the left on stimulation. Normal EEG without pathological graphoelements. Psychological evaluation: medium mental retardation, IQ = 57 (Raven Test). Slow thinking. Emotional immaturity. Genetic consult: particular phenotype, oblique palpebral fissure, hypertelorism. Narrow forehead, septum deviation. Geographic tongue (Fig. 2). Slow writing, chaotic dermographism, fifth finger clinodactyly (Fig. 3).

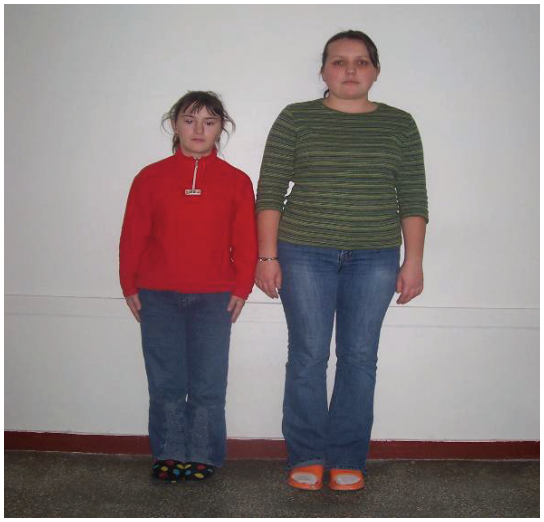

Figure 1. Staturo-ponderal delay.

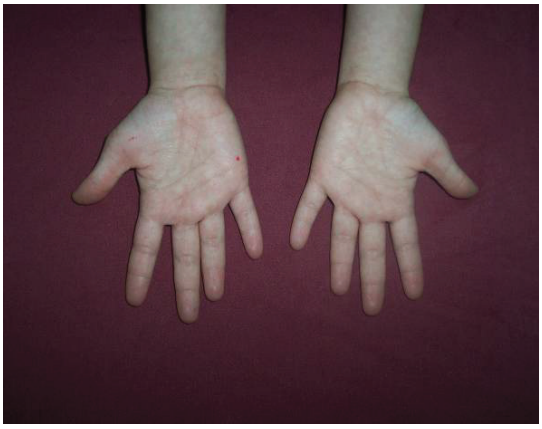

Figure 3. Fifth finger clinodactyly.

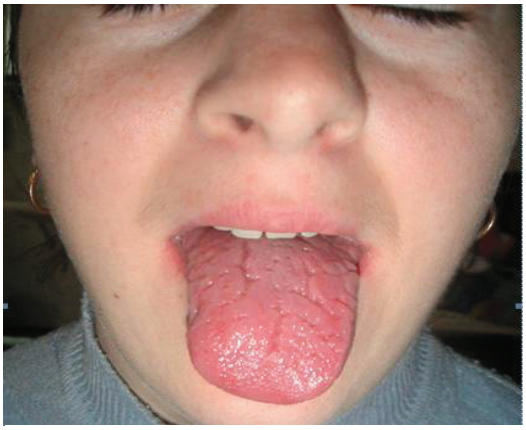

Figure 2. Geographic tongue.

Normal karyotype. The insulin-dependent diabetes mellitus diagnostic is confirmed and it is established venous perfusion with insulin and diet. Only after five days is resorting to subcutaneous injections insulin therapy + diabetes diet type divided into 6 meals/day. Since history shows that classic symptom onset diabetes (polyuria, polydipsia, weight loss) lags behind at least 4-5 months which is a contrast to the way the child onset diabetes!

Pathological personal history: Heart surgery in 1997 for: mitral insufficiency by mitral valve cleft of previous ventricular septal defect, persistent foramen ovale, pulmonary hypertension, the aberrant insertion of the secondary tendinous cords of the anterior mitral valve in the right ventricle.

In evolution: laboratory, positive C-reactive protein, positive ELISA HBS Atg, HbA1c = 8,8% oriented towards the diagnosis of chronic hepatitis with B type hepatitis. At 8 months after diagnosis of type 1 diabetes are seen: polynodular goiter, confirmed by ultrasound and hormonal dosages and it has been administered substitution treatment with L-thyroxine.

Simultaneously, the emergence of a progressive and rapidly developing bilateral cataracts which requiring surgery are seen (bilateral lens implant) at just 1 year after the onset of type 1 diabetes (Fig. 4). Pubertal retardation - Tanner I/II at the age of 14,5 years. Menstrual cycles are irregular (oligo/dysmenorrhea) at 4-5 months. Gynecological exam: normal. Bone age corresponding chronological age. Sella turcica X-Ray: normal shape and size. Following insulin replacement therapy in 4 injections/day, diabetes diet type divided into 6 meals/day, associated with thyroid substitution treatment, in the period 2004 to 2010 a weight increase of 5 kg (37-42 kg) and a stature increase of only 0,5 cm occurs.

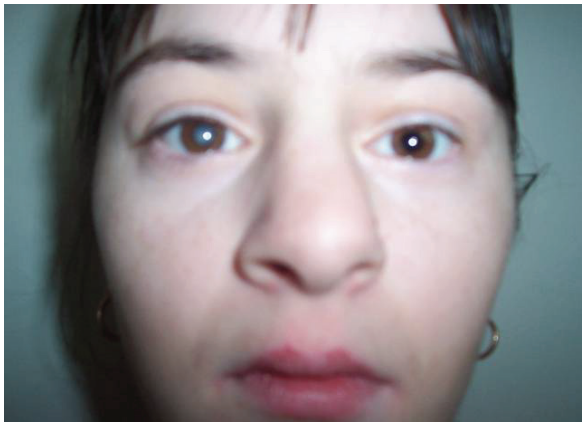

Figure 4. Rapidly progressive cataract (initially on the right eye).

*Photographs were made with mother agreement, respecting the ethical principles and protection of the minor.

Discussions

The presented case is extremely complex both in terms of symptoms presented, a variety of disease complications of the revolving rapidly especially in the first period, and that of the period of time stretches. Accumulating these things, looking back and comparing this case with similar cases in the literature, concludes that in this case the disease is prenatal undiagnosed congenital rubella by PCR of amniotic fluid [7] and involving classical triad:

- ✓ Congenital heart disease, especially patent ductus arteriosus (50% of patients) [8],
- ✓ Eye abnormalities, especially cataract and microphthalmia (43% of patients) [9],
- ✓ Sensorineural deafness (58% of patients) [5].

Other manifestations of CRS may include:

- ✓ Diabetes type III (!) - at this age, type 1 diabetes (insulin dependent diabetes) has classical clinical symptoms duration of maximum 30 days (intermediate onset type). Type 2 diabetes has a genetic load of 80-90% of cases [10], which **has not been found** in our case.
- ✓ Mental retardation
- ✓ Eye defects
- ✓ Low birth weight
- ✓ Developmental delay
- ✓ Growth retardation
- ✓ Learning disabilities
- ✓ Spleen, liver or bone marrow problems (some of which may disappear shortly after birth)
- ✓ Small head size (microcephaly)
- ✓ Thrombocytopenic purpura (presents as a characteristic blueberry muffin rash)
- ✓ Hepatomegaly
- ✓ Micrognathia
- ✓ Schizophrenia
- ✓ Glaucoma

The consequences of congenital rubella syndrome occurs during the whole life, at any time there is a risk for a new diseases to appear, such as thrombocytopenic purpura, paranoid schizophrenia [11], glaucoma or worsening the one that are already present. Once again we must emphasize the importance of preventing maternal-fetal infection during pregnancy because so far no one has developed an effective therapy for congenital rubella virus and the passive immunization with immunoglobulins does not guarantee fetal safety.

According to ISPAD Clinical Practice Guidelines, diabetes is classified as [10]:

I. Type 1

β -cell destruction, usually leading to absolute insulin deficiency

A. Immune mediated

B. Idiopathic

II. Type 2

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance.

III. Other specific types

Genetic defects in insulin action	Infections	Drug or chemical-induced
1. Type A insulin resistance	**1. Congenital rubella**	1. Vacor
2. Leprechaunism	2. Cytomegalovirus	2. Pentamidine
3. Rabson-Mendenhall syndrome	3. Others	3. Nicotinic acid
4. Lipoatrophic diabetes		4. Glucocorticoids
5. Others		5. Thyroid hormone
		6. Diazoxide
		7. β-adrenergic agonists
		8. Thiazides

Tabel 1. Specific types of diabetes, (*Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatric Diabetes 2009*).

Conclusions

This case presentation wants to be a looking back, a review of the case and an alarm sign pulled by us according to rubella congenital syndrome which can be very difficult to anticipate and to be diagnosed on a child in this stage.

The facts that we discussed in this paper are pleading for rubella congenital syndrome diagnose and unfortunately this doesn't change anything in the medical evolution of the case. This is why we tried to expose the facts chronologically to clarify other diagnostic possibilities, to explain for the clinicians the options, to understand, to recognize and to treat a similar case when they are in the position to do it.

Nevertheless, we want to highlight once more the importance of the screening for bacterial and viral infections in pregnancy.

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DENTAL AND CRANIOFACIAL ANOMALIES IN A PARTICULAR CASE OF TURNER PHENOTYPE

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Abstract

Turner syndrome (TS) is a genetic disorder associated with abnormalities of the X chromosome, occurring in about 50 per 100 000 liveborn girls. We present the case of a 9 year old girl, admitted to the Children's Hospital "Louis Turcanu" Timisoara, Pediatric Clinic I in november 2008, because of short stature and particular phenotype, in order to establish a complete diagnosis. The clinical and paraclinical features for the diagnosis of Turner syndrome were represented by: dysmorphic dwarfism, particular phenotype, karyotype - homogenous total X monosomy, renal malformation, hearing impairment. Dental clinical examination, extraoral and intraoral orthodontic investigation, cephalometric examination and pantomographic investigation revealed the following modifications: high palate, macroglossia, hypoplasic low face level, enamel hypoplasia, dental-alveolary dysarmony with squashing at the mandibular arch level, simple superficial caries of the occlusal face. Therapy included correction of short stature with growth hormone administration, treatment of caries and orthodontic treatment. Particularity of this case is due to the extremely rare renal malformation – "pancake kidney", and to the uterine agenesia, which is not characteristic for this syndrome.

Key words: Turner syndrome, dental and craniofacial anomalies, child

Introduction

Turner syndrome (TS) is a genetic disorder associated with abnormalities of the X chromosome, occurring in about 50 per 100 000 liveborn girls. TS is usually associated with reduced height, gonadal dysgenesis and thus reduce levels of female sexual hormones and sterility/infertility. The average intellectual performance is within the normal range.

The genetic background of the TS phenotype is highly variable, but includes complete or partial absence of the sex chromosomes (the X and/or Y chromosomes). In addition, mosaicism with two or more cell lines may be present. The first described cases were with the 'classical' karyotype 45,X. In more recent series the classical karyotype only accounts for 50% of cases; the remaining cases comprise mosaic karyotypes (i.e. has cells with 45,X and cells with 46,XX), karyotypes with an isochromosome of X—for example i(Xq) or i(Xp)—or karyotypes with an entire or part of an Y chromosome[1]. The genetic basis for the findings in TS is being further unravelled as the functions of the *SHOX* gene become clearer. Haploinsufficiency of *SHOX* explains the reduction in final height, changes in bone morphology, sensorineural deafness and other features. However, additional genes are thought to be involved in the pathogenesis of TS, but await new discoveries.

Case presentation

Giulia B., 9 years old, with a history of recurrent urinary tract infections (UTI), diagnosed with horseshoe kidney in 2003, is first admitted to the Nephrology Department, Paediatric Clinic I, Children's Hospital " Louis Turcanu" Timisoara, in 19.11.2008, presenting short stature and particular phenotype, in order to establish a complete diagnosis.

She is the first borne of a young, healthy couple, with good socio-economic background, pregnancy with abortion risk, periodically hospitalized for treatment, birth age 40 weeks, normal birth in cranial presentation, birth weight = 2000 g, height = 48 cm, Apgar score 8, no physiologic jaundice, formula nutrition from birth, ricketts prophylaxy and immunisation scheme complete.

Family history is not significant, personal medical history reveals a suspicion of malabsorbtion syndrome at 1 year of age, recurrent UTIs between 2 and 4 years of age (horseshoe kidney diagnosed by CT), at the age of 9 subperiostal fracture of 1/3 inferior right tibia, and an adenoidectomy before the admission; the otorhynologist also diagnosed hearing impairment and noticed the short stature, recommending further investigations.

1. Physical examination at admission reveals (Fig. 1,2):

- Real Height = 110 cm ; Age Height = 131,61+/-6,1 cm; Growth deficit = -16% (under 3rd percentile 3, -3,5 SDS)
- Chronological Age = 9 years 5 month; Height Age = 5 years

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• Real Weight = 24 kg; Weight corresponding to real Height = 18,59±2,76 kg; BMI = 19,8 kg/m2 (over 97th percentile)
• Morphogram reveals a dysmorphic dwarfism: Cranial perimeter = 53 cm (+0,8 SD); Thoracal perimeter = 66 cm (+0,7 SD); Abdominal perimeter = 63 cm (+1,4 SD) ; Pelvic perimeter = 66 cm (-0,7 SD); Biacromial distance = 29 cm (+0,4 SD) Manubrium-ground distance = 90 cm (-3 SD), Pubis-ground distance = 55 cm (+2,8 SD), Bitrochanterian distance = 27 cm (+2,3 SD).
• Phenotype features: microretrognathia, dental anomalies, high-arch palate, assymetric low-set ears, with a larger left ear, low M-shaped hairline, short neck, biacromial diameter > bitrochanterian diameter, Kosowitz sign present, broad chest (*shield chest*) and widely spaced nipples, genu valgum, increased weight. The rest of the physical exam revealed no modifications regarding the different organs and systems.

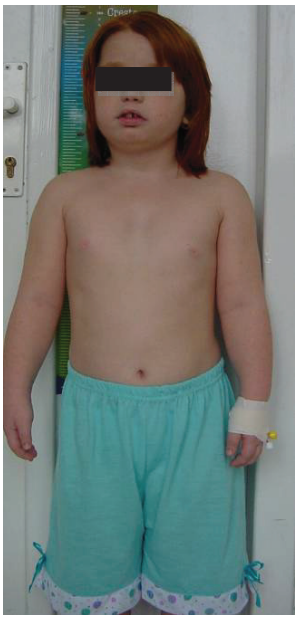

Fig. 1. Dysmorphic Short Stature.

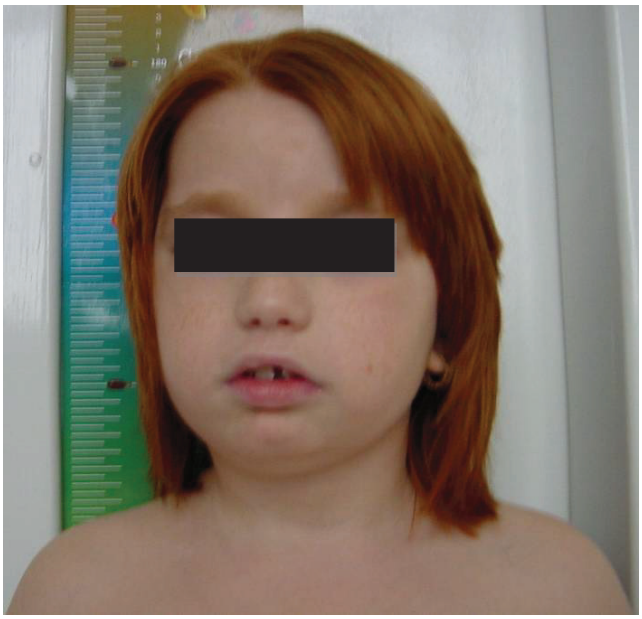

Fig. 2. Particular Phenotype.

2. Clinical diagnosis raised the suspicion of Turner syndrome (TS), based on the association of short stature + particular phenotype + hearing impairment + renal malformation.

3. Differential diagnosis was mainly made between the following syndromes, considering clinical features that are for or against the suspected diagnosis:

	FOR	AGAINST
TURNER SYNDROME	• only female affected • short stature • dental anomalies, high-arch palate • asymmetric, low-set ears, low M-shaped hairline • short neck • biacromial diameter > bitrochanterian diameter, Kosowitz sign present • shield chest • widely spaced nipples • genu valgum • *renal malformations, horseshoe kidney, ovarian dysgenesia, karyotype 45x*	• transient lymphedema of hands and feet • cranio-facial dysmorphism (triangular face shape, epicanthal folds) • pterigium coli • short metacarpian of finger IV, hyper convex, soft upturned nails • *cardiac malformations, karyotype 45x/46xx, 46xdel(x)*
NOONAN SYNDROME	• short stature 25 %	• both sexes equally affected • drooping of the eyelids, epicanthal folds, strabismus, hypertelorism • pectus excavatum or carinatum • *normal karyotype*

	FOR	AGAINST
DOWN SYNDROME	• short stature • short neck • bilateral hearing impairment	• up slanting palpebral fissures, small nose, microgenia, macroglossia, protruding tongue • strabism • short and wide hands, bradidactilia, clinodactilia of finger V, simian crease • *visceral malformations (duodenal atresia, anal imperforation), cardiac malformations, severe mental retardation, karyotype 47xx/47xy*
GH DEFICIENCY	• short stature	• doll face, retrognathia, thin skin with freckles • high voice • small genitalia • sexual development can be normal

We also took in consideration for the differential diagnosis several disorders such as: achondroplasia, pure gonadal dysgenesia, hypothyroidism, cortisole excess, chronic cardiac, pulmonary, renal and digestive diseases, all of them associated with growth failure.

4. In order to establish a complete and correct diagnosis we performed the following investigations:

- *Karyotype:* indirect method of chromosomes analyse was performed, using the GTG banding technique, a number of 20 metaphases were cytogenetically evaluated, and the karyotype was performed computer-assisted. The presence of a numeric chromosomial anomaly was established by the standard cytogenetic method: homogenous total X monosomy, no presence of any cell with normal karyotype, so a mosaicism is excluded. *Cytogenetic Diagnosis: homogenous total X monosomy*. (Fig. 3)
- *Bone age Xray:* bone age corresponding to the chronological age of 7,9 years, growth cartilages present.
- *Evaluation of glucides metabolism:* oral glucose tolerance test with 45 g glucose: a jeun glicemia = 57mg% (venous blood), 2h glicemia =122,5mg% (venous blood)
- *Hormonal status* – to exclude GH defficiency – normal values for IG F1 = 139 ng/ml (november 2008), and basal GH = 0,06 ng/dl were detected, insulin stimulation test with 0,1U/kgc showed no modifications.
- *Biologic investigations:* Leukocytes = 8.670/mm³, RBC = 5.030.000/mm³, Hb =13,2 g/l, Ht=41,2 %, Trombocytes = 418.000/mm³, ESR = 10 mm/h, GPT = 16 U/l, GOT = 40 U/l, Na = 140 mmol/l, K = 5 mmol/l,Ca++ = 1,17 mmol/l, Alkaline phosphatase = 156 U/l, pH = 7,38, pCO2 = 30,2 mmHg, pO2 = 54,3 mmHg, HCO3 = 17,5 mmol/l, BE = -7,5 mmol/l, BUN = 5,2 mmol/l, Creatinine = 40µmol/l, Uric acid = 334µmol/l, Cl creatinine = 134,4 ml/min, Urinalysis: albumine traces, frequent leukocytes, rare epithelia, frequent bacteria, Urine culture: >100000 germs/ml E.coli
- *Otorhynologic exam:* left chronic mucous otitis media, mild right chronic otitis media. Audiogram: *severe mixte hearing loss left ear.*
- *Cardiologic exam:* normal cardiac rhythm, 110-120 beats/min, systolic murmur grade I in Erb focus, perypheric puls present, BP=100/60 mmHg; *EKG:* sinusal tachycardia, 130/min, intermediary QRS axes, PR=0,12 sec.; *Cardiac Ultrasound:* normal.
- *Ophtalmologic exam:* hypermetropic astigmatismus
- *Psychologic exam:* polymorphic dislalia, anxious disposition, concentration deficit, QI=74 (Raven)
- *Abdominal ultrasound* (Fig. 4): liver with normal structure, right hepatic lobe = 95 mm, portal vein = 4,24 mm, free gallbladder, right kidney with no differentiated structure, situated anterior to the spinal cord, 50/20 mm, left kidney normal situated, 47/13 mm. Spleen with normal structure, splenic axe = 109 mm. Urinary bladder with normal walls. Conclusion: bilateral renal hypoplasia, ectopic right kidney. *Pelvis ultrasound:* no evidence of internal genitalia.
- *MRI:* reveals the "pancake" kidney, an extremely rare anomaly of renal ascent and subsequent fusion (Fig. 5a, 5b).
- *Pelvis MRI:* no visualisation of uterus and ovaries. Urinary bladder without parietal or intracavitary modifications. No ascites. No intrapelvic or inguinal adenopathies. Conclusion: agenesia of uterus and ovaries.
- *Dental examination* – clinical examination, extraoral and intraoral orthodontic investigation, cephalometric examination and pantomographic investigation revealed the following modifications (Fig. 6):
  - Dynamic and static occlusion instability, sagital inocclusion
  - High palate, small retrogenic mandible, macroglossia, hypoplasic low face level
  - Hypoplasia of enamel and changes in the shape of teeth's roots
  - Dental formula: mixt dentition, 21 rotated mesio-distal, 22 palatinised eruption, diastema
  - Dental-alveolary dysarmony with squashing at the mandibular arch level
  - 16, 26, 36, 46 – simple superficial caries of the occlusal face

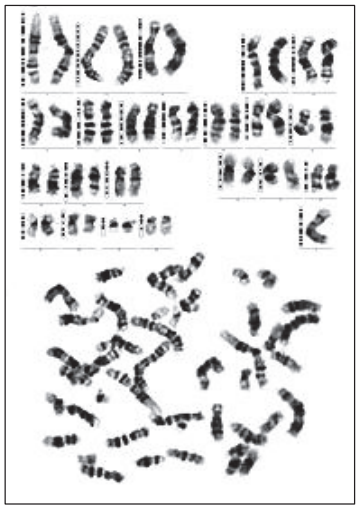

Fig. 3. Karyotype 45,X.

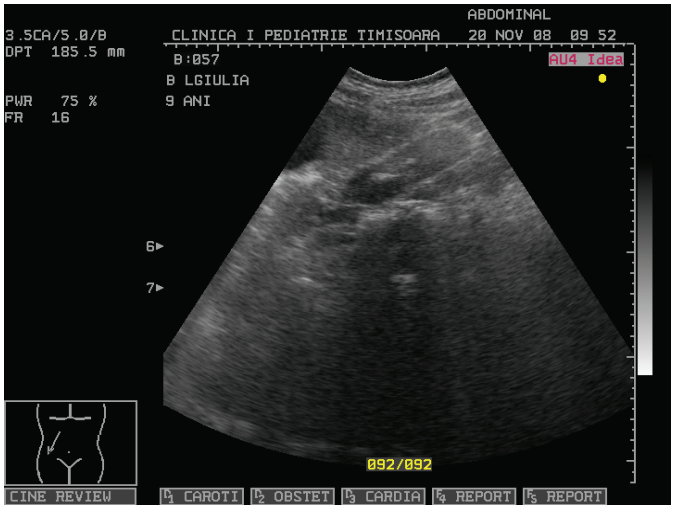

Fig. 4. Abdominal ultrasound.

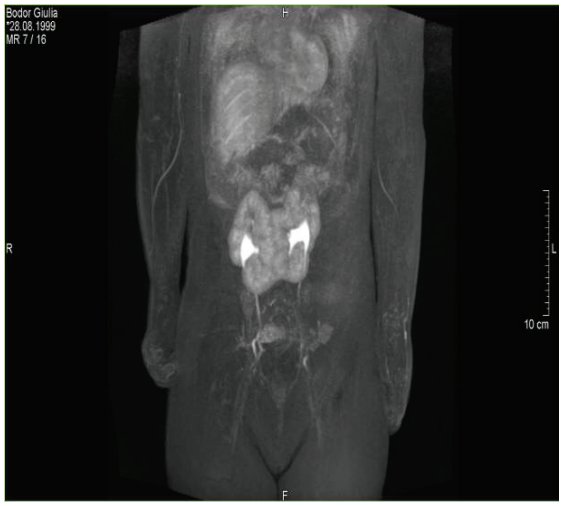

Fig. 5a. MRI.

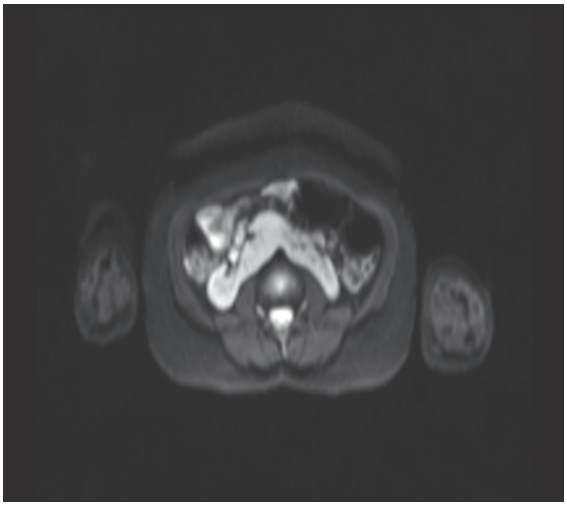

Fig. 5b. MRI.

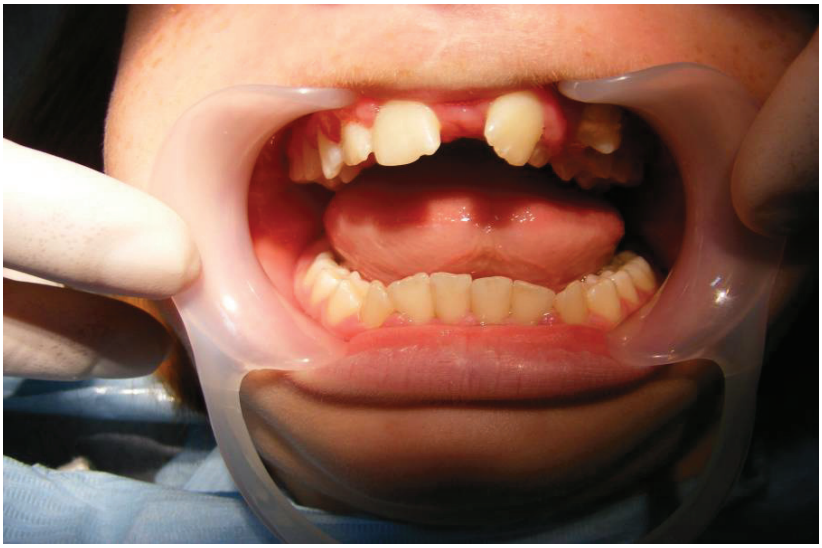

Fig. 6. Dental anomalies.

5. Diagnosis: *1. Turner Syndrome 2. "Pancake" Kidney 3. Urinary Tract Infection with E Coli 4. Severe Mixt Hearing Loss Left Ear 5. Obesity grade I 6. Uterine Agenesia 7. Hypermetropic Astigmatismus 8. Polymorphic Dislalia,* sustained by :

1. Turner Syndrome: characteristic clinical features, karyotype, renal malformation, hearing loss
2. "Pancake" Kidney: abdominal MRI
3. Urinary Tract Infection with E Coli: urine culture
4. Obesity grade I: BMI = 19.8 kg/m²
5. Uterine Agenesia: pelvic MRI
6. Hypermetropic Astigmatismus: ophtalmologic exam
7. Polymorphic Dyslalia: psychological exam

6. Treatment

- *prophylactic* – prenatal diagnosis:

– couples that already have a child with TS have a no significant risk of giving birth to another child with the same disease, but a genetic counseling before another pregnancy is recommended

– Turner syndrome may be diagnosed by amniocentesis during pregnancy, chorionic villus biopsy, or percutaneous umbilical cord blood sampling, followed by chromosomal analysis using classical or cytogenetically methods.

– triple test - second trimester maternal serum screening can check levels of alpha fetoprotein, β-hCG, inhibin-A, estriol, and h-hCG in the woman's serum. When alpha fetoprotein and estriol are low and hCG is high triple test is positive for TS.

- *diet:* hypocaloric, hypolipidic, avoiding food products with > 50% glucides, normoproteic
- *hormonal therapy* – there are different treatment schemes, related to age and possible complications, the main clinical features that will be concerned are *short stature and feminisation deficit*
- correction of short stature is made considering 3 age periods:

– childhood (2-10 years) overdoses of growth hormone (GH) are administered – initiation in January 2009 in our case

– after 11 years – Oxandrolone therapy for 1 – 1,5 years, (stimulates bone length growth)

– after 12-13 years - estrogen and progesterone administration, continuous replacement therapy up to normal menopause age (40-50 years)

– *GH dose: 0,045mg/kg/day*

- *feminisation deficit - etinilestradiole - 0,025µg/kg/day* – role in developing secondary sexual features, puberty onset (spontaneous in less than 10% of the cases), social integration, osteoporosis prophylaxis, uterine growth improvement.
- *dental therapy* – preventive measures of dental hygiene, caries treatment performed at 6 year molars level, orthodontic treatment was recommended.

7. Evolution – Life expectancy is almost normal, exceptions are the cases with severe cardiac anomalies or renal malformations with risk for developing chronic renal failure.

8. Complications - In the adult period the patient can develop high blood pressure, obesity, diabetes mellitus, cataract, Hashimoto thyroiditis.

9. Prognosis

- The only aspect that can not be corrected is infertility.
- Pregnancy is possible in cases with X monosomy mosaicism.
- Short stature and feminisation deficit can be corrected with proper therapy.
- Hearing impairment can be corrected by hearing aid - prosthesis
- Recurrent UTIs need prevention and follow-up.

10. Particularity of this case is due to the extremely rare renal malformation – "pancake kidney", and to the uterine agenesia, which is not characteristic for this syndrome.

Discussions

Turner's syndrome is defined as a congenital disease determining by quantitative and/or structural aberrations of one from two X chromosomes with frequent presence of mosaicism. Clinically it is characterized by growth and body proportion abnormalities, gonadal dysgenesis resulting in sexual infantilism, primary amenorrhoea, infertility, characteristic stigmata, anomalies of heart, renal and bones and the presence of some diseases like Hashimoto thyroiditis with hypothyroidism, diabetes mellitus type 2, osteoporosis, hypertension. Turner's syndrome occurs in 1:2000 to 1:2500 female livebirth. The most frequent X chromosome aberrations in patients with phenotype of Turner syndrome are as follows: X monosomy - 45,X; mosaicism (50-75%), including 45,X/46,XX (10-15%), 45,X/46,XY (2-6%), 45,X/46,X,i(Xq), 45,X/46,X,del(Xp), 45,X/46,XX/47,XXX; aberration of X structure: total or partial deletion of short arm of X chromosome (46,X,del(Xp)) isochromosom of long arm of X chromosome (46,X,(i(Xq)), ring chromosome (46, X,r(X)), marker chromosome (46,X+m). Searching of X chromosome and mapping and sequencing of genes located at this chromosome (such as SHOX, ODG2, VSPA, SOX 3) have made possible to look for linkage between phenotypes and adequate genes or regions of X chromosome[2].

The loss of the X chromosome in girls with Turner syndrome (TS) affects the shape and the size of craniofacial structures. Comparative studies performed on groups of TS patients versus control subjects have followed clinical parameters completed with caphalometric examination on teleradiogram of the head, periapical, occlusal, panoramic, and orthopantomograms[3,4,5]. The decayed, missing, and filled permanent surfaces index for teeth was statistically higher in TS patients versus control subjects. Orthodontic anoalies were more frequent and more severe in TS patients. Approximately 78% of TS patients presented hypoplasia of enamel, 65% shortening of the roots and bifurcated roots, and 100% high arch palate. Incisor asymmetry, reduced crown size, narrower but of normal length alveolar arch of the maxilla and shorter and broader mandibular arch were also observed.

Females with Turner syndrome (TS), are characterized with palates that are narrow in width, normal in height and which are commonly associated with the presence of lateral palatine ridges[6]. The distance of the tongue from the palate is significantly longer in the TS subjects compared with the controls, indicating a low tongue position in TS. The TS subjects with prominent lateral palatine ridges have significantly narrower posterior palates compared with the TS subjects without lateral palatine ridges.

Another study performed on a group of 25 patients affected by TS, aged from 4 to 18 years, was selected and the data were compared to those of an age matched control healthy group. The caries index values in TS patients are higher in the permanent (6.4 vs. 3.9), mixed (0.5 vs. 0.75) and primary dentition (0 vs. 1). The mesio-distal diameter in TS patients was significantly reduced for every tooth measured, in particular for the lower first permanent molar[7].

The investigations confirm that numeric aberration of the X chromosome most likely affects the quantitative and qualitative excretion of amelogenin, so that teeth often present enamel defects – reduced crown size and enamel hypoplasia. High caries index values (DMFT) highlight the demand of early preventive measures mostly focused on special care patients.

A broad cooperative effort is ideal with the involvement of a large number of specialties; for example, we enjoy the participation of departments of pediatry, genetics, cardiology, gynaecology, dentistry, otorhinology, ophthalmology, nephrology and gastro-enterology.

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THE MANAGEMENT OF THE TREATMENT OF CHILDREN WITH ASSOCIATED TRAUMA

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Abstract

Pediatric multiple trauma victims present a unique set of problems to the emergency physician, pediatrician, or surgeon. Children rarely sustain lethal injury; however, delayed recognition and inappropriate management of the common problems encountered in the pediatric trauma patient can lead to a poor outcomeThis study was designed as a retrospective descriptive study, using reviews of medical records of 289 injured children. All children aged from 1 to 15 years, who were admitted to the Republican Research Center of Emergency Medicine (RRCEM) and its branches in the 2000-2009 years. Caring for pediatric trauma patients requires an understanding of the distinct anatomy and pathophysiology of the pediatric population. Initial evaluation, management, and resuscitation require a multidisciplinary approach including trauma surgeons, anesthesiologists, and pediatric intensive care physicians.

Key words: Polytrauma management, Pediatric, Multiple trauma, Associated trauma, Pediatric trauma, emergency medical service (EMS)

Introduction

Trauma is still the most common cause of mortality in children, even in countries with the most advanced medical services. Severe head injury carries a high morbidity and mortality, whether isolated or in association with other trauma. However, a fatal outcome is usually the consequence of combinations of injuries. We define "real" polytrauma as two or more system injuries, involved at the same time endangering life as a result of one single or a combination of several injuries. Multiple trauma is always more than the sum of the single injuries; it should be considered as a systemic disease. Orthopaedic injuries account for a high proportion of the damage incurred by the polytraumatized child but are rarely life-threatening in their own right [3].

Pediatric multiple trauma victims present a unique set of problems to the emergency physician, pediatrician, or surgeon. Children rarely sustain lethal injury; however, delayed recognition and inappropriate management of the common problems encountered in the pediatric trauma patient can lead to a poor outcome.[7, 8, 10]

There are some effective models of emergency service in the world. Current guidelines of these models for polytrauma management are only partially applicable to the pediatric population. Associated trauma is one of the leading causes of death and disability in children and adolescents in Uzbekistan region. Therefore Ministry of Health of the Republic Uzbekistan supports our national emergency model development.

The emergency medical service (EMS) structure consist of the head center in Tashkent - the Republican Research Center The government program of public health services reforming in Republic of the Uzbekistan is defined by the Decree of President - 2107 from 10.11.2008, by a basic principle puts in of Emergency Medicine (RRCEM) – Trauma center I-st level, in each of 13 region there are regional branches – Trama center 2-nd level, in 175 settlements of the country at regional medical associations locate RRCEM`s subbranches - emergency medical units – Trauma center 3–rd level. These hospitals are the only hospitals in the region designated as a regional pediatric trauma center with 24-h emergency service, surgical service and intensive care, including burn and neurointensive care.

The aim of this study was to describe emergency service for the pediatric patients with associated trauma admitted in the RRCEM and its regional branches in Uzbekistan region during 2000-2009 periods.

Materials and Methods

This study was designed as a retrospective descriptive study, using reviews of medical records of 289 injured children. All children aged from 1 to 15 years, who were admitted to the Republican Research Center of Emergency Medicine (RRCEM) and its branches in the 2000-2009 years.

Definitions

The Abbreviated Injury Scale (AIS) system [1,4] classifies injuries according to body region, type anatomical structure, specific structure and level, and assigns severity in an ordinal scale from 1 to 6, where 6 is lethal. The Injury Severity Score (ISS) system [2,6] allocates the AIS scores into six body regions and calculates the highest AIS score from the three most severity injured ISS body regions to assigned the ISS score in an ordinal scale from 1 to 75, where 75 is lethal.

Statistical analysis was performed using Microsoft Excel 2007. Total numbers, percentages, and means±standart deviations are given.

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Results and discussion

Initial management of the pediatric trauma victim is similar to that of the adult trauma victim. However, it requires sufficient knowledge of the physiologic and anatomic differences between children and adults. Successful management requires adequate assessment and control of the airway, breathing, and circulation. Evaluation of the ABCs is a dynamic process that requires simultaneous assessment and resuscitation, as well as persistent reassessment until the child is hemodynamically stabilized.

To reduce mortality and optimize functional outcome in pediatric patients with severe head injury, it is necessary to minimize the progression or the effects of secondary injury and thereby maximize the potential for recovery. Successful management of severe pediatric head injury requires complete and rapid physiologic resuscitation, which begins with aggressive and organized resuscitation in the field; avoidance of hypotension and hypoxia; prompt diagnosis and removal of intracranial mass lesions; aggressive treatment of intracranial hypertension; and maintenance of normal physiologic parameters, such as cerebral perfusion, in order to facilitate adequate delivery of oxygen and metabolic substrates to the brain.

The group of physicians immediately responsible for the care of an injured child is made up of the surgical specialties. Pediatric general surgery includes within its training the care of the injured child. The pediatric surgical team must include a leader of that team whose responsibility it is to organize the team. In the ED, this trauma team is expected to meet the patient on arrival. Once the patient has been placed in the resuscitation room, the team begins its work. Hopefully, the ED has been notified by the pre-hospital personnel of the cause of the injury, e.g., motor vehicle crash, gunshot wound, stab wound, fall, and is prepared to start the resuscitation phase. Occurring simultaneously with the resuscitation phase is the diagnostic phase. However, the team should be trained to the important fact that the diagnosis is less important than saving the life of the injured child. Thus, the team should be aware that the lack of a diagnosis should never impede the application of an indicated treatment.

The composition of the team, in addition to the leader, is generally two other surgeons, an anesthesiologist or emergency medicine physician, and at least two nurses, one of who acts as the scribe. Absolute responsibility for the patient rests with the team leader. The team leader will have assigned specific duties to other members of the team Fig.1.

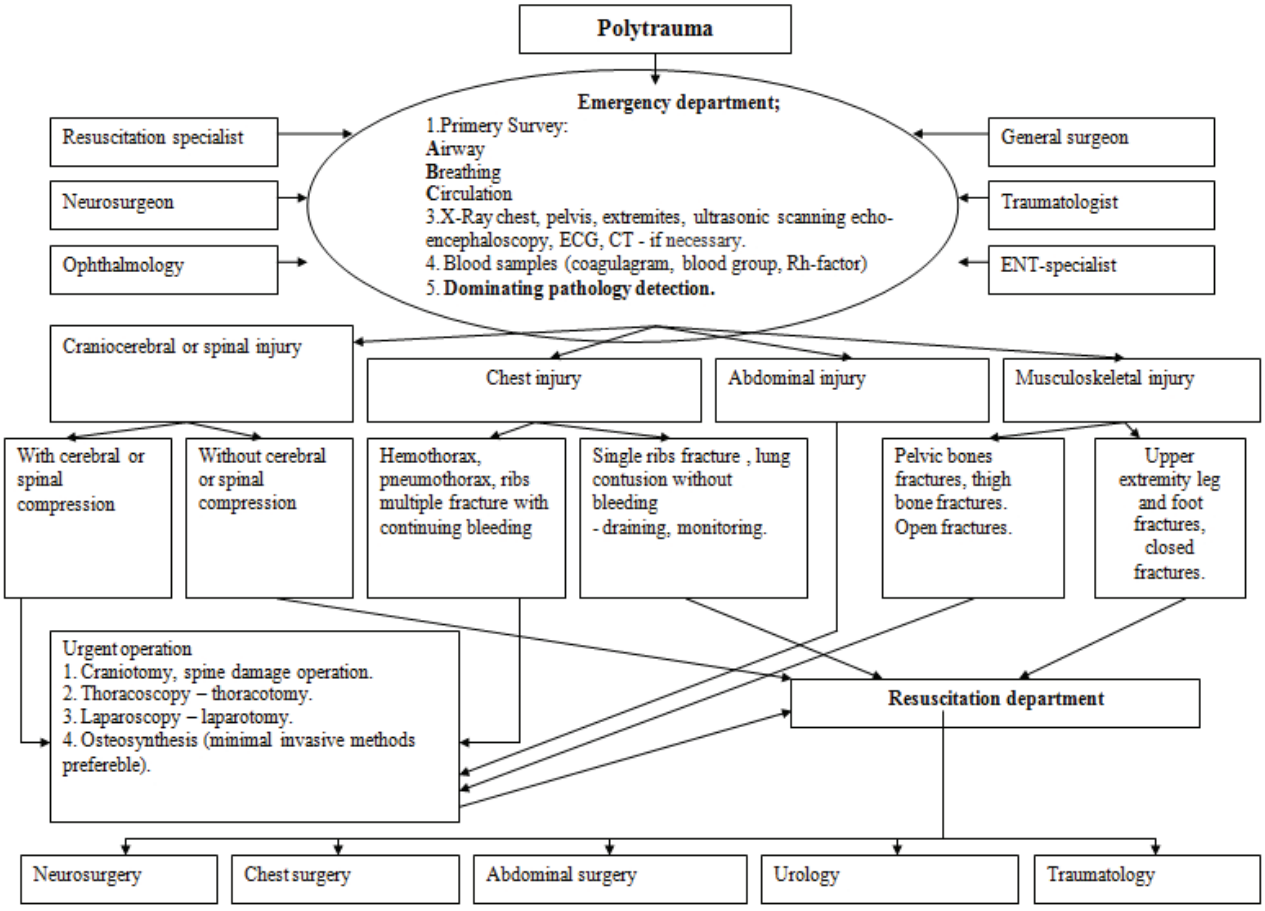

Fig.1. Polytrauma management.

Other physicians is part of the trauma team but not necessarily part of the physician group who initially responds upon the patient's arrival. Clearly, Orthopedic Surgery and Neurosurgery must be included in this group. Also, Plastic Surgery, Ear Nose Throat, Urology, and Ophthalmology will be required in specific cases. These individuals must be available on short notice at the behest of the trauma team leader. Nonsurgical physicians are also included in the requirements. Pediatric emergency medicine and pediatric intensive care physicians are included in this group, as are radiologists.

The ultimate common pathway leading to death in the injured child is profound shock: the inadequate delivery of oxygen to the tissues. It is therefore the goal of the initial phase of resuscitation to rapidly evaluate and treat any immediate life-threatening injuries that compromise tissue oxygenation. This is known in Advanced Trauma Life Support (ATLS) courses as the primary survey or the ABCs of trauma: airway, breathing, and circulation. Appropriate management of the ABCs is necessary for optimal outcome in pediatric trauma, regardless of whether it is managed in an adult or pediatric trauma center.

Patients with the dangerous body damages, being in traumatic shock condition or without consciousness, hospitalised in intensive care unit. Associated damage complicates diagnostics, both brain damages, and bone fractures. Carrying out of emergency reanimation actions was accompanied by diagnostic researches: craniography in two dimensions, roentgenography of locomotorium damages, ultrasonic examination of abdominal organs.

Diagnostics, first of all, should be referred on definition of the pathology demanding urgent operative intervention; bleedings of various localisation; a prelum of a brain with hematoma or osteal fragments; it is necessary to consider possibilities of development of a coma owing to a shock, hemorrhages, serious hypoxia, a hypo-hyperglycaemia which aggravate craniocerebral injures gravity, mask focal semiology.

It is important to estimate gravity of a cerebral coma on Glasgow scale. After carrying out of clinico-neurologic diagnostics all available agents arsenal involved: echoencephalography, a computer tomography, an axial computer tomography, ultrasonic research, modern noninvasive methods of a brain visualisation.

At a choice of a method of treatment of victims with a polytrauma we were guided by gravity of a condition of patients, degree of a traumatic shock, hemorrhage volume, other disturbances of vital functions of an organism and age, and then treatment tactics was defined. Treatment should begin in extremely early terms, that as shows our experience, essentially reduces number of lethal outcomes, both from immediate complications of a trauma, and from serious complications in the post shock period.

Further if the acute surgical pathology detected the patient translate in surgical resuscitation unit where the intensive cares proceed. In case of detecting of an acute surgical pathology the patient translate in operational, for emergency surgical intervention.

As indications to an emergency surgical intervention considered intra-abdominal bleeding, breath disturbance in a consequence of pneumo or a hemothorax, brain compression with dislocation syndrome, open not stable fractures of extremities. Presence of these indications or suspicion to them were an occasion to transfer of patients in operation room where simultaneously with antishock actions inspection proceeds. If results of research do not give the basis for an urgent surgical intervention the patient translate in intensive care unit. In cases when urgent operative treatment concerning craniocerebral trauma was required or damages of internal organs, in parallel operative stabilizations of long bone and pelvic bone fractures execute, so-called simultaneous operations.

The most frequent trauma causes at 1-3 year kids were falling from low places: tables, chairs, sofas, beds. Domestic trauma were the most frequent trauma causes at 4-5 year childs. The TV involves with colour pictures and puts the most serious damages after the falling. The child cannot understand the threats proceeding from such subjects. To protect it from such mutilations - a parents duty. Serious traumas of a head because of fights on changes and in court yard of schools at 7-12 age adjoin to road accident. Not casually on a traffic sign «children» are represented running schoolboys. Also often there are combustions of respiratory tracts and eyes from fireworks, fractures on an athletic field and falling from a bicycle. Complicates a situation a combination of various damages to one case. At children after twelve years the probability of serious traumas as a result of employment by extreme sports sharply increases Fig.2.

The greatest quantity of severe associated traumas (high ISS) becomes perceptible at children of early school age Fig.3.

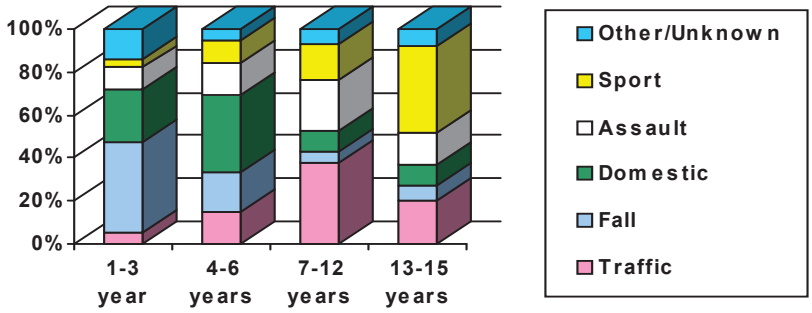

Fig 2. Injury mechanism.

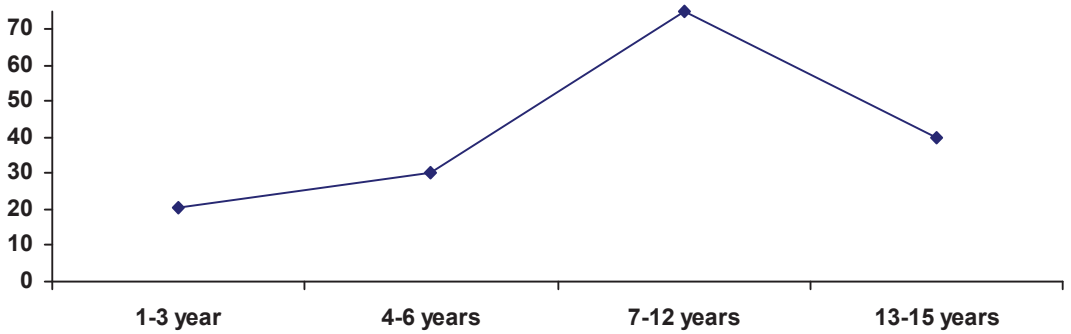

Fig. 3. ISS group.

Conclusion

Caring for pediatric trauma patients requires an understanding of the distinct anatomy and pathophysiology of the pediatric population. Initial evaluation, management, and resuscitation require a multidisciplinary approach including trauma surgeons, anesthesiologists, and pediatric intensive care physicians. Head injury severity is the principal determinant of outcome and mortality in polytraumatized children.

Application of above mentioned actions algorithm allow avoiding diagnostic fault and decreasing evaluation term.

This study indicates effectiveness of generated emergency medical service for children with associated trauma in Uzbekistan.

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POST-OPERATIVE EVOLUTION OF INTRA-ABDOMINAL INFECTIONS TREATED BY CARMELI SCORE

Elena Tuluc[1], SG Aprodu[1], Simona Rusu[2], Mihaela Ciornei[2]

Summary:

Acute appendicitis is the most frequent indication of abdominal surgery on pediatric population, and the appendicular perforation is a frequent complication of this condition. In order to avoid the abusive use of some last generation antibiotics and the occurrence of resistant germ strains, it was recently introduced a new intra-abdominal treatment scheme, according to Carmeli score. This study aimed to identify the risk factors of a potential adverse development and compare post-operative results depending on the received antibiotherapy. Thus a study was done on 53 patients with intra-abdominal infections by acute appendicitis or appendicular peritonitis who were treated in the Pediatric Surgery and Orthopedic Clinics of the "Sf. Maria" Emergency Clinic Hospital for Children, Iassy. The results of this study demonstrated that early age, male sex, associated conditions and a higher than 1 Carmeli score are poor prognosis factors in intra-abdominal infections in pediatric age patient.

Key words: acute appendicitis, intra-abdominal infections, Carmeli score, antibiotherapy.

Introduction

Acute appendicitis in a child is one of the most common surgical emergencies and the appendectomy has become the golden standard of therapy in this condition, associated or not to the antibiotherapy. Fitz et al. diagnosed and described for the first time the acute appendicitis in 1886, and McBurney did the first appendectomy in 1894. Since then, the appendectomy became the standard treatment of this condition (1), however 2-7% of the patients present complications such as peri-appendicular abscesses, appendicular insets or generalized peritonitis (2).

In emergency surgical interventions, due to local inflammation, adherences, peri-appendicular liquid collections or generalized peritonitis, the surgical wound healing process is delayed and many other complications may appear, in up to 26% of the these patients (3,4). The management strategy of patients with intra-abdominal infections is controversal, the aim of this study being that of identifying risk factors of adverse development and comparing patients' post-operative evolution depending on the received antibiotherapy.

Material and methods

For carrying this study there were taken in evidence 53 patients with intra-abdominal infections through acute appendicitis or appendiceal peritonitis treated in the Pediatric Surgery and Orthopedic Clinics of the "Sf. Maria" Emergency Clinic Hospital for Children, Iassy, for three months, from November 1st, 2010 to January 1st, 2011. The patients were monitored prospectively, being divided in two study groups depending on Carmeli score, receiving thus antibiotherapy in triple association, Cefort + Gentamicin + Metronidazole or Invanz ± another antibiotic, depending on the particularity of each case. There were analysed patients' data from the points of view of age, sex, disease severity, surgical approach, hospitalization duration, need for and duration of peritoneal drainage, post-operative complications and associated complications.

The obtained data were compared among them, not only regarding the differences between the two study groups, but also inside each group, depending on sex, age, associated affections, being used the *t* Student test, Chi square, multifactor analysis methods. The data were expressed as means ± standard deviations or as frequencies. The used threshold for statistical significance was $p \leq 0.05$. In order to achieve a permanent statistic analysis on the obtained data series, there were used specialised software applications, Statistics and Microsoft Excel.

Results

Of the 74 hospitalized and treated patients in our clinic during the three months for acute appendicitis, in 21 patients the post-operative diagnosis was that of acute catarrhal appendicitis or acute phlegmatic appendicitis, but which did not require antibiotherapy, thus being removed from the study. The remaining 53 patients were considered having post- acute appendicitis intra-abdominal infections and 49 of them fit in Carmeli Class 1, being treated with usual antibiotics, Cefort + Gentamicin + Metronidazole in adapted dosages to age and body weight. Four of the patients who previously received antibiotherapy for respiratory or digestive infections fit in Carmeli Class 2 and received Invanz (Ertapenem) in association to another antibiotic, depending on the associated affections.

Of the 49 patients with Carmeli score 1, 16 were girls aged from 5 to 17, with an average of 13.06±3.4 years old, and 33 were boys aged from 3 to 18, with an average of 10.84±3.7 years old (Fig. 1). For a $p \leq 0.05$ the age difference is significant from a statistic point of view. All in all, the patients' average age in the first class was of 11.57±3.7 years old.

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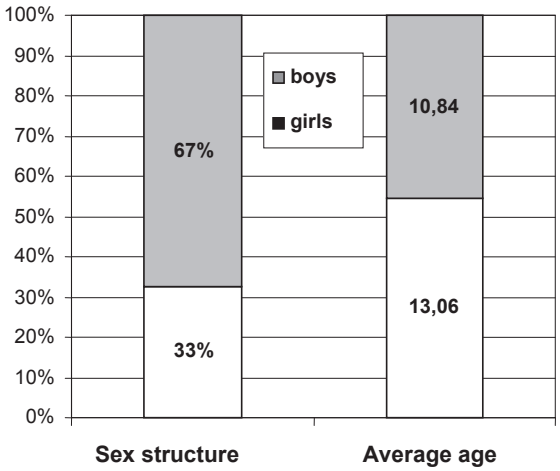

Fig 1. Carmeli score 1 patient distribution by age and sex.

The hospitalization duration varied between 4 and 13 days, with an average of 6.67±2.4 days and a median of 6 days, varying for girls with 6.5±1.8 from 6.75±2.6 for boys (a statistically insignificant difference for $p \leq 0.05$). Only 3 of 16 girls were diagnosed with peritonitis, while in boys the proportion was of 15 to 33 (Fig. 2). The days of peritoneal drainage were in an average of 6 ± 1.4, varying from 4 to 9 days and applying to 42.8% of the patients in this group. Only 31.2% of the girls required peritoneal drainage, to 48.4% of the boys.

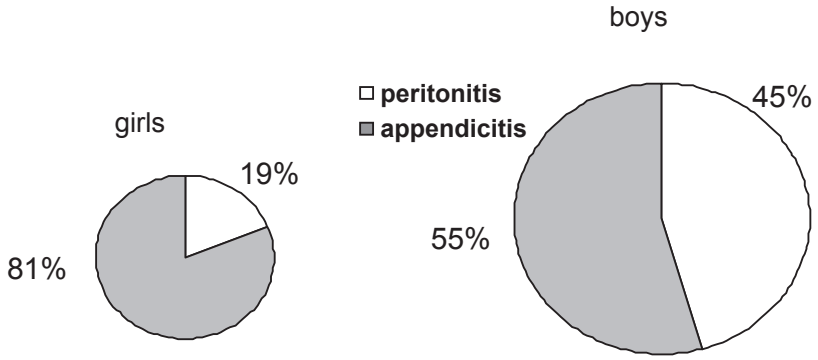

Fig 2. Carmeli score 1 patient distribution on disease severity.

In what concerns the Carmeli score 2 patients the average age was of 7.87±5.9 years old, a 3 year old boy and 3 girls, one aged 2.5 and the other two aged 13, respectively. The average hospitalization period was of 14.75±8.3 days, obviously longer than in the first patient group, all of them presented themselves with peritonitis and needed peritoneal lavage and drainage, on the other hand the drainage period did not differ significantly (6.5±2.5 days). In 3 of these 4 patients the evolution was difficult, 3 of the boys developing fever, 2 of them with suppuration of the operative wound and 1 requiring secondary suture.

In 49 of the 53 total patients (92.5%) there were surgical interventions by McBurney incision and in 4 of them by median laparotomy, the latter ones' diagnosis being that of localized peritonitis (2 patients) or generalized peritonitis (2 patients). Three of these patients (all boys) had Carmeli score 1 and one girl patient had Carmeli score 2. The average hospitalization period was of 8.7 for boys, and the girl had 22 hospitalization days, this one suffered another surgery for a retro-uterine abscess with rectal wall perforation, being put in colostomy. The evolution was difficult in 3 of the 4 patients with wound suppuration in the re-operated patient for retro-uterine abscess, with dehydration syndrome through vomiting in a small age patient (3 years) and because of a iatrogenic burn at the scrotum level (through electrocautery plaque) in another patient. All 4 patients needed lavage and drainage of the peritoneal cavity, but the drainage duration was comparable to that of the other patients, being of 6 days in average. In 2 patients, the peritoneal fluid culture was positive, *Pseudomonas* and *Enterobacter*, *Escherichia coli*, respectively, isolating themselves.

Ten patients also had other associated conditions, 6 boys and 4 girls, 3 of them were boys with Meckel

diverticulum discovered intra-operatively, but whose excision was delayed, one girl with right ovarian cyst which was punctured and evacuated, one girl with intestinal parasites and another one with ichthyosis. The last two ones belong to Carmeli score 2 patient group. The average age of patients with associated conditions was of 10.5 years, with variations between 2.5 and 16 years, and the average hospitalization period was of 9.8±6.5 days. Seven of the 10 patients needed peritoneal drainage, the average drainage duration being of 6.14 days. Four of the patients had a difficult evolution, with fever and suppuration of the operative wound in 3 of them.

It was also analysed early age patients' evolution, under 6, comparatively to the others, the results being the following: 6 patients (11%) aged under 6 (4.08±1.42) in average compared to the rest of 47 (89%), with an average age of 12.21±3.21years. The hospitalization period was of 9.83 days versus 6.95 days, 83% needed peritoneal drainage versus 42.5 %, with an average duration of 6.4 towards 6 days. Four of the 6 patients had a difficult evolution (66.6%) comparatively to 6 of 47, representing 12.7%. We mention that 2 of the 6 early age patients obtained a Carmeli score 2.

Discussions

Acute appendicitis is the most frequent recommendation for abdominal surgery in pediatric population, and the appendicular perforation is a frequent complication of this condition. The main objectives of the surgical management in these cases are minimizing morbidities, costs, hospitalization period and re-interventions. Post-appendectomy infectious complications are strongly related to all these parameters, on which the chosen antibiotic regime has a major influence. Broad-spectrum antibiotics are traditionally recommended, usually in triple association (5), although lately more and more authors prefer mono-antibiotherapy (6) in order to reduce costs and simplify the treatment (7). Yet, the occurrence of postoperative infectious complications has a multifactor determinism, depending on the patient, the peri-operator factors and the received antibiotics; this is why the research regarding the best treatment scheme continues (8).

For avoiding the abusive use of some last generation antibiotics and the occurrence of resistant germ strains, it was lately introduced a new infection treatment scheme, depending on Carmeli score (9). Thus, for knowing what antibiotic should be administered to each patient, the evaluation depending on this score is done. This one cannot have but the value of 1 if the patient obtained only answers rated 1, the value of 2 if the patient achieved one or more rated 2 criteria, or the value of 3 if he achieved at least one rated 3 criterion. So, the score value is offered by the maximum obtained value, and not by summing up the results. The meaning is the following: if the score value is 1, then the infection is considered to be communitarian and the patient will receive an usual antibiotic, here included fluorochinolone for respiratory infections; if the score is 2 means that the patient had previously got in touch with the health care system or received antibiotics in antecedents and now he will receive a superior class antibiotic, for example Ertapenem, Linezolid, Vancomycin; if the score is 3, this means an nosocomial infection, which will have to be treated with Imipenem, Meropenem, or an association of other antibiotics.

Risk evaluation - Carmeli score

- **A**.Contact with the health sector
  - 1) Without contact
  - 2) Contact with no invasive procedures
  - 3) Repeated contacts with invasive procedures
- **B**.AB treatment:
  - 1) Without AB
  - 2) With AB in antecedents
- **C**. Patient characteristics:
  - 1) Young- without comorbidities
  - 2) Elderly with comorbidities
  - 3) Immunocompromised patients (AIDS, BPOC, BMT, Cancer)

From the analysis regarding the first patient group in the present study one may notice the fact that acute appendicitis occurrence frequency is higher in boys and occurs at an early age, two thirds of the patients being boys with an average age of 10.84 years old, compared to one third girls aged 13.06. There are also differences concerning the condition severity, 45.5% of the boys developing acute peritonitis to 19% of the girls; 48.4% of the boys needed peritoneal drainage compared to 31.2% of the girls. The hospitalization period was not influenced by the sex variable, being of 6.67 days in average (Table 1).

Tabel no.1. Patients' evolution on disease severity.

Disease category	% of total	Average age(years)	Average hospitalization period (days)	Peritoneal drainage necessity (%)	Average drainage period (days)	Difficult evolution (%)
	49	11,2	5,7	8,3	4,5	4,2
Phlegmatic appendicitis	14	12,7	5,3	28,6	5,0	0,0
Localised peritonitis	25	12,2	8,4	91,7	6,1	33,3
Generalised peritonitis	12	10,6	8,6	100,0	6,7	33,3

From the data analysis after patients division into diagnosis groups one may notice, naturally, the raise of the hospitalization and peritoneal drainage periods once with the increased condition severity, but not necessarily associated with an increase of the frequency of complications or a difficult evolution. It can also be noticed the raise of the hospitalization period and the necessity of peritoneal drainage in patients who presented a series of associated affections, these being thus factors of negative prognosis.

It is evident a difficult evolution of patient with Carmeli score 2, this fact being explained by the early age, the peritonitis stage diagnosis in all these patients, the association of other pediatric conditions, the previous contact with health services or the recently administered antibiotherapy. The difficult evolution is reflected in a prolonged hospitalization, the necessity of lavage and of the peritoneal drainage in all cases, although the drainage duration did not differ significantly from the first patient group.

It is also observed that early age is an important factor in determining difficult evolution, with prolonged hospitalization periods and frequent postoperative complications.

Conclusions

Early age, male sex, associated affections and Carmeli score higher than 1 are unfavourable prognosis factors in intra-abdominal infections in pediactric age patient.

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THE IMPORTANCE OF EARLY DIAGNOSIS IN TRAUMATIC PATIENTS - CASE PRESENTATION

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Abstract

Introduction. Injuries arising from car accidents are problems that require a quick and accurate diagnosis, and when they occur in pediatric patients it becomes more difficult. This is often because children are unable to show the exact location of pain and lack precise communication, but working hard in these situations, formulating a diagnosis will be a critical step to determine the evolution (outcome?) of the patient**.** *Case report.* This paper presents the clinical observation of a patient involved in a car accident resulting in loss of consciousness and a series of complex trauma. After stabilizing the patient in the Emergency Room, he was transfered to our clinic with the suspicion of splenic rupture. After an emergency splenectomy followed, in another phase by the resolution of the orthopedic problem, the patient was discharged, about after a month of hospitalization, when the general condition improved. *In conclusion*, accidents are, regardless of their seriousness, an emergency where the exact diagnosis is mandatory and decisive.

Key words: accident, splenic rupture, femoral fracture, child

Introduction

Injuries are the leading cause of death in pediatric age. In England, the percentage of these deaths is around 20-40% for 1 to 15 years old age category. The spleen is the most commonly injured structure in abdominal trauma. Over the last two years, the efforts have been directed to preserve the splenic tissue (1, 2).

Case presentation

M.M., a 4 year, 3 month old boy, was transfered to the Department of Pediatric Surgery, Cluj-Napoca with the diagnosis of splenic rupture, for surgical treatment. The child was involved in a car accident and was projected through the windshield. He was hospitalized in the Emergency Room where he was in a state of coma, grade IV, without responding to auditory, tactile and painful stimuli. The fotomotor pupillary reflex was reduced bilaterally. Because of the general condition, he was intubated and then the doctors continued the assessment to formulate a diagnosis of all injuries.

The abdominal computer tomography revealed a 3,7/1,7 cm hypodense lesion of the spleen which was extended to the lower pole and intraperitoneal liquid in significant quantities. The description of this issue led to the diagnosis of splenic rupture.

Also, the imagistic evaluation highlighted bilateral mandibular fracture, left pleural effusion in small quantity, minor rib fractures and a fracture of the left femural in the metaphysic (Fig. 1). The diagnosis of spleen rupture made necessary the transfer of the patient into our clinic for surgical resolution. Physical examination during the admission to our clinic revealed: swelling on the left side of the face due to a hematoma around the orbita and a left eyebrow wound of about 1,5 cm. The jaw presented abnormal mobility and cracks when we tried to execute simple movements. The medial part of the thigh was deformed due to a hematoma in the lower third and at the same level we could detect bone cracks and the interruption of bone contour. Near the left rib there was a hematoma present measuring approximately 2 cm and the abdomen was relaxed, with a discreet muscular defense.

Laboratory investigation have revealed increased liver enzymes and amylase.

The computer tomography revealed a fracture of the medial and posterior superolateral walls in the left maxillary sinus; a displaced fracture in the lateral and the inferior wall of the left orbit, at the junction with the zygomatic arch; a fracture with the displacement of the mandible, between the two left incisors; a fracture of the mandible's vertical ramus, bilateral, extending on the right side up to the condyle.

We performed the surgial therapy under general anesthesia, practicing the splenectomy, with drainage and lavage of the peritoneal cavity. On the same occasion, we practiced a continued extension of his left leg. Three days after splenectomy was performed, we practiced a reduction of the paramedian fracture of mandible, a monomaxillary rigid immobilization with an acrylic tray and the mandibular fixation. During the same session we performed a manually reduction of the left malaria disjunction. After nine days in our clinic, the patient started to respond to verbal stimuli and on day twelve he was conscious and cooperative. Eighteen days after admission in our clinic, the patient underwent a new intervention regarding the left femorale fracture, during which we performed an intramedullary fixation with a special rod. Discharge was made on the 26th day after splenectomy, the patient being in a good general condition.

The patient returned to the clinic one year after the accident and the radiological examination demonstrated proper healing of the femur (Fig. 2).

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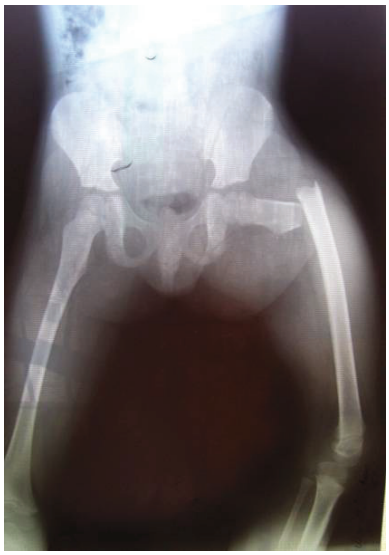

Figure 1. Antero-posterior radiograph of the pelvis and femur bilateral-fracture of the left femur in the upper third.

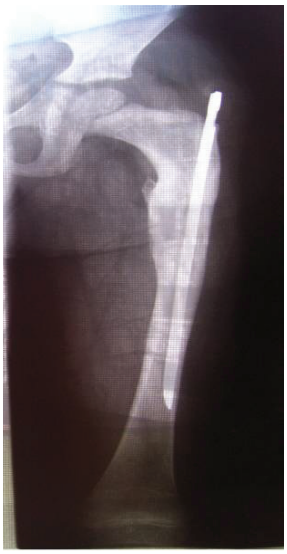

Figure 2. Antero-posterior radiograph of the pelvis and left femur.

Discussion

Traumatic rupture of the spleen is a medical emergency and the priority in these cases is to save lives and to resolve the other aspects leading to additional clinical improvement of the patient's clinical condition. The pediatric advanced life support guideliness, published in 1993 and revised in 1997, brought the therapeutic protocol of children with abdominal trauma (1).

Though protected by the chest, the spleen remains the most commonly affected organ in abdominal trauma, regardless of group age. Although the liver injuries in some cases are more frequent, the traumatic spleen injury remains the most common primary affected solid organ in the abdomen.

The clinical picture of splenic injury is very variable. Most patients with minor trauma to the spleen show a right lower quadrant tenderness in the upper abdomen. Sometimes there is a minor level of sensitivity in the right shoulder as a result of the subdiafragmatic nerve irritation. But in most cases the clinical picture is dominated by the presence of the hemoperitoneum, diffuse abdominal pain and peritoneal irritation. If the intra-abdominal hemorrhage is more than 5-10% of the patient's blood volume, clinical signs of early shock can be present. These include tachycardia, tachypnea and anxiety. Sometimes patients present pallor and the physical examination can detect a drop of pulse and time of recoloration. The increase in the amount of intraperitoneal blood leads to abdominal distension and peritoneal signs. Hypotension is another clinical manifestation that must be closely monitored.

The presence of a patient in the Emergency Room with splenic trauma involves two situations: the necessary and urgent splenectomy or the delay of this intervention, with a chance of preserving splenic tissue.

When the splenectomy is timed, it is recommended in the first stage to achieve a hemodynamic stability, by replacing no more than 40 ml per kg body-weight from the intravenously space. Most of these cases are associated with major bleeding, and careful observation of the evolution in this patient and frequent and accurate monitoring of fluids is essential (1, 2).

Patients which, despite appropriate therapy to rebalance, continue to present abdominal bleeding will be assessed by exploratory laparotomy, who will then decide whether a full or partial splenectomy is necessary (3).

A certain diagnosis of splenic injury is made using imaging methods. Computer tomography is the imaging investigation of choice, in cases of major abdominal trauma in children hemodynamically stable. This investigation is a method of a high sensitivity in detection of abdominal solid organs trauma (1, 2, 3, 5, 6).

Another imaging investigation is ultrasonography. This is a rapid diagnostic method, accessible and not exposed to radiation. Ultrasonography may be useful in patients who do not require surgery in the first stage an outcome which was initially assessed by computed tomography.

Despite an appropriate assessment of imaging, in one third of abdominal trauma, solid organ damage may not be diagnosed (7).

The decision of the therapeutic conduct in traumatic spleen rupture in a child, should be made based on the general condition of the patient's and the severity of the spleen injury. The situations in which we may preserv the splenic tissue are encouraging, but should not be overlooked as there are cases in which a splenectomy is essential.

Facial bone fractures are a rare pathology in pediatric age, particularly in children under 5 years, due to their increased resistance. This resistance is due to a high elasticity of the bone, a low pneumatisation, the fat tisue around bones, but also because of the stability of the mandible and maxilla.

More than a third of children who have facial fractures shows fractures of the mandible. This type of fracture can lead to airway compression because of the trauma itself and indirectly because of the hematomas or swelling.

Diagnosis is often difficult to formulate, and most times it can be suggested by the presence of an asymmetry of the face, facial bruising and swelling especially in the preauricular area. Opening and closing movements of the mouth are often limited and because of the muscle spasm and pain the patient may develop trismus (8).

Treatment of mandible fractures depends on factors such as location and type of fracture, the type of child's dentition, occlusal status. Time to immobilize the fracture is lower in children because of rapidity of healing and remodeling process. Most studies recommend immobilization for a period of 2-3 weeks (9, 10).

Fractures of the femur in children are common. The mechanism of injury varies from low-energy twisting type injuries to high-velocity injuries in vehicular accidents.

When suspecting a femural fracture, it is very important the physical examination in order to detect other injuries and to establish the neurovascular status. After clinical examination, the imaging is necessary to complete the diagnosis. Anteroposterior and lateral radiographs of the femure will show the fracture's path.

The treatment varies with age, from spica cast, tractions and spica cast to intramedullary rod, external fixator in open fractures and screw or plat.

This article highlights how trauma patients should be treated. The particularity of this case was represented first by the ruptured spleen which was a medical emergency, but also by the associated diseases-the femoral and jaw fractures and all its possible complications involved.

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PERSISTENT CLOACA: UROLOGICAL THERAPY

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Abstract

Purpose: To evaluate urinary tract function and continence in patients (pts) with persistent cloaca.

Materials and Methods: surgery was performed in 32 patients with cloaca, 3 months to 16 years old.

Group A. In 12 pts urethral and vaginal reconstructions and pull-through of rectum were done together during the primary operation. 5 pts had VUR, 3 neurogenic bladder (NB), 2 had solitary kidneys. Bladder augmentation n=1 and VUR-correction n=2 were done as secondary operations.

Group B. In 20 pts primary surgery for the cloaca was done at other institutions. They presented with persistent urogenital sinus (UGS) n=14, vesico-vaginal fistula n=2, vesico-urethral fistula n=2, reconstructed urethra n=2. Other urinary pathologies: VUR n=13 pts, NB n=7, solitary kidneys n=6, megaureter n=4. Only 2 pts were continent. Urethral reconstruction n=15, bladder augmentation/substitution n=5, vesico-cutaneostomie n=5, VUR-correction n=5 were performed.

Results: Group A. There are no pts with renal insufficiency. All patients are dry spontaneously n=7, or by catheterisation via urethra n=5. *Group B.* Reflux-nephropathy leading to renal insufficiency was seen in 3 pts. One patient had undergone renal transplantation. Another was transplanted after the re-do operation for cloaca and died 6 month after transplantation. The 3rd was lost to follow-up. 7 patients are continent, 9 are socially continent, and 2 are incontinent for urine.

Conclusions: The outcome of urinary tract function is better when urethral and vaginal repairs and the pull-through of the rectum are done together (group A). To prevent the damage of the urinary tract long-term follow-up is essential. Some of these patients need secondary operations to achieve urinary control or to correct reflux.

Key words: persistent cloaca, posterior sagittal approach, urinary tract function, incontinence

Introduction

Persistent cloaca is a complex malformation with a wide anatomical spectrum.

The surgical procedures enable the correction of cloacal anomalies with good prognosis regarding urinary and bowel control and genital function. However, persistent cloaca is a rare malformation and for many pediatric surgeons it is difficult to get substantial experience with this anomaly. Consequently the anatomy of malformation may be misinterpreted with inadequate timing of operation and inadequate procedures. The obtained results are frustrating both for patient and surgeon leading to frequent reoperations.

Material and methods

During a 12 year period (1993-2004), 32 girls with persistent cloaca have been operated. There were 12 primary operated children (Group A) and 20 reoperated patients (Group B). All children from group B presented after having had surgery for persistent cloaca elsewhere ranging from 1 to 14 previous surgical procedures.

A review of clinical and radiological records was undertaken. The parents and the patients were interviewed. All patients were seen in the last 5 years.

Group A: The age at the operation was between 2 months and 1 year with a mean of 7 month. Eleven patients had colostomies and 1 patient vaginostomy before definitive correction. There were 5 children with double vagina and double uterus (2 with hydrocolpos), one with vaginal agenesis and one with vaginal and uterine agenesis. One girl had a perineal lipoma, and one absence of both minor labia. In 5 children the common channel was longer than 3 cm. In 7 children sacral dysplasia was present. Five patients had VUR (8 renal units), 3 neurogenic bladder (NB) all with sacral dysplasia, 2 solitary kidneys, and one ureteral triplication with one megaureter. In all these patients urethral and vaginal reconstructions and the pull-through of the rectum were done together at primary correction. The reimplantation of the megaureter in the child with ureteral triplication was performed during primary correction of the cloaca.

Group B: All children underwent at least one correction for persistent cloaca before presentation to our institution: pull-through of the rectum in 12 patients, surgery for the UGS in 2, pull-through of the vagina instead of the rectum in 1, pull-through of the common channel in 1, multiple operations (up to 14) in 4 patients. Fourteen presented with UGS (one of them with bladder agenesis), vesico-vaginal fistula in 2 (one of them with urethral atresia), urethro-vaginal fistula in 2, reconstructed urethra n=2, both of them with low bladder volume.

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Thirteen patients had VUR (21 renal units), 7 NB (6 in combination with sacral dysplasia), 6 solitary kidneys, 4 megaureter, and one had bladder diverticula. There was no information about the common channel (CC) in 14 patients, in 6 the CC was more than 3 cm long. 12 patients had sacral dysplasia.

There were 11 girls with double vagina and double uterus, 4 with vaginal atresia, 3 with atresia of the cervix. One girl had stenosis of the vaginal substitute (ileum segment), 2 absence of both minor labia and one had no clitoris. Renal failure occurred in 3 girls as consequence of undetected hydrometrocolpos leading to obstructive uropathies. One of them already had renal transplantation at presentation, another girl had kidney-transplantation 6 month after the reoperation for cloaca.

The age at reoperation in Group B was between 7 months and 16 years with a mean of 7 years. In 15 patients urethral reconstruction was performed. Other undertaken procedures on urinary tract: bladder augmentation/neobladder in 5, continent vesicostomy according to Mitrofanoff procedure (1) in 5, VUR-correction in 5 (8 units).

The urethra was reconstructed together with the vagina and rectum in 14 girls, and together with the vagina in 1. All reconstructions were performed under protective colostomies or ileostomies. Bladder augmentation or bladder substitution were performed in 5 patients. The same number of patients received continent cystostomies and 3 were provided with MACE (2). Two patients had vaginoplasty only (Table 1).

Table I.

Re-do Procedures in "group B"	**Nr. of patients**
Posterior sagittal anorectovaginourethroplasty (PSARVUP)	4
PSARVUP, bladder augmentation (Mainz-Pouch I) and Mitrofanoff	1
Posterior sagittal anorectoplasty (PSARP) and TUM	5
PSARP, TUM, bladder augmentation and Mitrofanoff	1
PSARP, vaginal substitution with ileum, urethra substitution with ileum, and bladder augmentation with ileum	1
PSARP, vaginal substitution with sigma and urethroplasty	2
PSARP, vaginal substitution with ileum, Mitrofanoff and MACE	1
PSARP, vaginoplasty from UGS, neobladder from ileum, Mitrofanoff, and MACE	1
TUM	1
Vaginal introitoplasty, bladder augmentation with ileum, Mitrofanoff and MACE	1
Vaginal substitution with ileum	1
Vaginal introitoplasty of vaginal substitute (ileum segment)	1

Results

Only the urological status will be analysed in spite of the fact that all patients from group A and most patients from group B had simultaneously correction of urethra, vagina and rectum.

Postoperative evaluation was undertaken clinically in all and radiologically in most patients.

Group A: All patients have good renal function. In 1 girl the urethra retracted after TUM. She also has neurogenic bladder with VUR III in a solitary kidney. Although 7 patients from group A had sacral dysplasia, there are only 3 children with neurogenic bladder dysfunction.

Seven patients void with good urinary control and are dry. Five empty their bladder by intermittent catheterisation via the urethra and are also dry.

Group B: Obstructive uropathies leading to renal insufficiency were seen in 3 patients. All 3 girls had undetected hydrometrocolpos as newborns with obstructive uropathies. One patient presented with a transplanted kidney, another one was transplanted after re-do operation for cloaca, but died 6 months following transplantation. The 3rd patient waiting for transplantation, was seen 5 years ago before she was lost to follow-up. Other 5 girls had reflux nephropathies leading to nephrectomy in one.

There were 11 girls with sacral dysplasia, 6 of them with neurogenic bladder, 1 with ileum-neobladder and 1 with bladder agenesis, and 3 with normal bladder function. But there was also one girl with neurogenic bladder, without sacral dysplasia.

At last follow-up, there were 7 continent patients. Nine patients achieved continence by intermittent catheterisation via the urethra or a catheterisable channel, and 2 were still urinary incontinent.

Discussion

Persistent cloaca is an anomaly with an extremely complex anatomy. It consists of a spectrum of anomalies of the genitourinary tract and anus and rectum. All three organ systems have a common confluence, termed the cloacal channel (3).

The malformation can be corrected satisfactory in most patients, providing them with urinary and bowel control and good sexual function (4). But most patients need very sophisticated surgical procedures (4,5,6).

The surgeon must have vast experience in the treatment of anorectal and genitourinary malformations. Treatment of a newborn with cloacal malformation should start with a colostomy. Moreover, satisfactory evacuation of urine must

be achieved, as some children may present with infravesical obstruction due to hydrometrocolpos or obstruction of the common channel (7). Vesicostomy or vaginostomy should be considered in such cases. In our series, there were 3 girls (all in group B) in which unrecognised hydrometrocolpos led to urinary obstruction and subsequently resulted in renal failure.

The anatomy must be clarified by clinical examination, sonography, x-ray studies, MRI, and endoscopy (8, 9). The timing of surgery is important: the patients should be in good condition, having an accurate diagnosis before any procedure. A correct diagnosis will allow the experienced surgeon to repair the entire malformation and avoid a persistent urogenital sinus (5). In most patients from "group B" the cloacal malformation was misinterpreted as anal atresia with recto-vaginal fistula. Consequently 14 of them presented with persistent UGS. The other 4 presented with vesico-vaginal, or urethro-vaginal fistula. Only 2 girls had a functional urethra, but they also needed correction because of vaginal pathology.

As for primary operation, the posterior sagittal incision provides good exposure of the anatomy, protecting the nerves and vessels which enter the pelvis posteriorly and laterally. Yet scar tissue and the absence of organs, e.g. urethra, vagina, uterus, require other approaches and types of reconstructions (see Table I).

The re-do operations were performed by posterior sagittal approach in all patients from group A and in 16 patients from group B. To achieve urinary continence in one patient from group A and in 5 patients from group B, bladder augmentation or bladder substitution were carried out. There were 5 patients needing a Mitrofanoff procedure to become dry by intermittent catheterization. Additionally a bladder neck plasty in one and a colpo-wrap (10) procedure in an another girl were done.

Primary reconstruction of the urethra, the vagina and the rectum simultaneously during the first operation gave better results regarding urinary continence. All patients from group A are dry: 7/12 void spontaneously and 5/12 by intermittent catheterization.

In contrast, the results are less good in patients with multiple procedures regarding both, continence and renal function. In group B only 7/18 patients void spontaneously, 10/18 are on intermittent catheterization, 2/18 are incontinent, one child died after renal transplantation.

The likelihood of needing continuing intermittent catheterisation is greater in those with severe sacral anomalies (3). That was true also in our patients.

Accomplishment of definitive repair involves not only anatomical reconstruction, but also postoperative urinary control, including the initiation of intermittent catheterization under repeated urodynamic evaluations (11).

The well-being of the patients is markedly affected by incontinence and also by renal failure. The lack of compliance to regular catheterizations is an absolute contraindication for continent urinary diversion (12).

Therefore, before providing the patient with continent urinary diversion the surgeon has to be sure that the patients or their caregivers will be able to empty the bladder by intermittent catheterization.

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CONGENITAL ESOPHAGEAL STENOSIS: A REPORT ON TWO CASES

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Abstract

Introduction. Congenital esophageal stenosis (CES) is a very rare malformation, occurring in 1:25.000 – 1:50.000 live births.

Purpose. We report two cases of CES treated in our unit.

Materials and Methods. The charts of two patients having CES were retrospectively studied, special attention being paid for clinical aspects, radiological features, surgical treatment and results.

Results. Both of our patients were admitted for repeated episodes of vomiting and dysphagia. The esophagogram revealed the stenotic lesion, without any episode of gastro esophageal reflux. They initially underwent bougienage dilatation, with no significant effect. In one case we performed the stenotic segment removal followed by eso-esophageal anastomosis. In the other one we replaced the long stenotic portion of the esophagus with distal ileum. The histopathology study found fibro muscular thickening. The postoperatory esophagogram showed good results in both cases.

Conclusions. The curative treatment of our cases was represented by surgical removal of the stenotic esophageal segment. In cases with long, distal esophageal stenotic segment, the replacement with distal ileum is a good alternative.

Key words: congenital esophageal stenosis, esophageal substitution with ileum.

Introduction

CES is a consequence of a congenital malformation of the esophageal wall architecture (1). This rare condition was found in 1:25.000 – 1:50.000 live births, the incidence being higher in Japan (3,4). Associated anomalies, including esophageal atresia, cardiac anomalies, intestinal atresia, anorectal malformations, and chromosomal anomalies, were found in 17% - 33% of cases (1,2). More and more CES cases successfully treated with conservative meaning (bougienage or balloon dilatation) were reported, although with a significant consequent morbidity (5,6,7). In failed dilatation cases surgical removal of the lesion is mandatory.

Herein we report our experience with 2 CES patients treated in our hospital.

Materials and Methods

Between 2008 and 2009, two patients (4 months and 2 years of age) having CES were diagnosed and treated in our hospital (one boy and one girl). In both patients the diagnosis was made performing an esophagogram. In this retrospective study we reviewed the clinical picture, the therapeutic particularities and the results.

Results

The first case, a 4 month old female, was admitted in our unit for repeated episodes of vomiting, treated in another medical unit as GER. The esophagogram revealed a tight, stenotic, portion located in the middle of the thoracic esophagus, with no gastro-esophageal reflux (fig.1). A bougienage dilatation was attempted twice, without results. We performed the stenotic segment resection (about 2 cm) and end-to-end esophageal anastomosis (fig.2-4), with good results (fig.5,6). The pathological examination revealed a fibro muscular thickening of the resected esophageal segment.

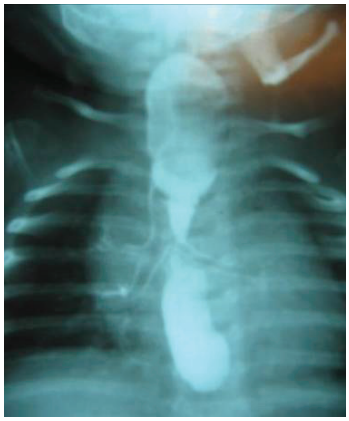
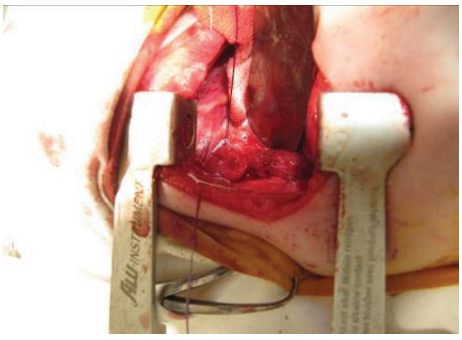


Fig.1: preop. esophagogram.



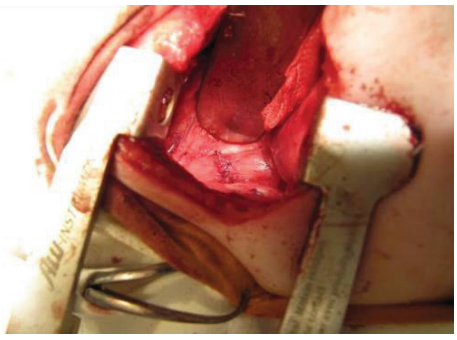


Fig.2,3: intraop findings, eso-esophageal anastomosis.

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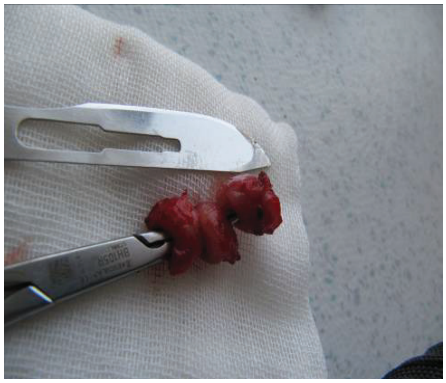


Fig 4: the stenotic segment removed.

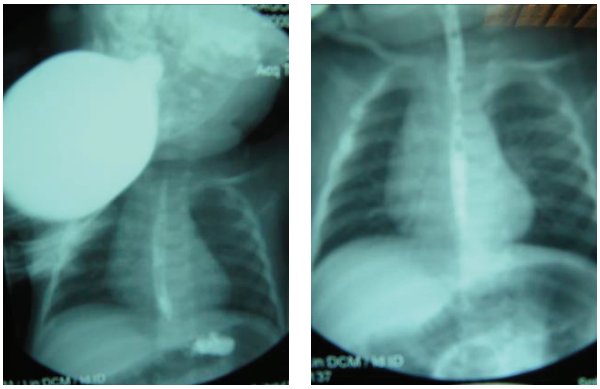


Fig. 5,6: postop esophagogram: no stenosis, no GER.

The second case was a 2 years old boy having Down syndrome associated with ventricular septal defect (previously operated) and cleft palate (previously operated). He was admitted in our department for repeated episodes of vomiting. The esophagogram (fig.7) showed a tight, long (about 4 vertebral bodies) stenotic segment. A bougienage was attempted, without results. In this circumstances we decided to operate him and to remove the stenotic segment (fig.10,11), performing a low esophageal substitution with distal ileum. The blood supply of the graft was given by the ileocolic a., preserving the junction with right colic a. We preserved the last 2 cm of the ileum and we performed an ileum-ileum anastomosis (fig.8,9). The postoperatory esophagogram (3 months postop) showed satisfactory results (fig.12).

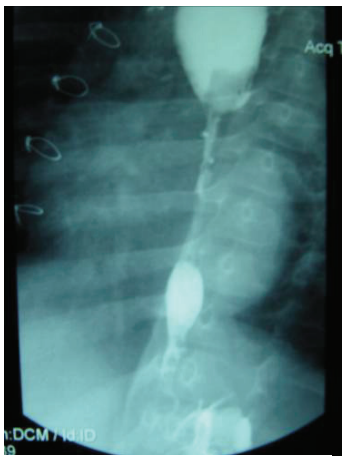


Fig.7: preop. Esophagogram.

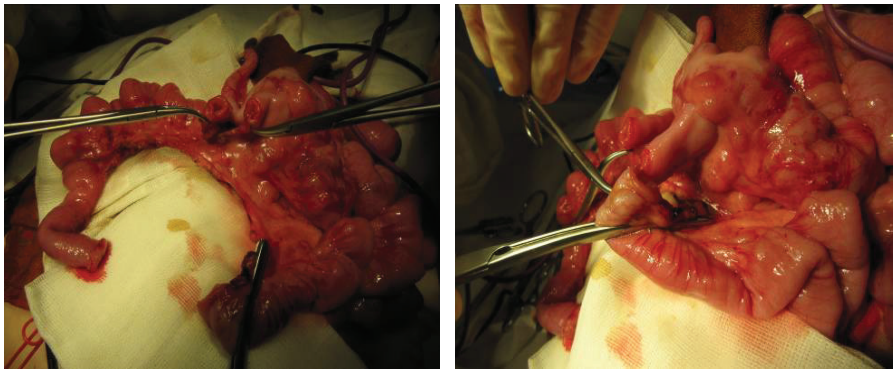
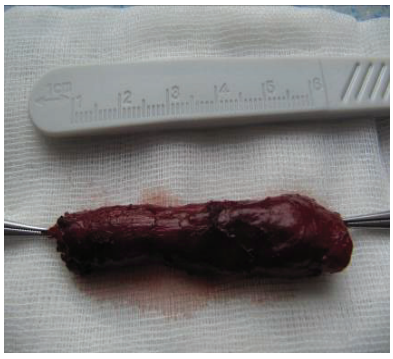


Fig.8,9:the ileal graft (the blood supply given by the ileocolic a.)



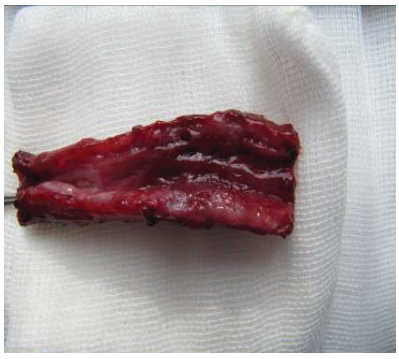


Fig.10,11: The esophageal stenotic segment.

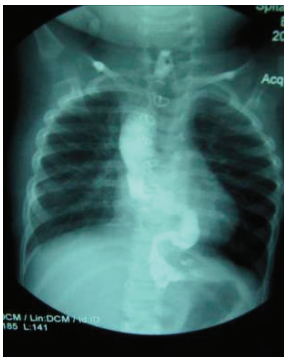


Fig.12: Postop esophagogram.

The pathologic exam revealed a fibro muscular thickening of the esophagus. An important aspect was that the distal thoracic and the abdominal esophagus removed together with the stenotic portion had a normal appearance, with no signs of reflux disease.

Discussion

Despite its rarity, CES must be taken into account in infants having repeated episodes of vomiting. The esophagogram, together with the clinical picture are highly suggestive for the disease. There are 3 histologically types of CES: 1-fibromuscular thickening, 2-tracheobronchial remnants, and 3-membranous webbing. There are 2 possible therapeutic options for this anomaly: dilatation (bougienage or balloon) and surgery. Shintaro and coworkers summarized, on 115 cases founded in 28 English-language studies that about 70% of the cases required surgical treatment (1). When the stenotic segment is relatively short, it is feasible to remove the lesion and to perform an end-to-end anstomosis. In this perspective, a very useful tool is represented by the traction sutures, as are described by Foker (8). When dealing with a long segment, involving the lower half of the thoracic esophagus, we found that esophageal substitution with distal ileum is an effective alternative, the blood supply being offered by the ileocolic a.

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IATROGENIC RETRACTION OF THE QUADRICEPS#

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Abstract

Quadriceps retraction after intramuscular injections requires a great attention, considering the fact that it causes a serious disability. The condition appears in children born prematurely or underweight that was hospitalized for a long time during the neo- natal period and in the first years of life. The knee's stiffness represents a surgical illness, but the general practioner (GP) has the duty to prevent it. The GP should be aware of the risk the intra-muscular injections have in new-born and disabled children (1,8,9). If, still, the disease has been identified and clinical signs are present, the pediatricians and family physicians have the duty to guide the earlier treatment of these children in a department of pediatric surgery and orthopedics.

Also, after being discharged from surgical departments, family physicians and pediatricians must pursue their rehabilitation for a long time because the post-operative evolution can be difficult, walking again can cause many problems, complications can occur, and relapses.

It is very important to be familiar with this disease in pediatric practice. The topic is of out most interest for the pharmaceutical industry because it brings forward the issue of creating new drugs to be administered by routes other than intramuscular one, but with the same efficiency and tolerance.

Key words: quadriceps retraction, intramuscular injection, neonates, extraperiostical desinsertion of the thigh muscle.

Introduction

The contraction of the quadriceps in childhood may be congenital or secondary to a different variety of reasons. This study discusses the femoral quadriceps muscle sclerosis, induced by injection in the thigh muscle and sclerosis resulting in a progressive painless limitation of knee flexion(2,10,11). All children had suffered from serious illnesses since the first weeks of life for which they had received intramuscular tigh injections. A thigh dimple was noticed in all patients (Lloyd Roberts and Thomas 1964).

The mechanism by which these injection induced contractures develop is speculative. In the case of infants and babies the muscle mass is small and, for most of those babies included in the study who were born prematurely, the muscle mass must have been even smaller. Due to the volume of injected drugs, the compression of muscles and capillaries can result in significant muscle ischemia.(Gray 1967).The experimental trauma of a single intramuscular injection seems to cause disruption of muscle fibers with local necrosis and subsequent muscle fibrosis (Engel 1967); local drug toxicity may, also, play an important part(Chiu et al1974). It is interesting to point out that the damage to the muscle after injection is different from the damage caused by vascular injury. Unlike the ellipsoidal forearm heart attack, described by Seddon (1972), where Volkman's contracture is immediately obvious, after the injection therapy there is a considerable delay before contractures develop in the thigh. In our study, the age at admission varied from1year to15 years.

Williams (1968) has suggested that injection induced contractures may be related to unequal growth of muscle and bone. At first the healthy distal muscle fibers can compensate for the bone growth and ,as a result, there is no visible effect on the knee for several years after the injection treatment.

Subsequently, it reaches a point where the healthy muscle can no longer lengthen in proportion to the bone growth and contracture becomes apparent.

The differentiated growth between bone and muscle cannot be the only one responsible for any worsening of the patient's condition.

If contractures of this type are left untreated, secondary changes may occur in soft tissues, cartilage and bone of the neighboring joint. (Bose and Chong, 1976).

Some authors have observed that good results are achieved through the surgery of reinsertion of thigh muscle for mobilization the knee.

In conclusion, we believe that the most appropriate surgical treatment for children with contractions of the quadriceps caused by infection is reinsertion of the thigh for knee mobilization. The surgery eliminates the complication of a persistent extension lag (3,12). Postoperative mobilization can be quicker and the scar produces a more acceptable cosmetic result. A satisfactory range of flexion has been achieved in all our patients.

Aim of the paper. Material. Methods

This paper is based on the casuistic of the Clinic of Orthopedics' and Pediatric Surgery in Bucharest and Galati, over a period of twenty years, between1989-2009.

A retrospective and statistical study was conducted based on:

- The observation sheets of 200 children operated for iatrogenic quadriceps retraction;
- Postoperative protocols;
- Histopathological examinations.

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Between 2004 -2009 active calls were made for medical check-outs in the same centres where the postoperative results were analysed:

- After the knee flexion obtained postoperatively;
- After patellar position;
- After the age at surgery;
- After the postoperative scar;
- After walking, running, climbing and gender distribution, environment origin and location of the disease;

These classifications have been made for the clinic of Pediatric and Orthopedic Surgery in Bucharest and Galati, to be used as acomparative test. The study takes into account the following aspects:

- Frecquency of the disease in years (table 1)
- Frequency index (table 2)
- Prevalence of the disease for each sex (table 3)
- Environment of origin (table 4)
- Location of the disease(table 5)
- age (table 6)

The social aspect is also of outmost importance, considering the fact that a great number of patients come from institutionalised centres.

One more reason for this paper is the observation that due to the increased popularization of this condition, the number of cases dropped for a certain period of time.

In order to be better understood and for achieving its goal, this paper was structured into a theoretical presentation of the disease and a detailed presentation of cases.

Catemnestic study

Frequency of the disease

Table 1, fig. 1 shows that frequency of cases has decreased progressively and the explanation would be both an absolute decrease in the number of cases but also a greater involvement of the competent services, which was the result of a better knowledge of the disease in the field.

Table 1: Frequency in years.

YEAR	NUMBER of CASES
1989	25
1990	20
1991	15
1992	20
1993	18
1994	19
1995	17
1996	10
1997	8
1998	6
1999	5
2000	5
2001	4
2002	4
2003	3
2004	4
2005	4
2006	4
2007	4
2008	3
2009	2
TOTAL	200

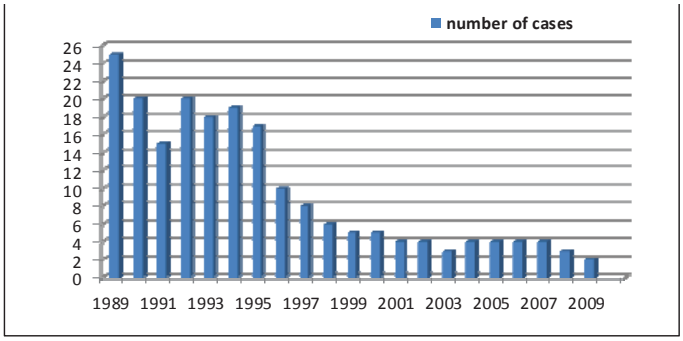

Fig. 1. Number of cases.

Frequency index (Table 2, Fig. 2), representing the number of reported cases of RIC from the total number of hospitalized children in the clinic, was 0, 31% in 1989, 0, 19% in 1993, 0, 09% in 2009. These figures reflect the incidence of the disease and are, also, a warning to pediatricians, imposing measures of prevention.

Table 2: Frequency index.

YEAR	NUMBER OF ADMISSIONS	NUMBER OF CASES	%
1989	10245	25	0, 31
1993	10773	18	0, 19
2009	11440	1	0, 09

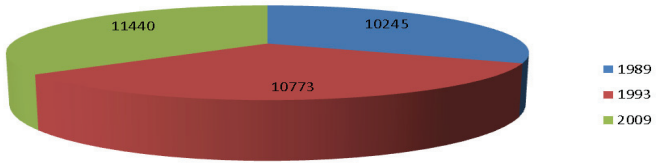

Fig. 2. Number of admissions / year.

Sex

One can note the prevalence of disease in females (Table 3, Fig. 3). Thus, from 200 cases of RIC, 165 were girls (62%) and 35 boys (38%). These data were found in the specialized literature, where the same ratio of 2 / 3 girls and 1 / 3 boys is mentioned. We do not have a scientific explanation of this scale, though some have blamed an unknown, constitutional factor, predominant in girls.

Table 3: Sex ratio.

BOYS	35	38%
GIRLS	165	62%

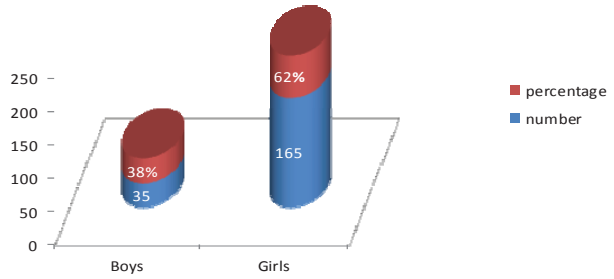

Fig. 3. Sex ratio.

Environment of origin (table 4,fig.4)

Statistics show an almost equal incidence, however, insignificant in relation to the social environment: 106 cases (53%) in urban and 94 cases (47%) in rural areas, indicating similarity of curative care. Important to mention, is that the disease occurs frequently in children from institutionalized centers (145 cases), aspect which requires informing the responsible factors in these institutions.

Table 4: Environment

URBAN	106	53%
RURAL	94	47%

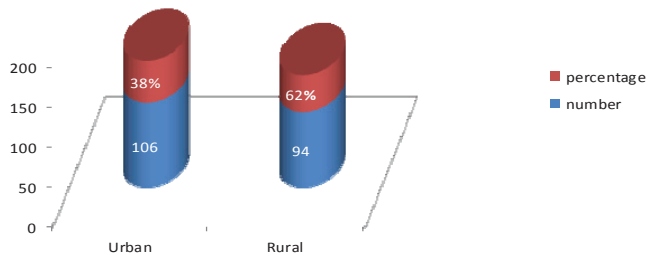

Fig. 4. Environment.

Location of disease (Table 5, Fig. 5) was as follows: 45 cases unilateral right, unilateral left 63cases, bilateral 71. Taking into account the bilateral cases, our cases make up a total of 249 operated hips.

Table 5: Location of disease.

BILATERAL	71	41%
RIGHT	45	26%
LEFT	63	33%
TOTAL	249	

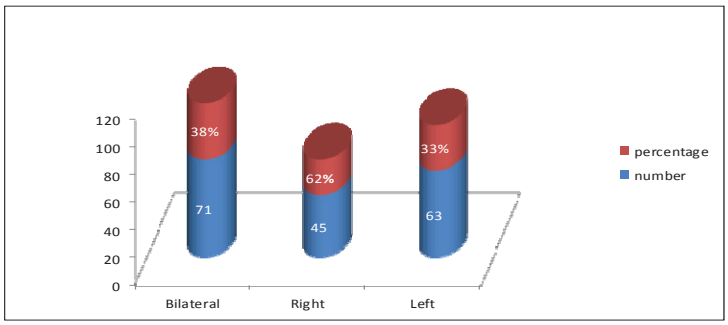

Fig. 5. Location of disease.

Age (table 6, fig. 6) has been the most difficult to establish because it relies only on their parents' assessment, subject to error, the onset of disease is often confused with a delay in walking due to other causes. We managed to get a statistics on age groups, both based on the history of the case report forms and on the history taken from parents in the checking.

Table 6. Age groups.

AGE	NO. OF CASES
0-1 years	24
1-2 years	77
2-3 years	44
3-4 years	36
4-5 years	8
5-8 years	6
Over 8 years	5

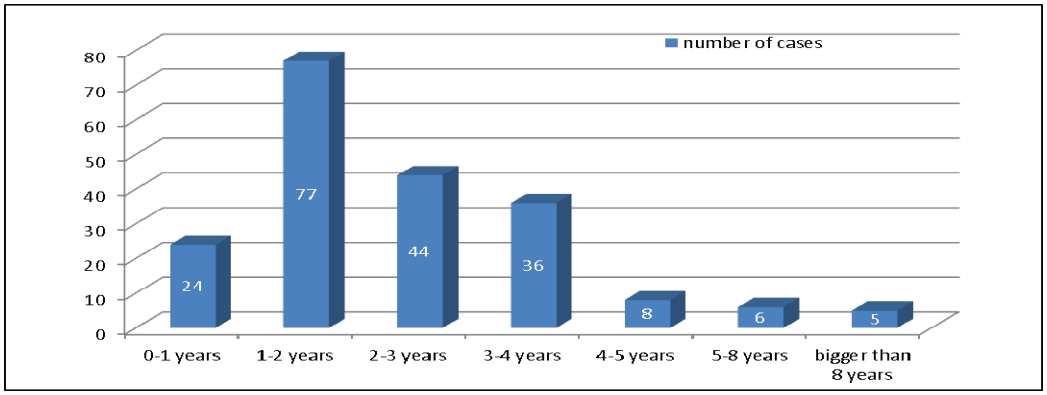

Fig. 6. Age groups.

We see from this table the frequency of the disease onset between 1-4 years (181 cases) as evidence of the consequences of the treatment carried out during the neonatal period and in the first years of life, therefore the importance that should be given to injection treatment in the thigh.

Surgical treatment

The technique (fig. 7) was inspired by Judet's method, but adapted to the knee's stiffness by iatrogenic quadriceps retraction, aiming to obtain better functional results and avoid as far as possible, the disadvantages of other techniques. The current technique is an extraperiostical reinsertion of the quadriceps and lowering associated with external patellar fin-clipping, in order to widen the strap that secures the patella and allows its lowering in a normal position through a single incision made in the postero-external side of the tight; groin incision iliac crest begins at 2 cm behind the anterior-superior spina, going down and backward to circle the great trochanter and then follows the septum between the anterior and posterior muscles up to one third of the lower thigh, where it curves backwards and ends just at the edge of the patella, 1cm from its external edge(4).

The incision involves the skin, subcutaneous tissue and fascia lata, which continues within the intermuscular septum. Vastus lateralis is detached from the intermuscular septum up to the rough line where it is detached from the femur. The reinserted fibres are cut with the scissors in order not to damage the periosteum.

The reinsertion is made on the whole surface of the vastus lateralis from the great trochanter up to the femoral condyle. Along with the vastus lateralis is also reinserted vastus intermedius. In the upper side of the incision we enter in the space between tensor fascia lata and buttocks, which is reinserted from the crest and anterior-superior iliac spine. The reinsertion of the tendon relaxes aponevrosis and enables exploring the direct and reflected tendons of the right femur. The direct and reflected tendon are sectioned from the anterior-inferior iliac spine which enables flexion of the knee(5,6).

This should be gently flexed and if it fails, the areas under tension should be examined and must be thoroughly and carefully identified and sectioned. Sometimes the reinsertion of the tailor muscle is very necessary and compulsory. We also don't want to damage the vascular – nerve bundles of the thigh and, especially, of the quadriceps(7).

Haemostasis must be done very accurately, in order to minimize bleeding which is quite significant. Examination of the leg flexion should be done with the hip in extension over the basin. If a flexion of 90 to100 is obtained, then it can be considered a successful intervention and then observe how the quadriceps lowers about 10-12cm. Only the skin is sutured with the knee in flexion, the muscle remaining at the level at which it had lowered. After applying the bandage, the leg is covered with a layer of wool, wrapped up in bud set, achieving as light compression on the thigh, following immobilization in pelvic-pediaplaster device with the thigh in extension over the basin with a flexion 90-100 on the thigh.

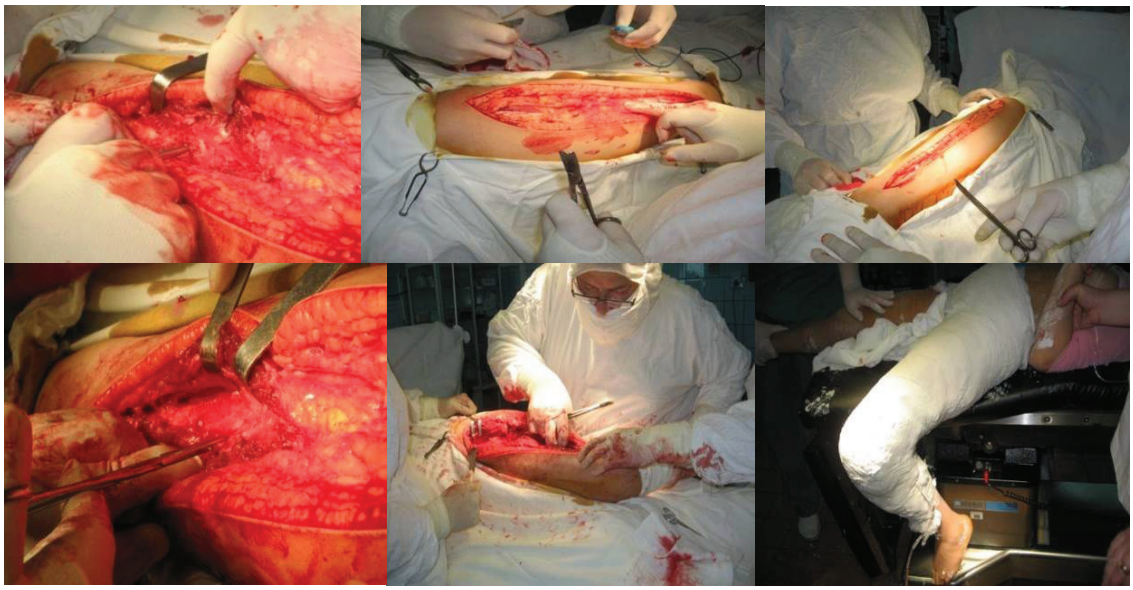

Fig. 7. Operatedcases of retraction of thequadriceps (personal archives).

Results

Postoperative results are mostly good or very good, especially in recent years, when the technique acquired an experimental and pathophysiological basis and was used as a treatment by many specialists.

Criteria of these results are:

1. passive and active flexion-extension movementmeasuredbygoniometry;
2. study of quadriceps strength (determination of muscle functional capacity after Iordanescu Baciu clinical scale);
3. position of the patella and the presence of the patellar reflex ;
4. walking;
5. climbing and descending stairs;
6. running;
7. physical education program;

8. local aspect, postoperative scar,symetry of the tights;

Analysis of the results after the above mentioned criteria:

after the knee flexion (active and passive movements) the assesment is made with a clinical goniometer. After the degree of active flexion, the classification of the results on groups vary by author:

Judetfor post- traumatic treatment of the knee:

Results	**Degrees**
excellent	**over 100^0**
good	**80-100^0**
satisfactory	**50-80^0**
Very poor	**Sub 50^0**

Pouliquenet al. for knee stiffness by R.I.C:

Results	**Degrees**
excellent	**over 140^0**
good	**up to 120^0**
moderate	**up to 90^0**

Enasel for knee stiffness by R.I.C.

Results	**Degrees**
excellent	**over 100^0**
good	**80- 100^0**
moderate	**under 80^0**

Our own interpretation after the following criteria:

Results	**Degrees**
excellent	**over 110^0**
good	**90- 110^0**
moderate	**70- 90^0**
poor	**under 70^0**

Resultsafteractive andpassiveflexionshow:

Qualifier	Degree	No. Of cases	**Percentage**
excellent	>110^0	22	**37,28**
good	90-110^0	27	**45,76**
moderate	70-90^0	8	**13,55**
poor	**<70^0**	**2**	**3,38**

It is interesting to point out that, although, through surgery is achieved between 90-100 range of flexion (with the knee immobilized in plaster), afterwards the child will improve movement and increase the degree of flexion. This happens because the quadriceps' contractile element is enhanced, unlike adults, where, as Judet says, the flexion obtained at operation remains the same. I saw children who, at ckeck-up, had achieved a flexion of 140-160.

1. **assesment of the quadriceps muscular functional capacity** with the help of Iordanescu -Baciu clinical scale with gradations from 0-5. The results were as follows: 4-5= 41cases; 3= 14 cases;2= 4 cases.

This method asses, practically, the value of the lowered muscles. It was more difficult to use this method with smaller children,even using the Spitzy technique; judging by their active and passive flexion, one could suspect that they have a greater strenght.

2. **patella as position and dimenssion** was found normal in 54 de cases,4 cases of upper outer dislocation and 1 case with permanent, complete external dislocation. Patellar reflex existent.

3. **walking, was possible even for those who achieved a knee flexion of only 70^0**, without any abnormal element. This can be explained by keeping the iliac psoas, the tailor muscle and by the horizontal contribution of the adductors in the thigh flexion. Generally, for the extension of the calf, the quadriceps, with its renewed functional

capacity is strog enough to ensure a fairly reasonable walking

4. **running,** highlighted some deficiencies in the recovery of the hip flexion, due to the reinsertion of the tensor fascia lata and , sometimes, even of the tailor muscle,especially,in more serious conditions. Those children cannot raise their swinging, leg rapidly, being aware that in running there's no double support. They run errantly, limping,throwing off their thigh.

5. **the sports and physical education program ,** required in schools as a sum of the movements examined above, could be easily and corectly executed by the great majority of children , who had over 90 of flexion, quadriceps strength of a 4-5, except for the serious conditions..

6. **postoperative scar** was found in16out of 59 cases, partially with a keloid aspect, on the whole surface of the scar or only, partially. This keloid formation adds to the inestetical aspect of the thigh. It seems to develop very quickly, if we take into account that 3 scars were found in only 1 year after the surgery.

7. **thigh assimetry** was constantly frequent, predominant in the unilateral cases,but also present in the bilateral ones, in which the injuries were never equal assurface or gravity.

Conclusions

1. The iatrogenic retraction of the quadriceps is a disease described in pediatric orthopedics, whose frequency and severity make it widely known. The iatrogenic etiopathogeny cannot be wrong. A careful and rigorous anamnesis, as well as the clinical examination of hips showed the existence, in the past, of prolonged injectable treatments. We can't blame those treatments because they have saved thousands of lives. But, if today we know that by injecting drugs in the thigh a series of compartmentalized syndromes are achieved, whose purpose is the retraction of the quadriceps in extension of the knee, we must do everything for preventing it.

2. The histo-pathological lesions observed in both biopsies collected after surgery, as well as during the experimental research have clearly showed the fibro sclerotic transformation of the muscle tissue, with the loss of mobile, contractile parts. The clinical correspondent of the quadriceps sclerosis is represented precisely by the knee biomechanics effect, stiffness in extension with or without patellar dislocation.

3. There are no problems of positive and differential diagnostic, to the extent in which the examiner knows the problem. This way, children are operated and explored by knee surgery (because there is suspected obstruction), or are recommended physical therapy (useless in the established disease stage). Therefore, we believe it is useful to inform the pediatric and orthopedic network about the disease.

4. The evolution of the disease is progressive up to a certain level where flexion is blocked, sometimes to the stage of genu recurvatum in very serious cases. The parents of such children should be advised not to wait more than 2-4 years to accept surgery because significant osteo- articular changes take place in the knee, and worsening of the quadriceps sclerosis that make the surgery and postoperative muscle re-education difficult.

5. The surgery is the only one capable of solving the disease. There are some surgeons in favour of lengthing the quadriceps tendon. Experience in the clinic shows that, in most of the cases this lenghting is not enough for obtaining a satisfactory flexion of the calf on the thigh and the postoperative rehabilitation can not recover completly the calf extension.

6. The Socolescu technique of extraperiostal reinsertion and lowering of the quadriceps, which is associated with the reinsertion of tensor fascia lata and sometimes of the tailor muscle, answers all the criticism of other surgical methods and is adapted to the very local situations resulting from muscle fibrous retraction. In addition, by reinserting tensor fascia lata, external rotation is corrected. Plaster immobilization for 3-4 weeks followed by careful rehabilitation, assisted and directed, provides very good results. The complications of this postoperative technique, when it is well performed, when hemostasis is done with full attention and the asepsis is treated as the "the surgery's golden rule" are minimal.

7. It's important to underline that after surgery, thorugh a sustained correction, the knee flexion increases in amplitude.

But the most important conclusion of this work remains the problem of the disease prophylaxis. The conjunction of all factors from the Ministry of Health is a necessary responsibility, until each person in the medical field is determined to do whatever it takes to avoid this iatrogenic disease seriously affecting small patients.

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

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

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ACADEMIA OAMENILOR DE ŞTIINŢĂ DIN ROMÂNIA – TRECUT, PREZENT ŞI PERSPECTIVE DE DEZVOLTARE –

Acad. Nicolae Gorun
(Bucureşti)

Sub prima sa denumire, aceea de „Academia de Ştiinţe din România", academia noastră s-a înfiinţat „de facto" la 11 martie 1935, din iniţiativa a 26 oameni de ştiinţă, dintre care unii erau membri ai Academiei Române.

Necesitatea acestei academii a fost susţinută de marele fiilozof P. P. Negulescu, încă din 1920, dar cel care a motivat această necesitate a fost Grigore Antipa, la acea vreme, directorul Buletinului Ştiinţific al Academiei Române, care a spus că „Academia Română singură nu poate să îndeplinească toate cerinţele culturii noastre".

Primul preşedinte a fost ales prof. dr. C. Angelescu, personalitate marcantă a vieţii ştiinţifice medicale şi organizator al învăţământului românesc, demn continuator al marelui său înaintaş Spiru Haret.

În ciuda protestului vehement al preşedintelui Academiei Române din acei ani, Ludovic Mrazek, acest demers s-a încheiat în mod fericit.

Activitatea Academiei de Ştiinţe din România a fost marcată de obstrucţii şi împliniri.

Primul război mondial şi apoi Marea Unire din 1918, au fost urmate de o prodigioasă activitate a membrilor Academiei de Ştiinţe. În acest context, participarea României la viaţa internaţională şi libera circulaţie de valori au asigurat prezenţa activă a oamenilor de ştiinţă români la numeroase congrese şi conferinţe internaţionale, obţinerea unor brevete şi traducerea unor lucrări în limbi de circulaţie internaţională, lucrări care au putut astfel intra în patrimoniul intelectual al Europei şi al lumii.

În cadrul acestui înalt for ştiinţific, au activat, timp de 14 ani, mari personalităţi ale ştiinţelor medicale din România. Academia şi-a îndeplinit misiunea cu entuziasm şi profesionalism desăvârşit şi în anii grei ai celui de al II-lea război mondial.

Regimul comunist a desfiinţat abuziv, în 1948, Academia Română, Academia de Ştiinţe şi Academia de Ştiinţe Medicale, înfiinţând Academia R.P.R., cu întreg patrimoniul mobil şi imobil al celorlalte.

Ca o reparaţie morală pentru momentul 1948, din iniţiativa unor distinşi oameni de ştiinţă (M. Ralea, Şt. Milcu, Şt. Bălan, Gr. Moisil, Şt. Nicolau, Al. Codarcea, s-a constituit, sub conducerea lui Traian Săvulescu, preşedinte în exerciţiu al Academiei Române, Asociaţia Oamenilor de Ştiinţă din România având, la început, un nivel ridicat, în mod treptat, nivelul academic a scăzut semnificativ. De fapt, Academia de Ştiinţe, ca academie, a intrat într-un adânc con de umbră, care a durat peste 45 de ani. Şi după 1989, încercările făcute de valoroşi oameni de ştiinţă de a reînfiinţa această academie au întâmpinat oprelişti incredibile. Criticul literar Eugen Simion, preşedintele Academiei Române, s-a opus cu înverşunare şi dispreţ, obligându-ne să purtăm din nou denumirea de Asociaţia Oamenilor de Ştiinţă, care s-a reînfiinţat în 1994, sub conducerea marelui matematician, academicianul Nicolae Teodorescu. La primul său congres, după reînfiinţare, domnul prof. dr. general (r) actualul preşedinte, a propus schimbarea titulaturii din Asociaţie în Academie, schimbare rămasă definitivă, prin hotărârea judecătorească din 3 octombrie 1996.

Desfăşurând o largă şi valoroasă activitate, în noile condiţii, membrii celor 13 secţii ale AOŞ-R, secţia a 8-a fiind secţia medicală, instituţia şi-a recăpătat prestigiul şi locul pe care îl merită din plin.

În prezent, AOŞ-R se axează pe câteva direcţii strategice, atât pe plan intern, cât şi pe plan extern, pe produse şi servicii oferite comunităţii ştiinţifice, rezolvarea unor complexe probleme de infrastructură.

Obiectivele AOŞ-R pentru 2011 sunt numeroase şi precise, iar rezultatele cercetărilor noastre vor fi la înălţimea eforturilor depuse.

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REZUMATUL CARACTERISTICILOR PRODUSULUI

1. DENUMIREA COMERCIALĂ A MEDICAMENTULUI ZOMACTON, liofilizat şi solvent pentru soluţie injectabilă, 4 mg (12 UI) **2. COMPOZIŢIA CALITATIVĂ ŞI CANTITATIVĂ** Un flacon cu liofilizat pentru soluţie injectabilă conţine 4 mg (12 UI) somatropină produsă prin inginerie genetică din E. Colli. O fiolă cu solvent pentru soluţie injectabilă conţine: clorură de sodiu, alcool benzilic 31,5 mg, apă pentru preparate injectabile. Pentru lista tuturor excipienţilor, vezi pct. 6.1. **3. FORMA FARMACEUTICĂ** Liofilizatul: liofilizat de culoare albă sau aproape albă. Solventul: soluţie limpede, incoloră. **4. DATE CLINICE 4.1 Indicaţii terapeutice** Zomacton este indicat în tratamentul de lungă durată al copiilor: cu deficit de creştere produs de insuficienţa hormonului somatotrop; cu deficit de creştere produs de disgenezia gonadală (sindrom Turner), confirmată prin analiză cromozomială. **4.2 Doze şi mod de administrare** Zomacton trebuie prescris doar de către medici specialişti care posedă cunoştinţe despre indicaţia terapeutică pentru care a fost recomandat. Doza trebuie individualizată, stabilindu-se în funcţie de răspunsul pacientului la tratament. Durata tratamentului, în mod obişnuit de câţiva ani, depinde de maximul de beneficiu terapeutic dorit. Administrarea subcutanată poate provoca reducerea sau creşterea ţesutului adipos subiacent de la nivelul locului de administrare. Din această cauză se recomandă alternarea locurilor de administrare. Dozele recomandate: *Deficitul creşterii, produs de insuficienţa hormonului somatotrop (nanism hipofizar)*: doza uzuală recomandată este de 0,17-0,23 mg somatropină/kg, echivalent cu 4,9-6,9 mg/m2 pe săptămână divizată în 6-7 prize de injecţii subcutanate, corespunzând la 0,02-0,03 mg somatropină/kg şi pe zi sau 0,7-1,0 mg/m2 şi pe zi. Doza maximă recomandată care nu trebuie depăşită este de 0,27 mg/kg sau 8 mg/m2, corespunzând la 0,04 mg/kg pe zi. *Sindrom Turner*: doza uzuală recomandată este de 0,33 mg somatropină/kg şi pe săptămână, echivalent cu 9,86 mg/m2 divizată în 6-7 prize de injecţii subcutanate, corespunzând la 0,05 mg /kg şi pe zi sau 1,40-1,63 mg/m2 şi pe zi. **4.3 Contraindicaţii** Hipersensibilitate la somatropină sau la oricare dintre excipienţi; Orice tumoră malignă evolutivă sau neoplasm intracranian în antecedente sau recidivă a procesului tumoral, deoarece există posibilitatea creşterii tumorale. Anterior iniţierii terapiei cu Zomacton neoplasmele trebuie să fie inactive iar terapia antitumorală să fie completă; copii ale căror epifize de creştere s-au închis; Pacienţi cu complicaţii acute critice, ca urmare a unor intervenţii chirurgicale pe cord deschis, intervenţii chirurgicale abdominale, politraumatisme prin accidentare, insuficienţă respiratorie acută; sarcina şi alăptarea. **4.4 Atenţionări şi precauţii speciale pentru utilizare** Deoarece conţine alcool benzilic, Zomacton nu trebuie administrat la prematuri sau nou-născuţi. Alcoolul benzilic poate provoca reacţii toxice şi anafilactoide la sugari şi copii sub 3 ani. Tratamentul cu Zomacton va fi efectuat sub supravegherea unui medic endocrinolog cu experienţă în tratamentul nanismului hipofizar. În timpul tratamentului cu somatropină este necesar controlul glicemiei, deoarece hormonul poate produce intoleranţă la glucoză prin creşterea rezistenţei la insulină. Se recomandă prudenţă la pacienţii diabetici şi la cei cu antecedente familiale de diabet zaharat. Este necesară monitorizarea glicemiei şi glucozuriei. La copiii diabetici poate fi necesară creşterea dozei de insulină. Hipoglicemia à jeun care poate să apară la copiii cu insuficienţă hipofizară este ameliorată în timpul tratamentului cu somatropină. La pacienţii cu insuficienţă hipofizară secundară unei leziuni intracraniene sunt necesare controale regulate pentru evaluarea afecţiunii de bază. Tratamentul cu somatropină trebuie întrerupt dacă se constată agravarea afecţiunii. Se recomandă prudenţă la pacienţii cu antecedente de boli maligne, deoarece semnele şi simptomele pot să reapară. Au fost raportate rare cazuri de apariţie a hipertensiunii intracraniene. Examenul fundului de ochi pentru depistarea edemului papilar trebuie efectuat la iniţierea tratamentului şi, periodic, pe tot parcursul acestuia, în special la pacienţii care prezintă cefalee recurentă, tulburări de vedere, greaţă sau vomă (simptomatologie ce poate indica apariţia hipertensiunii intracraniene). Dacă edemul papilar este confirmat, diagnosticul de hipertensiune intracraniană trebuie luat în considerare, iar tratamentul cu hormon de creştere va fi întrerupt. Somatropina poate induce uneori insuficienţă tiroidiană. Hipotiroidismul netratat corespunzător scade eficienţa tratamentului cu somatropină. Pe toată perioada tratamentului este necesară supravegherea funcţiei tiroidiene şi, în caz de hipotiroidism trebuie instituit tratamentul corespunzător. La un număr mic de pacienţi cu deficit de hormon de creştere, dintre care unii au fost trataţi cu somatropină, au fost semnalate cazuri de leucemie. Pe baza datelor existente din studiile clinice pe 10 ani este improbabil ca somatropina să fie responsabilă pentru acest fenomen. Luxaţiile de cap femural apar mai frecvent la bolnavii cu endocrinopatii. Pacienţii trataţi cu somatropină care prezintă claudicaţii, dureri de şold sau de genunchi trebuie examinaţi de un medic specialist. Efectele tratamentului cu hormon de creştere au fost observate în cadrul a două studii clinice controlate placebo care au inclus 522 pacienţi adulţi cu complicaţii acute critice, ca urmare a unor intervenţii chirurgicale pe cord deschis, intervenţii chirurgicale abdominale, politraumatisme prin accidentare, insuficienţă respiratorie acută. Mortalitatea a fost crescută 42% la pacienţii trataţi cu hormon dew creştere faţă de 19% la pacienţii trataţi cu placebo. Deoarece nu există date despre siguranţa administrării de hormon de creştere la pacienţii cu afecţiuni acute severe, continuarea tramentului în aceste situaţii trebuie făcută după evaluarea raportului beneficiu terapeutic-risc potenţial implicat. La toţi pacienţii cu afecţiuni acute, beneficiu terapeutic trebuie să depăşească riscul potenţial implicat. **4.5 Interacţiuni cu alte medicamente şi alte forme de interacţiune** Glucocorticoizii pot reduce eficienţa tratamentului cu somatropină. Administrarea de glucocorticoizi la pacienţii cu deficit asociat de ACTH impune prudenţă şi ajustarea dozelor de glucocorticoizi. Dozele mari de estrogeni, hormoni androgeni sau anabolizante steroidiene pot accelera procesul de maturare osoasă, favorizând oprirea creşterii în înălţime. Somatropina are efect antagonist competitiv faţă de insulină, ceea ce obligă uneori la creşterea dozei de insulină la copiii diabetici care sunt trataţi concomitent cu Zomacton. Date din studiile de interacţiune efectuate la adulţii trataţi cu hormon de creştere arată că somatropina poate creşte clearance-ul medicamentelor metabolizate pe calea citocromului P4503A4, cum ar fi steroizi, corticosteroizi, anticonvulsivante, ciclosporină, rezultând concentraţii plasmatice reduse ale acestora. Semnificaţia clinică a acestui efect nu este cunoscută. **4.6 Sarcina şi alăptarea** Deoarece nu există studii preclinice şi clinice care să demonstreze siguranţa tratamentului cu somatropină la gravide, medicamentul nu va fi administrat în timpul sarcinii. Nu se ştie dacă somatropina se excretă în laptele matern, de aceea nu se administrează la femeile care alăptează. **4.7 Efecte asupra capacităţii de a conduce vehicule şi de a folosi utilaje** Somatropina nu influenţează capacitatea de a conduce vehicule sau de a folosi utilaje. **4.8 Reacţii adverse** Au fost raportate cazuri rare de reacţii adverse cum ar fi rritem, prurit, durere la locul injecţiei. Injectarea repetată în acelaşi loc poate produce fenomene de lipodistrofie - se recomandă schimbarea locului injecţiei de fiecare dată. În primele săptămâni de tratament este posibilă apariţia unei hipertensiuni intracraniene benigne. Simptomele obişnuite sunt: cefalee, greaţă, vărsături, tulburări de vedere şi impun examinarea fundului de ochi pentru depistarea edemului papilar. În majoritatea cazurilor simptomele sunt tranzitorii şi nu necesită întreruperea tratamentului. În cazuri severe se recomandă reducerea dozei sau întreruperea tratamentului. La aproximativ 1% dintre pacienţi a fost observată apariţia anticorpilor. Capacitatea de legare a acestor anticorpi este scăzută şi nu au fost observate manifestări clinice asociate cu formarea de anticorpi. Au fost raportate cazuri foarte rare de leucemie la copii cu deficit de hormon de creştere trataţi cu somatropină, dar incidenţa apariţiei leucemiei este similară cu cea constatată la copii fără deficit de hormon de creştere. Clasa organ sistem: Foarte frecvente (>1/10): Tulburări generale şi la nivelul locului de administrare; Tulburări ale sistemului imun; Tulburări metabolice şi de nutriţie; Afecţiuni musculo-scheletice şi ale ţesutului conjunctiv; Tumori benigne, maligne şi nespecificate (incluzând chisturi şi polipi); Tulburări ale sistemului nervos. Frecvente (>1/100, <1/10): Tulburări generale şi la nivelul locului de administrare - Reacţii la nivelul locului de injectare; Tulburări ale sistemului imun - Formare de anticorpi; Tulburări metabolice şi de nutriţie - Hipoglicemie; Afecţiuni musculo-scheletice şi ale ţesutului conjunctiv; Tumori benigne, maligne şi nespecificate (incluzând chisturi şi polipi); Tulburări ale sistemului nervos. Mai puţin frecvente (>1/1000,<1/100): Tulburări generale şi la nivelul locului de administrare - Edeme periferice; Durere şi erupţie cutanată tranzitorie la nivelul locului de injectare; Tulburări ale sistemului imun; Tulburări metabolice şi de nutriţie - Diabet zaharat tip 2; Afecţiuni musculo-scheletice şi ale ţesutului conjunctiv - Mialgii; Tumori benigne, maligne şi nespecificate (incluzând chisturi şi polipi); Tulburări ale sistemului nervos - Cefalee; Hipertensiune intracraniană. Rare (>1/10000, <1/1000): Tulburări generale şi la nivelul locului de administrare; Tulburări ale sistemului imun; Tulburări metabolice şi de nutriţie; Afecţiuni musculo-scheletice şi ale ţesutului conjunctiv; Tumori benigne, maligne şi nespecificate (incluzând chisturi şi polipi) - Leucemie; Tulburări ale sistemului nervos. **4.9 Supradozaj** Dozele recomandate de Zomacton nu trebuie depăşite. Nu s-au raportat cazuri de supradozaj. Este de presupus că supradozajul acut poate produce iniţial hipoglicemie urmată de hiperglicemie. Nu se cunosc efectele pe termen lung ale administrării repetate a unor doze mai mari decât cele recomandate. Este posibil să apară aceleaşi efecte ca şi în cazul hipersecreţiei de somatropină (gigantism, acromegalie). **5. PROPRIETĂŢI FARMACOLOGICE 5.3 Date preclinice de siguranţă** Studiile preclinice de toxicitate acută efectuate cu doze de 50-100 de ori mai mari decât cele terapeutice pentru om nu au evidenţiat efecte toxice la niciuna din speciile supuse experimentării. Studiile de toxicitate cu doză unică efectuate la şobolani cărora li s-a administrat intramuscular o doză de 10 mg/kg, câini şi maimuţe cărora li s-a administrat intramuscular o doză de 5 mg/kg nu au evidenţiat efecte toxice semnificative la nici o specie. Studiile de toxicitate la doze repetate efectuate la şobolani cu doze de 1,10 mg/kg şi pe zi timp de 30 zile şi 0,37 mg/kg şi pe zi timp de 90 de zile nu au evidenţiat efecte toxice semnificative. Studiile preclinice nu au evidenţiat efecte mutagene. Somatropina obţinută prin inginerie genetică este identică cu somatropina endogenă şi are aceleaşi proprităţi biologice dacă este administrată în doze fiziologice. Nu se cunosc efectele asupra funcţiei de reproducere, sarcinii şi alăptării şi nu este de aşteptat un potenţial efet carcinogenetic. **6. PROPRIETĂŢI FARMACEUTICE 6.1 Lista excipienţilor** *Liofilizat:* Manitol. *Solvent:* Clorură de sodiu, alcool benzilic, apă pentru preparate injectabile. **6.2 Incompatibilităţi** În absenţa studiilor privind compatibilitatea, acest medicament nu trebuie amestecat cu alte medicamente în aceeaşi seringă. **6.3 Perioada de valabilitate** Medicamentul în ambalajul intact: 2 ani. Soluţia după reconstituire: 14 zile la temperaturi între 2ºC-8ºC, la frigider. **6.4 Precauţii speciale pentru păstrare** A se păstra la temperaturi între 2ºC-8ºC, la frigider, în ambalajul original, pentru a fi protejat de lumină. Soluţia reconstituită se va păstra la temperaturi între 2ºC-8ºC, la frigider, maxim 14 zile. **6.5 Natura şi conţinutul ambalajului** Cutie cu un flacon cu liofilizat şi o fiolă a 3,5 ml solvent pentru soluţie injectabilă. **6.6 Precauţii speciale pentru eliminarea reziduurilor** Zomacton trebuie preparat numai cu solventul prevăzut. Reconstituirea se face cu 3,2 ml solvent. Pentru obţinerea unei concentraţii mai mari (10 UI/ml) reconstituirea se face cu 1,3 ml solvent. Introducerea solventului în flacon se face dirijând jetul către peretele flaconului şi nu direct spre pulberea liofilizată, pentru a evita spumarea soluţiei. Flaconul se agită uşor până se dizolvă conţinutul. Datorită structurii proteice a Zomacton, nu se recomandă agitarea energică a flaconului. Soluţia obţinută trebuie să fie clară, incoloră. Dacă se observă prezenţa unor particule sau flocoane, soluţia se aruncă. Dacă se observă prezenţa flocoanelor în cazul soluţiei păstrate la frigider, se aşteaptă încălzirea produsului la temperatura camerei; dacă flocoanele persistă sau apare o coloraţie anormală, soluţia se aruncă. Doza de Zomacton se administrează utiliz-nd ZomaJet 2 Vision sau alte instrumente convenţionale de administrare. Instrucţiunile de utilizare pentru ZomaJet 2 Vision sunt disponibile în ambalajul acestuia. Orice produs neutilizat sau material rezidual trebuie eliminat în conformitate cu reglementările locale. **7. DEŢINĂTORUL AUTORIZAŢIEI DE PUNERE PE PIAŢĂ** FERRING GmbH, Wittland 11, D-29109 Kiel, Germania. **8. NUMĂRUL(ELE) AUTORIZAŢIEI DE PUNERE PE PIAŢĂ** 8263/2006/01 **9. DATA PRIMEI AUTORIZĂRI SAU A REÎNNOIRII AUTORIZAŢIEI** Decembrie 2006. **10. 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1. Rezumatul caracteristicilor produsului.

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Zomacton®
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