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JURNALUL PEDIATRULUI – Year XIX,
Vol. XIX, Nr. 73-74, january-june 2016
www.jurnalulpediatrului.ro
ISSN 2360 – 4557

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RECURRENT CONVULSIVE SYNDROME - CAUSES OF NEUROLOGICAL SEQUELAE

Aniko Manea^{1,2}, Oana Bilav², Daniela Cioboata², Florina Doandes², Marioara Boia^{1,2}

Abstract

The seizures represent the most common clinical manifestation and distinct neurological disorder in newborns with a frequency of 0.05% in newborns and 25% in preterm infants. The main causes of seizures are hypoxic-ischemic encephalopathy (EHI), intracranial hemorrhages and intracranial infections but there are some causes less common that make difficult to establish the etiology of the seizures. A 15 days old newborn baby girl was admitted with dyspnoea, subcostal and intercostals draft. During the hospitalization period she develop tonic-clonic seizures with high frequency of the episodes in 24h, reaching from 2-3 episodes per day to 10-12/ 24h, changing their features, becoming generalized, with spasm in flexion (flexible arms and legs). Because of the small age of the patient and the complexity of the case makes it difficult to establish the etiology of the convulsive episodes been associated both metabolic and hypoxic-ischemic causes. Conclusions - during the neonatal period the etiology of the seizures is difficult to establish and most of the children develop multiple comorbidities such as tetraspastic, severe psychomotor retardation accompanied by eating disorders leading to deficiency anemia, protein-calorie malnutrition, rickets.

Key words: convulsive syndrome, seizures, new born

Introduction

The seizures represent the most common clinical manifestation and distinct neurological disorder in newborns. The frequency of seizures in the neonatal period is variable from 0.05% in newborns to 25% in premature infants (1,2). The incidence of seizures increases to 50% in cases of associated with seizures (3). The most common physical cause of the seizures is the hypoxic-ischemic encephalopathy (EHI) - 50-60% of cases; intracranial hemorrhages cause about 10% of neonatal convulsions. Intracranial infections causing 5-10% of neonatal seizures are most commonly nonbacterial. Other causes of neonatal seizures include genetic metabolic disorders (metabolic disorders of amino acids, urea cycle enzyme, abnormalities leucinos, biotinidasis deficit, peroxisomal anomalies – Zellweger syndrome). Septicemia, and toxic metabolic

abnormalities can also produce seizures in the neonatal period. (20)

Case report

The 15 days old newborn baby girl was admitted to the ICU Premature Children's ward at "Louis Turcanu" Emergency Hospital for dyspnoea, subcostal and intercostals draft, and distended abdomen volume. The physiological personal history shows that the infant comes from dispensarised evolving physiological pregnancy, naturally born at a gestational age of 38 weeks, with 2900g birth weight, APGAR score 10/1' with good neonatal adaptation. Since the third day of life, overall condition worsens respiratory functional syndrome, fever ($T = 38^{\circ}C$) despite the antibiotic treatment.

On admission she presented an overall influenced general state, pale skin, heart rhythm disturbances CF180b/min, SaO₂ 94% and respiratory draft with RF 60 b/min, distended abdomen volume, generalized hypotonia. Laboratory data on admission revealed a mixed anemia, positive inflammatory markers (PCR=71.77mg/L, PCT=0.686 ng/ml) with positive blood cultures for *Acinetobacter baumannii/haemolyticus* at 72 hours.

On the second day of hospitalization appear the tonic-clonic seizures with decreased SaO₂<50%, with perioronasal cyanosis, spontaneously reversible. On the fifth day of hospitalization the patient shows a feverish spurt ($T = 38^{\circ}C$) therefor CSF is harvested in order to rule out the meningitis suspicion. The inflammatory markers become negative under the antibiotic treatment. Convulsive episodes are maintained throughout the hospitalization lasting <1min, their frequency in 24h reaching from 2-3 episodes per day to 10-12/ 24h, changing their features, becoming generalized, with spasm in flexion (flexible arms and legs), horizontal nystagmus, then look on the sunset, oculogyric.

To confirm the seizure etiology other biological investigations were made (table 1, 2). The cytogenetic report indicated karyotype 46, XX. Transfontanelar ultrasonography: minor bleeding of bilateral choroid plexus (Fig. 1).

Brain MRI and MRI angiography reveal normal appearance.

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It was established anticonvulsant therapy with Keppra syrup, initially 20mg/ kg/ day after reaching therapeutic dose of 40mg/ kg/day and Phenobarbital 10 mg/ kg/ day increasing the dose to 15mg/ kg/ day. The number of convulsive episodes intensifying it is decided to replace

Phenobarbital with Phenytoin, initially in continue IV infusion thereafter administered orally. Evolution under anticonvulsant therapy was stationary, reducing convulsive episodes/ 24h, without their final cropping.

<i>Alanine</i>	2.1mg/dL	<i>Leucine</i>	1 mg/dL
<i>Alphaaminobutyricacid</i>	0.1 mg/dL	<i>Lyzine</i>	1.3 mg/dL
<i>Arginine</i>	1 mg/dL	<i>Mehtionine</i>	0.3 mg/dL
<i>Asparagine</i>	0.7 mg/dL	<i>Ornithine</i>	0.6 mg/dL
<i>Aspartic acid</i>	0.3 mg/dL	<i>Phenylalanine</i>	0.7 mg/dL
<i>Carnosine</i>	<0.1 mg/dL	<i>Phosphoethanolamine</i>	<0.1 mg/dL
<i>Citruline</i>	0.2 mg/dL	<i>Proline</i>	1.8 mg/dL
<i>Cystine</i>	0.2 mg/dL ↓	<i>Sarcosine</i>	<0.1 mg/dL
<i>Glutamine</i>	6.1 mg/dL	<i>Serine</i>	1.5 mg/dL
<i>Glutamic acid</i>	3.3 mg/dL ↑	<i>Taurine</i>	0.7 mg/dL
<i>Glycine</i>	1.9 mg/dL	<i>Tronina</i>	0.9 mg/dL
<i>Histidine</i>	1 mg/dL	<i>Tryptophan</i>	1.1 mg/dL
<i>Hidroxioproline</i>	0.3 mg/dL	<i>Tyrosine</i>	1.2 mg/dL
<i>Izoleucine</i>	0.5 mg/dL	<i>Valine</i>	1.3 mg/dL

Table 1. Plasma amino acids

<i>CMV IgG</i>	>500 U/ml	<i>ToxoIgG</i>	187.6 UI/ml
<i>CMV IgM</i>	0.247	<i>ToxoIgM</i>	0.315 UI/ml
<i>Creatinkinaza</i>	325 U/L		↑
<i>Orotic acid</i>	4 mg/g		
<i>Ammonia</i>	143.9 μmol/L		↑
Na	137		138
K	4.3		4.2
Ca⁺⁺	1.1		1.2
Ca total	2.39		2.49
Mg	0.81		0.9

Table 2. Biological investigations

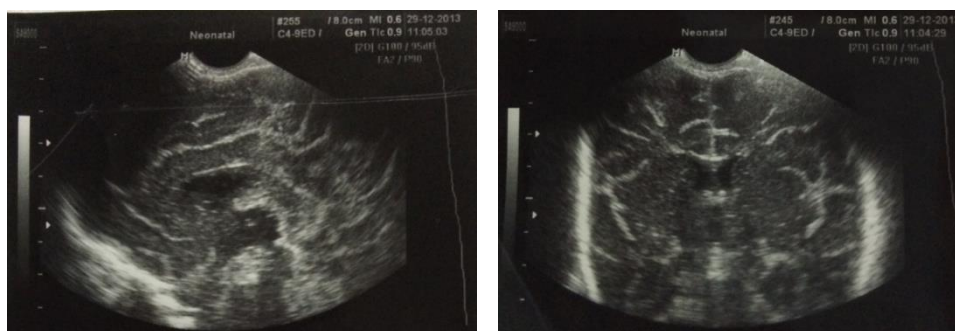


Fig.1: Transfontanelar ultrasound

Discussion

In recent years, significant advances in diagnosis and treatment in terms of neonatal seizures came into practice in neonatal intensive care.

The large majority of seizures in our population is due to perinatal asphyxia, known more correctly as hypoxic-ischemic encephalopathy, characterized by clinical evidence and laboratory investigations show acute or subacute cerebral abuse.(4) Asphyxia may be accompanied by hypoglycemia, hypocalcemia, hyponatremia due to antidiuretic hormone hypersecretion, especially in the first 3 days of life, and each of them individually can cause seizures. The onset seizures occur in the first 24 hours of life, being isolated at first and then become frequent and repetitive. Seizures show various appearances: sharp, clonic seizures (focal and multifocal), tonic (focal and generalized), myoclonic (focal, multifocal and generalized).

Our infant showed no signs of hypoxia intra and postpartum, early neonatal adaptation is good. Transfontanelar ultrasonography reveals a choroid plexus hemorrhage, but no signs of cerebral ischemia.

Intracranial hemorrhage as only etiology is estimated at 10% of neonatal seizures, but the true incidence of it is not known because most newborns with intracranial hemorrhage show no clinical symptoms, including hemorrhages moderate to severe. (5) Symptomatic intracranial hemorrhage is much less frequent at the newborn at term - 4 per 10,000 live births. (6) The incidence is higher, however, if the fetal delivery is instrumental. (7) In 50% of cases bleeding occurs on the first day of life and 90% in the first four days. In the case of subarachnoid hemorrhage seizures occur more frequently in premature babies starts in the second day of life and between seizures newborn is in good general condition and 90% have a favorable prognosis. Seizures of intraventricular hemorrhage occur in premature babies in third day of life and tonic convulsions are associated with respiratory deterioration and death. Subdural hemorrhage determine onset seizures within 24 hours, associated trauma, usually with cerebral contusion. In this context they are focal seizures. Choroid plexus hemorrhage occurs in newborn at term, leading to complications with neurological sequelae in 15% of cases. (8)

Bacterial meningitis or viral encephalitis usually occur in sepsis, representing another common etiology of neonatal convulsions. The most common causes of nonbacterial infections include toxoplasmosis, CMV infection and less rubella. *Escherichia coli* bacterial pathogens common and *Streptococcus pneumoniae*. These causes should be excluded in any patient with seizures in the neonatal period, analyzing the TORCH complex and CSF. (9) The clinical and paraclinical background (fever, convulsions, positive inflammatory samples) raised the suspicion of infection of the central nervous system as a possible etiology of convulsion. Lumbar puncture was performed, and the TORCH serology refute the diagnosis of CNS infection.

Seizures can be caused by transient metabolic disorders including hypoglycemia, hypocalcemia and hypomagnesemia. Hyponatremia may be the result of inappropriate antidiuretic hormone secretion, due to trauma,

infections and cerebral hypoxia being an unusual cause of neonatal convulsions. These metabolic disorders are often diagnosed early and treated quickly and effectively. The severity of neurological manifestations is directly correlated with the duration of the metabolic disorder.

Metabolic disorders are rarely among the causes of seizures in newborn babies, but should be considered if there is no evidence of hypoxic-ischemic injury, infection or bleeding. In many cases, etiological treatment is not available and the antiepileptics are used but unsuccessful. Seizures are rarely specific for a certain metabolic disorder likewise the EEG pattern.

Amino-acidopathy and organic acidemia are the result of amino acid and fatty acid metabolism dysfunction and can be manifested by seizures, movement disorders, cognitive and behavioral disorders.(10) Many of them produce epileptic encephalopathy. The seizure types and EEG pattern changes are variable, the myoclonic epilepsy being more common and the EEG shows slow wave dominated conduct. The most typical EEG changes in metabolic encephalopathies have the appearance of "burst suppression" hyperarhythmia and generalized unloading wave/peak.

The Ohtahara syndrome also known as early infantile epileptic encephalopathy with the EEG pattern of "suppression-burst" type is characterized by onset of seizures since the first 10 days of life, the most common being flexed tonic spasms lasting a few seconds. Some patients may experience partial seizures and myoclonic attacks. (11) The Ohtahara syndrome is determined by a variety of structural abnormalities of the CNS (developmental abnormalities, defective neuronal migration, microcephaly, hemimegalencefaly, hypoxic-ischemic encephalopathy), although metabolic disorders are also reported and include glycinic encephalopathy and abnormal mitochondria.(12) The EEG picture consists of a suppression-burst pattern with diffuse hot flashes peaks and ample sharp waves separated by periods of a few seconds of underactive EEG appearance. (13) They may present between 30 and 100 spasms per day. The prognosis is very severe with insufficient response to treatment.

In our case the convulsions started at 17 days of life, not exceeding 12 episodes/24 hours, the EEG pattern has changed, initially looking for "suppression-burst" after presenting an aspect of slow dysrhythmia causing wave extensive derivate tile from left of center. During pregnancy no echographic aspects showing structural abnormalities of CNS were highlighted. The amount of glycine was normal. Symptoms improved under anticonvulsant therapy.

The prognosis varies depending on the underlying disease. A brain injury is proved that generally predicts a lower prognosis. EEG activity may serve as a prognostic marker, a normal activity correlates with a better prognosis. Seizures that occur within the first 3 days of life were associated with an increased risk of intraventricular hemorrhage, injury to the white matter of the brain and an increased death risk. (14) The risk of developing epilepsy after neonatal seizures varies in different studies, 2 % to 56%. Persistent seizures despite anticonvulsant therapy to children who had received two or more AEDs had an

unfavorable prognosis. 3 or 4 treatment failure AEDs, unlike two AEDs increase the risk of an unfavorable outcome. (15,16). Symptomatic neonatal seizures suggests a serious condition, the mortality rate is 15% in developed countries and up to 40 % in developing countries, and one third of survivors develop epilepsy. (17,18) Recurrent and prolonged neonatal convulsions may act on an epileptogenic substrate, causing further injuries, which are responsible for further clinical expression of epilepsy. (19)

Conclusions

The complexity of the case makes it difficult to establish the etiology of the convulsive episodes.

During the neonatal period, despite intensive therapy increasingly more specialized, the doctors treating seizures

have difficulties in terms of prognosis and finding adequate solutions to therapeutic problems.

In our center, all children with a history of neonatal seizures are followed at least during the first year of life and are evaluated by a multidisciplinary team of experienced pediatric neurologists, developmental psychology specialists and physiotherapists.

The case was multidisciplinary evaluated, requiring repeated hospitalizations in the pediatric ward and infantile neuropsychiatry because of multiple associated complications, the patient reaching age 2 with multiple comorbidities: tetraspastic, severe psychomotor retardation accompanied by eating disorders leading to deficiency anemia, protein-calorie malnutrition, rickets. All these pathologies are associated with a severely unfavorable long-term prognosis

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Archives of Disease in Childhood-Fetal and Neonatal
Edition 2004 89 (1), F37-F40

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TREATMENT OF ABDOMINAL SOLID ORGAN INJURIES IN CHILDREN

Alexandra Elena Popa^{1,2*}, C Tica^{2,3}, FD Enache^{2,3}

Abstract

Trauma is the leading cause of death in pediatric patients between 1 and 18 years old. Abdominal lesions in children are mostly due to car accidents, falls from heights or sport-related injuries. In this study it is discussed the therapeutic management of abdominal parenchymal organ injuries in polytrauma in children. The material used for this 5 year retrospective statistical study represents two lots of polytrauma children who associate abdominal trauma and solid organ injuries, hospitalized in the Pediatric Surgery and Orthopedics Constanta County Hospital, one group treated surgically and the other group with conservative treatment. Conservative treatment methods are assessed and they prevailed before the surgical treatment.

Key words: children, trauma, conservative treatment, surgical treatment

Introduction

Even today trauma represent the major cause of death in children [1]. Abdominal lesions due to car accidents, falls from heights or sport-related injuries cause a lot of damage and substantial mortality from injuries of the solid organs or hollow viscus [2,3].

Polytrauma is an emergency in Pediatric Surgery. The results are better if the lesion is determined faster and the therapeutic intervention is proper, but in order of priorities.

Purpose

This study aimed the therapeutic management of abdominal parenchymal organ injuries in polytrauma in children. Conservative treatment methods are assessed and they prevailed before the surgical treatment.

Material and method

The material used for this retrospective statistical study represents the two lots of polytrauma children who associate abdominal trauma, hospitalized in the Pediatric Surgery and Orthopedics Constanta County Hospital from January 2011 - December 2015. Of which:

- a group of 36 children who required abdominal surgery, of which only 27 had abdominal parenchymal organ injury;
- a group of 212 children remained under medical supervision for abdominal trauma and with the appropriate treatment of associated injuries.

Results

Following the retrospective statistical study it was observed that out of 565 children with polytrauma between 2011-2015, only 248 associated abdominal trauma.

Concerning the total number of patients hospitalized in the Clinic of Pediatric Surgery during this time, the frequency of polytrauma who associates abdominal trauma is 1.19%.

The frequency is higher in urban than in rural areas (145 cases in urban areas, compared to 103 cases in rural areas) and in males.

As in adults, the first place in the etiology of trauma in children are road accidents, followed in frequency by falls from heights, play accidents or aggression [4].

Combined lesions amplifies the severity of the case (Fig. 1), thus associating a brain injury increases the risk of death of the child over 30% [5], and if the brain injury is accompanied by coma, risk increases to over 75%.

Studying the period in which occurred most polytrauma, we noticed that more than 50% of polytrauma occurred in during summer,

- when children are on holidays,
- when they are playing most of the time outside, without parent supervision.

In comparison, the distribution by age group showed the highest frequency was recorded equally in preschool and school age groups (11 cases), in the group treated surgically, but the dominant group was of school age (8-14 years) in the 212 children who were treated conservatively (93 cases).

The worst cases in terms of abdominal trauma, those who required surgery had a serious overall condition at admission in rate of 74.07%, and only 23.11% in those treated medically.

In both groups, the clinical picture was dominated by abdominal pain, diffuse or localized, but the association of meteorism and peritoneal inflammation was significantly lower in the case group treated medically.

Rectal exam, a compulsory examination in all the cases of abdominal trauma, showed a bulging and painful Douglas in all operated cases.

An important element of differentiation is also the present state of shock at admission, to varying degrees, as the state of coma (Table 1).

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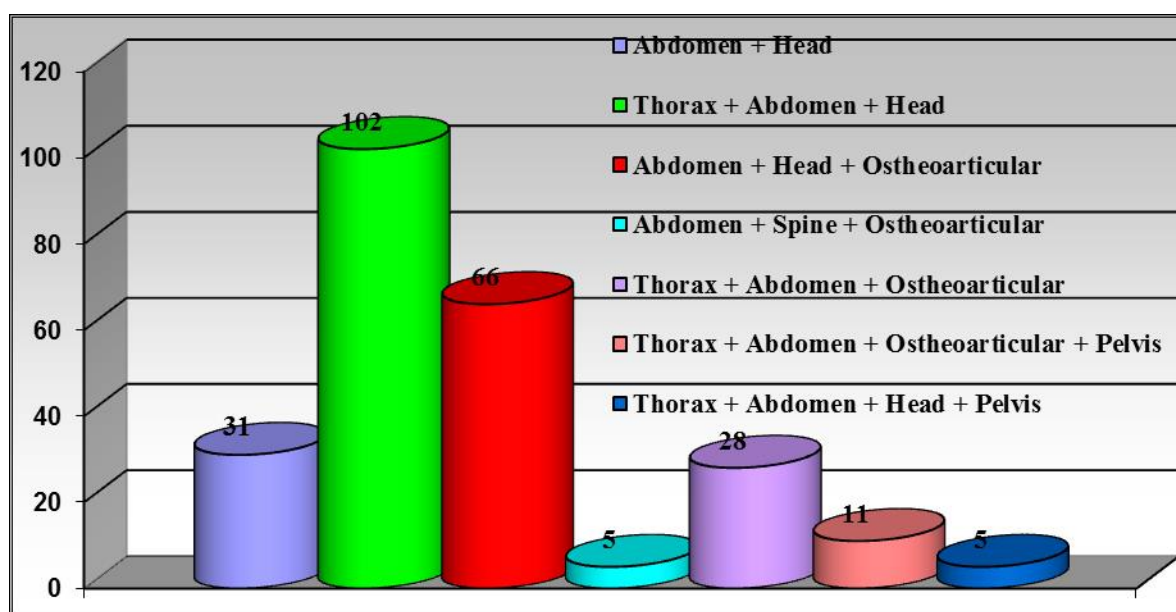


Figure 1 – Distribution of combined lesions in our study.

Table 1 – State of shock in our two groups of patients.

STUDY GROUP	SHOCK	COMA	TOTAL
Surgical	20	5	27
Conservative	45	19	212

The presence of hemodynamic instability was observed in 23 children in the operated group and in 45 children in the other group. This finding leads to the conclusion that the presence of hemorrhagic shock due to hemoperitoneum is a plus sign in guiding diagnosis and therapy for acute surgical abdomen.

However the presence of hypotension, tachycardia, tachypnoea was observed in different percentages in 212

children. Thus, we can think that the presence of associated fractures, the presence of chest and/or headtrauma lead to changes in vital signs, and any injury is an assault on the body.

As in literature, in this retrospective statistical study we found that the most common associations of abdominal injuries in polytrauma were head trauma, thoracic trauma and limb trauma (Fig. 2).

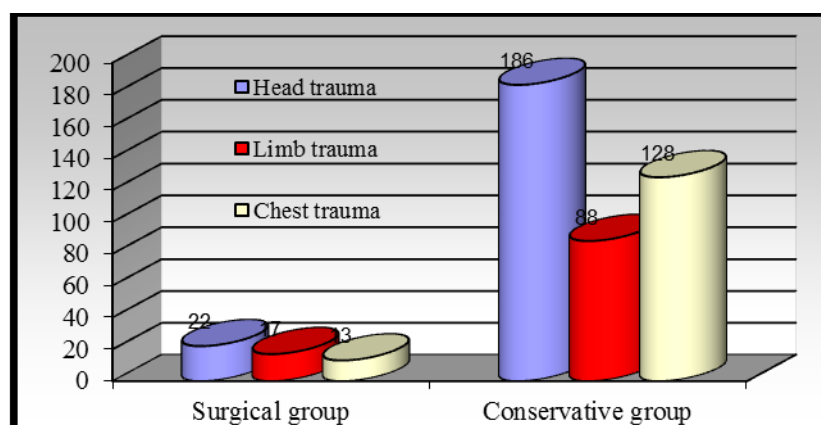


Figure 2 – Most common combined lesions in our study.

Thus it was found that chest trauma, although sometimes with fatal serious events was more frequent in children treated conservatively, outpacing limb trauma. Thoracic trauma, although several, have threatened life in just 20 cases, associating rib fractures, and requiring pleurotomy in 10 cases, with favorable outcome.

Diagnosis of acute surgical abdomen was difficult to assess in cases associated coma, especially two of them which had at clinical examination a normal abdomen. The stability of the patient is of paramount importance. Patients requiring transfusion of more than 40% of blood volume must be treated operatively [6].

For children receiving medical treatment, clinical picture was dominated by abdominal trauma in 90 cases by traumatic brain injury in 19 cases and trauma of the chest in 20 cases, and the other children was a combination of symptoms and clinical signs of multiple trauma, without a net dominance of any trauma.

On paraclinical state, although necessary for the evaluation of the lesions, we can say that surgical

emergencies were diagnosed with clinical and imaging (abdominal ultrasound, CT or MRI). CT has become the investigation of choice for the stable trauma patient [7]

Ein et al. said that non-operative management of haemoperitoneum depends on the results of CT scans. [8]. This investigation can discover specific organ injuries, and determine the severity of liver, spleen or kidney lesions, especially lacerations [9-12]. Indications for CT examinations include clinical suspicion of abdominal injury, unexplained blood loss, and unreliable physical examination (e.g. central nervous system damage or in very young children) [10-12].

Abdominal ultrasound, a higher indication in children than in adults, was conducted for the group treated medically, just to confirm parenchymal organ damage, and the confirmation was obtained by abdominal computed tomography. Ultrasonographic examination is used for detecting free fluid in the peritoneum [13,14].

Performed in emergency for all children: hemoglobin, hematocrit, white blood cell count, showed (Table 2):

Table 2 – Paraclinic exams in the study groups.

EXAM	CASES FOM SURGICAL GROUP	SURGICAL GROUP	CASES FROM CONSERVATIVE GROUP	CONSERVATIVE GROUP
Low hemoglobine	13	27	65	212
Low hematocrit	13	27	65	212
Leucocitosis	20	27	68	212

Particular importance was given to laboratory tests for the correct diagnosis of extra-abdominal associated lesions. Radiographs of those areas had priority in all cases.

In comatose children we've made cranio-cerebral tomography, for the etiological diagnosis of coma. We remind once again that the clinical abdominal picture is sometimes hidden by the comatose state.

Difficulties in diagnosis of abdominal trauma and injury of abdominal parenchymal organs in children, depends on body condition and severity of associated trauma.

Without being able to do comparison, analyzing the results of surgery, we found that there were dominated by splenic ruptures (15 cases), followed by liver lesions (8 cases), pancreatic lesions (8 cases) and ultimately renal lesions (6 cases).

Parenchymal organ injuries dominated, compared to the hollow viscus. Thus after surgery this state was found in 36 cases, and only 12 had injuries of the hollow viscus, of which 3 cases also associated parenchymal organ damage.

Rebalancing fluid, electrolyte and acid-base metabolism, although in general was performed in all patients equally, offered the following particular features:

- liver ruptures - requiring administration of protecting liver solutions Arginine, Aspatofort, Multiglutin.

- those who associate necrotic hemorrhagic pancreatitis - required a more intense metabolic rebalancing; 10% glucose solution, human albumin solution and Aminosteril, along with other crystalloid, colloid and electrolytes administered in much higher amounts.

Abdominal parenchymal organ ruptures prognosis associated to polytrauma, depends on several factors, among which are listed:

- multiple organ injuries;
- time elapsed from the accident;
- a lack of pre-hospital care or caregivers that don't come at the hospital with the child immediately after the accident [15];
- a lack of anesthetic-surgical comfort.

Evolution was generally favorable, demonstrating that an intensive treatment started as soon as possible, and properly administered and supervised, it has a key role in the prognosis of the case.

It is known that in children it is always preferred a conservative therapy initially, non interventional, hepatic and renal regeneration being proper.

As a result of the 27 cases in the group treated surgically, there were 3 deaths due to:

- association with other complications of abdominal and extra-abdominal injuries, being unable to rebalance the volume metabolism,

- a long period of time elapsed since the accident up to the treatment.

The percentage of deaths was 11.11%.

The prognosis depends on the same factors as in the group treated conservatively, but where there was no deaths.

Most were discharged in improved clinical status, being called to regular inspections required for preventing possible complications.

Conclusions

Polytrauma child is in a very critical condition, shocked with complex pathophysiological disorders. Concerning the etiology of polytrauma which combines abdominal trauma in children, the first is road accidents, followed by falls from heights.

Removing the child from the accident site, delaying transport to a hospital with a minimized mobilization of the patient, the evaluation as soon as possible and providing first aid in order of priority, are vital for further prognosis of the child.

We always have tried conservative treatment, rebalancing vital functions and keeping them normal as possible, and we passed to surgery, when it appeared unstable hemodynamic signs of acute surgical abdomen even under correct intensive treatment.

Because traumatology is increasing compared to previous years, especially through increased traffic and hence the number of traffic accidents, aggression polytrauma on the body, also is increasing, we can say that although there has been notable progress in recent years in methods of diagnosis and therapy, multiple accidental trauma mortality is increasing.

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BACTERIAN AGENTS IMPLICATED IN NECROTISING ENTEROCOLITIS

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Abstract

Introduction: Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in the preterm infant [1]. NEC affects 5-15% of all infants born at less than 30 weeks gestational age or <1500g birth weight. However, up to 10% of all neonates who develop NEC are born at term [2]. The main objective of this retrospective study is to describe antimicrobial utilization for NEC and identify organisms most frequently isolated from patients with NEC at our institution. **Material and Methods:** A retrospective study of all infants with a confirmed diagnosis of NEC and a positive culture (from the peritoneal cavity) collected within 72 hours in the Pediatric Surgery Department, Emergency Children's Hospital, Cluj-Napoca Romania between January 2010 and December 2015, was performed. A total of 61 medical charts were reviewed; 26 patients with suspected NEC and no microbiological data available were excluded. From the 35 patients included, 28 underwent laparotomy and 7 had peritoneal drainage. **Results:** An associated bacteremia/fungemia was found in 7 (20%) of the cases. Candidemia was present in 2 cases, Enterobacteriaceae bacteremia in 4 cases and CONS bacteremia in 1 case. Polymicrobial sepsis was present in 1 case. The results of peritoneal fluid cultures changed antibiotic selection in 10 (28%) of 35 cases. These changes were attributable to the growth of candida or CONS in all but 1 case, in which methicillin-resistant Staphylococcus aureus was identified.

Discussion: The first line choice of antibiotics for babies with suspected NEC consisting of Ampicillin, Gentamicin and Metronidazole failed to adequately cover the 4 coagulase negative Staphylococci, the Staphylococcus aureus and Candida species. Also, this combination of broad spectrum antibiotics (Ampicillin, Gentamicin and Metronidazole) only adequately treated 20 of the 35 cases of NEC and 3 positive blood cultures patients. From our limited data it would appear that only the combination of Meropenem and Vancomycin would have adequately covered all the isolated organisms. While it is often presumed that the infectious agent associated with NEC is bacteria, a number of other organisms, particularly viral have been implicated. **Conclusions:** Due to the limitations of this study we are unable to make general recommendations on the first line antibiotic choice for babies with suspected or confirmed NEC. Our current regime of Ampicillin, Gentamicin and Metronidazole failed

to adequately treat 5 of the 8 organisms subsequently isolated in blood cultures.

The only combination of antibiotics that would have adequately treated all the bacteria identified was Vancomycin and Meropenem. The concern with this approach is the possible emergence of multidrug resistant bacteria. Further research is required to determine the best antibiotic regime for babies with suspected or confirmed NEC.

Key words: newborn, necrotising enterocolitis, antibacterial agents.

Introduction

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in the preterm infant [1]. NEC affects 5-15% of all infants born at less than 30 weeks gestational age or <1500g birth weight. However, up to 10% of all neonates who develop NEC are born at term [2].

The initial clinical presentation is variable but may include general deterioration in the patients condition, lethargy, temperature instability, apnoea, shock, peritonitis, pallor, skin mottling, jaundice, bleeding and mild feed intolerance [3]. The classic presentation of NEC is a triad of abdominal distension, bloody mucous stools and bile stained aspirates [3].

The exact aetiology of NEC is unknown, however multiple risk factors have been identified including prematurity, hypoxia, exchange transfusion, intrauterine growth restriction, loss of mucosal integrity, patent ductus arteriosus, indomethacin, enteral feeds and microbial infection [1, 4]. A large number of organisms have been isolated from babies with NEC in both epidemics and sporadic cases [3, 4-7].

More recently, Gram-negative bacteria that form part of the normal flora are now speculated as important factors in triggering the injury process in a setting where there is a severe paucity of bacterial species and possible lack of protective Gram-positive organisms [9].

The current clinical practice for infants with suspected or confirmed necrotising enterocolitis is to: cease enteral feeds; commence intravenous fluids; aspirate the nasogastric tube regularly; collect a blood culture; commence antibiotics (Ampicillin, Gentamicin and Metronidazole); perform an abdominal radiograph and arrange paediatric surgical evaluation [8]. Antibiotic regimes are adjusted according to organism culture sensitivities once available.

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The main objective of this retrospective study is to describe antimicrobial utilization for NEC and identify organisms most frequently isolated from patients with NEC at our institution.

Material and methods

A retrospective study of all infants with a confirmed diagnosis of NEC and a positive culture (from the peritoneal cavity) collected within 72 hours in the Pediatric Surgery Departement, Emergency Childrens Hospital, Cluj-Napoca Romania between January 2010 and december 2015, was performed. Confirmed NEC is defined as symptoms of NEC with abdominal radiograph changes including any of the following: bowel wall oedema; pneumatosis intestinalis; portal vein gas and pneumoperitoneum (includes all Bell[10] stage 3 and some stage 2). A total of 61 medical charts were reviewed; 26 patients with suspected NEC and no microbiological data available were excluded. From the 35 patients included, 28 underwent laparotomy and 7 had peritoneal drainage. Data recorded included: demographic data, surgical data, microbiological data (peritoneal fluid

specimens and susceptibility to antibiotics), antibiotic management (initial therapy, changes in therapy, and duration of treatment) and outcomes. Blood culture bottles were placed in the BacT/ Alert® microbial detection system (bioMérieux Inc.) Swabs and catheter tips are directly plated on enrichment broth and then incubated at 35 degrees. They are examined for growth at 24 hours, 38 hours and 7 days. Positive cultures are then inoculated onto Horse Blood agar, Chocolate agar, MacConkey agar and Brain Heart Yeast agar. Antibiotic sensitivity testing was done using the Vitex®2 (bioMérieux Inc, Hazelwood, USA) method. Disc sensitivity or resistance was determined using CLSI (Clinical and Laboratory Standards Institute) standards.

Results

From a total of 35 patients included in this study, 21(60%) were male and 14 female(40%). The birth weight of patients with NEC ranged between 528g and 3410 g (median=1282) and the gestational age ranged between 24 and 40 weeks (median=27 weeks). Clinical characteristics are illustrated in Table.1

Total number of NEC patients	n=35
Birth weight, g, median (range)	1282(528-3410)
Gestational age, wk, median (range)	27(24-40)
Age at perforation, d, median (range)	15(3-40)
Male gender, n (%)	21(60%)
Case fatality, n (%)	12(34%)
Laparotomy	28(80%)

Table 1. Clinical Characteristics of Neonates With Peritonitis Associated With NEC

Pathogens	n (%) (N=35)
Gram-positive	
CONS*	4 (12)
S aureus	1 (1)
S epidirmidis	2(5)
Enterococcus species	8 (23)
Diphtheroids	1(3)
Gram-negative	
Enterobacteriaceae	21 (60)
E Coli	7 (20)
Klebsiella species	7 (20)
Enterobacter species	6 (17)
Citrobacter species	1(3)
Anaerobes	4 (12)
Bacteroides species	4 (12)

Table 2. Peritoneal Isolates Recovered From Neonates With NEC

Discussion

The first line choice of antibiotics for babies with suspected NEC consisting of Ampicillin, Gentamicin and Metronidazole failed to adequately cover the 4 coagulase negative Staphylococci, the *Staphylococcus aureus* and *Candida* species. Also, this combination of broad spectrum antibiotics (Ampicillin, Gentamicin and Metronidazole) only adequately treated 20 of the 35 cases of NEC and 3 positive blood cultures patients.

First, the large distribution of pathogens when dealing with NEC supports the need to obtain peritoneal fluid cultures in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient. Second, it sheds light on which organisms should be targeted by antimicrobials when empirically treating neonates with documented NEC.

From our limited data it would appear that only the combination of Meropenem and Vancomycin would have adequately covered all the isolated organisms. While it is often presumed that the infectious agent associated with NEC is bacteria, a number of other organisms, particularly viral have been implicated (3,5,11). The retrospective nature of this study has limited the search for other possible infecting organisms as viral cultures and rectal swabs are not routinely collected. The small number of babies with a positive blood culture is also a concern however a long time period was examined to identify these cases. Another limitation is that the study is confined to one centre and the external validity of the results is therefore poor.

The standard of care for patients with documented NEC continues to include broad-spectrum antimicrobial coverage; however, the agents of choice vary between centers. Lee and Polin(12) recommended ampicillin, gentamicin, and clindamycin, with the possible substitution of vancomycin for ampicillin as a result of the increasing prevalence of CONS. Others have proposed ticarcillin and an aminoglycoside, usually gentamicin(13). Foglia(14) endorsed amikacin and Flagyl in place of gentamicin and clindamycin. Neu(15) advocated starting ampicillin and gentamicin after a blood culture is obtained, substituting vancomycin for ampicillin when CONS is suspected and then adding either clindamycin or metronidazole, for anaerobic coverage, when perforation is suspected or has occurred. This lack of agreement within the medical literature confirms that peritoneal fluid cultures should be obtained in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient.

In neonates with culture-positive peritonitis, 14% with NEC showed evidence of *Candida* species peritonitis, emphasizing the need to address the use of antifungal agents in cases of bowel perforation in the NICU. We identified associated candidemia in only 2 (40%) of the 5 cases of culture-proven candidal peritonitis; therefore, it is imperative that the clinician be aware of patients who are at risk for fungal disease.

Bond et al(16) described 3 cases of fatal candidal enteritis seen on pathologic evaluation and therefore

recommended “review of pathologic specimens for invasive fungal enteritis with institution of aggressive combination therapy in confirmed cases.”

In a previous publication, Karlowicz (17) proposed that amphotericin B be considered in neonates who weigh <1000 g and have stage IIIB NEC, “especially in those with a history of prolonged umbilical vessel catheterization, prolonged antibiotic therapy, and prolonged intubation.” In a report on neonates with NEC, Smith et al(18) recommend amphotericin B for patients who remain symptomatic despite negative bacterial cultures. The most current recommendations from Benjamin et al.(19) based on a study of neonates with birth weight <1250 g, encourage consideration of empiric antifungal therapy pending culture results on the basis of noted risk factors: <25 weeks’ estimated gestational age, thrombocytopenia at the time of blood culture, or 25 to 27 weeks without thrombocytopenia but with a history of third-generation cephalosporin or carbapenem exposure in the preceding 7 days. It has been suggested that earlier institution of antifungal therapy may alter outcome in infants with *Candida* peritonitis(17,15). We conclude that a peritoneal culture obtained at the time of surgical intervention is reasonable, as it may allow more rapid identification of fungal peritonitis and allow initiation of antifungal therapy as promptly as possible.

Importantly there were 28 infants who had no organism identified on blood culture. A large number of babies would therefore need to be treated with Vancomycin and Meropenem to adequately cover the few with positive blood culture. The use of such broad spectrum antibiotics may lead to the emergence of multi resistant bacteria and the initial choice of narrow spectrum antibiotics has been recommended (21, 22).

It has been shown that coagulase negative Staphylococci have a relatively long incubation time (median 28.9 hours) and thereby continuing with our current antibiotic choice for NEC may significantly delay the commencement of an appropriate antibiotic (23). Due to the limitations of this study we are unable to make general recommendations on the first line antibiotic choice for babies with suspected or confirmed NEC. Our current regime of Ampicillin, Gentamicin and Metronidazole failed to adequately treat 5 of the 8 organisms subsequently isolated in blood cultures. The only combination of antibiotics that would have adequately treated all the bacteria identified was Vancomycin and Meropenem. The concern with this approach is the possible emergence of multi drug resistant bacteria. Further research is required to determine the best antibiotic regime for babies with suspected or confirmed NEC.

Conclusions

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AUDIT OF PATIENT'S RECORDS REGARDING THE DIAGNOSIS AND TREATMENT OF ASTHMA IN CHILDREN

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Abstract

Asthma is a common chronic pathology in children, with a growing prevalence and morbidity. The diagnosis of asthma is mainly a clinical one, but is difficult to sustain, especially for children under five years old. *Objective:* analysis of quality of medical records regarding the criteria that were used for supporting diagnosis and choosing the treatment of asthma in children, to identify nonconformities and take action to remedy them. *Methods:* The audit asked questions about the correctness of filling medical documents regarding patients demographics, asthma risk factors, diagnostic criteria, investigations performed, treatment and asthma education for children aged 3 to 15, diagnosed with asthma, who presented for an evaluation in the Pediatric Pneumology Service, in the second semester in 2015. *Results:* We observed deficiencies regarding risk factors/triggers of asthmatic crisis identification, especially related to food allergy, pet exposure, exercise and smoke exposure. More accurate reporting is needed about the criteria for determining the severity and the level of disease control using GINA guidelines classifications for asthma in children as well as Asthma Control Questionnaires. Furthermore, we insist on training and evaluation of inhaled medication administration technique, medical education on asthma prophylaxis and the issue of a written personalized asthma action plan at the end of the visit to the specialist. *Conclusions:* Audit is an important instrument for any clinician used to measure the outcomes, improve the quality of medical practice and decrease the burden of the disease.

Key words: Celiac disease, HLA DQ2/DQ8 typing, children

Introduction

Asthma is more and more becoming a common chronic pathology in children, with a growing prevalence and morbidity related to increasing prevalence of atopy and allergic diseases [1]. In Romania, the prevalence of asthma is approximately 5-7% [2], but varies according to the area or various countries between 1 and 18% [3]. The disease is diagnosed in more than half of cases in childhood, up to 10

years old, initially being more common in boys [2,4]. Diagnosis is difficult especially for children under 5, has a variable evolution and symptoms disappear with age in a considerable percentage, with the possibility of recurrence after 40 years [1]. Even though in most cases of children with asthma (80%), symptoms occur under the age of 5, these are not recognized or, frequently, child's evolution is monitored for a longer period, before supporting the certain diagnosis of asthma [5]. In children, the diagnosis is supported by a detailed history of specific symptoms like wheezing, cough, breathlessness, and chest tightness with an episodic pattern, in relation to presence of risk factors (airborne indoor and outdoor allergens, secondhand cigarette smoke, viral upper respiratory infection, chronic sinusitis and pneumonia with *Mycoplasma pneumoniae* or *Chlamydia* species, exercise, weather changes) [3,6]. Given the fact that asthma has a genetic predisposition, is very important to identify the presence of special conditions, such as personal and family history of atopic disease (atopic dermatitis, food allergy, allergic rhinitis, asthma) [7-12]. The physical examination could be very suggestive in acute exacerbation or asthma attack (wheezing, prolonged expiration, and sibilants with or without signs of rhinitis, conjunctivitis, sinusitis, eczema), but could be normal between asthma attack [2-4,13]. Documentation of reversible obstruction on spirometry is possible after 5-6 years of age or older [14]. A positive bronchodilator response in children younger than 12 years old is considered an increased FEV₁ with 8% [14-15]. Demonstration of peak expiratory flow limitation variability and an elevated value of total serum immunoglobulin E (IgE) may be suggestive for asthma diagnosis after the age of 3 [3]. Exclusion of another diagnosis is also essential, especially for other wheezing illnesses [16]. Asthma is known as a chronic inflammatory disorder with an excellent response at inhaled corticosteroids [1,4,6]. The treatment is chosen by severity and frequency of asthma symptoms, and includes avoiding asthma triggers, rescue and controller medications (inhaled glucocorticoids, leukotriene modifier, and long-acting bronchodilator), medical education and personalized asthma action plan [6].

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Objective

Is to analyze the quality of medical records regarding the criteria for supporting diagnosis and choosing the treatment of asthma in children, to identify nonconformities and take action to remedy them. Thus, we monitor if age, BMI, symptoms and crisis characteristics, risk factors, the condition of atopy, results of clinical examination of functional respiratory exploration and level of eosinophils and IgE, the severity, and level of asthma control, prescribed treatment, are registered. The recommendations resulting from medical audit will be submitted and put into to improve the quality of medical act and compliance with guidelines in force.

Methods

We retrospectively evaluated medical records belonging to children aged 5 to 15, diagnosed with asthma, who presented for an evaluation in the Pediatric Pneumology Service, in the second semester in 2015. The audit asked questions about the correctness of filling medical documents regarding age, body mass index, risk factors, diagnostic criteria, investigations performed, treatment and advice received by patients or their parents. At the same time, we observed demographic, clinical and treatment characteristics of children diagnosed with asthma.

Results

The table below shows the audit results, and the missing data from medical records were identified (table 1). The data were collected from 40 children, with an average age of 11.82 years, diagnosed with asthma, which addressed the pediatric pulmonology service for a consult. 62.5% of children were male, and only 5% were under five years old, the rest being in relatively equal proportions between 5 and 12 years old and over 12 years old (27.5% vs. 30%). Girls, although significantly fewer in number than boys (15 (37.5) vs. 25 (62.5)) had the same distribution by age group (5% under 5 years old). Our data showed that the weight of male children was slightly higher than of girls' (19.52 vs. 18.18), suggesting that obesity may be a risk factor for asthma [1]. All medical documents contained demographics of children (100%). Regarding identification of trigger factors for asthma attacks, as well as predisposition to develop asthma, we found that there was nothing stated about the presence of pets in home in 67.5% of cases, the data about possible food allergies were missing in 57.5% of cases, and second-hand cigarette smoke exposure in home environment in 25% of cases.

All cases had completed symptoms history and clinical exam. The most frequent symptoms described by children were: 40% dyspnea, 28% dry or a productive cough, 27.5% wheezing, and 37.5% had a clinical examination suggestive of asthma. Spirometry with bronchodilator test was used in 82.5% of cases, but it was not applied to children under five years old. There are studies showing that the bronchodilator test with short-term betamimetics can be performed when the ventilatory function is normal, in some cases bronchodilation being highlighted [1,16]. Unfortunately, in

40 % of cases it was not mentioned whether the spirometry technique was correct or not, if forced vital capacity-FVC and forced expiratory volume in 1 seconds-FEV1 data met ATS/ERS acceptability and repeatability criteria. In 30% of cases, detailed explanations were needed about the severity of asthma and control level. Asthma Control Questioner was not currently used. All patients had indications for therapy: 50% received a combination of inhaled corticosteroid with long active bronchodilator, 30% inhale corticosteroids, 52% anti-leukotriene and 45% salbutamol as reliever medication. In 25% of cases, it was neither specified if the correct inhalation technique had been used, nor if patients had been instructed on the administration of medication inhaler. In 65 % of cases written personalized asthma action plan was missing.

Discussion

Medical audit is a systematic analysis of the quality of medical care that evaluates the tools used in diagnosis, the treatment prescribed, and management of disorders [17-20]. Auditing is an essential instrument for any clinician used to measure the outcomes, to improve the quality of medical practice and decrease the burden of the disease. As we know, this study is among the first medical audits in pediatric asthma in our county. A correct diagnosis and treatment of asthma reflects in a normal lifestyle, with no exacerbations or hospitalizations, lack of symptoms and a normal respiratory function under minimal inhale treatment [4,16]. In children, especially under the age of five, the diagnosis is supported by clinical symptoms related to the conditions of developing the disease (trigger factors), repeatability, personal and family atopic status, as it is one of great medical responsibility. For this reason, a detailed record of historical data is extremely important. Only 4 children under five were evaluated, one possible explanation could be the type of phtisio-pediatric ward, which lacks an intensive care unit. As specified in other studies, asthma prevalence was higher in boys (62% vs. 37%) [18,21]. In the medical records of patients evaluated, while revising the diagnostic criteria, symptoms recording can be observed in 100% cases, suggestive clinical examination in 37.5% of cases, and the presence of atopy in 50% of cases. Heart rate and oxygen saturation should be also recorded, as well as the degree of dyspnea, and use of accessory muscles. We found a reduced ability to identify and record the history of allergies, especially the food ones, pet presence in homes or exposure to parental smoking. In general, risk factors history is reduced to questions about what the children or their parents think that could trigger asthma attacks, such as dust, pollen, molds and viral infections. Food allergies, as well as exposure to hair and pet droppings (cats, dogs, fish aquarium, budgerigars) are important in children. Children exposure to parental smoking may also represent both a trigger factor of asthma crises followed by admission to hospital, and a cause of the lack of disease control under treatment [20]. It is necessary on consultation date be clearly set out if children are passive smokers, and parents be motivated to quit smoking.

Table 1. Characteristics of asthma.

N= (%)	Asthma cases n=40; (100)	Male n=25 (62.5)	Female n =15 (37.5)	Missing data n=0 (0)
Mean Age:	11.82	11.4	12.53	0 (0)
BMI kg/m²	19.5	19.52	18.16	17 (42.5)
< 5,	4 (10)	2 (5)	2 (5)	0
5-12,	18 (45)	11 (27.5)	7 (17.5)	0
>12.	18 (45)	12 (30)	6 (15)	0
Risk factors and special condition				
Present personal atopy	20 (50)	11 (27.5)	3 (7.5)	15 (37.5)
Present family atopy	8	5 (12.5)	3 (7.5)	29 (72)
History of asthma (month)	36.15	52.36	13.87	20
Smoker	2 (5)	2 (5)	0	0
Secondhand cigarette smoke exposure	4 (4)	2 (5)	2 (5)	10 (25)
Pet exposure	0	0	0	0
Food allergy	5 (12.5)	3	2 (5)	27 (67.5)
	6 (15)	3	3 (7.5)	23 (57.5)
Symptoms				
Dyspnea	16 (40)	11 (27.5)	5 (12.5)	0
Dry Cough	12 (30)	7 (17.5)	6 (15)	0
Productive Cough	16 (40)	9 (22.5)	7 (17.5)	0
Wheezing	11 (27.5)	9 (22.5)	2 (5)	0
Chest tightness	3 (7.5)	2 (5)	1 (2.5)	0
Suggestive Clinical exam	15 (37.5)	7 (17.5)	8 (20)	0
Repeatability	15 (37.5)	10 (25)	5 (12.5)	0
IACRS related	6 (15)	5 (12.5)	1 (2.5)	10 (25)
Functional respiratory test				
Spirometry	33 (82.5)	20 (50)	13 (32)	3 (7.5)
Bronchodilator test	9 (22.5)	7 (17.5)	2 (5)	0
Correct technique - yes	19 (47.5)	13 (32)	6 (15)	16 (40%)
Analyses (present data)				
Eosinophils	16 (40)	8 (20)	8 (20)	24 (60)
IgE	4 (10)	2 (5)	2 (5)	36 (90)
Severity/ control of asthma	28	15	13 (32.5)	12 (30)
Treatment				
SABA	18 (45)	11 (40)	7 (17.5)	0
ICST (inhale corticosteroid)	12 (30)	6 (15)	6 (15)	0
Correct inhaler technique	10 (25)	4 (10)	6	10 (25)
Combination LABA/ICST	20(50)	12 (30)		
Salmeterol-fluticasone	7 (17.5)	3 (7)	4 (10)	0
Formoterol- budesonide	13 (32.5)	9 (22.5)	4 (10)	0
Anti-leukotriene	21 (52)	12 (30)	4 (10)	0
Antiallergic	10 (25)	5 (12.5)	9 (22.5)	0
Written personalized asthma action plan	14 (35)	9 (22.5)	5 (12.5)	26 (65)

Physical exercise and sleep disordered breathing are scarcely mentioned in medical letters, even if they play a significant role in child's asthma. It is also known that asthma is an inherited disease, the risk that a child becomes asthmatic is 2.6 times greater if a parent is asthmatic [22, 23]. Between 37 and 72% of cases we had no information about family history of atopy and personal atopy, these being important criteria for suspicion of asthma in children. Spirometry was used in children over 8 years old for documenting obstruction, and a FEV1 reversibility over or

equal to 8% was considered significant, different from the value of 12% (200 ml) in adults. It is very important to note all ERS/ATS validity and repeatability criteria of flow / volume curve. In patients already diagnosed with asthma, clinical evaluation should include data about the frequency of daytime and nocturnal symptoms, identification of exacerbations, daily asthma medication (control and reliever), and level of obstructive dysfunction, in order to classify the severity of the disease. Monitoring diurnal variability of PEF represents another indicator of severity in

asthma, and no PEF-meter evaluation was specified. Patients with less 75% predicted PEF and variability over 25% have a higher risk of exacerbation [18]. We propose to check the inhale technique for every drug device during every medical visit. The disappearance of symptoms under treatment is a criterion for a positive diagnosis of asthma, but an incorrect technique can lead to a lack of disease control and patients' poor adherence to treatment. The assessment of each patient must be followed by recommendations for asthma prophylaxis, with identification and avoidance of

precipitation triggers, explanations regarding self-monitoring and written asthma personalized control plan.

Conclusions

Medical audit studies identify deficiencies in medical activity and their correction leads to an improved quality of medical practice. Adoption of protocols in the ward, in accordance with international guidelines, results in a better management of the disease, an increased quality of patients' life and a decrease in medical costs.

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CLINICAL-IMAGING CORRELATION AND EARLY DIAGNOSIS IN BRAIN MALFORMATIONS

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Abstract

The malformations of the brain represent a serious pathology in the neonatal period, with major implications for subsequent psychomotor development of children. Thanks to the advanced technology, the diagnosis is established early, even in the prenatal period (fetal ultrasound, or even more recently fetal MRI or early neonatal MRI)-a very important thing for the introduction of the specific therapy and also the anticipation of the short-term and long-term prognosis. The authors are proposing a review of the most frequent brain malformations: encephalocele, myelomeningocele, Arnold-Chiari malformation, holoprosencephaly, the absence of cavum septum pellucidum, septo-optic dysplasia, proliferation and neuronal migration disorders, corpus callosum agenesis, Aicardi syndrome, porencephaly, median line defects, some vascular malformations. Also, the authors want to establish a correlation between the clinical, anamnestic and imaging data for the anticipation of short-term and long-term prognosis in every group that malformations have been identified. Conclusion: Brain malformations represent an important part of neonatal pathology, either due to the emergency situation with life-threatening prognosis or because of the high risk of sequelae which threatens social-integration.

Key words: Brain malformations, diagnostic, prognosis

Introduction

Due to increased morbidity and mortality in the neonatal period and also in infancy and toddlerhood, brain malformation represent a major concern. Short term and long term complication depend primary on the time and severity of the malformation but also on the stage of the cerebral maturity. Those that develop early, during intrauterine development, are usually severe types, with high degree of complexity.

In the pathogenesis of brain malformation, several factors are involved: genetic (chromosomal abnormalities, and genetic mutations), congenital infections (rubella, toxoplasmosis, CMV), radiations, chemical agents, drug consumption, vitamin deficiency or excess, nutritional deficiencies. Brain ischemia may intervene in various stages

of neurological development, leading to different types of brain malformations.

Neural tube defects

Anencephaly – severe damage which involves the absence of the cranial vault, meninges, scalp and cerebral hemisphere. Can be detected intrauterine from 12 weeks gestation. The prevalence is approximately 1 in 2000 births and the risk of recurrence is 4%.

Encephalocele – represent in the bag shaped herniation of the intracranial structures through the frontal or occipital (more frequent) cranial bones defect. Occipital encephalocels – depending on the size of the defect and the herniated structure may be accompanied by microcephaly, visual and auditory disorders. If a stenosis in the aqueduct of Sylvius or Dandy-Walker syndrome is associated, hydrocephaly may occur. Frontal Encephalocele – may have multiple locations (nasal, orbital) or may not be visible – with basal location (sphenoid, nasal cavities, deep in the orbital cavities) with a good prognosis.

Myelomeningocele – it's a neurotube defect which occurs after the closure of caudal neuropore. Often associated with hydrocephaly and Arnold-Chiari II malformation. The vertebral defect – most common in the lumbar and sacral region; it contains dura, leptomeninge and medullary structure. Clinical may associate from motor damage to paresis, absence of skin sensitivity, intestinal motility disorders.

Arnold-Chiari Malformation – consists in the cerebellum hypoplasia, the herniation of the cerebral vermis into the foramen magnum with the posterior displacement of the cerebellum and different degrees of cerebellar dysplasia. Three types of malformation are known, but the most common type is type II associated with myelomeningocele. Classic:

- Type I consist in inferior displacement of the cerebellar tonsils and inferior cerebellum. Without affecting the spinal cord and IV ventricle.
- Type II – inferior displacement (in the superior region of spinal canal) of the inferior cerebellum, tonsils, pons, spinal cord and IV ventricle. This type almost always is associated with myelomeningocele.

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- Type III – the displacement of the spinal cord, IV ventricle and cerebellum into a cerebral and occipital encephalomeningocele. The ultrasound signs are represented by: the inferior displacement of cerebellum, IV ventricle – hard to visualize; cisterna magna obstruction (1). Third ventricle appears dilated with increased intermediate mass. Lateral ventricles (LV) with dilated posterior horns. An anterior and inferior extension of the frontal horn is visualized, with a specific aspect of a “bat wing”* (fig.1a and fig.1b) (2).

Hydrocephaly in Arnold-Chiari malformation is caused by: cerebellum malformation, which leads to the obstruction of IV ventricles, blocking the leakage of cerebrospinal fluid in the posterior fossa; the stenosis of the aqueduct leads to hydrocephaly in 75% of cases (fig.3 and fig.4)

Ventral induction disorders

Holoprosencephaly is the complex and severe brain malformation characterized by the absence of cleavage of the prosencephalon into telencephalon and diencephalon (3). The ventral separation process occurs in the fifth week intrauterine (4). The frequency of the disease is 1 in 10000 living newborns (5, 6, 7) but the incidence is 60 times higher in the aborted embryos.

Depending on the differentiation and severity degree there are known three types of holoprosencephaly (De Mayer classification: alobar, semilobar and lobar). Literature cites different incomplete disease versions.

- Alobar holoprosencephaly (fig.4) – the most severe form characterized by the complete absence of septation, with a unique ventricle on the midline continued by a dorsal bag, fusiform thalamus and undifferentiated brain parenchyma. The cerebellum and the cerebral trunk are present and may have a normal aspect.
- Semilobar holoprosencephaly (fig.5) – consists of a unique ventricle with a fused thalamus. The interhemispheric cleft is present but partially developed, especially in the posterior region. Third ventricle is small or absent, fourth ventricle, cerebellum, cerebral trunk are usually normal. Sometimes a total or partial agenesis of the corpus callosum may be present.
- Lobar holoprosencephaly (fig.6a and 6b) – the least severe form, characterized by the absence of the septum pellucidum, which leads to the development to a unique squared frontal horn with flat roof and rectangular corners. The bodies of the LV are midline joined but the posterior horns are separated, with normal aspect as well as the thalamus and the posterior interhemispheric groove. The anterior interhemispheric groove is present but shallow and incomplete developed.

Clinically, patients with holoprosencephaly, have facial malformations directly correlated with the severity and the cerebral lesions, from major defects of the midline like cyclopia, the absence of the nasal septum, dehiscence of facial bones, hypotelorism, to micrognathia, fissured palate. The mild form of disease clinically is accompanied by the facial bones hypoplasia and moderated forms of hypotelorism (14%). The least severe forms of disease are

accompanied by dental vicious eruptions and coloboma (36%). Long-term neurological prognosis is correlated with the type of brain malformation. All forms of disease associate muscular tone disorders and dysmotility. (8,9,10) Neurological sequelae like mental retardation, epilepsy, spasticity, dystonia, chorioretinitis, as well as endocrine disorders, diabetes insipidus, may be present in a clinical variable intensity.

The absence of cavum septum pellucidum and septo-optic dysplasia

The absence of septum pellucidum is associated with many brain malformations including holoprosencephaly, septo-optic dysplasia, schizencephaly and corpus callosum agenesis (fig.7a and 7b). Severe hydrocephalus and holoprosencephaly are associated with destructive lesions of the septum pellucidum that can be diagnosed by the ultrasound in the early intrauterine period. (11)

Isolated absence of septum pellucidum with an intact corpus callosum is seen in septo optic dysplasia. This condition is characterized by a triad: the absence of septum pellucidum, optic nerve hypotrophy and pituitary gland dysfunction. Clinical is a severe disorder with decreased visual acuity, endocrine dysfunctions – cholestasis and mental retardation (11). Septo-optic dysplasia may be associated with other brain malformations: cortical dysfunctions, corpus callosum agenesis, schizencephaly. (fig. 8a and 8b)

Cell proliferation and neuronal migration disorders

Microcephaly is defined as decreased head circumference with 2 standard deviation (SD) compared to children of the same age and sex. Usually associated with microencephaly, which is followed by mental retardation. May be primary or secondary to some genetic disorders.

Megalencephaly consists in the diffused neuroepithelial proliferation and increase number of cells in the brain. The term is similar with macrocephaly in contrast to macrocephaly which refers only to the increased head circumference more than 2 SD for the same age and sex.

Can be primary, dominant autosomal form, with normal or minimally affected intelligence. Literature cites many genetic syndromes associated with megalencephaly: Sotos syndrome (cerebral gigantism), fragile X syndrome, autism, neurocutaneous syndrome. It also may be found in some metabolic diseases like: Tay-Sachs, Canavan, Alexander disease, which does not debut at birth.

Learning disorders, neuropsychomotor retardation and epilepsy are found in megalencephaly.

Hemimegalencephaly it's a rare brain malformation characterized by the unilateral enlargement of a part of the brain. Only a hemisphere or only the frontal lobes can be affected, with abnormal cells proliferation. Clinically, a non-responsive to treatment epilepsy can be found, hemiparesis, psychomotor retardation. (12) It can be associated with neurocutaneous diseases, hypomelanosis, neurofibromatosis.

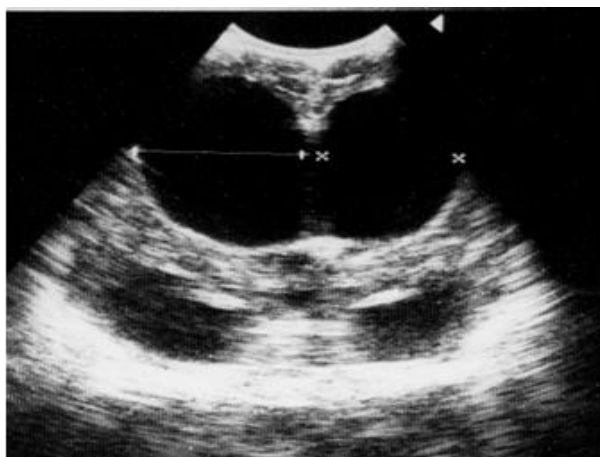


Fig. 1a Progressive hydrocephalus secondary to the myelomeningocele. LV dilatation



Fig. 1b Medium coronal section. Arnold Chiari type II malformation. Anterior horns dilatation of the LV, distant from the midline.

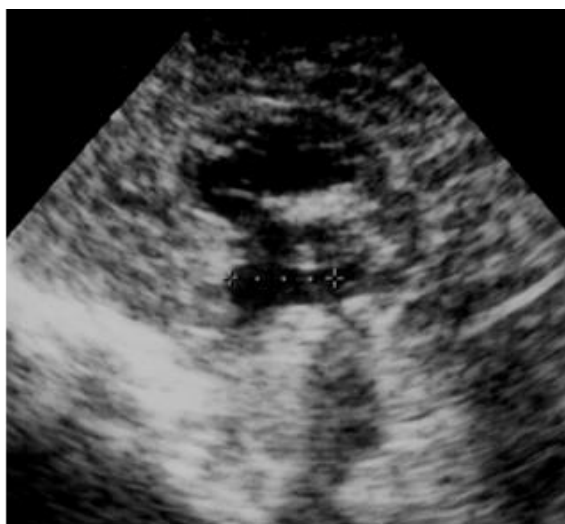


Fig. 2 Medium sagittal section. Third ventricle dilatated with intermedia mass present.

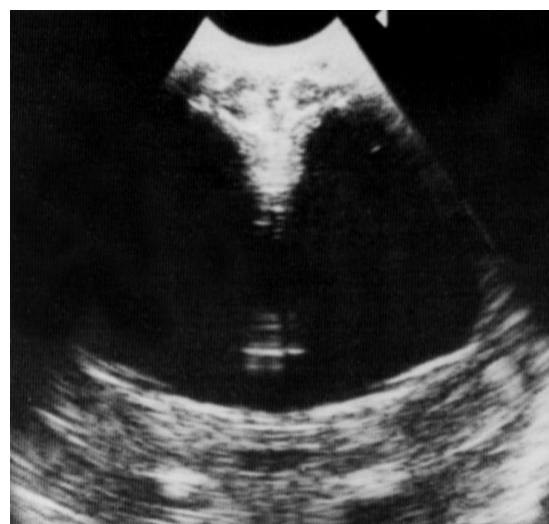


Fig. 3 Progressive severe hydrocephalus. Emphasized dilation of LV especially anterior

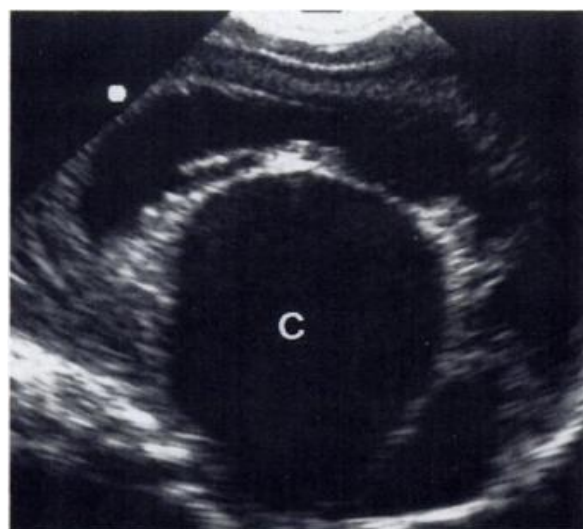


Fig. 4 Alobar holoprosencephaly

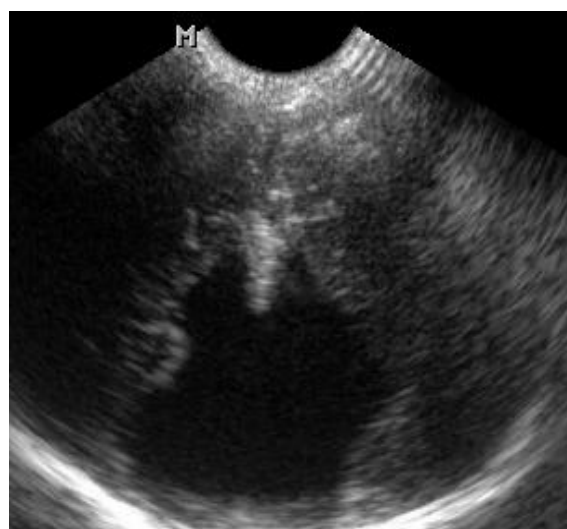


Fig. 5 Semilobar holoprosencephaly

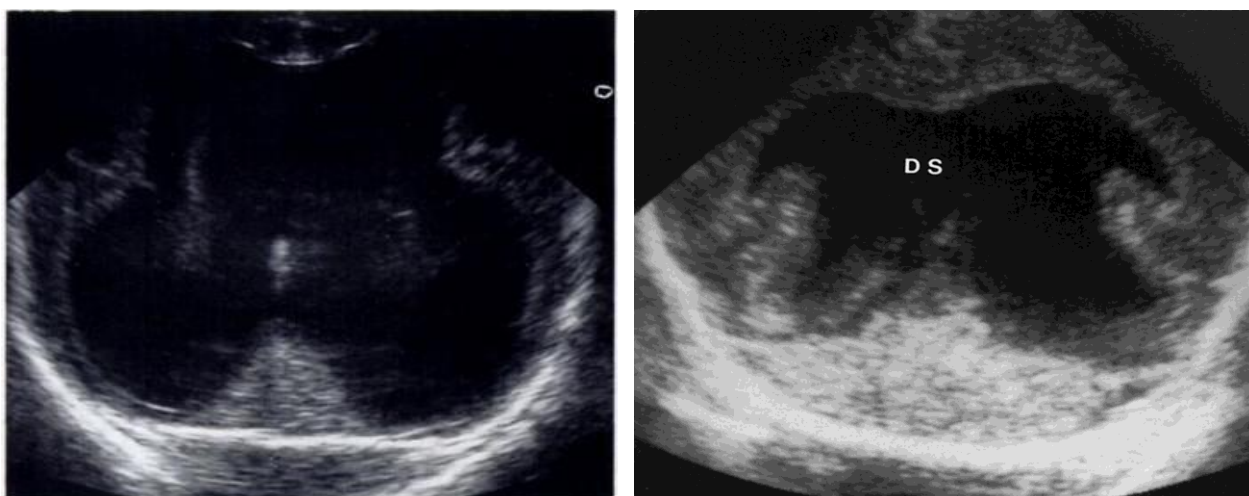


Fig. 6 a and 6b Lobar holoprosencephaly

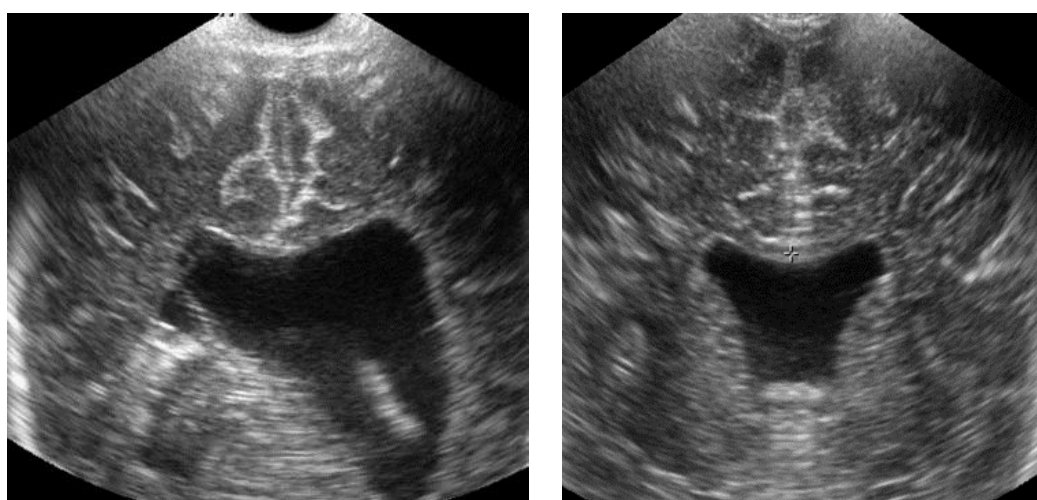


Fig.7a and 7b Absence of cavum septum pellucidum

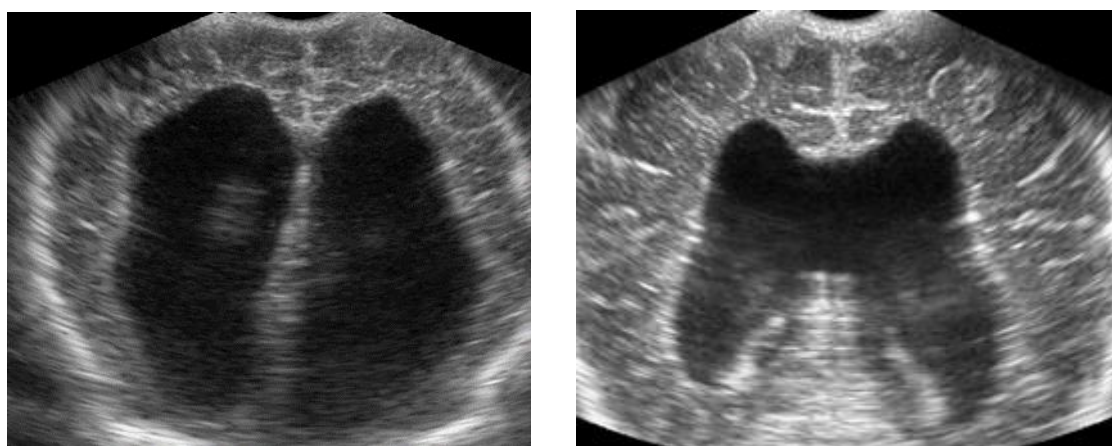


Fig.8a and 8b Septo optic dysplasia

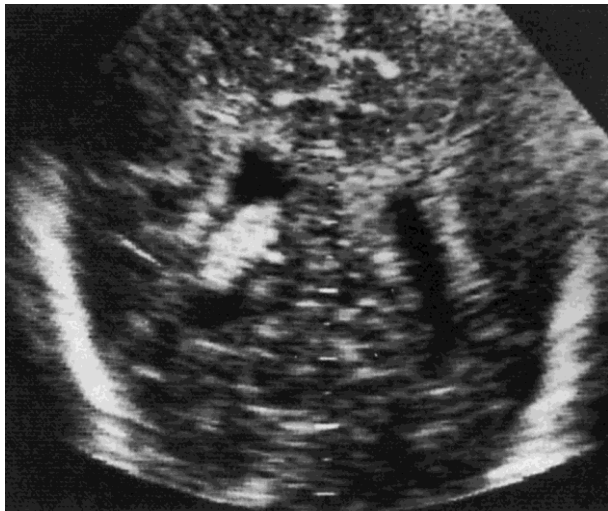


Fig. 9 Lissencephaly-widened Sylvian fissure and subarachnoid space

Neuronal migration disorders

Neuronal migration begins at 40-41 days of gestation until approximately six months of embryonic development, when the neuroblasts from the germinal matrix radially migrates into the cerebellum cortex, cerebellum and spinal cord. At the same time it also take place a tangential migration towards the interior of the cortex. Neuronal migration disorders cause the disorganization of the cortical structure, creating neuronal gaps which leads to the modification of the cerebral cytological architecture. The absence of the neurons in the periventricular areas lead to ventricular heterotopy.

Neuronal migration errors leads to the occurrence of several disorders: lissencephaly, schizencephaly, enterotopy and polymicrogyria. (13)

Lissencephaly and agyria/polygyria

Lisencephaly is defined as deficitary neuronal migration forming the cerebral cortex (fig.9), with few or no gyri ("smooth brain").

Polygyria is defined as a reduction in size of the gyri and grooves usually appears at the same time with lissencephaly. Clinically patients present growth disorders, microcephaly, major neurological retardation and severe form of epilepsy. There are three types of lissencephaly known:

- Type I: characterized by microcephaly and facial dysmorphism (14)
- Type II: characterized by hydrocephalus, retinal dysplasia and muscular dystrophy (12).
- Type III: characterized by microencephaly but without facial dysmorphism.

Gray matter heterotopia

Represents a local anomaly of neuronal migration disorders. The heterogeneous gray matter can be located anywhere along the neuronal migration ray.

Polimicrogyria is characterized by an abnormal thickening of the cortex with a larger number of gyri, fused

to the surface. Histologically is about a four layer cortex and a diagnosis can be established only by biopsy (15,16).

Schizencephaly is characterized by unilateral or bilateral septation of the cerebral hemispheres, with occurrence of irregular cracks of varying sizes that extend from the LV to the cerebral cortex. These cracks have thickened edges made of gray matter in the form of microgyria. The disorder occurs due to the faulty migration of the neuroblasts from the germinal matrix producing local cortical agenesis or hypoplasia. Clinically it can be found: microcephaly, motor retardation, seizures, hyper/hypotonia, epilepsy, developmental disorders. In the severe forms of disease that occurs in the neonatal period preceded by apnea, aspiration syndrome, halting growth (17). Ultrasound viewing reveals wide grooves, filled with liquid, communicating with lateral ventricles. The edges are hyperechoic, because of the thickened brain tissue. Anterior horn of the lateral ventricles are joined due to the absence of the septum pellucidum.

Tuberous sclerosis it's a dominant autosomal transmitted disorder which consists in the presence of tumoral formations in different organs, including the brain, skin, bones, kidneys. Brain tuberousities are formed by subependymal nodules, astrocytoma, giant cells astrocytoma and hematomas.

Affected children clinically describe early onset epilepsy and delayed neuropsychomotor development. The presence of hypopigmented patches and facial angiofibromatosis may lead to clinical suspicious diagnosis but accurate diagnosis is established by cerebral MRI and ultrasound. Subependymal tuberousities are visualized as small heterogeneous formations located in the walls of the LV, sometimes dilated.

In terms of ultrasound, the differential diagnosis is with neurofibromatosis type I, Sturges-Weber disease and neonatal cerebral tumors. (18) Sturges-Weber disease have early onset in the neonatal period and starts with facial hemangiomas. The cerebral abnormality occurs in the lobar region (frontal and occipital). In time, ipsilateral choroid plexus undergoes hypertrophy and around the LV the deep collateral venous branch develops. The necrosis of the adjacent cerebral parenchyma takes place and the intralobular calcifications arise even in the neonatal period. Inside the cortex and the subcortical white matter are found diffused hyperechoic formations hard to distinguish from tuberous nodules.

Complex brain disorders

Corpus callosum agenesis

Is a fibrous structure which connects the two cerebral hemispheres. The development takes place between 6-8 weeks of gestation until 18-20 weeks of gestation.(19) The corpus callosum agenesis can be caused by various factors: infections, congenital metabolic errors, genetic syndromes. In the specialty literature there are known 50 types of congenital syndromes which associate the corpus callosum agenesis (20) and it can be found in chromosomal abnormalities like trisomy 8, 18. The prevalence of the

disease is 0,1-0,7% and increases to 2,3% in patients with various disorders.

The agenesis can be partially, when only the posterior side is missing, and totally when the whole corpus callosum is absent. The ultrasound diagnosis is based on the absence of the corpus callosum and a marked separation of the anterior horns of the lateral ventricles which are pushed sideways by the powerful Probst fascicle (Fig 10 a and 10 b). Posterior horns are more dilated and lead to colpocephaly. This occurs because of the absence of a great number of fibers from the posterior commissure. Other ultrasound signs are: the anterior displacement of the third ventricle between the two lateral ventricles creating a cystic formation, the distortion of the cerebral gyri and grooves with a radial orientation from the bodies of the lateral ventricles. (21, 22)

Aicardi syndrome

Is a malformative complex syndrome defined by the triad: total or partially corpus callosum agenesis, lacunar chorioretinitis and infantile spasms. Other associated signs are: coloboma, polymicrogyria, periventricular heterotopy, choroid plexus cyst, intracranial cysts and brain tumors. The diagnosis is possible through MRI when it's associated with major ocular and brain malformations.

Cystic brain lesions

Hidranencephaly

Is considered to be a severe disorder characterized by the flattening to absence the cerebral hemispheres and replacing them with a bag with thin, membranous walls filled with cerebrospinal fluid (fig. 11). The external layer of the bag is formed by leptomeninges, and the internal layer is formed by the rest of the cerebral cortex and the white matter. The structure of the median brain and cerebellum are usually intact, and the cerebral trunk can be atrophic. (23) Hidranencephaly is produced by an intrauterine destruction, when, under the action of the pathogenic factors (ischemia, haemorrhage, infections, vasculopathy) occurs a liquefactive necrosis (20-27 weeks of gestation).

Porencephaly

Consists in the presence of a congenital or inherited focal cavity in the cerebral parenchyma which communicates with the subarachnoid space (external porencephaly) or with the lateral ventricles (internal porencephaly) or the midline (central porencephaly). Porencephalic cyst appears like a small cavity with walls full of liquid, without interior septa. In the specialty literature are present more types of classification: embryonic porencephaly or schizencephaly, early fetal porencephaly (fig.12) and perinatal porencephaly (fig.13a and 13b).

Midline brain malformations

Dandy Walker Malformation

The classic form of disease is characterized by: cerebral vermis complete or incomplete agenesis, cystic dilatation of the posterior fossa which communicates with the fourth ventricle and tentorium abnormalities with the enlargement of the posterior fossa.

Posterior brain fundamental anomaly is related to improper forming of the cerebellar vermis and the roof of the fourth ventricle. The starting point can be partially or totally obstruction of the Magendie orifice, which leads to the accumulation of CSF and the dilation of the fourth ventricle. Despite the further opening of the Luschka orifice (usually opened in Dandy Walker malformation), the cystic dilatation of the fourth ventricle persists and a deterioration of the leakage of CSF (24). Clinically, infants present hydrocephalus with occipital prominence growth and the emphasized dilatation of the fourth ventricle and the enlargement of the posterior fossa. The ultrasound signs of the disease are better visualized in the sagittal sections (20) and are represented by: large homogeneous cyst of the posterior fossa, full of liquid, which actually is the dilated fourth ventricle extending posteriorly; partially or complete absence of the vermis; cerebral hemispheres hypoplasia; abnormally high tentorium (fig.14 and 15)

Dandy Walker version

Consists in moderate hypoplasia of the cerebellar vermis, less developed tentorium and posterior fossa dilatation. Neurological impairment of the infants is less intense than the malformation but it also depends by the associated lesions (25). Sometimes marked enlargement of the cisterna magna can be found and in the absence of a cerebral abnormality the prognosis is good.

Joubert syndrome

Is a complex recessive autosomal disorder, characterized by: cerebellar vermis hypoplasia, thickening and widening of the cerebellar peduncles and the deepening of the interpeduncular fossa. Clinically, the newborn presents marked hypotonia and apnea or tachypnea (26). Psychomotor retardation, ataxia, nystagmus, ocular motor apraxia.

Conclusions

1. Positive diagnosis is relatively easy since the antenatal period using ultrasound, but a certain diagnosis is established by brain MRI.
2. Cranio-cerebral dysraphism although shows a good short-term prognosis immediately after rapid therapeutic intervention, have a high degree of long term sequelae, especially those associated with Arnold Chiari type II malformation.
3. Cell proliferation and neuronal migration disorders are severe due to early damage, neuropathogenic associations, which in the end lead to complex clinical syndromes resistant to treatment, with unfavorable outcome.
4. In ventral induction disorders long term neurological prognosis is correlated with the type of disease, neurological signs are present from the neonatal period and the evolution in the severe forms of disease is unfavorable, leading to death.
5. Generally, brain malformations, represents an important part of the neonatal pathology either due to the vital risk or because of the high risk of sequelae, threatening the social integration.

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NEONATAL PNEUMOTHORAX IN THE “BEGA” NEONATOLOGY CLINIC BETWEEN 2014-2015

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Abstract

Pneumothorax is a medical and surgical emergency. The most incriminated risk factors in the neonatal pneumothorax are: mechanical ventilation, pulmonary tissue anomalies, respiratory distress syndrome, sepsis; pneumonia; aspiration syndromes (meconium, blood), congenital malformations. In 0.07% of the cases pneumothorax can occur spontaneously in an apparently healthy new born infant.

This is a retrospective study of the pneumothorax cases in the “Bega” Neonatology Clinic from Timisoara through a period of 2 years (2014-2015). We found important aspects regarding maternal pathology, pregnancy related pathology and incidents during birth.

During 2014-2015 there were 4891 births in our Clinic, 378 of the new born infants were admitted in the Neonatal Intensive Care Unit (NICU). 12 of these infants had pneumothorax, which means an incidence of 2.38% and a prevalence of 0.24%. More than a half were unilateral pneumothorax cases. The gestational age of the new born infants included in the study is between 27-39 weeks, with a prevalence of the premature born infants, with an approximately equal ratio between sexes. 56% of the cases needed surgical intervention for pleural drainage. There is an increased proportion of the cases that needed invasive mechanical ventilation, cases with severe respiratory distress and also an increased proportion of the cases diagnosed with maternal-fetal infection. The evolution and the prognosis of the infants depended on the gestational age and associated pathology. The majority of the infants had a favorable evolution, with remission after 48 hours. By the pulmonary point of view the prognosis was good. The cases with intraventricular hemorrhage can be considered as a complication secondary to the fluctuations in the cerebral vascular circulation and blood pressure, the disturbance in the venous return, of hipercapnia, hypoxia and acidosis.

Key words: pneumothorax, new born, gestational age.

Introduction

Pneumothorax is a medical and surgical emergency. The most incriminated risk factors in the neonatal

pneumothorax are: mechanical ventilation, pulmonary tissue anomalies, respiratory distress syndrome, sepsis; pneumonia; aspiration syndromes (meconium, blood), congenital malformations. In 0.07% of the cases pneumothorax can occur spontaneously in an apparently healthy new born infant.

Objectives

We analyzed the frequency of pneumothorax in “Bega” Neonatology Clinic from Timisoara during 2014-2015, sex and gestational age related distribution and any correlation with mechanical ventilation and maternal pathology during pregnancy. We were also interested in the associated pathology and therapeutical management.

Material and method

We did a retrospective study analyzing patients observation sheets from “Bega” Neonatology Clinic over a period of 2 years (1st January 2014-31st December 2015). During this period there were born 4891 infants, 378 were admitted in the NICU and 12 of them had pneumothorax.

Results and discussions

In the scientific literature the incidence of pneumothorax in new born infants is 1 – 2 % and it can increase until 30% in the patients with pulmonary disease or who received mechanical ventilation [1-4]. Also pneumothorax is more frequent in boys and term or postmature new born infants than in premature infants [1, 5-8].

During the analyzed period, in our Clinic, there were 4891 births, 378 of the new borns were admitted in the NICU. 12 of these had pneumothorax, which means an incidence of 2.38%/year and a prevalence of 0,24%.

As a comparison in 2014 there were 2357 births and 2534 births in 2015. 173 of these new born infants were admitted in the NICU in 2014 and 205 in 2015. We noticed that the incidence of pneumothorax was relatively constant during the two studied years and it was very close to the published data. [1,2,9,10].

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It is known that neonatal pneumothorax is more frequent in boys than girls [1, 11-14]. In the studies that we found in the scientific medical literature 65-70% of the pneumothorax cases were boys.

By the sex related distribution point of view, we also had a slightly predominance of pneumothorax in boys in our study (56%) compared to the female sex (44%). But if we make a comparison between the two years we notice that in 2014 the ratio is in girls favor (75%), opposite in 2015 when the ratio is 80% for boys.

The worldwide studies from the last years show an increased incidence of pneumothorax in infants born by cesarean section (approximately 60-70%) compared to those from vaginal delivery which means approximately 1/3 of the cases [1,14-17].

The study we did in our Clinic confirmed the literature data mentioning that the percentage of the infants with pneumothorax born by cesarean section exceeded the anterior published data reaching 90% of the cases, vaginal deliveries representing only 10%.

By the gestational age point of view, in the medical scientific literature, first place is occupied by the term and postmature infants, the percentage varies among the studies between 44% and 83% [1,9].

In contrast to these data the gestational age of the infants included in our study was between 27 -39 weeks, with a prevalence of premature infants (78%) while only 22% of the infants that developed pneumothorax were at term (fig. 1). We had no cases of pneumothorax in postmature infants.

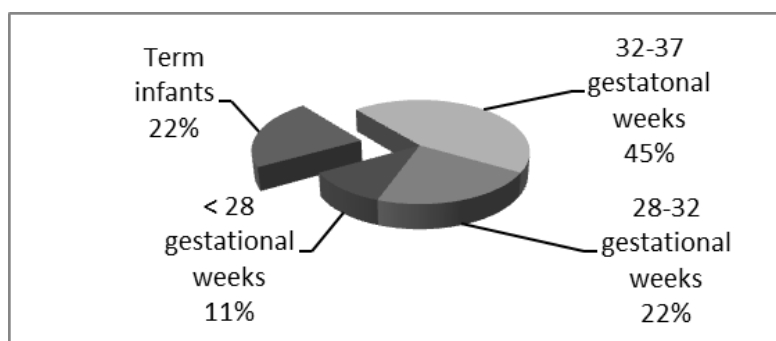


Fig.1- Gestational age related distribution of the infants with pneumothorax.

In the study lot 1/3 were normal birth weighted, the rest had a birth weight less than 2500 grams. Among the latter the highest percentage (33%) was represented by the infants with a birth weight 2000 and 2500 grams (fig.2). In contrast with our results, other studies cited in the literature

mentioned a higher percentage of the normal weighted infants. [1,9,14]

Analyzing maternal pathology during pregnancy we noticed the presence of: 22% infections, 11% preavia placenta, metrorrhagia, 11% history of dead fetus (fig. 3).

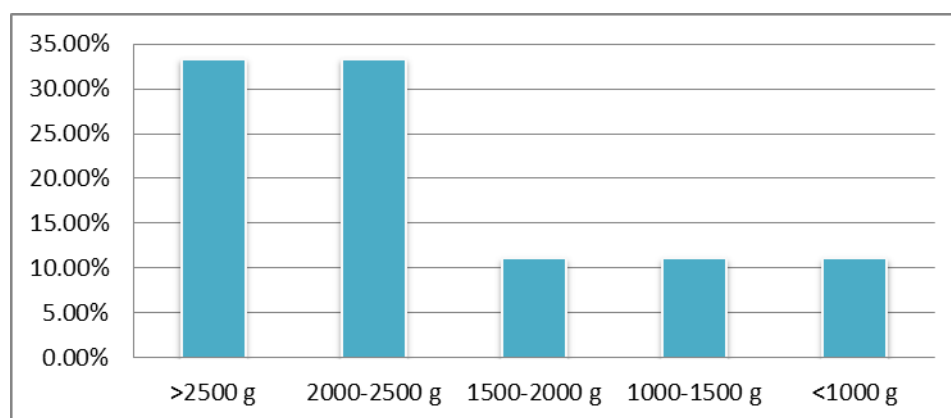


Fig. 2- Birth weight related distribution of the infants with pneumothorax.

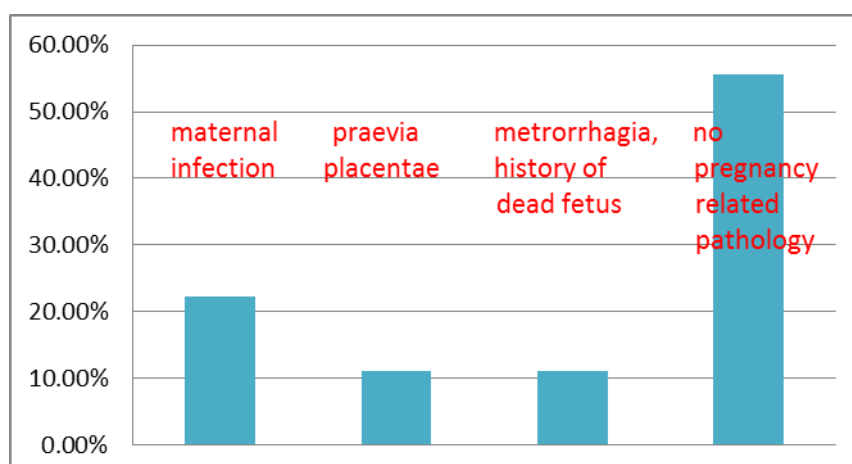


Fig. 3- Pathological history of the mother before and during the pregnancy.

The use of mechanical ventilation and the presence of respiratory distress syndrome were incriminated as risk factors for pneumothorax [1,9,14,18]. 89% of the pneumothorax cases occurred in the infants with severe respiratory distress syndrome and mechanical ventilation.

In the scientific medical literature it is mentioned that 2/3 of the unilateral pneumothorax cases involve the right

lung, [12,19] and bilateral pneumothorax represents 15 to 25% of the cases [1,9,14,18]. Our study confirms these data as almost 80% of the cases are unilateral pneumothorax, the most of them being localized on the right lung, while bilateral pneumothorax is seldom diagnosed (fig. 4).

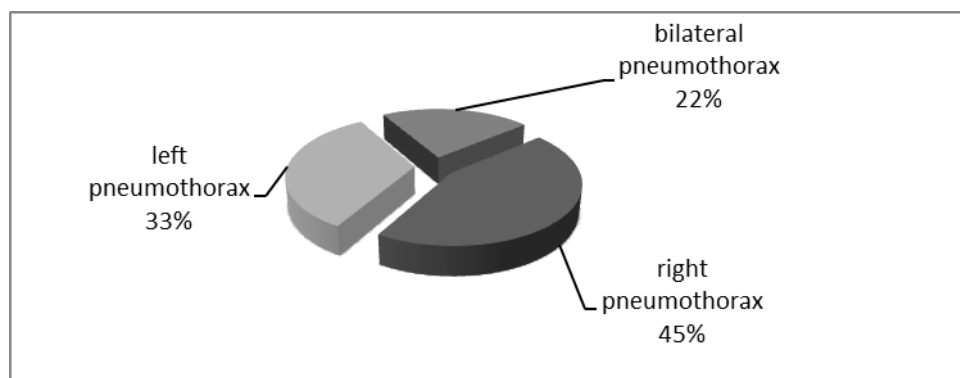


Fig. 4- Localization related distribution of the neonatal pneumothorax.

Small dimension pneumothorax usually resolve spontaneously. In contrast pneumothorax that affects > 20% of the lung surface and in tension pneumothorax need pleural drainage for evacuation [18,19]. In literature the percentage of the latter is between 79-93% [1,14]. In our case 56% needed pleural drainage, in the rest of the cases pneumothorax resorbed spontaneously.

Studying the associated pathology, we observe that the most frequent association was that with respiratory distress syndrome (RDS) (66%), followed by the intraventricular hemorrhage (IVH) (50%), perinatal hypoxic-ischemic encephalopathy (HIE) (44%), maternal fetal infection (40%) and in a lower percentage by pneumonia, congenital

hypothyroidism, cardiac and respiratory failure and seizures (fig. 5).

Also in the scientific literature in the first place as comorbidities is RDS followed by meconium aspiration syndrome [1,14,18,19]. There have been also mentioned: pneumonia, cardiac failure, hyaline membranes disease, neonatal asphyxia, multiple organs dysfunction, congenital malformations etc.[1,9,14]. Pneumothorax associated with RDS increases the risk for IVH, chronic pulmonary disease and death [3,21].

The evolution was favorable under therapy with recovery in 89% of the cases. We had only one decease in 2014, a new born infant from a pregnancy at risk, the mother

being diagnosed with uterine fibroids, metrorrhages during the pregnancy, with a history of a dead anencephalic fetus.

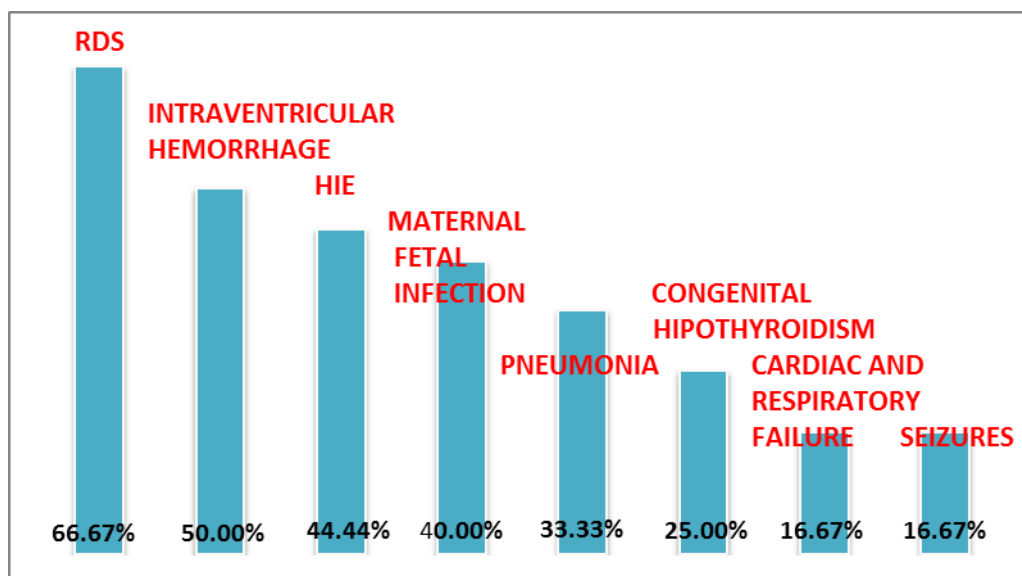


Fig. 5- Associated pathology.

Conclusions

1. The majority of the pneumothorax cases were unilateral.
2. Cesarean section is a supplementary risk for pneumothorax appearance.
3. Respiratory distress syndrome is one of the most frequent causes of pneumothorax.
4. The evolution and the prognosis of the infants with pneumothorax depends on the gestational age and associated pathology.
5. The majority of the infants had a favorable evolution with the remission of the pneumothorax in 48 hours.
6. Long term prognosis regarding the respiratory function was good.
7. The IVH can be considered as a complication secondary to the fluctuations in the cerebral vascular circulation and blood pressure, the disturbance in the venous return, of hypercapnia, hypoxia and acidosis.

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CLINICAL STUDY OF CIRCUMCISION IN THE PEDIATRIC POPULATION AGED 0 TO 15 YEARS

Ada Savin^{1,2*}, Tica C^{2,3}, Enache FD^{2,3}

Abstract

Introduction: Despite the fact that almost 1/6 of the total male population of the world is circumcised it has been a long time since it has been forgotten the origin of this intervention. The procedure was practiced for religious beliefs, cultural or medical, the latter being fashionable in modern surgery in the last century. **Material and method:** The trial was conducted in the Clinic of Pediatric and Orthopaedic Surgery of "St. Andrew" Emergency County Hospital of Constantza, between 2011 and 2015. During this period we verified the cases of phimosis and separated them in two age groups. We looked at those who were circumcised and those who had conservative surgery of the foreskin. **Results:** During those five years, we had 1,196 cases of phimosis. Some of them were circumcised, and at others the foreskin was kept. For circumcision, there were different aspects:

- Biological circumcision has been practiced for different pathologies that needed this type of intervention;
- Psychological: presence or absence of the foreskin perceived like a state of well-being;
- Social: in terms of cultural, religious or social or when an individual wishes to be circumcised.

Conclusions: Surgery of the foreskin, unless required by medical reasons, should not be performed in the first 4 years of life, taking into account the development of the glans-foreskin system during this period. Western trends about the integrity of the human body have their justification in the light of new investigations conducted (microscopic anatomy, immunology, etc). For circumcision it must be considered a multitude of factors that are not only medical, but also social, cultural, religious, etc. Regarding statistics in our country and especially in Dobrogea, there isn't an accuracy because of the inconsistent practice of the intervention in hospital. Rural population and the urban one of both Muslim origin, turn to alternative services for circumcision, which does not include statistical views.

Key words: children, phimosis, circumcision.

Introduction

Despite the fact that almost 1/6 of the total male population of the world is circumcised it has been a long time since it has been forgotten the origin of this

intervention. The procedure was practiced for religious beliefs, cultural or medical, the latter being fashionable in modern surgery in the last century. The worldwide global rate of male circumcision is about 13.3 million annually despite increasing evidence of its negative functional consequences [1-9].

There is no country in the world that accepts as protocol male circumcision, especially for infants [10]. The prepuce plays an important role in local sensitivity. It contains the highest concentration of nerve endings in the penis and thus it serves not only a protective role, but also a sensory one for sexual function [11]. Its removal during circumcision doesn't go to great benefits in this situation.

Purpose

The aim of this study is to compare therapeutic results obtained in the treatment of foreskin pathology in children between 0 and 15 years.

Material and method

The trial was conducted in the Clinic of Pediatric and Orthopaedic Surgery of "St. Andrew" Emergency County Hospital of Constantza, between 2011 and 2015. During this period we verified the cases of phimosis and separated them in two age groups. We looked at those who were circumcised and those who had conservative surgery of the foreskin.

We studied the methods of approach of the foreskin pathology, postoperative complications occurred, both early and also the late ones.

Results and discussions

In the Clinic of Pediatric and Orthopaedic Surgery of "St. Andrew" Emergency County Hospital of Constantza, between 2011 and 2015, we have grouped patients with foreskin pathology in 2 series by age. First group consists of patients between 0 and 4 years old and the other group between 5 and 15 years old (fig. 1). We used the 4 years border because of the fact that around this period, the prepuce-glans system defines and the foreskin will start to retract by itself [12].

The distribution per year of the cases is shown in table 1.

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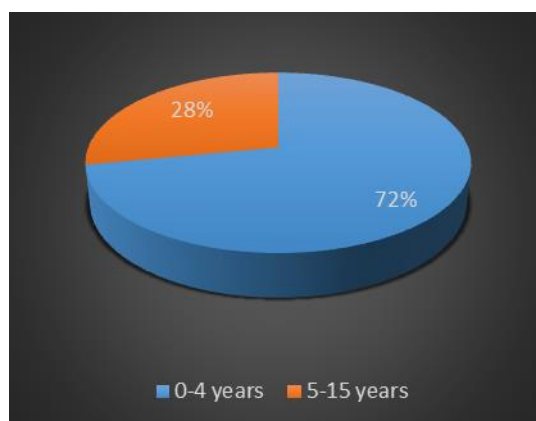


Figure 1 – Distribution of patients in two study groups.

Table 1 – Distribution per year of foreskin pathology cases.

	0-4 years	5-15 years	TOTAL
2011	106	101	207
2012	141	127	268
2013	127	119	246
2014	164	85	249
2015	101	125	226
TOTAL	639	557	1196

We considered the ways of treating phimosis by surgery. These are circumcision, dorsal debridement and elimination of preputial adhesions.

The cases treated by circumcision are presented in figure 2.

The total cases of circumcision performed in the study is 127. From 1196 cases studied, that means about 10,6% (Table 2). This is a little bit more then the percentage of muslims who live in Constantza area.

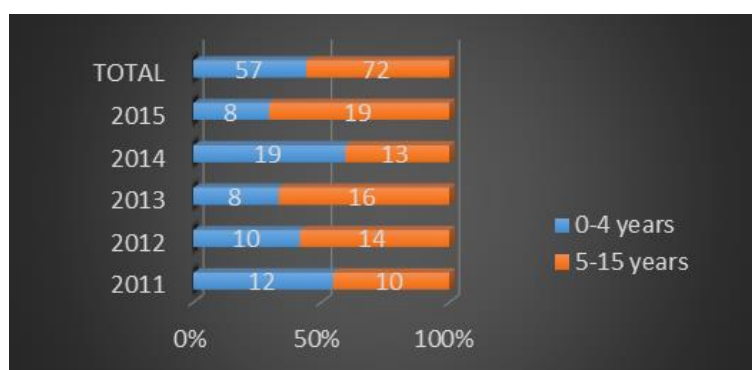


Figure 2 – Cases treated by circumcision in our study group, by age and year of treatment.

Table 2 – Distribution of cases treated by circumcision.

Type of treatment	No. of cases	Percentage
Circumcision	127	10,6%
Other treatment	1069	89,4%
TOTAL	1196	100%

According to the 2002 census, 67,566 people, approx. 0.3% of the total population of Romania, indicated that their religion was Islam [13,14]. The vast majority of Romania's believers in Islam are Sunnis who adhere to the Hanafi school. Ethnically, they are mostly Tatars (Crimean Tatars and a number of Nogais), followed by Turks, as well as Muslim Roma (as much as 15,000 people in one estimate) [13,15], Albanians (as many as 3,000) [13,16], and groups of Middle Eastern immigrants. Members of the Muslim community inside the Roma minority are colloquially known as "Turkish Romani" [13,15]. Traditionally, they are less religious than people belonging to other Islamic communities, and their culture mixes Islamic customs with Roma social norms [13,15].

Ninety-seven percent of the Romanian Muslims are residents of the two counties forming Northern Dobruja: eighty-five percent live in Constanța County, and twelve percent in Tulcea County [13,17], forming 6% of local population [18]. The rest mainly inhabit urban centers such as Bucharest, Brăila, Călărași, Galați, Giurgiu, and Drobeta-Turnu Severin [13,19].

So, if we are comparing the percentage of muslim population in the area where the study was conducted and circumcision performed, there is a slightly resemblance. The difference stands in the fact that a part of circumcisions were made for therapeutic reasons or on parents' demand.

Health, as defined by the World Health Organization, is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity [20].

Circumcision involves all three of these components of health:

- Biological circumcision has been practiced for different pathologies that needed this type of intervention;

- Psychological: presence or absence of the foreskin perceived like a state of well-being;
- Social: in terms of cultural, religious or social or when an individual wishes to be circumcised.

Although circumcision is one of the simplest procedures, the complexity of notions resulted from new research, makes it questionable, especially concerning it's timing.

Conclusions

For circumcision it must be considered a multitude of factors that are not only medical, but also social, cultural, religious, etc.

Surgery of the foreskin, unless required by medical reasons, should not be performed in the first 4 years of life, taking into account the development of the glans-foreskin system during this period.

Western trends about the integrity of the human body have their justification in the light of new investigations conducted (microscopic anatomy, immunology, etc).

The religious factor is much stronger than the factors resulting from the perception of small groups (cultural or scientific), circumcision being a custom of the Muslim population or an existential necessity of Jewish population, so for these groups, circumcision practice will be unchanged regardless of the evolution of human thinking.

Regarding statistics in our country and especially in Dobrogea, there isn't an accuracy because of the inconsistent practice of the intervention in hospital. Rural population and the urban one of both Muslim origin, turn to alternative services for circumcision, which does not include statistical views.

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A RARE CASE OF GROW RETARDATION ASSOCIATED TO DISGENETIC SYNDROME

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Abstract

Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract and retinal detachment. It can also cause hearing loss that is both conductive and sensorineural. Under-development of the middle part of face, ogival palate, spondylo-epiphyseal dysplasia and/or precocious arthritis can also occur. The authors present the case of a 7 months old infant with failure to thrive associated to a particular phenotype; facial dysmorphism and congenital cataract, who was referred for admission presenting an upper respiratory tract infection. Corroborating the clinical examination with the paraclinical evaluation and genetic assessment, including the karyotype, the authors established in this case the diagnosis of Stickler syndrome.

Key words: Stickler syndrome, congenital cataract, myopia, conductive and sensorineural hearing loss.

Introduction

Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Variable phenotypic expression of Stickler syndrome occurs both within and among families; interfamilial variability is in part explained by locus and allelic heterogeneity. Stickler syndrome is the commonest inherited cause of retinal detachment in childhood and although the systemic features are widespread, the sight threatening complications are the most serious manifestations. (1)

Case report:

T.V., a 7 months old boy, was admitted in hospital in June 2015 for an upper respiratory tract infection.

The personal history showed that T.V. was a young couple's first child from rural area. T.V. was born at term, in cranial presentation, with weight at birth 3250 grams and height at birth of 49 cm. Apgar score was 10, and the infant presented good neonatal adaptation. His diet consisted of breast milk for one month and after that he was fed with

cow's milk. The complementary feeding was incorrectly initiated at the age of three months. He has been vaccinated only with BCG and Engerix in maternity and the other vaccinations were not performed by the age of 7 months when he presented in our clinic. In infancy he presented several episodes of upper respiratory tract infections treated at home.

The interesting aspect of this case was the fact that the family history showed an involvement of ocular disorders in two maternal uncles with acquired amblyopia of unknown etiology, one of whom died in a car accident and the other being alive and presenting blindness. (Figure 1)

Clinical examination upon admission revealed an infant with mild failure to thrive, presenting the following anthropometric indices: weight of 6300 g, high 63 cm, 43 cm cranial perimeter, thoracic perimeter of 47 cm and 45 cm abdominal perimeter. Particular facial phenotype was characterized by underdevelopment of the middle part of face, micrognathia, ogival palate.

The infant presented a pronounced horizontal nystagmus and the skin was pale. The pharynx was congested, the baby presented nasal obstruction and a rare irritating cough but presented normal lung auscultation. On auscultation a second degree systolic murmur was heard. The infant showed generalized hypotonia with pronounced tendon reflexes in the legs. The baby maintained its own head, was not sitting upright, not able to stand alone or with support or say polysyllabic words. He presented chaotic eye movements, was not able to follow the examiner face, nor respond to his mimic, nor follow moving objects with his eyes. No other changes were detected in the rest of examination.

Laboratory examinations revealed severe iron deficiency anemia, hypochromic microcytic, hypocalcemia, hypomagnesemia, hipogammaglobulin and moderate elevation of liver transaminases. (Table 1).

TORCH serology was negative, we excluded cytomegalvirus infection, toxoplasma gondii, treponema pallidum and HIV infection, chronic B and C hepatitis. Skull radiography revealed normal thickness cap, suture according to age, Turkish saddle according to age.

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	17.06.2014	23.06.2014	01.07.2014
Hemoglobin	6.8 g/dl	10.2 g/dl	11.5 g/dl
RBC	$1.87 \times 10^6 / \mu\text{L}$	$3.80 \times 10^6 / \mu\text{L}$	$4.0 \times 10^6 / \mu\text{L}$
WBC and leukocytes formula	$6.6 \times 10^3 / \mu\text{L}$ Sg=27%, E=1%, Ly=63%, M=9%	$8.8 \times 10^3 / \mu\text{L}$	
Platelets	175.000 / μL	220.000 / μL	
Inflammation	ESR=6mm/h CRP: negative		
Electrolytes	Na=134, K=3.99, Ca=2.2, Cl=98, Mg=0.76 mmol/l	Na=138, K=4.33, Cl=104 mmol/l	
Astrup	pH = 7.34, pCO ₂ = 17.6mmHg BE = -9.6mmol/l HCO ₃ = 9.8mmol/l		
Proteinemia and electrophoresys	60 g/l; A = 66.7%, $\alpha 1$ =3.2%, $\alpha 2$ = 10.4%, β = 10.8%, γ = 8.9%	64.6g/l	
LDH	820 U/L		
Liver tests	GPT = 65U/l GOT = 76U/l GGT = 22 U/L	GPT = 71U/l GOT = 73U/l	GPT = 16 U/L GOT = 12 U/L
Renal tests	BUN = 6.87mmol/l Serum creatinine = 45 $\mu\text{mol/l}$		
Serum Glucose	3.5 mmol/l		
Microscopic examination of urinary sediment	Absent albuminuria, 1-3 WBC per high power field, rare hyaline cylinders, rare epithelial cells		
Stool parasitology test	NEGATIVE		
Stool culture	NEGATIVE		

Table 1. Laboratory results

A pediatric cardiology examination was performed. Echocardiography showed aorta = 12.7 mm, opening aorta = 7.14 mm, left atrium = 14.4mm, left ventricle = 16.6 / 23.6 mm, ejection fraction = 0.59, shortening fraction = 29.79 mm, interatrial septum = 5.18 mm, apparently without defects, right atrium = 17.1 mm, right ventricle = 13.5 mm. The anterior mitral valve presented protosystolic prolapse with regurgitation. The examiner detected aortic insufficiency. There was no fluid in pericardium.

Ophthalmologic examination showed microphthalmia in both eyes. Cornea transparency was reduced in size in both the horizontal and vertical axis. Normal iris. Pupil

round, central. Anterior subcapsular crystalline opacities, white color. Ocular pressure was normal (Figure 2).

- Papillary and photomotor reflexes were present.
- Ophthalmometry = 8 mm
- Ophthalmoscopy (Dilated Fundus Exam - DFE): no shine.
- Neurologic exam showed muscular hypotonia, horizontal nystagmus; opsoclonus; psychomotor retardation with stereotypy.
- Electroencephalogram (EEG Test) showed theta-delta rhythm, with many artifacts.
- Ear, nose and throat (ENT) examination was normal.

- Audiogram revealed mixed hearing loss, conductive and sensorineural.

A genetic consultation was performed. The karyotype was 46 XY 1qh+, 21s+, yq +; with chromosomal heteromorphysm with elongation of secondary constriction of chromosome 1, increase satellites on chromosome 21 and heteromorphysm of the Y chromosome.

Taking into consideration clinical and laboratory criteria: ophthalmic, otic, cardiac and cranio-facial changes and the karyotype, we sustained the diagnosis of Stickler syndrome.

During hospitalization in our clinic, the infant presented several episodes of watery diarrhea, possibly of viral etiology, which resolved under medical and dietary treatment (lactose-free milk, Racecadotril, Smecta, probiotics), without dehydration syndrome and electrolyte disorders. Pale skin was associated with pronounced low values of hemoglobin and the number of red blood cells, which required red blood cells transfusion. The treatment for upper respiratory tract infection was performed with acetaminophen syrup orally and 1% ephedrinated serum intra-nasal. For muscle hypotonia Cerebrolizyn treatment was initialized which was well tolerated. For transient hepatocytolytic syndrome accompanying the viral enterocolitis, the infant received intravenous infusion of Arginine and Aspatofort and transaminases return to normal in 14 days. Roborant treatment given to infant was consisted from group B vitamins (B1, B6, C) and gluconic calcium 10% in slow iv injection.

Discussions

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations affecting one of three genes: COL2A1, COL11A1, COL11A2 have been associated with a disease. Because a small number of families with Stickler syndrome features showed no mutations in these three mentioned genes, it appeared the hypothesis of mutations occurred at the level of other genes.

Given the autosomal dominant mode of transmission of the disease, affected patients shows a 50% risk of transmitting the mutant gene to each of successors. Because of the wide clinical variability of the disease that can occur within the same family, it must be assessed the relative risk of developing the disease and providing genetic counseling, like in the case of infant T.V. (Figure 3)

The Stickler syndrome diagnosis is mainly established on clinical data. There is currently no consensus on the minimum number of clinical criteria that must be met for a diagnosis.

Prevalence

There have been no studies done to determine the exact prevalence of Stickler syndrome. However, an approximate incidence among newborns can be estimated given the data regarding the incidence of Pierre-Robin syndrome (1:10 000) and taking into account the percentage of those infants who develop signs or symptoms of secondary Stickler syndrome (35%). Summing these datas, it was obtain an

approximate incidence of 1:7500 of Stickler syndrome in newborns. (1)

Diagnosis

There is not a specific clinical diagnosis criteria for Stickler syndrome however its diagnosis takes into account subjects who have two or more of the following conditions: (2, 3, 4, 5, 6)

1. Ophthalmologic disorders: congenital cataract or early onset in infancy, myopia greater than - 3 diopters, abnormal vitreous, retinal detachment. Usually, babies are farsighted (1 diopter or more), so the discovery of a degree of myopia in newborns at risk (with Pierre-Robin phenotype or with a parent affected) is suggestive for the diagnosis of Stickler syndrome. Among patients with this disease, there were observed two types of vitreous abnormalities. Type I, which is most commonly seen, consists of a persistent vestigial vitreous gel in the retrolental space, bounded by a membrane. Type II which is rarer, is characterized by the presence of bands thickened, irregular, and dispersed into the vitreous cavity. In our case, infant T.V. showed the phenotype Pierre-Robin described above and ocular changes: mycrophthalmia, corneal decreased in size in horizontal and vertical axis, and crystalline opacities, subcapsular above, white color.

2. Ear disorders: hearing loss, conductive or sensorineural. The degree of hearing damage is variable and can grow progressively. Approximately in 40% of the studied cases it has been described sensorineural deafness typically with loss of hearing for high tones. The exact mechanism is unclear and has been linked to the expression of collagen type II and IX in the inner ear. In type I Stickler syndrome, sensorineural hearing impairment is mild and with no progressive evolution, and is less severe compared with the audiological degradation in types II and III Stickler syndrome. Conductive deafness in some cases may be secondary to recurrent ear infections favored by ogival vault or due to a defect of the middle ear ossicles. Infant audiometry performed for T.V. infant showed mixed hearing loss, conductive and sensorineural.

3. Craniofacial changes: hypoplasia of the middle part of the face, deepened nose base, sharp nose, with nostrils anteversion, long filter, uvula bifida, ogival palate, micrognathia, Pierre Robin phenotype (micrognathia, ogival arch, glosptosis). Flat facial profile, caused by underdeveloped jaw and nose base, can cause telecanthus and epicanthus folds. Hypoplasia of the middle face is more pronounced in infants and young children, some subjects may have a normal facial profile.

T.V. baby facies was characteristic for Pierre-Robin phenotype, involving extra microcephaly.

4. Articular changes: Skeletal manifestations consist of early-onset osteoarthritis, hypermobility (joint laxity), short stature and radiographic changes of medium spondylo epiphyseal dysplasia. Some individuals may have "marfanoid" features, but with no tall stature. Joint laxity can be found in children and become less important with age. Stickler syndrome common spinal abnormalities

(scoliosis, kyphosis) can lead to chronic back pain. In T.V.'s case no skeletal changes were detected on admission.

5. Cardiac disorders: In the literature there were reported associations with mitral valve prolapse in 50% of the cases studied in a clinical trial and in a much smaller proportion of cases in another series (3, 5). This malformation – prolaps of mitral valve, was associated in our case.

According to recent studies, not all criteria are needed to comply with Stickler syndrome.



Fig. 1. The two maternal uncles of T.V. infant with

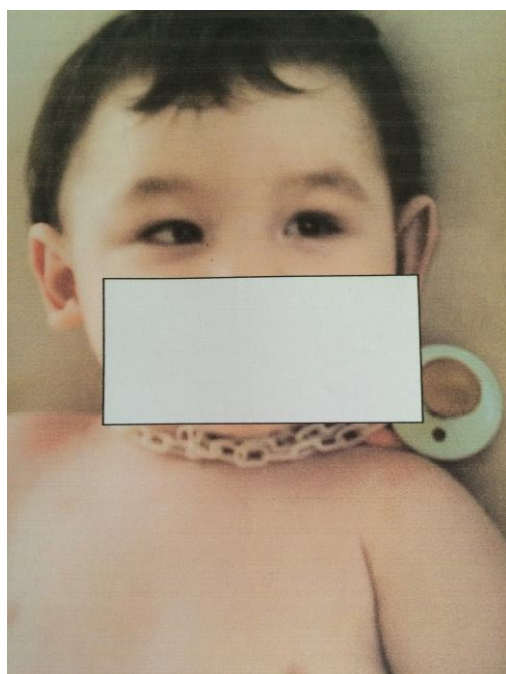


Fig. 2. T.V. clinical aspect

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations produced in the following three genes were associated with the appearance of type I, II and III Stickler syndrome: COL2A1 (chromosome 12, 12q13.11-q13.2 locus), COL11A1 (chromosome 1, 1p21 locus), COL11A2 (chromosome 6, 6p21.3 locus). (Table 2)

In some families with characteristic clinical changes of Stickler syndrome were not uncovered any one of these three mutations mentioned. It has been hypothesized the existence of mutations in other genes, still unidentified, present also in this disease.

Most patients diagnosed with Stickler syndrome presents the type I of the disease, with mutations in COL2A1 gene, while mutations in the gene COL11A1 (type II) were only recently described. Lately, in a few cases have been describing mutations in COL11A2 gene that causes Stickler syndrome type II, where all eye changes are missing.

Normal results of the COL2A1 gene activity is represented by chains of type II collagen, a major structural component of cartilage tissue. Mutations in this gene cause the premature termination of translation and consequently reduces type II collagen synthesis.

COL11A1 gene encode α chain synthesis of collagen type XI, which is supposed to play an important role in collagen fibrils genesis, controlling the lateral growth of collagen II fibrils. COL11A1 gene mutations alter the synthesis and function of collagen type XI.

COL11A2 gene encode α 2 chain synthesis of collagen type XI, expressed in cartilage, but not at the level of liver, skin and tendons. COL11A2 gene mutations also cause abnormal synthesis of collagen XI.

Genotype-phenotype correlations

In the COL2A1 gene appears a premature stop mutation that causes failure of the normal gene product synthesis, type II collagen. Most patients shows the type I vitreous anomaly and are at increased risk of retinal detachment, do not present hearing impaired or have a mild form of sensorineural deafness and shows early arthritis and craniofacial changes are variable.

COL11A1 gene mutation was observed in patients with typical phenotype of Stickler syndrome. Usually these patients have a more severe hearing impairment and type II congenital vitreous anomaly.

Gene mutation in COL11A2 cause Stickler syndrome without eye changes. (7, 8, 9, 10, 11, 12)

Clinical examination, biological investigations, laboratory and karyotype, performed in conjunction with interdisciplinary exams excluded a number of related genetic disorders. The karyotype of the case presented described mutations in the gene COL11A1 - locus 1p21 (46 XY, 1qh +, 21s +, yq +; chromosomal heteromorphism with elongation of secondary constriction of chromosome 1, increase satellites on chromosome 21, and heteromorphism of the Y chromosome), framing the presented case as Stickler syndrome type II.

Type of disease	Mutant gene	Mutant locus	Synthesis product of the gene
Stickler syndrome type I	COL2A1	12q13.11-q13.2	$\alpha 1$ chain of type II collagen
Stickler syndrome type II	COL11A1	1p21	$\alpha 1$ chain of type XI collagen
Stickler syndrome type III	COL11A2	6p21.3	$\alpha 2$ chain of type XI collagen

Table 2. Stickler syndrome's types

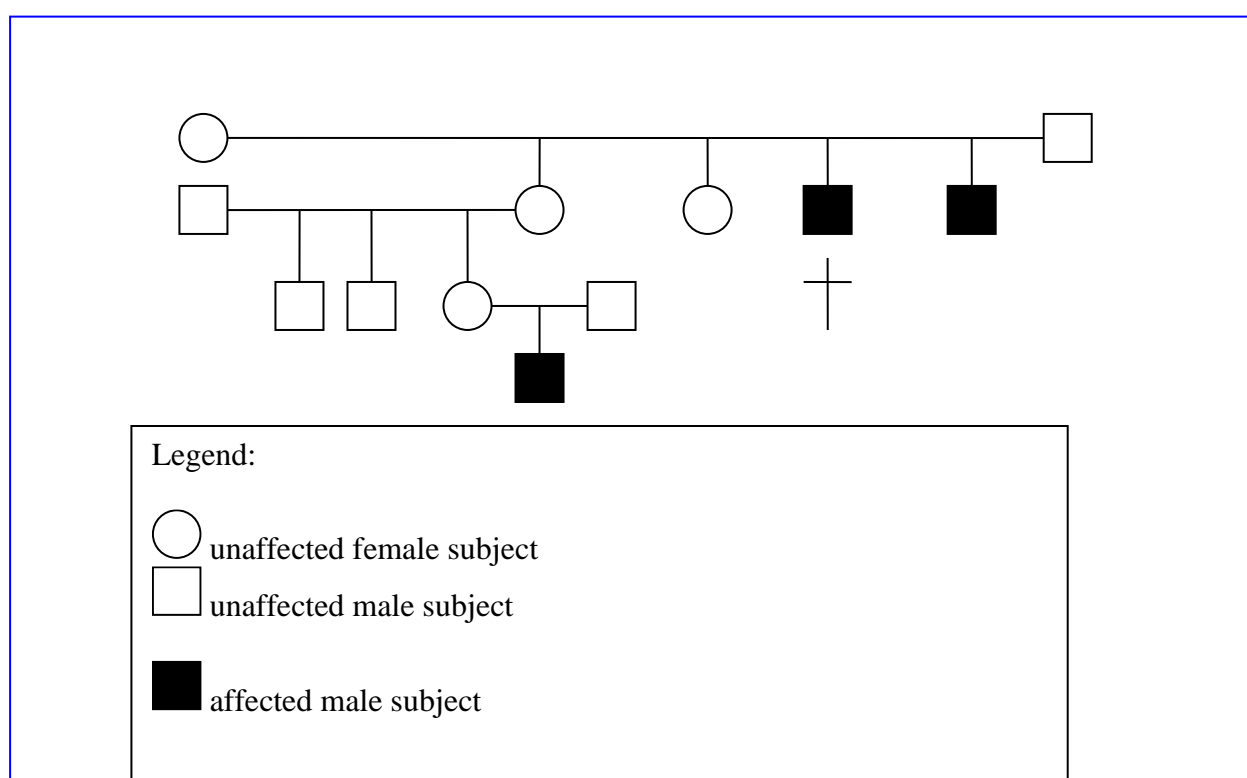


Fig. 3. Genetic family tree of T.V. infant

Conditions that show phenotypes associated with COL2A1 and COL11A2 gene mutations were excluded; in our case it is not type I or III of Stickler syndrome according to the karyotype.

For the differential diagnosis, we ruled out the following conditions:

1. Phenotypes associated with mutations in COL2A1 gene:
 - Achondrogenesis type II: characterized by virtual absence of ossification of the spine, sacrum and bin, with the consequent appearance of shortening of the trunk and limbs, with prominent abdomen and dropsical issue. Death occurs in utero or in early neonatal period.
 - Hypochondrogenesis - term used for describing a medium form of achondrogenesis
 - Congenital spondylo epiphyseal dysplasia: although skeletal changes are similar to those described in Stickler syndrome, these are more severe and cause significant

short stature. In addition, affected subjects may present flat profile, myopia or vitreous and retinal degeneration.

- Kneist dysplasia: affected subjects may present disproportionate short stature, flat facial profile, myopia, vitreous and retinal degeneration, ogival palate, kyphosis scoliosis, and multiple radiological spinal changes.
- Early-onset arthropathy: the disease is transmitted autosomal dominant, in 1990 being identified the COL2A1 gene mutation incriminated in the disease - the substitution of arginine to cysteine in position 519 of the $\alpha 1$ chain of type II collagen.
- 2. Phenotypes associated with mutations in COL11A2 gene:
 - Autosomal recessive spondylo-metaepiphyseal dysplasia: the disease is characterized by flat facial profile, sharp hard palate and severe deafness. Recently it has been hypothesized that type III Stickler syndrome - a form

without eye changes could be considered a type of this disease.

- Weissenbach-Zweymuller syndrome (WZS) was described as “neonatal Stickler syndrome”, but now is a distinct entity, characterized by hypoplasia of the middle part of face, clogged nose and top with the sharp nose, micrognathia, sensorineural hearing loss and limb shortening. Radiological changes include the femur and humerus in the form of “weightlifting”. Skeletal changes are less obvious in their lives and resume growth after 2-3 years of life is common.
 - Non-syndromic sensorineural deafness: in 1999 were described mutations in the COL11A2 gene in two unrelated families suffering from non-syndromic nonprogressive deafness.
3. Stickler syndrome type II seen in infant T.V. and must be differentiated from other similar genetic diseases that present similar phenotype and also associate mutations in the gene COL11A1:
- Marshall syndrome: Affected individuals present hypertelorism, maxillary hypoplasia and hypoplasia of the nasal bones as well as a clogged nose and a pointed nasal tip. Unlike Stickler syndrome, flat facial profile is more evident in adults. Eyes’ impairment includes: myopia, vitreous humor fluid and early onset cataracts. Sensorineural hearing loss is common and may progress. Nanism and early

arthritis may occur. Skin manifestations are also described - hipotricosis and hipohidrosis.

T.V. baby did not have early cataracts, skin manifestations or early onset arthritis, but the differential diagnosis remains questionable, taking into consideration the opinions of some authors which categorizes Marshall syndrome as a variant of Stickler syndrome II. (13, 14, 15, 16, 17, 18, 19, 20)

Conclusions

Stickler syndrome is often under-diagnosed in neonates with particular facial dysmorphism.

There are not any established precise clinical diagnosis criteria for Stickler syndrome. The diagnosis should be considered in children who presents two or more of the following conditions: ophthalmologic disorders, ear affections, particular craniofacial phenotyp, articular injuries or cardiac disorders.

Medical family history, clinical examination and karyotype assessment are necessary for diagnosis of Stickler syndrome.

The particularity of the presented case was the delay in diagnosis until the age of 7 months in a child with particular phenotype with facial dysmorphism, failure to thrive, microcephaly, congenital cataracts and mild psycho-motor retardation.

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PSYCHOLOGICAL DISTRESS OF PATIENTS AND THEIR FAMILIES IN CELIAC DISEASE

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Abstract

The aim of this paper was to discuss patient support in celiac disease, with a more attention to children. We point the physical and psychological problems related to this chronic disease and the fact that a proper medical surveillance of the patient should be doubled by strong psychological and educational guidance. Family support increases the adherence to gluten-free-diet and also assures a better quality of life. Some data also indicate that psychological stress may be involved in the development of celiac disease and primary stress and secondary stress should be taken into account regarding the therapy for this disease. Successful management of celiac disease both from the medical and the psychological aspects requires proper education of patients and their families and use the most efficient coping mechanism. Even if quality of life of these patients is relatively positive comparing to other chronic disease, patients should be empowered regarding the fact that not all symptoms will vanish after diagnosis and gluten-free-diet.

Key words: celiac disease, coping mechanisms, stress, child, adult, quality of life.

Introduction

Celiac disease (CD) is a chronic inflammatory immunomediated disease from which we know the environmental trigger: gluten. It is a common condition with prevalence in the western world of about 1: 100 and can be diagnosed at any age. CD is a digestive disease characterized by intolerance to gluten, a protein composite found in wheat, rye, and barley. Even minimal exposure to gluten results in small intestinal injury that can lead to a variety of symptoms, including abdominal pain, weight loss, diarrhea and irritability, and long-term complications such as osteoporosis, infertility, and malignancy (1).

The exact causes of celiac disease have not been identified yet. The existence of a family member suffering from this disease increases risks by 5-10%.

The key treatment is lifelong adherence to gluten-free diet (GFD) with dietary restrictions requiring constant management. Because celiac disease is a multisystemic

disorder, physicians need to be aware of the potential autoimmune, nutritional and malignant complications.

A proper team must approach to the follow-up of the newly diagnosed patient and should include regular supervision by an interested physician, medical nutritional counseling by a dietician and access to local and national support programs (2). Psychological and educational support must doubled medical support in order to increase the adherence to GFD.

Physical and psychological development

Early CD diagnosis correlates with better physical health, lower Celiac disease associated burden and fewer social problems. So, medical diagnosis done as soon as possible is a must in case of this chronic disease (3).

Adult presentations of CD are more common than children cases and there are even patients now being diagnosed and recognized who are elderly. Most cases of celiac disease in children are detected between 6 months and 2 years of age, because food diversification and the introduction of new foods throughout this stage may determine reactions from the child's body, which may easily be observed by the parents (malabsorption and poor growth).

Celiac disease is a chronic issue; it can appear and disappear throughout life, so that some people will only be diagnosed with this disease late in life.

Some of the common symptoms of celiac disease are diarrhea, decreased appetite, stomach aches and bloating, slowing growth rate in children and weight loss. The symptoms can often be mistaken for other medical problems, but a mere blood test can eliminate or confirm the suspicion of celiac disease. Detecting this disease as early as possible is important, because its effects on the physical and mental development of the organism are important. From a physical point of view, celiac disease causes a deficiency in the absorption of nutrients and vitamins that reach the small intestine. Without their contribution, the organism cannot develop harmoniously and it cannot maintain a normal growth rate.

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In addition, the effects of celiac disease may determine other imbalances at the level of the body. For instance, iron absorption deficiency will determine iron deficiency anaemia. Iron is important not only for the physical development of the organism, but also for the optimal functioning of the human psyche. It is well known that iron contributes to the myelination of the axon sheath. An intact myelin sheath facilitates a much faster transmission of information than an intermittent one. Thus, iron deficiency anaemia has consequences on the person's ability to retain and update information. The absence of iron up to the age of 2 may have important consequences on the child's intellect, determining thinking latency, decreased intellectual capacity, memorization difficulties, and decreased ability to maintain focus.

Family support and adherence to GFD

The effects of celiac disease on family functioning are not to be neglected. The role of the family in diet is of course even greater when the patient is a child. In the beginning, the mother is extremely disconcerted by the fact that the ingestion of considerable quantities of food cannot be noticed in the child's weight. The child can eat large quantities of food, but this ingestion is followed by weight loss. On the one hand, mother is feeling guilty about her skills. Mothers should be informed that "lack of breast-feeding" is never the sole reason for developing CD. On the other hand, mother should be also assisted in monitoring other members of the family (siblings) in order to diminish her fear about the CD among the family members.

Finding out the diagnosis is the second stage the parents must face. On the one hand, there is the diagnosis in itself. On the other hand, there is the difficulty to permanently create a menu according to medical indications, that is, a gluten-free diet. The parents must constantly preoccupy themselves with the daily menu, which makes it more difficult to provide meals, to socialize during meals within or outside of the family, precisely because of the difficulty of respecting the restrictions imposed by the diagnosis. The younger the child, the less (s)he understands and respects the dietary restrictions. If there are other children in the family, the process of preparing meals also becomes difficult. Healthy and balanced nutrition must be ensured for all family members, without depriving them of the foods necessary for healthy growth and development. For the child suffering from celiac disease, it is precisely the removal of many foods that ensures development without many complications, such as stomach aches, bloating and diarrhea. A gluten-free diet considerably reduces these symptoms. Many studies have shown the positive effects of GFD on children's muscle mass and weight, even a year after starting the diet.

The health-related quality of life of children with celiac symptoms improved significantly after 1 year of gluten-free diet. Ten years after screening, the health-related quality of life of children with celiac disease was similar to that of the reference population (4). So, in general, the children reported an adequate quality of life, similar to that of the reference sample (5).

Depression, anxiety and psychological disorders

The association of celiac disease with various psychological disorders has generated many controversies in scientific studies, as early as the 1950s, when behaviors such as tantrums, irritability and a negative attitude were described in a group of children suffering from this malady, behaviors which disappeared after the introduction of the GFD (6).

In adults, the symptoms were connected to sleep disorders, depressions and headaches. The numerous studies have identified a series of psychological disorders associated with CD, but many of these had also been present before the diagnosis and continued after the introduction of the GFD. For this reason, researches associating psychological illnesses with CD have often reached the conclusion that, in what concerns psychological disorders, they are hereditary in nature. Depression, often associated with CD, actually has a genetic nature (7). Some data indicate that psychological stress may be involved in the development of CD.

Depression has been reported to be more prevalent and severe in celiac patients than in the general population. The rates of depression proven in various studies show a 21-50% prevalence of depression in subjects with CD (8). Depressive symptoms have been identified in various researches as being independent from CD and the GFD treatment: reactivity, pessimism, asthenia and anhedonia. There is an inverse relationship between depressive symptoms and adherence to the diet. As emphasized by researches on CD, depressive elements are closely linked to this disease.

These two symptoms, anxiety and depression, are important for quality of life (QoL). Assessments of physical and psychological well-being depend on the level of anxiety and depression. Both anxiety and depression determine somatic reactions. Depression has a biological component (associated with CD), but it is also a consequence of the lifestyle which the diseased person must adopt: dietary restrictions (limited participation in family meals, difficulties related to travel and problems in the workplace), but also the effects on one's personal and social life caused by temporary relapses and the accompanying pains. Anxiety may also be related to the ongoing fear of food being gluten-contaminated and, thus, of reactions to it making a tempestuous return. A lot of studies show that, compared to other groups of chronic patients, those who suffer from CD have a very good score during the first years after the diagnosis, as well as higher adhesion to treatment, after which the level of QoL diminishes as the years go by.

Gender differences within the disease emphasize that there is an important difference in the way of experiencing the disease between female and male subjects. Hallert et al. found that women with celiac disease had a lower level of subjective health than men; they were less satisfied with the outcome of treatment and expressed more concern with the impact of their disease on socialization and having to abandon important things in life. Such differences have not been emphasized for other chronic diseases. The emotional experience of the disease is harder to bear for women. Some

studies show that the most affected activities are: work, shopping, travelling, eating out and at home. On the other hand, patients, especially female ones, feel guilty, isolated, and avoid becoming a burden to those around (9).

The purpose of medical and psychological therapy is to make the patient adapt to the disease and increase the level of QoL. Coping is the conscious, active effort to regulate emotions, actions, thoughts and the environment in response to different sources of stress.

The psychotherapy should inform the patient that not all symptoms will vanish in all patients and prepare for health-related problems from time to time.

Coping with CD

Successful management of CD both from the medical and the psychological aspects requires proper education of patients and their families; even it is about children or adults.

Coping with illness can be divided into the following: active or primary control coping (acting on the source of stress or one's emotions); accommodative or secondary control coping (adapting to the source of stress); and passive or disengagement coping (avoiding or denying the source of stress). Adaptive mechanisms are linked to the type of locus of control, external or internal. The internal locus of control seems to characterize children and teenagers with a high degree of adherence to treatment (10). Good knowledge of celiac disease and dietary treatment was found in 87% of children, while dietary compliance was 81%. Girls and younger children (aged 12-14) were more compliant than boys and older children (aged 15-17) (11).

The practice of checking food labels and, when unsure, asking questions about gluten content can be described as "primary control coping", as a problem-solving response to coping with CD and GFD.

Regarding coping mechanisms, avoiding behavior creates the most complicated problems. It seems that this disclosure avoidance, which has been used in order to maintain solidarity and a sense of belonging to the group, in reality has increased the feeling of being an outsider and different (12).

Quality of life correlates with the subjective experience of the disease and the acceptance of the diet. In addition, the personality structure and the coping mechanisms which the person uses to adapt to disease-related situations serve as a guarantee of psychological and physical well-being.

Despite the abundant literature on this theme, which proves the negative effects of the disease on physical and psychological health and on the patient's behavior, there are few studies focusing on ways of individual psychological counseling and on couple or family relationships. The effects of CD are important both at a personal level and for intrafamily balance. Some studies show that gender and cultural factors are as important as individual factors. CD patients adapt to the disease by two mechanisms: coping with food and coping with social situations. The support received within the couple and the family ensures a better level of QoL (13). For example, some studies indicate a correlation between CD and eating disorders. High bulimia

scores have been registered in CD patients, without being linked to the presence of anxiety and depression; the higher results have been encountered especially in male subjects (14).

Quality of life

The findings of some studies further delineate the importance of caregiver vigilance regarding the recognition of eating disorders in celiac patients; therefore, the life partner's involvement and family members' support are important factors for ensuring quality of life in CD patients. The patients (especially children and teenagers) and their parents sometimes minutely prepare socialization situations, taking an interest in menu options beforehand or proposing an alternative to what has already been settled by the hosts or those who celebrate an event. Successful diet adherence strategies used by families include planning ahead and taking their own food to social functions (15). More than half of the families with children who are on a GFD avoid restaurants all or most of the time, and 83% always carry gluten-free food (16).

Strategies of adapting to social life are most important during childhood and adolescence. Sometimes, intending to avoid embarrassing situations, patients break the rules of the gluten-free menu, bearing the consequences. Noncompliance to the gluten-free dietary regimen is seen in 18% of cases. Dietary noncompliance is more common in the adolescent age group, in joint families and in those who have a large number of siblings (17).

The diagnosis in itself is an important event in the person's life, and changing one's lifestyle may sometimes be traumatic. Optimistic and pessimistic coping strategies are important factors in assessing the level of QoL (18). Incidentally, results are sometimes contradictory. Some recent studies performed on large student populations show that health-related quality of life is not impaired in children with either undetected or diagnosed celiac disease (19). Chronic fatigue was identified in patients on partial diet; anemia and delayed puberty were identified only in noncompliers. Moreover, data regarding noncompliers proved that this specific diet posed a major burden to such patients and that they usually did not visit a gastroenterologist on a regular basis (20). Studies indicated several areas of negative impact in maintaining a gluten-free diet. They included the difficulties of dining out (86%), travel (82%) and impact on family (67%), but less of a negative impact on career or work (41%) (21).

The studies aimed at the importance of school integration for children suffering from CD have proven that optimal school integration significantly improves good compliance. A better understanding within the school environment about issues related to this chronic disease improves motivation to follow the GFD. Children included in the study of Errichiello et al. (22) reported, to a great extent, good family relationships (88.7%), social relationships (91.2%), school integration (88.2%). On the other hand, adolescent subjects claimed that their social life had limitations (54.5%). The study proved good compliance

in patients who reported higher rates of school integration and social relationships.

In what concerns adults' quality of life, researches have only focused in the past few years on stressful events which may decrease the level of psychological and physical well-being. A poor social network and unemployment are additional important factors of vulnerability to stress. A study of Ciacci et al. (23) revealed that life events are associated, to some degree, with the recent diagnosis of celiac disease in adults. Rather than the severity of events, their number appeared to be the determining factor. Researches on pregnant women with celiac disease have indicated that stressful events preceding the diagnosis are frequent among women. The study proved that pregnancy is

defined as a stressful event only by celiac women comparing it to other diseases, like gastroesophageal reflux.

Conclusions

Celiac disease involves many changes in various aspects of the life of patients suffering from it. The main goal is to ensure their physical and psychological well-being, to diminish the negative physical symptoms and the psychosocial consequences of CD. Medical treatment should be doubled by psychotherapy in order to increase the adherence to treatment and to individually find the best coping mechanism. One's family, profession and social network are important factors in countering vulnerability and ensuring a high QoL.

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A RARE CASE OF GASTRIC PERFORATION IN AN ADOLESCENCE AFTER AN ALCOHOL ABUSE

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Abstract

Nowadays the diagnosis of gastro-duodenal ulcers has been made easy due to the discovery of CT scan and endoscopy. Gastric ulcer is rare in children compared to adults, *Helicobacter pylori* infection is the main cause of gastro-duodenal ulcer in children. Other risk factors are none steroidal anti-inflammatory drugs (NSAIDs), steroids, immunosuppressive drugs and stressful events

Key words: Alcohol abuse, antisecretory medication, gastric resection, *helicobacter pylori*, perforated gastric ulcer.

Introduction

Gastro-duodenal ulcer can be defined as gastric or duodenal mucosa discontinuity with penetration of muscular mucosa and sub-mucosa. Primitive ulcer causes gastric dysfunction (an increase in gastric hydrochloric acid production): it is mainly a single lesion located in the minor curvature of the stomach and on the antrum. Secondary ulcer is caused by the use of certain drugs and also by stress. It has multiple locations in different parts of the stomach.

About 20% of duodenal ulcers are hereditary: with increased basal acid output, increased maximal acid output and rapid gastric emptying. Alarm signs for perforated ulcer with gastro-duodenal hemorrhage are: sudden abdominal pain, black or red stool or “coffee ground” vomit.

The major cause of ulcer is *Helicobacter pylori* infection, followed by the use of NSAIDs (aspirin, ibuprofen etc.), steroids, antineoplastic drugs, stressful events (shock, sepsis, burns, major trauma, intracranial hypertension, surgical interventions and chronic diseases).

The reduction of prostaglandin protective effect on the gastric mucosa is the principal pathogenic mechanism.

Symptoms appears after 3-6 days prior to the causative event and it is mainly abdominal pain and hematemesis (sometimes). The major symptom in gastric ulcer is epigastric pain, shortly after meal. In duodenal ulcer a burning pain sets in 2-3 hours after meal. Alarm signs in the case of perforated gastric or duodenal ulcer with high digestive system hemorrhage are sharp and strong abdominal pain, “coffee ground” vomit and melena. Other alarm signs are anemia, dehydration, weight loss without, dysphagia, and family history of gastric cancer. Laboratory test: Serum pepsinogen A and C, gastrin 17 (G17), gastrin

34 (G34, large gastrin), anti-*Helicobacter pylori* antibody. Endoscopy is preferred in case of active bleeding for hemostasis and for the localization of the bleeding site and evaluation of the grade of the bleeding. ¹³C- urease breath test (UBT) has a high specificity and sensibility, it is to be trusted and none invasive for detecting *Helicobacter pylori*. Detecting anti *Helicobacter* antibody (IgG and IgA) in the blood, urine and saliva has no clinical significance. *Helicobacter pylori* culture has a low sensibility and 100% specificity. Urease breath test and stool test for detecting *Helicobacter pylori*, combined with endoscopy helps in diagnosis.

HP fecal antigen detection is a non-invasive test which can be reliable to determine the success of HP eradication. Fecal antigen detection technique may include monoclonal and polyclonal EIA, also immune-chromatographic tests. It is not age-dependent, but easier to perform on children. Anti-HP antibodies are resistant to degradation.

Differential diagnosis of peptic ulcer: acute cholangitis, acute coronary syndrome, acute gastritis, cholecystitis, cholecystitis and biliary colic in emergency medicine, chronic gastritis, diverticulitis, emergency treatment of gastroenteritis, esophageal rupture and tears in emergency medicine, esophagitis, gallstones (cholelithiasis), gastroesophageal reflux disease, inflammatory bowel disease, viral hepatitis, acute appendicitis and peritonitis, Crohn disease, Zollinger-Ellison syndrome.

If treatment is carried out in the right way the prognosis is excellent. Complications are 1-2% in children and the mortality rate is just 1 in 100.000 cases. Prevention is important and necessary and reduces the risk of gastric and duodenal ulcer. NSAIDs has to be stopped immediately. Stressful events has to be reduced in children with gastro-duodenal ulcer. Alcohol abuse in adolescence is a serious problem and has to be discouraged. Ulcer treatment has better results in boys than girls. *Helicobacter pylori* is a risk factor for gastric cancer, so the treatment is sine qua non. In order to deal with this pathology pediatric surgery departments has to be well equipped with the right instruments (CT scan, endoscopy, MRI, and laparoscopic surgery apparatus).

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Treatment: The first line of treatment has to abide by the guidelines of the European and the American Society of Pediatric Gastroenterology (the proton pump triple standard therapy, the bismuth based quadruple therapy and the sequential therapy) as mentioned below. *Helicobacter pylori* is treated with 3 different types of antibiotics combined with antiacids and gastric mucosa protection medications.

The following therapeutic guidelines were issued by the European and the American Society of Pediatric Gastroenterology as the first line of treatment:

1. Standard therapy with proton pump inhibitor-PPI (1-2mg/kg/day), Ampicillin –AMPC (50mg/kg/day), Clarithromycin –CAM (20mg/kg/day) and Metronidazole –MNZ (20mg/kg/day).
2. Quadruple therapy based on bismuth: Subsalicylate bismuth (8mg/kg/day) for 5 days. AMPC (50mg/kg/day), Clarithromycin-CAM (20mg/kg/day) and Metronidazole-MNZ (20mg/kg/day).
3. Sequential therapy: PPI (1-2mg/kg/day), AMPC (50mg/kg/day) for 5 days, CAM (20mg/kg/day), MNZ (20mg/kg/day), for 5 days.

Gastrointestinal endoscopy helps us to locate the bleeding site in case of hematemesis. This involves thermic cauterization (laser mono- or bipolar or argon coagulation) and none thermic (vasoconstriction and sclerosant injections). Agents used are epinephrine (1: 10.000), thrombin and fibrin reduces the need of surgical intervention and also the need of transfusion in the case of bleeding of non-perforated ulcer.

Laparoscopic surgery, omentoplasty and peritoneal lavage are the gold standard and the results are very good when properly done.

Transluminal endoscopic surgery is an alternative non-invasive intervention for selected patients. Delay in decision for surgical intervention is very crucial in the survival of perforated peptic ulcer patients. Initial biopsy, endoscopic follow up and repeated biopsies are essential not to omit a possible gastric ulcer malignancy.

Complication: Complications of peptic ulcer are: slow long term bleeding, leading to anemia, rapid and sever bleeding, blood vomiting, blood in the stool (pinkish or black stool) melena, peritonitis, gastric outlet obstruction

Case presentation

Patient B.A., age 17, admitted at the pediatric surgery department, in a serious condition. Patient was under the influence of alcohol (coming from a party), and with acute abdominal pain, nausea, bilious vomiting, fever, and very combative. On clinical examination the following was observed: dry cough, no passage of stool or wind, rales, dyspnea, tachycardia, palpitation, severe abdominal pain localized at the right abdominal quadrant (abdominal rigidity), no passage of stool or wind. Rectal examination: no sign of rectal bleeding (no stool). Abdominal x-ray: no pneumoperitoneum, no air-fluid levels. Lab tests: leukocyte 17.000/m, neutrophil 75.30%, CRP 49, blood sugar 132mg/dl. Other aspects were within normal limits. Abdominal CT and endoscopy was not considered necessary because of the absence of high digestive system (HDS)

bleeding. No family history of gastroduodenal ulcer. Patient was in a stable condition though serious and an emergency sub-umbilical laparotomy was performed because we suspected appendicular peritonitis, based on the right abdominal quadrant pain, the incision was later prolonged (supra-umbilical), upon discovery of bile in the abdominal cavity. On exploration we discovered a perforated small curvature of the stomach of about 3 cm diameter. We performed ulcer excision with single layer suture Starr and Judd procedure, pyloroplasty, omentoplasty, peritoneal lavage and drainage.



Photo 1. Abdominal ultrasound: moderate amount of fluid in the pelvis, other aspects were within normal limits

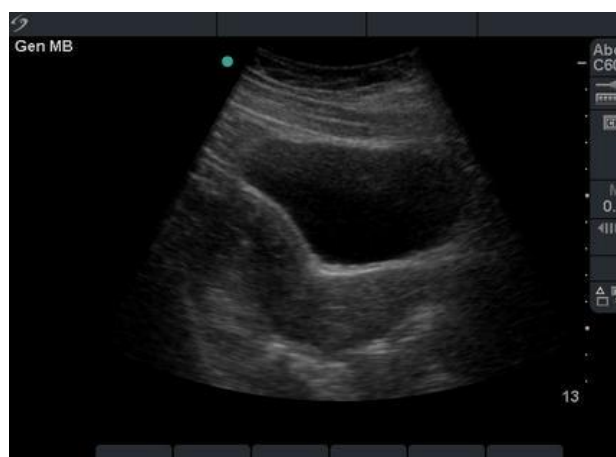


Photo 2. Ultrasound signs mimicking an acute appendicitis

Post-operation treatment: antisecretory drugs (Arnetin), antibiotics: (Ceftriaxone and Gentamicin), antiemetic (Metoclopramid), analgics (Acupan, Metamizole), correction of fluid and electrolyte imbalance (Glucose 5% and NaCl 0.9%), antithrombotic drug (Clexane).

Postoperative status was good, no complication. Patients condition after 2 years was good and without complication.

Discussion

Gastric ulcer is known as an adult disease, it is very rare in children and mainly in adolescence (90.4%), especially in boys (80.7%). Gastric ulcer is classified according to its location and its relationship with duodenal ulcer:

Type 1: Located on the body of the stomach and generally characterized by its low gastric acid secretion, especially at night. This reflects gastric mucosa inflammation with reduced functional parietal cellular mass.

Type 2: located at the gastric antrum and characterized by low, normal or high acid secretion.

Type 3: situated 3 cm from the pylorus, sometimes associated with duodenal ulcer and characterized by high gastric acid secretion.

Type 4: situated at the gastric cardia and characterized by low acid secretion.

The farther the ulcer is to the pylorus, the lower the basal acid secretion.

Because of this concept distal gastric ulcer is managed by resection drainage and vagotomy, while proximal gastric ulcer is simply treated by just resection.

Forrest classification describes four types of peptic ulcer based on endoscopic characteristics and associated upper gastrointestinal bleeding:

Forrest 1a: spurting arterial bleeding;

Forrest 1b: oozing arterial bleeding;

Forrest 2a: non hemorrhagic dilated large vessels;

Forrest 2b: adherent clot;

Forrest 2c: the presence of hematin at the ulcer base;

Forrest 3: lesion with sign of recent bleeding.

Perforated gastric ulcer is difficult to diagnose in children with acute abdomen (abdominal pain and peritoneal irritation). In children we always have the tendency of thinking about acute appendicitis or peritonitis especially in

the absence of epigastric pain. X-ray helps us with diagnosis in 82.7% cases of anterior bulboduodenal perforation. About 90% of adolescence with ulcer have no history of ulcer. Pneumoscrotum is a rare condition described as the presence of gas in the scrotum, often associated with pneumoperitoneum in smaller children. Pneumoscrotum may be a sign of recurrent peptic ulcer after laparoscopic surgery. Contrary to duodenal ulcers, patients with gastric ulcer have normal or low basal or stimulated acid production. This suggests that altered gastric acid defense is the cause and this explains why NSAIDs induces gastric ulcer (Schubert and Peura).

Diagnosis can be determined by rapid urease test and stool test to detect *Helicobacter pylori* combined with gastrointestinal endoscopy. *Helicobacter pylori* culture has a low sensitivity and 100% specificity (Schubert).

Delay of surgery in perforated ulcer favors complication and mortality in some cases. Antisecretory drug treatment (proton pump inhibitors), reduces the necessity of vagotomy practiced in the past. Eradication of *Helicobacter pylori* infection reduces recurrence. New drugs in this field has really helped in reducing mortality and morbidity.

Laparoscopic surgery remains the gold standard in the treatment of perforated ulcers, exception being critical patients or patients that has undergone past abdominal surgery.

The role played by *Helicobacter pylori* has to be further investigated and the issue still remains open.

Conclusions

1. Early presentation of patients at the doctor and change of life style reduces morbidity and mortality of patients with perforated peptic ulcer.

2. Urease breath test (UBS) is essential for detecting *Helicobacter pylori*.

3. Some studies suggest a strict selection of patients for conservative treatment. On a short term the result of this method of treatment can be compared with gastrectomy. The long term result of patients that benefited from conservative cannot be estimated.

4. Alcohol consumption and surgical resection are of statistical importance for postoperation prognosis, morbidity and mortality.

5. Decision to operate should be without delay.

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FIBROMA OF TENDON SHEATH OF THE POPLITEAL FOSSA IN THE CASE OF A 15 YEARS OLD PATIENT

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Abstract

We present the case of a 15 years and 6 months teenager with palpable mass (superficial) in the right knee (popliteal fossa). The paraclinical investigations (CT and MRI) led to the diagnosis of a benign tumor formation (with tissue structure). The histopatological examination concluded with the diagnosis of a fibroma of tendon sheath. The tumor formation was treated surgically.

Key words: Teenager, palpable superficial mass, benign tumor, fibroma of tendon sheath (extremely rare tumor), surgical treatment.

Introduction

The knee tumor represents a pathological crossroad where many lesions regarding the bone and the soft parts may occur. (5)

The tumor lesions of the knee are benign, benign with malignant potential or malignant from the beginning. Benign tumors are dominant in case of children and teenagers (70% of the cases). (5)

Fibroma of tendon sheath (FTS) is a slow-growing benign pathology which appears on tendons, especially on the distal extremity of the upper limb. (1)

In 2015 there were less than 30 cases reported in the literature, related to the knee. (1) This aspect shows the extreme rarity of the pathology (FTS in the knee).

The fibroma of tendon sheath (FTS) may occur at any age, most frequently between the ages of 20-50, especially in males. (1)

70% of the cases present discomfort or/and pain in the knee, only 30% present palpable mass. (1)

Goal of the work

Presentation of clinical, imagistic aspects and of the therapeutic approach in the cases diagnosed (anatomically and pathologically) with fibroma of tendon sheath of the popliteal fossa.

Case report

Clinical data

Male patient at the age of 15 years and 6 months that presents a slow-growing voluminous and superficial palpable mass in the right knee (popliteal fossa) with hard, adherent consistency and painful on palpation.

Imagistic data (CT aspects, also confirmed by the MRI aspects)

- Oval tumor formation dimensions: 95mm/66mm/68mm.
- Relatively clear margins of the tumor formation
- Relatively inhomogeneous structure of the tumor formation, with tissue density, respectively 40 HU – 80 HU (in the sequences with contrast agent)
- Peritumoral edema, bleedings and intratumoral calcifications are absent.
- The tumor formation displaces the popliteal artery posteriorly and laterally (clear aspect revealed by the CT angiography).
- There are no bone changes (of margins and structural changes) and no expansion in the joint space.

CT images are presented in figures 1, 2, 3 and 4.

Therapeutic approach

The tumor formation was surgically removed by femoral-popliteal bypass, respectively the right popliteal artery was partially reconstructed through an end-to-end interposition venous graft (internal saphenous).

Discussions

Differential diagnosis

The density of the tumor formation (40 HU-80 HU, in arterial time, with contrast agent) leads to a tissue etiology and excludes the lipidic or fluid etiology. CT angiography excludes a vascular pathology (aneurysm or arterial-venous malformation) (2).

The absence of calcifications (CT examination) is a counterargument to Myositis ossificans and synovial sarcoma (6,7).

CT malignancy aspects, respectively the peritumoral edema, necroses and the intratumoral bleeding (7) are absent.

MRI malignancy aspects, respectively the fast (in arterial time) and consistent capture of the tumor formation with contrast agent and the continuous invasion (3,4) are absent.

MRI is rarely used for benign tumors of the knee to children (6).

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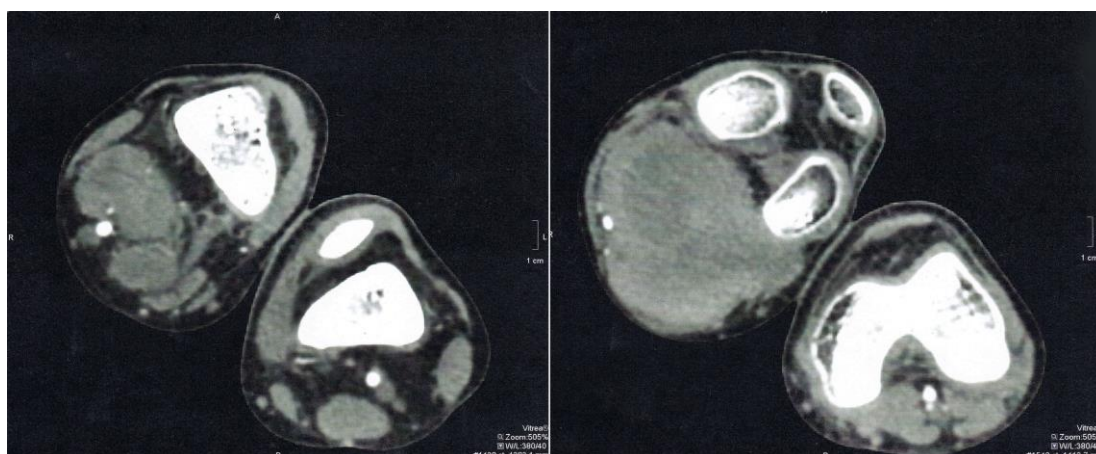


Fig. 1. Axial section

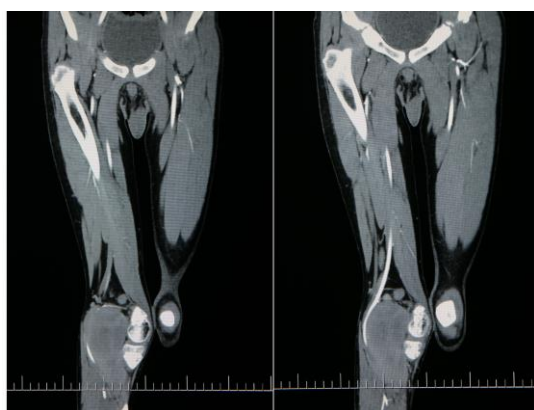


Fig. 2. Frontal section

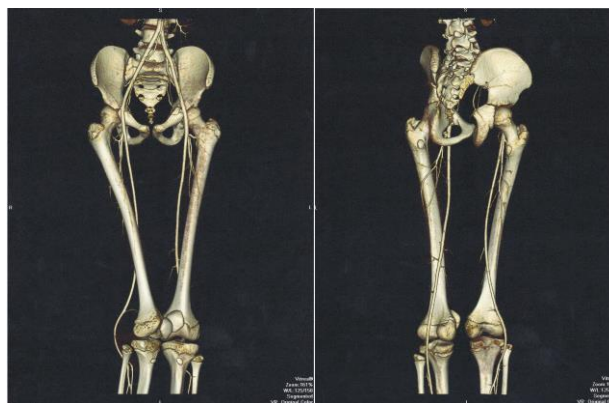


Fig. 3. Angio CT

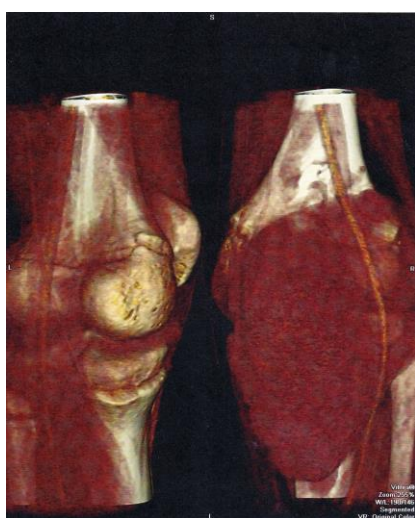


Fig. 4. 3D reconstrucction

Therapeutic approach

The irritation of the surrounding tissues, also mentioned in the literature (1), has been also confirmed in our case.

The detachment of the entire path of the popliteal artery during the surgery has failed (due to tumor adhesion on a portion of the popliteal artery) and a femoral-popliteal bypass has been performed.

Conclusions

The case of a teenager with a voluminous palpable mass in the knee (popliteal fossa) has been presented.

The imagistic examination (CT and MRI) proves the nature of the benign tissue and the histopatological examination has led to the diagnosis of fibroma of tendon sheath.

The surgeon was forced to perform a femoral-popliteal bypass in order to remove the tumor formation, adherent to the popliteal artery wall.

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DIAGNOSTIC DIFFICULTIES OF NON IMMUNOLOGICAL CONGENITAL ASCITES- CASE REPORT

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Abstract

Neonatal ascites is commonly the result of hematologic disorders that lead to hydropsfetalis; less frequently it may be caused by non-immunological disorders. One of the rare causes of non-immunological disorders are metabolic diseases. We hereby present the case of a 5 month old infant in which 4D ultrasound performed at 24 weeks of gestation revealed increased fetal abdominal circumference by fluid accumulation in peritoneal cavity. The presence of congenital isolated ascites along with the peculiar aspect of the infant - dysmorphic features that included frontal bossing, depressed nasal bridge and broad nasal tip, large low-set ears, long philtrum, macroglossia, broad hands and feet, brachydactyly and joint contractures, coarse skin, hepatosplenomegaly, and inguinal hernia, along with biochemical analysis of β -galactosidase enzyme in leucocytes lead to the diagnosis of GM1 gangliosidosis.

Key words: congenital ascites, β -galactosidase, GM1 gangliosidosis.

Introduction

Ascites in the neonate is usually a feature of hydropsfetalis, caused by hematologic disorders. Less frequently, isolated ascites is the dominant feature. Various mechanisms have been incriminated in the pathogenesis of ascites, that include abnormal lymphatic drainage, obstruction of venous return, cardiac failure, decreased plasma oncotic pressure, as in fetal anemia, hepatic failure (storage disease) or congenital nephrosis, increased capillary permeability, urinary tract obstruction, or meconial peritonitis [1]. Far less common causes are infections such as congenital syphilis, cytomegalovirus (CMV), varicella, toxoplasmosis, and hepatitis A [2].

We report a case of GM1- gangliosidosis, in which isolated persistent ascites was the dominant clinical feature.

Case report

A 5 months old infant girl was referred to the Intensive Care Unit presenting with increasing abdominal girth.

The infant was born to a 32 year-old woman after a gestation of 35 weeks. The data gathered revealed that the

infant was the result of a second pregnancy (first ended in spontaneous abortion at 6 weeks). Routine prenatal testing revealed positive anti-Toxoplasma IgM between 8 and 20 weeks gestation, leading to oral treatment with Rovamicine. Particular prenatal phenotype detected by ultrasound prompted further evaluation; however the karyotype performed revealed no abnormalities. 4D Ultrasound performed at 24 weeks gestation revealed increased fetal abdominal circumference by fluid accumulation in peritoneal cavity.

Upon admission in our Unit the physical examination revealed an ill appearing malnourished infant with mottled, pale dark-green skin, peri-oral cyanosis during crying, facial dysmorphism with coarse features; (fig.1) low grade fever (37,9C), fed with difficulty, marked psychomotor agitation, discrete palpebral and lower limbs edema; polypnea (60 rpm), discrete intercostal retractions, no pulmonary rales upon auscultation; bradycardia, AV = 86 bpm, systolic murmur; the abdomen was distended and tense, with shifting dullness without visible collateral circulation, (fig.2) liver edge palpable at 3.5 cm below the right costal margin, spleen at 3 cm below the left costal margin; accelerated intestinal transit, with watery stools. Initial laboratory tests revealed sepsis with staphylococcus epidermidis, moderate metabolic acidosis, hypoglycemia, high levels of alkaline phosphatase, and coagulopathy. Abdominal ultrasound (fig.3) and computed tomography revealed hepatosplenomegaly and moderate amounts of ascitic fluid. Bone marrow aspirate revealed low cellularity and vacuolated lymphocytes. Biochemical analysis of β -galactosidase enzyme in leucocytes revealed very low enzyme levels consistent with a diagnosis of GM1 gangliosidosis.

Fresh frozen plasma, packed red blood cells, platelet transfusions, broad spectrum antibiotherapy, maintenance fluid with appropriate glucose and electrolytes failed to maintain normal homeostasis of the infant as the patient developed bronchopneumonia requiring mechanical ventilation and an increased requirement for inotropic support. Persistent coagulopathy and poor perfusion resulted ultimately in her demise at one month of hospital day.

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Fig. 1 Facial dimorphisms with coarse features



Fig. 2 Shifting dullness without visible collateral circulation

Discussion

Although inborn errors of metabolism and other single-gene defects represent merely 1 percent of cases of nonimmune fetal hydrops, their importance resides in the substantial risk of recurrence in subsequent pregnancies [2]. Most of these disorders, such as Hurler's syndrome, mucopolysaccharidosis type I, GM1 gangliosidosis type I, Gaucher's disease, Niemann–Pick disease, and β -glucuronidase deficiency are lysosomal storage diseases [2-7].

GM1 gangliosidosis is a rare lysosomal storage disorder characterized biochemically by deficient beta-galactosidase activity [8] and clinically by dysmorphic features, visceromegaly, dysostosis multiplex and neurological alteration [9].

Prevalence at birth is estimated to be approximately 1:100,000 to 200,000 live births [10].

Based on the age of onset there are three types of GM1 gangliosidosis: type I (infantile), type II (late infantile/juvenile), and type III (adult) [11]. The severe infantile phenotype (type I) is characterized by psychomotor regression by the age of 6 months, visceromegaly, cherry red spot, and facial and skeletal abnormalities [11]. Disease severity seems to be related to the level of beta-galactosidase activity [12].

It is interesting to note our patients' extremely early onset of symptoms (24 wk of gestation). GM1

gangliosidosis does not usually have a prenatal presentation, but when it happens, the most common finding is, as in our case, fetal or neonatal ascites, for reasons that remain yet unclear. Storage material in Kupffer cells, sinusoidal obstruction and subsequent portal hypertension, or hypoproteinemia due to hepatocellular dysfunction, have been hypothesized as possible explanations [13]. However, in our case, liver ultrasound and hepatic function were normal.

The clinical manifestations are the result of the accumulation of ganglioside in the lysosomes. Clinical suspicion is based on signs of storage such as facial coarsening, hypertrophic gums, cherry-red macula, visceromegaly, dysostosis and psychomotor delay [11]. Bony deformities include stubby hands, broad wrists, anterior beaking of the lumbar vertebrae, thickening of the midshaft of the humerus, and spatulate ribs [14]. There is usually rapid progression of symptoms with the development of spasticity, seizures and general neurologic deterioration with death typically occurring by age 2 [11]. In our case, the infant exhibited dysmorphic that included frontal bossing, depressed nasal bridge and broad nasal tip, large low-set ears, long philtrum, macroglossia. Additional anomalies were broad hands and feet, brachydactyly and joint contractures, coarse skin, hepatosplenomegaly, ascites and inguinal hernia. The infant exhibited no macular cherry red spot, however this feature is seldom present under the age of 6 months [15]. There was no ultrasonographic evidence of dilated and/or hypertrophic cardiomyopathy or valvulopathy. The infant developed seizures during the course of his stay in Intensive Care.



Fig. 3 Abdominal ultrasound

Peripheral blood smear (testing vacuolated lymphocytes) and urine oligosaccharides represent orientation tests [16]. Gaucher-like foam cells have been

reported on bone marrow examination [16]. Diagnosis is confirmed by biochemical assay of beta-galactosidase activity in peripheral blood leukocytes and/or by molecular genetic testing [17]. Patients with the infantile form have almost no enzyme activity, whereas patients with the adult form may have residual activity of 5-10% of reference values [11]. In our case enzyme testing for beta-galactosidase activity revealed significantly diminished activity 0,06%, consistent with classical GM1-gangliosidose.

Differential diagnosis includes mucopolysaccharidoses, sphingolipidoses and oligosaccharidoses, but the disease resembles mostly with Mucopolysaccharidosis type IVB (Morquio B). Infantile GM1 gangliosidosis shows features of mucopolisaharidosis at birth [10]. GM1 gangliosidosis and Morquio B are autosomal recessive storage disorders caused by the deficiency of β -galactosidase (GLB1), a problematic partition between Morquio B and juvenile GM1 gangliosidosis phenotypes being long discussed in literature [18].

There are currently no effective therapies for GM1 gangliosidosis, only symptomatic and supportive

treatment. A main obstacle is the blood-brain barrier, which prevents the passage of therapeutic enzymes and proteins into the brain. Substrate reduction therapy is a potential approach for clinical trials in late-onset forms [19].

Prognosis depends on the type of GM1 gangliosidosis and is extremely poor in the severe infantile form and variable in the chronic adult form of the disease [11].

Conclusions

Gangliosidosis does not usually have a prenatal presentation, but, at our patient, it is interesting to note the extremely early onset of symptoms (24 wk of gestation).

Even the neonatal ascites may have as a possible explanation the storage material in Kupffer cells, sinusoidal obstruction and subsequent portal hypertension, or hypoproteinemia due to hepatocellular dysfunction, in our case liver ultrasound and hepatic function were normal.

There are currently no effective therapies for GM1 gangliosidosis, only symptomatic and supportive treatment, as it has an extremely poor prognosis in the severe infantile form.

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ORBITAL COMPLICATIONS OF RHINOSINUSITIS

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Abstract

Introduction: Acute rhinosinusitis is a very common disorder that at one time or another affects most people. From a temporal standpoint acute rhinosinusitis lasts for up to 4 weeks. *Streptococcus pneumoniae* (20%-45%) and *Haemophilus influenzae* (22%-35%) are the predominant organisms in acute bacterial rhinosinusitis in adults. An external ethmoidectomy is an alternative approach for treating orbital complications of acute rhinosinusitis, such as a subperiosteal abscess. Complications include diplopia from injury to the trochlea or medial rectus, blindness, exposure keratitis, corneal abrasions, skull base injury, and CSF leak. **Case Report:** We present the patient V.G. 18 years old which first addressed to the Infectious Diseases Department and 2 weeks later to the ENT Department with the following diagnosis: Left Fronto-Ethmoido-Maxillary Acute Bacterial Rhinosinusitis, Left Subperiosteal Abscess with Exophthalmia, Left Upper Eyelid Abscess, Left Chemosis, Left Lower Eyelid Inflammatory Edema. The blood cultures were negative. The treatment consisted in administration of i.v. broad spectrum antibiotics for 15 days. On ENT clinic and nasal rigid endoscopic 0° exam revealed purulent material at the level of left middle meatus, which is blocked, bilateral normal aspect of the inferior turbinates, rhinopharynx with purulent material from the left middle meatus. We performed a maxillary sinus puncture with lavage (+++) and silicon tube insertion. The patient was addressed for a contrast enhancement CT exam. In ENT Department we performed left external ethmoidectomy, left subperiosteal and upper eyelid abscesses drainage followed by Phenoxymethylpenicillin potassium 2g./day – 7 days. As postoperative protective antibiotic was used for 7 days Cilopen (Phenoxymethylpenicillin potassium) 2g./day. At seven postoperative days the signs (left subperiosteal abscess, exophthalmia, left upper eyelid abscess, left chemosis, left lower eyelid inflammatory edema) were resolved. The evolution was favorable with almost complete remission of the symptoms and signs. One month after the surgical procedure the patient presented a slight left proptosis and a slight divergent strabismus. Control CT exam was performed one month postoperative and showed a normal aeration of the paranasal sinuses. **Conclusion:** Orbital and nasal signs and symptoms at one month after the surgical procedure were resolved, the patient presented a slight left proptosis and a mild divergent strabismus..

Key words: orbital complication, external ethmoidectomy, subperiosteal abscess, upper eyelid abscess.

Introduction

Acute rhinosinusitis is a very common disorder that at one time or another affects most people. From a temporal standpoint acute rhinosinusitis lasts for up to 4 weeks.[1] The disorder is almost always due to an infectious process, both viral or bacterial, viruses accounting for the majority of the cases. Acute bacterial rhinosinusitis (ABRS) has been defined as sudden in onset and with duration of less than 4 weeks.[1]

Streptococcus pneumoniae (20%-45%) and *Haemophilus influenzae* (22%-35%) are the predominant organisms in ABRS in adults, whereas *S. pneumoniae* (30%-43%), *H. influenzae* (20%-28%), and *Moraxella catarrhalis* (20%-28%) are the predominant organisms in ABRS in children.[2,3]

In daily clinical practice, however, cultures are rarely performed unless there has been a failure of treatment. The severity of the symptoms and radiographic findings may help identify different pathogens, in that patients infected with *S. pneumoniae* have been found to have more significant symptoms and worse radiographic findings than those infected with *H. influenzae*. [4]

S. pneumoniae decreased from accounting for 43% to 25% of isolates, whereas *H. influenzae* increased from 35% to 41%. The rate for *M. catarrhalis* remained stable, changing from 13% to 14%. The rate for *Streptococcus pyogenes* increased from 7% to 12%, and that for *S. aureus* from 4% to 8%. [5]

Acute complications, both orbital and intracranial, that are unresponsive to medical therapy require immediate surgical intervention. External procedures are used because nasal edema and inflammation may compromise endoscopic exposure. However, in experienced hands, ESS is safe and effective. [6]

An external ethmoidectomy is an alternative approach for treating orbital complications of acute rhinosinusitis, such as a subperiosteal abscess. Complications include diplopia from injury to the trochlea or medial rectus, blindness, exposure keratitis, corneal abrasions, skull base injury, and CSF leak [7].

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Case report

The patient V.G. 18 years old, addressed to the Infectious Diseases Department with the following signs and symptoms: left exophthalmia, left subperiosteal and upper eyelid abscess, left chemosis, left lower eyelid inflammatory edema, nasal obstruction, fever 38,5°C, predominantly left headache. The patient underwent an MRI exam (figure 1) which revealed: left paranasal sinuses with thick mucosa and gadophilic irregular walls, left maxillary and frontal sinuses fluid/parafluid collection, left periosteal and upper eyelid abscess 2.7/1.2/2.4 and 1.1/0.8/1.3 cm., with irregular gadophilic contour, left orbital cellulites and left exophthalmia, edema of the left superior and right lateral muscles, left lower eyelid fluid collection, left hemifacial subcutaneous connective tissue and temporal and masseter muscles diffuse edema. Bilateral frontal and left temporal lobes contrast enhancement of the meninges (meningitis). Left parasagittal frontal epidural abscess 1.5/0.6 cm. The cultures were negative. The treatment consisted in administration of i.v. broad spectrum antibiotics for 15 days.

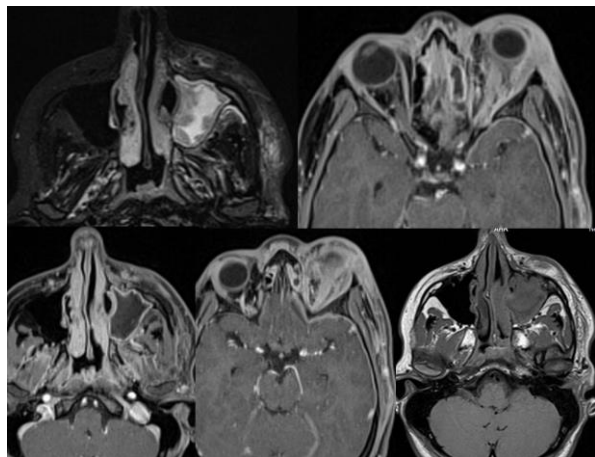


Fig. 1. MRI exam

Abnormal bioassays was represented by ESR 30 mm/h, PCR 61,07 mg/L (0-5 mg/L), WBC 14,54 *10³ /μL (4-10*10³ /μL), NEUT# 12,96 *101/ μL (2,2 – 6,60*101/ μL), LYMPH# 1,01 *101/ μL (1,2 – 4.40*101/ μL), NEUT% 89,2% (55,0 – 65,0%) and LYMPH% 6,9% (30 – 40,0%).

Two weeks later the patient was addressed to the ENT Department with the following diagnosis: Left Fronto-Ethomoido-Maxillary Acute Baterial Rhinosinusitis, Left Subperiosteal Abscess with Exophthalmia, Left Upper Eyelid Abscess, Left Chemosis, Left Lower Eyelid Inflammatory Edema.

ENT clinic and nasal rigid endoscopic 0° exam revealed purulent material at the level of left middle meatus, which is blocked, bilateral normal aspect of the inferior turbinates, rhynopharynx with purulent material from the left middle meatus. Bucopharyngoscopy: saburral tongue and purulent material at the level of posterior wall. Inspection showed left exophthalmia, left upper eyelid abscess, left chemosis, left lower eyelid inflammatory edema (figure 2).



Fig. 2. Preoperative aspect

We performed a maxillary sinus puncture with lavage (+++) and silicon tube insertion. The patient was addressed for a contrast enhancement CT exam.

CT exam with enhancement (figure 3): left maxillary, ethmoid and frontal sinuses with thick mucosa, with fluid, parafluid and haematic collection. Medial wall of the left maxillary sinus presents a 12 mm. osseous discontinuity with a wide communication with ethmoidal cells. Silicon drainage tube present in left nasal fossa and maxillary sinus. It was notice a left subperiosteal parafluid density collection (2.7/1.2/2.4 cm) with slightly irregular wall and left superior eyelid (1.1/0.8/1.3 cm) iodophilic parafluid collection, a left hemifacial subcutaneous connective tissue and temporal and masseter muscles diffuse edema and left exophthalmia, respectively.

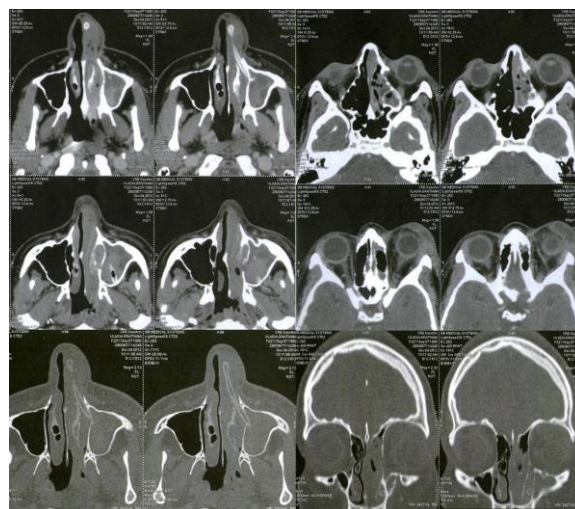


Fig. 3. Enhancement CT exam



Fig. 4. Intraoperative aspects

Ophthalmologic exam did not show any visual loss or eye movement impairment.

The patient was admitted in the ENT Department Timisoara the second day and the external ethmoidectomy (figure 4) was performed under General Anesthesia with OroTracheal Intubation. The patient was placed in a reversed Trendelenburg position with 1.5" of head-up tilt.

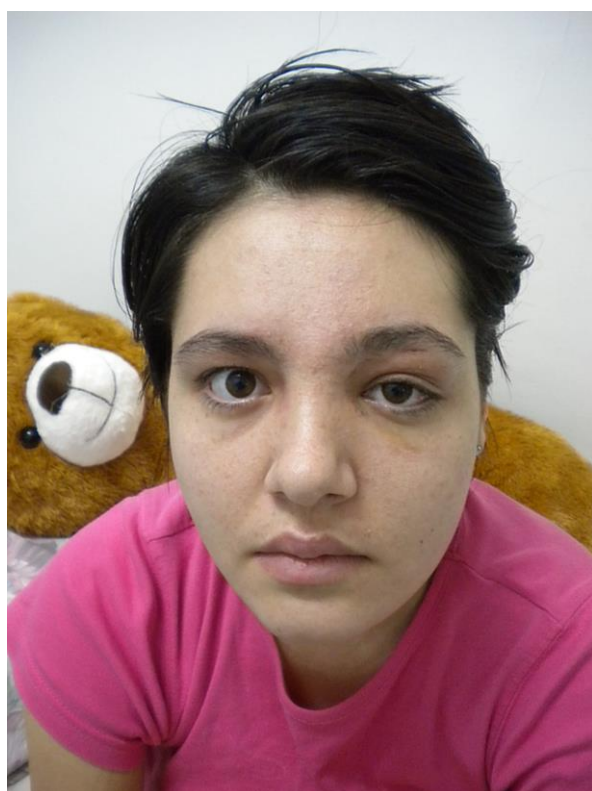


Fig. 5. Postoperative aspect

We removed the silicone drainage tube. A curved incision cutting down to bone was performed from the left medial canthus, mid-way between the medial canthus and the nasal bridge. The periosteum was elevated with a Freer's elevator exposing the nasal process of the maxilla, frontal bone and medial wall of the orbit. The trochlea was sharply dissected with a 15 blade scalpel. The lacrimal sac was elevated and laterally displaced; we exposed the lamina papyracea posteriorly to the level of the anterior ethmoidal artery. Through lamina papyracea we entered and cleared anterior and middle ethmoidal cells, from anterior to posterior, using a Blakesley-Wilde forceps. The medial floor of the frontal sinus was removed and extended laterally. The left subperiosteal abscess was drained. An additional incision of 1 cm. was performed at the upper eyelid midorbit level to drain the abscess.

The periosteal layer was sutured with non-resorbable material. The skin was subcutaneously sutured with fine silk 4.0. The left eye was washed with Betabioptol (Cloramphenicolium + Bethametazonum). As postoperative protective antibiotic was used for 7 days Cilopen (Phenoxymethylpenicillin potassium) 2g./day. Seven days postoperative aspect is showed in figure 5.

The evolution was favorable with almost complete remission of the symptoms and signs. One month after the surgical procedure the patient presented a slight left proptosis and a slight divergent strabismus. Control CT exam was performed one month postoperative (Figure 6).

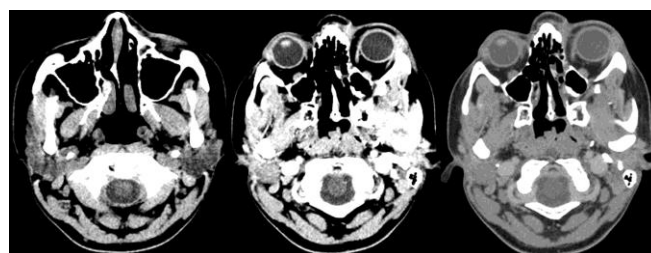


Fig. 6. Control CT exam

Discussion

Orbital cellulitis is usually a complication of paranasal sinus infection. Either the infection may dissect under the periosteum and lead to subperiosteal abscess or intraorbital abscess may be formed secondary to a progressive and localized cellulitis. Without appropriate treatment orbital infection may lead to serious complications, even death [8].

External approach indications are represented by frontoethmoidal mucocoeles, orbital complications of acute frontoethmoiditis, chronic infection unresponsive to conservative medication and surgery, recurrent polyposis, access for ethmoidal artery ligation in the treatment of epistaxis, transethmoidal hypophysectomy, dacryocystorhinostomy, repair of cerebrospinal fluid (CSF) leaks and orbital decompression. Many of these conditions can be managed by an endoscopic approach but it is not technically possible to use this in all cases. It may also be necessary to employ an external approach as an emergency procedure if an orbital haematoma occurs during endoscopic

sinus surgery. As a consequence, an important role still exists for this approach [9,10,11].

Our patient first addressed to the Infectious Diseases Department and 2 weeks later to the ENT Department, the cultures were negative.

The treatment consisted in administration of Cefort (Ceftriaxonum) 4 g./day – 4 days, Meronem (Meropenemum) 6 g./day – 13 days, , Metronidazol (Metronidazolium) 1.5 g./day – 15 days, Levofloxacin (Levofloxacinum) 0.5 g./day – 13 days, Vancomicina (Vancomycin) 2 g./day – 15 days, Hydrocortisone hemisuccinate 0.2 g./day – 11 days.

In ENT Department we performed an external ethmoidectomy, 0° rigid nasal endoscopy, left subperiosteal and upper eyelid abscesses drainage followed by Cilopen (Phenoxymethylpenicillin potassium) 2g./day – 7 days.

In a study Olwoch I.P. isolated a total of 233 micro-organisms from 163 patients (72.1%), and in 63 cases (27.9%) the cultures were negative. The study was retrospective, performed in 2 referral hospitals. The number of the patients was 226 consecutive surgical cases with acute complicated sinusitis, which underwent external fronto-ethmoidectomy with maxillary sinus washout and 13 had a concurrent craniotomy. One hundred and fifty-nine were males and 67 females, with a mean age of 16.5 (standard deviation 0.7) years. Positive cultures revealed *Streptococcus milleri* (18.5%), *Staphylococcus aureus* (12.4%), beta-haemolytic streptococci (10.8%), coagulase-negative staphylococci (8.6%), *Haemophilus influenzae* (8.6%) and the anaerobes, *Peptostreptococcus* (6.4%) and *Prevotella* (4.7%) species. The prevalences of *S. pneumoniae* (2.6%), methicillin-resistant *S. aureus* (MRSA) (1.3%) and *Moraxella catarrhalis* (0.4%) were low. Polymicrobial disease was present in 56 patients (34.4%). There was a significant difference between the two hospitals in the prevalences of some bacteria ($p < 0.05$). Antibiotic resistance was highest towards the penicillins (64.3%) and cephalosporins (12.5%). Effective empiric treatment was achieved with metronidazole and a choice of amoxicillin-clavulanate or ampicillin plus cloxacillin or penicillin plus chloramphenicol. The author concluded that the polymicrobial nature and severity of complicated sinusitis warrants a de-escalation approach to antimicrobial therapy.

The combination of beta-lactamase-resistant penicillins and metronidazole is a reasonable choice for initial empiric antibacterial therapy. Selection of drugs for empirical antibiotic therapy in patients with acute complicated sinusitis should be supported by knowledge of the local prevalence and antimicrobial susceptibilities of bacteria isolated from patients [12].

Strek P. et al. [13] stated that subperiosteal inflammatory disease, subperiosteal abscess and orbital cellulitis are the most common sequelae of both acute and chronic sinusitis.

Early, appropriate evaluation and management observing signs and symptoms of orbital inflammation are required to prevent blindness. CT is the investigation of choice.

Cellulitis does not require drainage of the orbit on a routine basis. Conventionally, the orbital abscess is drained via an external incision and sinus surgery is performed at the same time to remove the focus of infection. More recently, successful treatment both of the sinuses and decompression of the orbit has been accomplished endoscopically via an intranasal approach. Their experience suggests that the optimal method of treatment consists in surgical endoscopic removal of the focus of infection located in the sinuses with simultaneous drainage of the abscess in the orbit [13].

We performed an endoscopic evaluation of the ethmoid and maxillary sinuses and an external ethmoidectomy approach followed by the subperiosteal and upper eyelid abscess drainage.

Subperiosteal abscess should be early and appropriately evaluated and managed, by observing signs and symptoms of orbital inflammation in order to prevent blindness. Hatano A. et al. [14] reported 5 cases of subperiosteal abscess caused by paranasal sinus problems. The treatment consisted in endoscopic ethmoidectomy with puncture or endonasal endoscopic drainage of the abscess. In 4 cases they found orbital complications, using conservative therapy in 1 case with no visual acuity. Three of 4 patients with mild visual acuity and treated with surgical procedure were cured without sequelae. They managed the superior subperiosteal abscess with an endoscopic endonasal approach. One of 4 patients who had severe vision loss, however, was cured without any recovery of loss of vision after surgical drainage to decrease orbital pressure. In their hands the endoscopic endonasal approach is more useful in managing both sinus disease and orbital complications than external ethmoidectomy [14].

In our patient we did not encounter any complication: vision loss, vertical diplopia, incision webbing or paraesthesia of the supratrochlear nerve.

Conclusions

Orbital and nasal signs and symptoms at one month after the surgical procedure were resolved. External ethmoidectomy is a useful alternative approach in cases with orbital complications of suppurative anterior sinusitis with good cosmetic and functional results regarding the postoperative eye movements.

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COMPLICATIONS OF CIRCUMCISION IN THE PEDIATRIC POPULATION AGED 0 TO 15 YEARS

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Abstract

Circumcision is considered one of the oldest surgical procedure in the world. About 25% of all the men in the world are circumcised. Because of this reason, we can also say that circumcision is the most common surgical operation. Most circumcisions are performed for religious beliefs and only a few for medical reasons or cosmetic ones.

Between 2011 and 2015 we have evaluated all children who were treated in our Clinic for phimosis, undergoing different surgical interventions, among which circumcision has been included.

From 127 circumcisions performed in a group of 1196 children, there were 14 complications: preputial haematoma, partial glandular amputation, urethral injury, infections after wound suture opening, immediately seen and necrosis of the glans and fusion between glans and prepuce, late ones.

In spite of the fact that is one of the most common surgical procedures, we must be aware of great risks if this procedure is not performed properly, with care.

Key words: children, circumcision, complications.

Introduction

Circumcision is considered one of the oldest surgical procedure in the world. About 25% of all the men in the world are circumcised [1]. Because of this reason, we can also say that circumcision is the most common surgical operation. Most circumcisions are performed for religious beliefs and only a few for medical reasons or cosmetic ones [2].

Literature mentions a complication rate between 1 and 15% for circumcisions, including all procedures [3]. Most of them are minor and easily repaired complications, like haematoma, infections after suture opening, others are very severe like amputation of the glans or glans necrosis, both of them with urethral injury.

Purpose

The aim of this study is to study complications occurred in circumcision in children between 0 and 15 years.

Material and method

The trial was conducted in the Clinic of Pediatric and Orthopaedic Surgery of "St. Andrew" Emergency County Hospital of Constantza, between 2011 and 2015. During this period we verified 1196 cases of phimosis. We looked at those who were circumcised (127 cases), especially those with complications (14 cases). All cases taken in discussion were between 0 and 15 years old. We have investigated only children between this age and have not extended our study over the age of 15 years. The study concluded a great number of circumcision because of the fact that ninety-seven percent of the Romanian Muslims are residents of the two counties forming Northern Dobruja: eighty-five percent live in Constanța County, and twelve percent in Tulcea County [4,5], forming 6% of local population [6].

Results and discussions

In the Clinic of Pediatric and Orthopaedic Surgery of "St. Andrew" Emergency County Hospital of Constantza, between 2011 and 2015, we have studied patients with foreskin pathology aged between 0 and 15 years. There were 1196 patients treated by different methods. 127 of them were circumcised for religious beliefs, social or medical causes.

Among those 127 circumcised patients we have found 14 complications, early and late ones. Complications are shown in table 1 below. The rate of complications (figure 1) is similar with the one mentioned in the literature [3].

Table 1 – Distribution of complications in our study.

Complication	No. of cases
Preputial haematoma	8
Partial glandular amputation	1
Urethral injury	2
Infections after wound suture opening	3
Necrosis of the glans	2
Fusion between glans and prepuce	1

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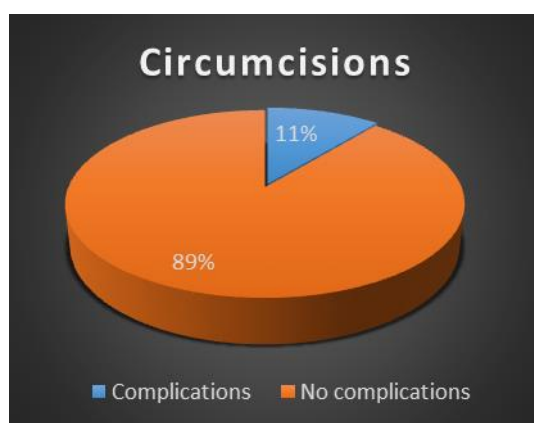


Figure 1 – The rate of complications after circumcision in the study group.

Among those with haematomas, 3 of them developed an infection with opening of the wound. The incomplete glans was patched with buccal mucosa (fig. 2).

One case with fistula of the urethra was close by double layered suture and the other case of urethral injury with total distal urethral amputation (fig. 3) was solved

using the Duplay style and a hypospadias repair was performed, with a tubular incised plate urethroplasty technique with buccal mucosa as a patch graft.

The fusion between glans and prepuce was treated by freeing the adhesions. Infections were treated locally by daily dressing and with systemic antibiotherapy.

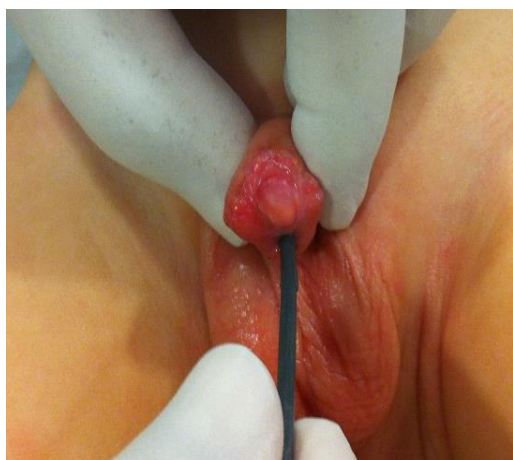


Figure 2 – Incomplete glans amputation after circumcision, with stenosis of the meatus.



Figure 3 - Total distal urethral amputation after circumcision.

Discussion

If we compare the frequency of our complications with the one in the literature, we find that indeed bleeding and haematoma is the most frequent one [7-10]. In most of the cases bleeding is minor and haemostasis can be achieved by pressure on the area or electrocoagulation. Excessive bleeding may be due to abnormal vessels [10] or systemic blood coagulation disorders [9].

Concerning infected haematoma or simple infection of the wound, this is mentioned in up to 10% of cases [7,11]. Usually it may appear local inflammatory changes, but occasionally there may be ulceration and pus. Most infections are treated locally, but in some cases systemic antibiotherapy is needed to prevent sepsis and even death [12-14].

The etiology of urethral fistulas is various in the literature. It may appear due to a misplaced suture at the frenulum for haemostasis [15], infection [16] or very rare anomalies of the penis, such as megalourethra [17].

Stenosis of the meatus of the urethra, complication found in our study, may be caused by meatal ulceration [18,19]. If not treated in time by meatotomy or other enlargement procedures, stenosis may be the cause of recurrent pyelonephritis and obstructive uropathy [20].

Partial or total amputation of the glans of the penis or the penis itself is a very important and serious complication, with a very difficult management of correction, with poor results [21,22].

Other complications mentioned in the literature, but not found in our study are carcinoma of the penis [23], erectile dysfunction [24], psychological complications [25,26], skin and mucosal dystrophies, etc.

Due to all these possible complications and of the fact that the majority of boys don't need circumcision, the

identification of ones who don't need this procedure is very important. Contraindications for circumcision include preterm children, those with blood disorders, people with a family history of clotting disorders, and those with birth defects such as hypospadias, or chordee. Abnormalities often missed are those with poor body skin, such as newborns with congenital penoscrotal skin or buried penis. Circumcision of these children often leads to trapped or hidden penis, which requires frequent reinterventions [27].

Conclusions

Complications after circumcision are somewhat rare, but some of them very severe. While most acute complications can be managed quickly and easily with minimal morbidity, others may be catastrophic.

Most of the boys do not need an intervention on the prepuce. It is considered that only about 1,5% need some kind of intervention to treat phimosis [28].

Because of the fact that, even in present days, a lot of boys are circumcised for religious beliefs by different individuals at home or during communal circumcisions, most of them inexperienced, the risk of complications is high.

For these reasons, before surgery, parents should be informed of the procedure and especially of its risks and should be required to provide their informed consent for the intervention. They must know the possible health benefits of childhood circumcision in balance with the complication rate.

Overall these procedures should only be done by qualified personnel, to reduce as much as possible potential complications.

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DIAGNOSTIC APPROACH TO GOITER IN CHILDREN

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Abstract

Introduction: Common causes of goiter in children include autoimmune disease and iodine deficiency. **Purpose:** The current study aims to frame goiter according to etiology in the pediatric population. **Methods:** A retrospective study was conducted over a period of 1 year and 6 months (January 2013-August 2014) in the Emergency Hospital for Children "Louis Țurcanu" Timisoara. The study group included a total of 36 patients aged between 4 to 18 years with a mean age of 12.3 years. Thyroid volume (Vt) was determined by ultrasound measurements and the diagnosis of goiter was established based on Vt > 97th percentile using diagrams adapted for age, gender. **Results and Discussion:** We found a high prevalence of Hashimoto thyroiditis, 21 patients (representing 58.33% of total). Of these, 14 patients (66.7%) associated type 1 diabetes, thyroiditis being the second autoimmune disease. Basedow's disease was diagnosed in 2 patients (5.55%), and one showed a solitary thyroid nodule. The other 14 patients (38.9%) with goiter had negative serology for autoimmunity, thus being labeled as diffuse nonimmune goiter. The mean age of these patients was 12.2 years with the limits 4.9-18 years, 75% of whom were girls. All patients from this category had euthyroid; most (62%) came from Timisoara. In 5 patients (38%) coming from endemic areas, thyroglobulin was determined. All patients had normal levels of thyroglobulin and iodine deficiency could not be demonstrated. Urine iodine was not determined in the patients included in the present study. **Conclusions:** The autoimmune pathology is the most common cause of goiter in children. Nonimmune diffuse goiter was found at pubertal age, mostly in girls. Children with goiter, regardless of its etiology, require treatment with thyroxine during puberty even if they are euthyroid. Studies are needed on urine iodine in the West of Romania in the pediatric population.

Key words: diffuse goiter, child, thyroiditis

Introduction

Thyroid disorders are one of the most common endocrine problems in children and adolescents; it affects 3.7% of children between the ages of 11 and 18 years (1). Children with thyroid disorders usually present with an enlargement of the thyroid gland, with or without symptoms

of thyroid hormone deficiency or excess. Common causes of goiter in children include autoimmune disease and iodine deficiency. Benign colloid goitre is also a common cause.

Hashimoto thyroiditis is uncommon in children younger than four years of age; the peak age of onset is in early to midpuberty. In adults 90% of cases occurs in females; in children the ratio female: male is 2 to 1 (2). A genetic inheritance has been established (30% of patients have family history of thyroiditis). Also a higher prevalence has been observed in individuals with chromosomal abnormalities: Turner syndrome, Klinefelter syndrome and Down syndrome (3). There is also an increase in association with other autoimmune diseases; thyroid antibodies often are detected in children with type 1 diabetes at onset (4, 5).

An endemic goitre is the most common cause of hypothyroidism. Iodine deficit should be considered in patients with a goitre and negative thyroid antibodies (6). Also high iodine intake has been associated with goiter (7). The pathophysiology of endemic goitre caused by excessive iodine intake is not well defined. By interacting with the immune system, iodine excess may trigger the development of autoimmune thyroid disease such as Hashimoto's thyroiditis (8).

Graves's disease is the most common cause of hyperthyroidism in children and adolescents. Thyromegaly is almost invariably present and the thyroid has a smooth, rubbery texture. Declining school performance and behavioural manifestations often predominate. Exophthalmos occurs in only one-third of children, and it is generally mild (9, 10).

Thyroid enlargement that is not caused by inflammatory, infectious or neoplastic causes is termed a colloid goitre, also referred to as a sporadic or idiopathic simple goitre. Histological findings include enlarged thyroid follicles filled with abundant colloid. The cause remains controversial; although TSH is the principal growth-stimulating factor for the thyroid, TSH levels are normal in patients with colloid goitre (11).

Aim

The current study aims to frame goiter according to etiology in the pediatric population.

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Material and methods

A retrospective study was conducted over a period of 1 year and 6 months (January 2013-August 2014) in the Emergency Hospital for Children "Louis Țurcanu" Timisoara.

The study group included a total of 36 patients aged between 4 to 18 years with a mean age of 12.3 years. Thyroid volume (Vt) was determined by ultrasound measurements using Brunn formula (12). The diagnosis of goiter was established based on $Vt > 97$ th percentile using diagrams adapted for age, gender (13). The patients were divided into two groups according to presence or absence of thyroid antibodies. Group I- immune goiter consisted of 21 patients (61.1%) and group II nonimmune goiter included 14 patients (38.9%). One case with solitary thyroid nodule was excluded from the group.

Results

Etiology of goiter: We found a high prevalence of Hashimoto thyroiditis, 21 patients (representing 58.33% of total). Of these, 14 patients (66.7%) associated type 1 diabetes, thyroiditis being the second autoimmune disease. Basedow's disease was diagnosed in 2 patients (5.55%), and one showed a solitary thyroid nodule, which was excluded from the group. The other 14 patients (38.9%) with goiter had negative serology for autoimmunity, thus being labeled as diffuse nonimmune goiter (Figure 1).

Group II which included patients with nonimmune goiter was older than group I: mean age in group I was 8.9 years, group II 12.2 years (Figure 2).

Most patients came from urban areas than from rural areas, 41% of patients with immune goiter respectively 50% patients diagnosed with nonimmune goiter lives in area with medium iodine deficiency (Figure 3 a, b). Most of the patients were females (Figure 4 a, b). Based on thyroid hormone values, we noticed in the immune group all the possible thyroid manifestations (from subclinical hypothyroidism to hyperthyroidism). All patients from the nonimmune goiter category were in a euthyroid status (Figure 5). In 5 patients (38%) coming from endemic areas, thyroglobulin was determined (Figure 6). All patients had normal levels of thyroglobulin and iodine deficiency could not be demonstrated. Urine iodine was not determined in the patients included in the present study.

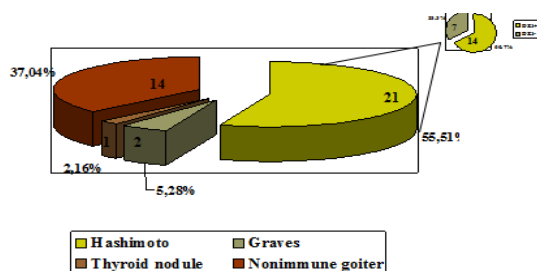


Fig. 1 Causes of goiter

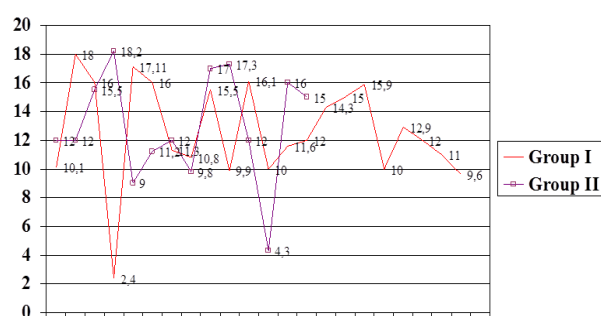


Fig. 2 Age in both groups

Discussion

Hashimoto's thyroiditis is the most common cause of thyroid disease in children and adolescents (14). In our study, autoimmunity was also the most common cause of goiter in children (61.1%).

Nonimmune diffuse goiter was found at pubertal age, mostly in girls. From the nonimmune group we will discuss one case. Female at puberty, coming from an endemic area, thyroid ultrasound suggested Hashimoto thyroiditis (Figure 7). Antibodies were negative (TPO antibodies = 0.3 N.V. < 5.6 and remained negative during her multiple exams. Thyroglobulin was also normal (thyroglobulin = 34.5 ng/ml N.V. 1-78 ng/ml). Hormone levels TSH, FT3 and FT4 normal (TSH=1.73 uUi/ml (N.V. 1.24-5.6) FT3=4.2 pg/ul (N.V. 2.2-4.7), FT4=1.2 ug/dl (N.V. 0.92-6.8)). Urine iodine was not determined. First she received iodide supplement with no improvement in goiter size, after that thyroxine plus iodide medication with normalisation of thyroid size (thyroid volume at the age 11 years= 7.8 cm³ > percentile 97 and after 2 years 7.9 cm³- between percentile 50 and 90).

The etiology of simple goiter remains not known, although TSH is the principal growth-stimulating factor for the thyroid, TSH levels are normal in patients with colloid goitre and some other mechanism can be involved in the development of goiter (15). Thyroxine treatment may improve thyroid size especially during puberty as seen in our case (16,17). A prospective study of 11- to 18-year-old school children found simple goitres in 1.9% of students. On re-examination 20 years later, 60% of patients were normal, 20% were unchanged and a few (10%) developed thyroiditis (18).

Conclusions

The autoimmune pathology is the most common cause of goiter in children. Nonimmune diffuse goiter was found at pubertal age, mostly in girls. Children with goiter, regardless of its etiology, require treatment with thyroxine during puberty even if they are euthyroid. Studies are needed on urine iodine in the West of Romania in the pediatric population.

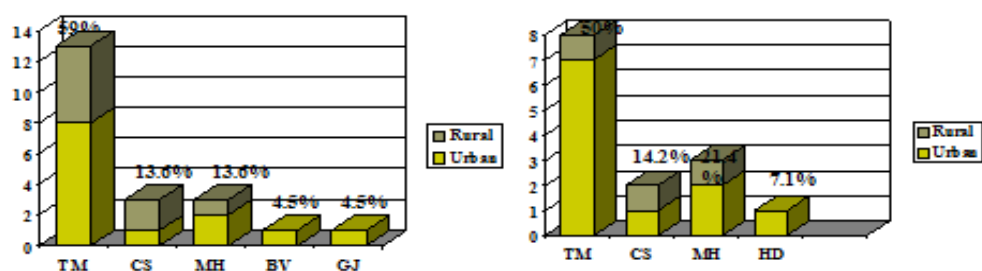


Fig. 3 a. Geographic area distribution group I **b.** Geographic area distribution group II

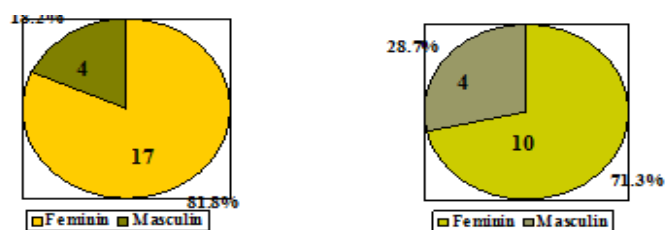


Fig. 4 a. Sex distribution group I

b. Sex distribution group II

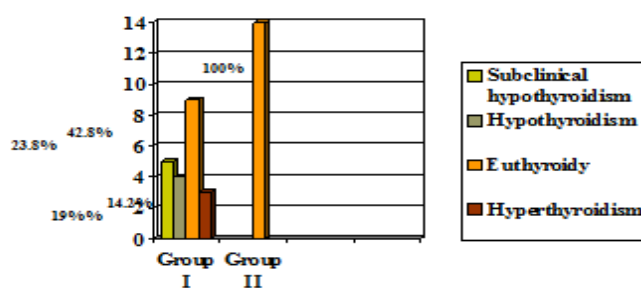


Fig. 5. Thyroid status in both group

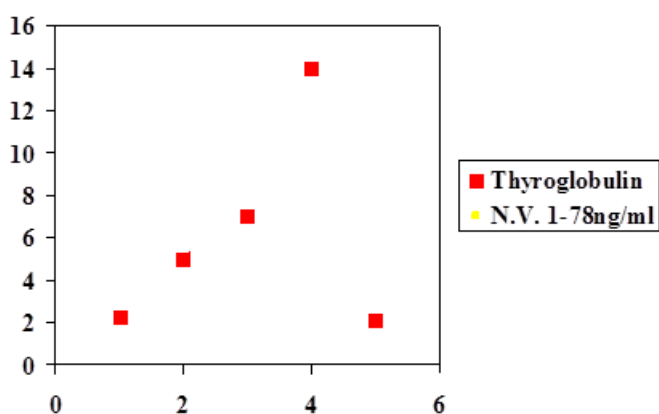


Fig. 6. Thyroglobulin values in 5 patients

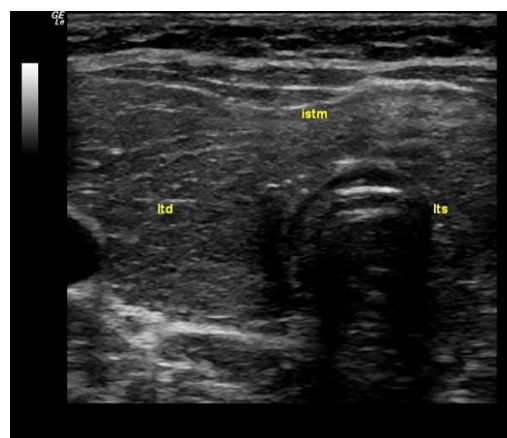


Fig. 7. Thyroid ultrasound revealing enlarged thyroid with inhomogeneous structure, echogenic septum within the gland, normal vascularisation.

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KIDNEY ECHO IN POLYTRAUMA – PEDIATRIC LESIONS VERSUS ADULT ONES

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Abstract

Traumatic kidney injuries are an important life threatening situation following blunt or penetrating abdominal lesions. At every age, the goal of renal trauma management is preservation of renal function with minimal morbidity. It is imperative that these patients are treated urgently and efficiently to prevent renal damage.

We present a series of patients (adults and children), treated in our department for kidney traumatic lesions on a period of 10 years. It will be discussed the main aspects of management of these patients and the similarities or differences between the two categories of age.

Key words: children, adults, trauma, kidney, management

Introduction

Within polytrauma, the urinary system occupies a considerable percent (between 10-12%) [1,2], which follows the same upward curve frequency as polytrauma itself.

In children, trauma is responsible for 90% of the genitourinary lesions, with approximately 90% having coexisting injuries of other organs [3,4]. Traumatic injury to the kidney accounts for greater than 60% of the pediatric genitourinary injuries [5-8].

In great polytrauma, urinary involvement is often ignored because the attention of the doctor who performed the first examination is captured by the obvious injuries, to which it is given more importance.

Today, thanks to the precision offered by modern investigations of the urinary system, the modern means of resuscitation, the surgical opportunities, it has come to change tactics in therapeutics, at least in some forms of urinary tract trauma. Thanks to them, it appreciably shortens the early recovery of the urinary tract, the patient's suffering and enables good quality of healing. [9,10].

Purpose

The aim of this study is to compare therapeutic results obtained in renal trauma, either closed or open, conditioning these results of exploration opportunities in the emergency room and to reconsider the attitudes to treat kidney lesions that are not necessarily life-threatening (in case of polytrauma), dealt as secondary affections. We have observed that these injuries must be recognized, acknowledged and treated by an urologist, even from the beginning.

Finally we would like to show the contribution of medical observation, assessment, diagnosis and treatment of kidney trauma for the main groups of patients – children and adults, the similarities or differences between the two categories of age.

Material and method

My study is conducted over a period of 10 years, from 2006 to 2015, and comprises a group of 218 patients, adults and children who were hospitalized for evaluations, investigations, monitoring and treatment, including kidney lesions. The study was conducted retrospectively for the period 2006-2010 and prospectively for the period 2011-2015. For the retrospective study we took into account the observation charts, controls carried out regularly to the part of patients who respected timing controls or answered calls for individual checks. The prospective study took into account the diagnostic protocol, clinical evaluation and treatment. To this group we were able to apply and track primary and secondary evaluation phases of the diagnostic protocol and imaging investigations following a specific algorithm.

Results

Of the 1117 polytrauma who were hospitalized, only 74 cases had only a renal lesion, confirmed by imaging or during surgery, the remaining 1043 had associated injuries to other organs or systems.

The most common associations found in our study were spleen ruptures with head trauma and musculoskeletal injuries in general, or the association of these lesions among themselves, but also with other injuries listed in Table 1.

Head trauma, when it had a severity above average, greatly influenced the evolution of the case, and in some cases even the vital prognosis, as shown by the literature [11].

In our study there were more patients from urban areas and also more females than males. This is due to specific activities or car accidents, more frequent in urban areas than in rural ones.

Kidney injuries occur most frequently between the ages of 16-40, representing the maximum of physical activity, basically belonging to social groups at risk through activities they are involved. In this group an important role play car accidents or sport injuries.

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Table 1 - The association of renal trauma with lesions of other organs or systems.

Frequent associations	Cases
Kidney trauma + spleen rupture	22
Kidney trauma + head trauma	28
Kidney + head + spleen	26
Kidney + osteoarticular	28
Kidney + head + osteoarticular	22
Kidney + head + spleen + osteoarticular	16
Others	2
Isolated kidney trauma	74

It seems that the majority of renal trauma arose from car accidents, following a high percentage of fall from heights, and

sports accidents, aggressions occurring in a small number of cases in our study (Table 2).

Table 2 – Distribution by age and ethiology.

Age group	Cases	Ethiology			
		Car accidents	Fall from heights	Sport injuries	Aggressions
0-3 years	2	2	0	0	0
4-9 years	8	6	2	0	0
10-15 years	38	20	12	6	0
16-40 years	102	28	40	22	12
41-60 years	60	26	30	0	4
> 60 years	8	2	6	0	0

In our study we observed a higher frequency of trauma on the right, and an explanation is that the right kidney is located lower than the left. Some put this higher frequency on the right and on behalf of the defense reflex, which automatically displays the individual right in front of an aggression, protecting it on the left.

18 patients suffered trauma on an ectopic, polycystic, tumoral, hydronephrotic or lithiasic kidney. These injuries are more serious because pathological kidney is more fragile and exposed to vulnerable agents even of lower intensity.

We had 212 kidney contusions and 6 ruptures.

Closed kidney trauma was more often observed. Child's kidneys are more likely to suffer closed trauma because they did not support the defense of perirenal fat and there is no well developed rib ossification. Concussion is the most common renal damage seen in children [12-14].

Section of the ureteropelvic junction and parenchymal lesions on preexisting abnormalities are next in frequency. These are caused by direct hit. The concept of conservative treatment (nonoperative), was greatly expanded and included also renal lesions [15].

The distribution of kidney lesions is illustrated in table 3.

Table 3 – Distribution of kidney lesions.

Cases		Minor kidney trauma		Major kidney trauma		
Closed	Open	Grd. 1	Grd. 2	Grd. 3	Grd. 4	Grd. 5
212	6	88	64	52	12	2
218		152		66		

Minor kidney traumas were treated conservatively in all age groups (grd. 1 and 2). Treatment of renal lesions is highly controversial for grds. 3, 4 and 5. Absolute indication for surgical exploration is the presence of pulsatile or expansive hematoma. Other indications are urinary extravasation, vascular lesions, devitalized tissues.

The presence or absence of hematuria and its degree of intensity, does not correlate with the degree of the lesions. Some grd. 4 lesions can be treated conservatively [16]. In contrast to adults, in children, hematuria is a very unreliable sign in determining the need to screen for renal injuries. In some studies there is no evidence of gross or microscopic hematuria in up to 70% children sustaining grade 2 or higher renal injury [17].

Therapy consists of bed rest, drainage by catheter, extravasation of urine, evaluated by CT and sonography. Ureteral stent and catheter drainage can be used for urinary extravasation. Allgrd. 5 kidney lesions require surgery and in 30% of cases the kidney can be saved [18,19].

Nephrectomy was the main procedure for surgical cases, with complications in only 9% and 2% deaths. The most common immediate complications were urinary fistulas, which resolved conservatively, with only 2 reinterventions. Late complications were hydronephrosis, lithiasis, hypertension. The data are similar with those in literature [19,20].

In the group of patients less than 18 years of age, 92% of them were treated conservatively, only two patients with

grd. 4 lesions were treated surgically but only with suture of the kidney. There were no complications for this group of patients, with both treatment types.

Conclusions

Management of polytrauma in emergency should be done after a written protocol which follows well defined steps. Attention should be directed towards potential injuries, quickly evolving, likely to lead to vital complications: pneumothorax, intra and retroperitoneal hemorrhage. Multidisciplinary team may highlight secondary lesions. Kidney lesions often are in the background unnoticed and are detected in the stage of complications or sequelae. Kidney response is largely masked by clinical violent associated lesions. A severe polytrauma, almost always present a kidney lesion, so we have to think about it. Recovery of blood pressure by perfusion, will allow making the required investigations. Lack of response to tensional treatment, done properly, requires emergency surgery to stop bleeding. Conservative treatment is applied in grade I-II and in most cases in grade III lesion. A small percentage of grade III injuries may require intervention.

The pediatric kidney is believed to be more susceptible to trauma because it is protected by an immature, more pliable thoracic cage and weaker abdominal musculature. The child has less perirenal fat and is positioned in a lower area in the abdomen than in adult.

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HLA DQ2/DQ8 TYPING IN THE DIAGNOSIS OF CELIAC DISEASE IN SYMPTOMATIC CHILDREN

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Abstract

Background: A strong association between celiac disease (CD) and human leukocyte antigens (HLA) -DQ2 and HLA-DQ8 molecules was demonstrated and therefore DQ typing is nowadays used in CD diagnosis. We aimed to evaluate the usefulness of HLA DQ2/DQ8 typing in CD diagnosis of symptomatic patients with positive anti-tissue transglutaminase antibodies (anti-tTGA) and histologic findings compatible with CD.

Methods: We performed a retrospective study including patients investigated for CD who underwent HLA DQ2/DQ8 typing and intestinal biopsy. We selected patients that presented with CD suggestive symptoms, positive anti-tTGA and specific histologic findings. We extracted from the medical records: age, clinical symptoms, anti-tTGA titers and histologic findings (according to Marsh-Oberhuber classification). Regarding anti-tTGA titers, three groups were defined: anti-tTGA < 3-fold the upper limit of normal range, anti-tTGA between 3-fold and 10-fold the upper limit of normal range and anti-tTGA > 10-fold the upper limit of normal range. According to the clinical response to gluten free diet (GFD), we defined two groups: responsive (disappearance of symptoms or significant improvement under GFD) and non-responsive (mild improvement or persistent symptoms).

Results: Thirty seven patients were found to be HLA DQ2/DQ8 positive (29 children had mildly/moderately increased anti-tTGA; 8 cases had anti-tTGA>10-fold the cutoff) and 8 patients were HLA DQ2/DQ8 negative. We compared two groups: patients HLA DQ2/DQ8 negative with anti-tTGA mildly/moderately elevated values and patients HLA DQ2/DQ8 positive with anti-tTGA mildly/moderately elevated values. Mildly elevated or borderline anti-tTGA were found in 100% HLA DQ2/DQ8 negative patients vs. 37.9 % HLA DQ2/DQ8 positive patients. All HLA DQ2/DQ8 negative patients had mild/moderate intestinal lesions, while in HLA DQ2 and/or DQ8 positive patients mild/moderate enteropathy was the histologic finding in 62.1% of cases.

Conclusions: Patients with high anti-tTGA were HLA DQ2 and/or DQ8 positive and intestinal biopsy could have

been avoided. HLA DQ2/DQ8 typing was useful in the evaluation of patients with mildly increased anti-tTGA, especially at young age, with mild/moderate histologic lesions and unresponsive to GFD. These data show that HLA testing plays an important role in the diagnostic algorithm of CD.

Key words: Celiac disease, HLA DQ2/DQ8 typing, children

Introduction

The involvement of genetic factors in celiac disease (CD) was observed many years ago, but is still under evaluation. The association of certain human leukocyte antigens (HLA) and CD was discovered by Falchuk et al. in 1972 [Error! Reference source not found.]. A decade later a strong association between CD and HLA-DQ2 and HLA-DQ8 molecules was demonstrated [Error! Reference source not found.-Error! Reference source not found.]. Forty loci have been identified to be involved in the etiopathogeny of the disease. All disease loci have been characterized as low-penetrance, with the exception of the high-risk genotypes in the HLA-DQA1 and HLA-DQB1 genes [6].

In consequence, DQ genotyping is used in CD diagnosis. The majority of celiac patients carry DQ2.5 heterodimers (DQA1*05 and DQB1*02) and a small percentage express HLA-DQ8 (DQA1*03 DQB1*0302). About 5% of celiac patients carry DQ2.x heterodimers (DQA1*05 and DQB1*02) [Error! Reference source not found.,8].

CD appears very rarely in patients negative for these DQ predisposing markers. So testing for their presence has high negative predictive value for the diagnosis. HLA DQ2/DQ8 typing is recommended for patients with uncertain diagnosis.

In the last two decades, the clinical picture of celiac disease became broader and new, improved diagnosis techniques were developed. Therefore, revision of the second ESPGHAN guideline was considered necessary.

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The present ESPGHAN guideline recommends HLA DQ2/DQ8 typing for asymptomatic patients from risk groups, for symptomatic patients with uncertain diagnosis: positive anti-tissue transglutaminase antibodies (anti-tTG), but mild enteropathy on histologic examination or negative anti-tTG and mild infiltrative changes in small-bowel specimens and also for children with high anti-tTG titers in order to avoid intestinal biopsy [9].

Aim

The aim of the study was to evaluate the usefulness of gene testing for HLA DQ2 and DQ8 haplotypes in CD diagnosis of symptomatic children with positive anti-tTG antibodies and histologic findings compatible with CD.

Material and method

We performed a retrospective study including patients investigated for CD in the Pediatric Gastroenterology Department of "Grigore Alexandrescu" Emergency Children's Hospital, Bucharest, patients who underwent HLA DQ2/DQ8 typing.

We reviewed the medical records of all patients that underwent HLA DQ2/DQ8 typing and intestinal biopsy. We selected patients that presented with CD suggestive symptoms and signs, positive anti-tTG and specific histologic findings.

Exclusion criteria were: asymptomatic patients from risk groups (first degree relatives with CD or patients with CD-associated diseases), patients with negative specific antibodies or patients that were only tested with anti-gliadin antibodies (the latter were patients diagnosed years back when other serological markers were not available) and patients with normal intestinal biopsy.

In selected patients, we extracted from the medical records: age, clinical symptoms and signs, anti-tTG titers and histologic findings (according to Marsh-Oberhuber classification) [10]. Regarding anti-tTG titers, three groups were defined: anti-tTG < 3-fold the upper limit of normal range, anti-tTG between 3-fold and 10-fold the upper limit of normal range and anti-tTG > 10-fold the upper limit of normal range.

The clinical response to gluten free diet (GFD) was evaluated in patients that did not undergo HLA DQ2/DQ8 typing at the moment of initial diagnosis and were already under exclusion diet when tested. According to the clinical response, we defined two groups: responsive (disappearance of symptoms or significant improvement under GFD) and non-responsive (mild improvement or persistent symptoms).

Typing methodology was polymerase chain reaction with sequence-specific primers (PCR-SSP); we used the commercial kits "HISTO TYPE Celiac Disease" (BAG Health Care GmbH - Germany). The kit contains 23 amplification primers that identify DQB1*02:01 to *02:05 alleles; DQB1*03:01 to *03:17 and DQA1 *02:01; *03:01; *05:01 to *05:09 alleles.

Statistical analysis was performed using SPSS. The characteristics of HLA DQ2/DQ8 positive patients were

compared to those of DQ2/DQ8 negative patients. Statistical significance was calculated using Fisher exact test. Values of $p < 0.05$ were considered significant.

The study was approved by the Ethics Committee of the "Grigore Alexandrescu" Emergency Children's Hospital.

Results

174 children investigated for CD underwent HLA DQ2/DQ8 typing. After we applied the exclusion criteria, we analyzed the medical records of 77 symptomatic patients that also had intestinal biopsy performed.

Patients with normal findings on intestinal biopsy, patients with negative celiac serologies or patients that were only tested for anti-gliadin antibodies were all excluded, so 45 patients fulfilled the inclusion criteria. The mean age was 34 ± 29.5 months ($p=0.03$).

Thirty seven patients were found to be HLA DQ2/DQ8 positive and 8 patients HLA DQ2/DQ8 negative.

Out of HLA DQ2/DQ8 positive cases, 8 patients had anti-tTG > 10-fold the cutoff values. Mean age was 41.6 ± 40.2 months. 7 out of 8 children had gastrointestinal symptoms. Histological findings corresponded to Marsh 3 in all patients, 5 out of 8 children exhibiting severe intestinal damage (Marsh 3b or 3c).

We compared two groups: patients HLA DQ2/DQ8 negative with anti-tTG positive, mildly to moderately elevated values (mean age: 19.5 ± 6.3 months) and patients HLA DQ2/DQ8 positive with anti-tTG positive, mildly to moderately elevated values (mean age: 41.6 ± 40.2 months). Gastrointestinal manifestations were reported for 75% of patients without HLA DQ2 or DQ8 vs 68.9% of patients with HLA DQ2 and/or DQ8 ($p=1$). Mildly elevated or borderline anti-tTG (< 3-fold the cutoff) were found in 100% HLA DQ2/DQ8 negative patients vs. in only 37.9 % HLA DQ2/DQ8 positive patients ($p=0.003$). All HLA DQ2/DQ8 negative patients had mild to moderate intestinal lesions (Marsh 2 - 2 cases and Marsh 3a - 6 cases), while in HLA DQ2 and/or DQ8 positive patients mild to moderate enteropathy was the histologic finding in just 62.1% of cases ($p=0.04$) and Marsh 3b and 3c in 37.9% cases. Poor clinical response to GFD exhibited 5 out of 7 HLA DQ2/DQ8 negative patients (71.4%) and 16 out of 22 HLA DQ2/DQ8 positive patients (27.3%) ($p=0.07$). These were patients that were already under GFD and therefore, for them, an evaluation of the clinical response could be made.

The results are presented in table 1.

Among patients with anti-tTG > 10-fold the cutoff, we found: one patient DQ2 and DQ8 positive, one patient DQ2 positive with a double dose of *DQB1*02*, one patient DQ8 positive and 5 patients DQ2 positive, with a single dose of *DQB1*0*. Among patients with mildly to moderately elevated anti-tTG, the distribution was as follows: one patient DQ2 and DQ8 positive, 4 patients DQ2 positive, with a double dose of *DQB1*02*, 6 patients DQ8 positive and 18 patients DQ2 positive with a single dose of *DQB1*02*. $P=0.47$.

Table 1: Characteristics of symptomatic patients with mild/moderate positive anti-tTGA.

	HLA DQ2/DQ8 positive	HLA DQ2/DQ8 negative	p
Age (mean age, SD) months	41.6 ± 40.2	19.5 ± 6.3	0.03
Typical symptoms (number, %)	20 (68.9)	6 (75)	1
Anti-tTGA < 3-fold (number, %)	11 (37.9)	8 (100)	0.003
Histology – Marsh 1, 2, 3a (number, %)	18 (62.1)	8 (100)	0.07
Not responsive to GDF (number, %)	6/22 (27.3)	5/7 (71.4)	0.07

Discussions

The study aimed to evaluate in a retrospective manner the usefulness of HLA genotyping in CD diagnosis in symptomatic patients, based on the experience of a single centre of pediatric gastroenterology.

All patients with anti-tTGA > 10-fold the cutoff had positive HLA DQ2 and/or DQ8. The majority had the classical form of the disease; two of them presented as celiac crisis, situation rarely encountered in clinical practice nowadays. In all patients, villous atrophy was the histologic finding. In all these patients with high level of anti-tTGA, the confirmation of genetic risk through HLA DQ2/DQ8 typing might have been sufficient for the diagnosis; the biopsy could have been avoided, according to recent studies [Error! Reference source not found.-Error! Reference source not found.].

Among patients with mildly or moderately increased anti-tTGA, we found a relatively high percentage (27.5%) of negative HLA DQ2/DQ8 cases, for which CD was practically excluded. The potential of a bias due to the fact that the study conducted was retrospective must be taken into consideration. Not all symptomatic patients investigated for CD underwent HLA testing, the indication being decided by the Pediatric Gastroenterology specialist.

All HLA DQ2/DQ8 negative patients had mildly increased or borderline anti-tTGA titers. Although anti-tTGA testing is now the most commonly used and recommended diagnosis test, some authors discuss its limits [16]. Anti-tTGA may have false positive values related to the technique used or a high rate of false positives in antibody testing may be related to pathological situations such as inflammatory bowel disease [Error! Reference source not found.].

All HLA DQ2/DQ8 negative patients had mild to moderate enteropathy on biopsied specimens; two patients had Marsh 2 lesions and is obvious that HLA DQ testing is useful for exclusion of CD in patients with minor mucosal changes [Error! Reference source not found.,Error! Reference source not found.]. Still, 6 patients had Marsh 3a lesions.

Partial villous atrophy is currently encountered in small children related to different pathologies. In our study the cases of non-celiac enteropathy were young age children

(mean age 19.5 months, ranging from 11 to 26 months). Two patients were diagnosed with cow's milk protein allergy. One case had Giardia lamblia infestation, chronic mucosal inflammation in children being sometimes related to this parasite. Considering the relatively high incidence of this infection in our country setting, Giardia may possibly be the etiology of the villous atrophy in some other patients diagnosed with CD [20]. Some authors consider that in these cases the villous atrophy is not associated with intraepithelial lymphocytes, specific to the histologic aspects of CD, and this could be considered a differentiation criteria. Other authors found a large number of intraepithelial lymphocytes related to Giardia infection [21, 22], so the diagnosis may be sometimes difficult [23,24].

Among children for which CD was infirmed, a higher number of patients had a poor response to GFD compared to the CD confirmed patients. It is considered that subjective response to gluten free diet has poor predictive value for coeliac disease, but the persistent or insignificant improvement of symptoms makes the initial diagnosis uncertain.

The large number of cases for which CD was infirmed may be explained through the existence of false positive anti-tTG antibodies due to technical difficulties. Errors in the interpretation of biopsy specimens may appear; false-positive results concerning small bowel biopsies may occur due to poorly oriented biopsies or inter-observer variation in interpretation [Error! Reference source not found.,Error! Reference source not found.].

Due to its high negative predictive value HLA DQ2/DQ8 typing allowed the diagnosis of CD to be excluded in a number of patients that were initially diagnosed with CD according to the ESPGHAN guideline (suggestive symptoms, anti-tTGA positive, histologic findings compatible with CD). Nevertheless these patients were of young age, had mildly to moderately increased anti-tTGA values and histologic lesions at most Marsh 3a and the majority didn't respond to GFD.

Conclusions

All symptomatic patients with high values of anti-tTGA were HLA DQ2 and/or DQ8 positive; in these CD confirmation through intestinal biopsy could have been

avoided. HLA DQ2/DQ8 typing also proved useful in the evaluation of patients with mildly increased anti-tTGA, especially at a young age, with mild to moderate histologic

lesions and poor response to GFD. These data show that HLA testing plays an important role in the diagnostic algorithm of CD.

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RARE CAUSES OF CHILDHOOD OSTEOPOROSIS

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Abstract

Gabriela, 8 years old, was admitted in the 1st Pediatric Clinic, Timisoara for the evaluation of cholestasis syndrome. She was known with hypotonic cerebral palsy, epilepsy with polymorphic seizures partial controlled by anticonvulsants and 5 atraumatic leg fractures occurred in the last 3 years. At admission, she had pale skin, absent subcutaneous tissue and muscle atrophy with muscle atrophy. She had splint cast in the left lower limb and pseudoarthrosis in the 1/3 distal of the right leg. The biological investigations revealed normal liver enzymes except alkaline phosphatase, an abnormal coagulation and bone markers and the presence of starch and fiber in the stool, while the other tests were normal. The radiography of extremities showed osteolysis injuries and old left clavicle, upper third diaphysis of left humerus and femur and lower third diaphysis of right tibia fractures, with vicious callus secondary to Osteogenesis Imperfecta. We considered that all these fractures were manifestations of osteoporosis secondary to malabsorption syndrome, malnutrition, vitamin D and K deficiencies, chronic anticonvulsant therapy and Osteogenesis Imperfecta. The evolution was favorable under treated with calcium gluconate, vitamin D and K with the reduction of alkaline phosphatase and normalization of coagulation. The initiation of bisphosphonate therapy was taken into account. Case particularity: The association of osteoporosis and Osteogenesis Imperfecta responsible for the production of fractures in a patient with cerebral palsy and epilepsy.

Key words: osteoporosis, osteogenesis imperfecta, cerebral palsy

Introduction

For a long period of time, osteoporosis has been considered a health problem specific to postmenopausal women and elderly. According to the medical literature, the incidence of osteoporosis in persons with their age under 50 years old predisposed to developed fracture is increasing up to 30% of women and 13% of men.

Recently, it has been recognized worldwide that osteoporosis could affect also children and adolescents as a primary pathology resulting from intrinsic skeleton abnormalities or as secondary where factors external to the skeleton impair mineralization (various conditions or medications), with ramification that extend during adulthood

life. A common presentation of childhood osteoporosis is recurrent long bone fractures, produced by low impact trauma and represents an important cause of morbidity, disability and mortality.

Sometimes, symptomatic osteoporosis may be the first manifestation of an underlying chronic disease such as leukemia or Crohn's disease

Case presentation

The authors want to present the case of Gabriela, 8 years old aged admitted in the 1st Pediatric Clinic of "Louis Turcanu" Children Emergency, Timisoara, in May 2015. She was sent by her general practitioner for a complex evaluation of cholestasis syndrome, which was identified during the routine investigations.

Regarding her personal history, she is the second child of a healthy young family, naturally delivered at the gestational age of 38 weeks with weight of 3550g. The Apgar score was 6 due to a complicated delivery, the patient being reanimated in the delivery room. She has an elder brother with Down syndrome and a healthy younger sister. At the age of 3 month, she had an afebrile seizures treated with Depakine, occasion with whom she was diagnosed with hypotonic cerebral palsy and epilepsy with polymorphic seizures. Also she was known with 5 fractures of the left lower limb (femur and tibia) cured with vicious callus and one fracture of right femur, all these fractured occurred in the last 3 years and were produced without trauma, during her seizures. Her anticonvulsant treatment consistent in high doses of Depakine (500mg/day), Phenytoin (200mg/day), Levetiracetam (700mg/day) and Levomepromazin (6mg/day), which partial controlled these seizures.

At hospital admission, the clinical examination revealed the presence of pale skin, muscle atrophy with muscle contractures and absent subcutaneous tissue. The oral cavity had dental abnormalities. She had a splint cast in the left lower limb and pseudoarthrosis in the 1/3 distal of the right leg, being 3 cm shorter compared with the other extremity, kyphoscoliosis, while the thorax was asymmetric. Cardiopulmonary examination was normal with painless abdomen, with normal liver and spleen size. She has problem with swallow of solid and liquid food, so she was feed by nasogastric tube. The intestinal transit was slow and the diuresis was presented. She was spastic and she didn't speak, sit upright or walk, being immobilized to bed.

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Parameters tested	Value obtained	Normal limit
25OH vitamina D3	16.01 µg /l	20-70 µg /l
Intact parathormon	613.9 pg/ml	15-65 pg/ml
Bone alkaline phosphatase	1174.0 µg/l	36.3 - 159.4 µg /l
B crosslaps	> 6,00 ng/ml	0.566 - 1.690 ng/ml
Osteocalcin	78.86ng/ml	73,0- 206,6 ng/ml

Table 1. Parameters of bone metabolism tested in this patient

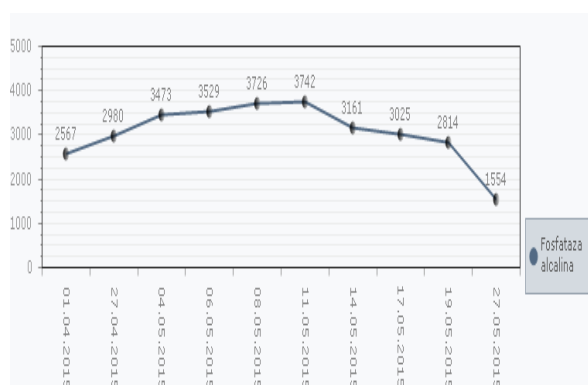


Fig. 1. Evaluation of alkaline phosphatase level under the treatment

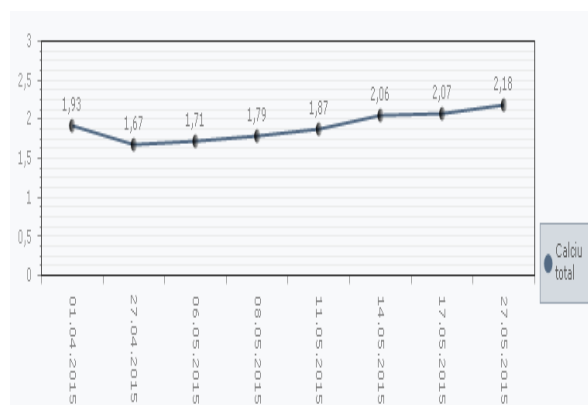


Fig. 2. Evaluation of total calcium level under the treatment prescribed

Anthropometrical parameter were body weight=12kg, body height=103 cm, body mass index=11.32 kg/m² (under the percentiles of 5 for age and sex).

The biological investigations were complex and were performed on dynamic. The blood tests performed revealed the presence of the iron deficiency anemia, while the other investigations reflecting renal functions, lipid metabolism, proteins, immunoglobulin, and hormones were normal. The evaluation of the cholestasis syndrome consisted in the analysis of the main liver enzymes that were within normal range (TGP=11U/l, TGO=20U/l, GGT=46U/l) except the alkaline phosphatase that was highly increased (2980U/l). These results imposed a detailed phosphor-calcium metabolism evaluation, which underlined decreased value of ionic calcium (0.81mmol/l), total calcium (1.67mmol/l) and

phosphorus (0.89 mmol/l). The further investigations regarding the bone metabolism are presented in the table 1.

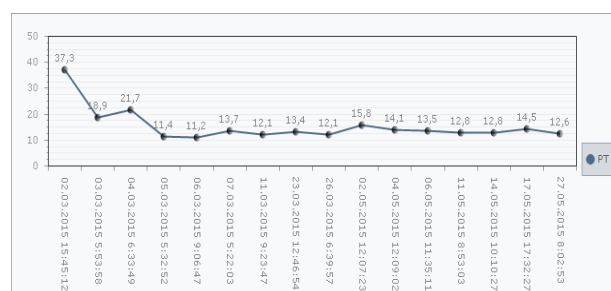


Fig. 3. Evaluation of prothrombin under the treatment with Fitomenandion

The urine examination was normal, while the stool examination identified the presence of starch and fiber in the stool, highly suggestive for malabsorption syndrome.

One day, during the changing of nasogastric tube, Gabriela developed a gastric hemorrhage, fact that imposed the coagulation evaluation which revealed increased values of prothrombin (15,8seconds) and INR- international normalized ratio 1,43 and decreased values of prothrombin activity (55,3%).

The abdominal ultrasound was normal while the radiographies of the superior and inferior limbs showed old left clavicle and upper third diaphysis of left humerus and femur, all cured with vicious callus and lower third diaphysis of right tibia fracture in healing. Also, osteolysis injuries characteristic to Osteogenesis Imperfecta were observed on this investigation. The genetic test for osteogenesis imperfecta is in working.

Based on anamnesis, clinical examinations, biological tests and imagistic investigations, we considered that all these symptomatic and asymptomatic fractures were manifestations of osteoporosis secondary to malabsorption syndrome, malnutrition, vitamin D and K deficiencies, chronic anticonvulsant therapy and Osteogenesis Imperfecta.

The treatment recommended to this patient consisted in the immobilization in splint cast of the right tibia fracture and in prescription of medication address in especially to the vitamin D and K deficiencies and anticonvulsant drugs. So the treatment consisted in the administration of calcium gluconate (100mg/kg/day IV) for 10 days follow by oral micronized calcium (250mg) associated with Vitamin D (increasing doses, from 800 UI/day till 4000UI /day). In parallel, the vitamin K deficit was substituted using Fitomenandion (10mg/day), for 10 days, then orally in

association with other liposoluble vitamins. The evolution under this treatment was good with the decrease of the value of alkaline phosphatase till 1500U / l and normalization of the coagulation factors vitamin K dependent, as shown in figures no. 1, 2 and 3. The initiation of bisphosphonate therapy was taken into account

Discussions and conclusions:

Osteoporosis is a systemic disorder produced by the decreased of bone strength, involving low bone mass and microarchitectural deterioration and it predisposes patients to bone fragility and fracture.

In the year 2013, definition of osteoporosis in children was established based on a combination of clinical and radiographic features. According to The International Society for Clinical Densitometry, pediatric osteoporosis can be diagnosed on the basis of a DXA BMD Z-score less than -2 associated with a clinically significant fracture history, defined as: the presence of a) 2 or more long bone fractures by age 10 years or b) 3 or more long bone fractures by age 19 years, or c) vertebral compression fracture.

In our case, unfortunately, DXA (dual-energy X-ray absorptiometry) was not performed, because in children younger than 12 years old, the soft used for the interpretation of DXA results was not adequate. Instead, the increased number of atraumatic fractures in the patient presented stands for this diagnosis. Also, we want to underline the fact, that the performance of DXA in patients with cerebral palsy is a unique challenge because the muscle contractures may prevent patients from lying in the proper position and lumbar spine evaluation may be hindered by scoliosis, the lateral distal femur being an alternate imaging site for these patients.

Based on clinical findings (abnormally of her teethes, kyphoscoliosis, long bone deformities, pseudoarthrosis and multiple fractures produced in the last 3 years in absence of trauma) and the radiological aspect of her bones, Gabriela was diagnosed with osteogenesis imperfecta type IV, an important cause of primary osteoporosis in children. There is an underlying abnormality in bone matrix composition, usually due to defective synthesis of type I collagen α chains produced by a mutation in COL1A1 or COL1A2 genes.

One of the most common physical disabilities of childhood, cerebral palsy represents a group of permanent disorders which arise from anomalies in the motor center of the brain due to perinatal infections, asphyxiation, and stroke. It consists in abnormalities of the development of movement and posture associated with disturbances of sensation, cognition, communication and behavior, epilepsy, and secondary musculoskeletal problems. Almost 80% of patients diagnosed with severe cerebral palsy have osteoporosis, with an annual fracture incidence of 4%.

There are a multiple factors which may adversely affect bone density and metabolism in patients diagnosed with cerebral palsy.

The motor disorders of cerebral palsy are often accompanied by immobilization to the bed. In is well known that reduced mobility and muscle load are major cause of reduced bone mass and strength. In this situation, the most

common site of fracture in children with reduced mobility is the femur, fact being seen also in the patient presented. In this case, her long bones tend to be slender with thin cortices and reduced trabecular density, and the lower limbs are usually more subjected to trauma from accidents or handling.

Outdoor activities may be significantly diminished in this patient with bone metabolism consequences. So, the limitation of the seasonal sunlight exposure is an important factor for the serum 25-hydroxy vitamin D level.

In the our patient, oral-motor dysfunctions with swallowing difficulties and feeding by naso-gastric tube are important risk factors for the feeding difficulty, poor nutrition and low calcium, vitamin D and K intakes. All these problems are frequent encountered in patients with such pathology and may contribute to poor mineralization.

The deficit of vitamin K is responsible in the case presented both for abnormality of coagulation factors vitamin K dependent and osteoporosis. The recent researches had shown the role of the vitamin K2 in the activation of osteocalcin – the protein responsible for binding calcium ions to the matrix of bone- and of Matrix Gla Protein protein circulator implicated in the cartilage and bone metabolism and in reducing the risk of osteoporotic fractures. According to Prabhoo and van Summeren, vitamin K2 is safety and can be used for prevention and treatment in those pathologies known to contribute to osteoporosis.

The treatment of epilepsy in this patient consisted in an association of 4 anticonvulsants in order to control the seizures, which according to the medical literature may adversely affect bone mineralization. Some of them can induced childhood osteoporosis throw the following mechanism such alteration of liver metabolism of 25-OH vitamin D resistance to PTH, inhibition of calcitonin secretion, and impaired calcium absorption or by the direct effects on bone cells.

Many medical studies have shown that under the correct therapy secondary osteoporosis in childhood can be reversible with remission or optimization of the primary causative condition responsible for its development.

There is a complex strategy regarding the treatment of osteoporosis in a patient with cerebral palsy and osteogenesis imperfecta. We initiated the treatment for osteoporosis with an association of calcium and vitamin D and K supplements. According to the medical literature, this association increase bone density by 2% to 10% and decrease the rate of fractures by 35% to 50%. Also mobility and exercise should be encouraged, because of their great beneficial. We take into account bisphosphonate therapy.

Bisphosphonates are the most used medications for the treatment of childhood osteoporosis. They are potent antiresorptive agents that disrupt osteoclastic activity¹⁷. In children and adolescents with osteogenesis imperfecta, pamidronate treatment had improve the muscle force, vertebral bone mass and size, bone pain, fracture rate and growth, while in patient with cerebral palsy, biphosphonates had a significant effect on improving bone mineral density

and reduce fragility fractures in children who have a history of fractures.

The treatment with intravenous pamidronate (bisphosphonates) consisted in 0.5mg/kg -first dose followed by 1mg/kg/cycle - next doses over a period of time of 5-6 hours, every 3 months. A cycle is represented by a period of 1-2 days of administration.

In these days, pediatricians have to face new challenges in order to ensure the maintenance of bone health

throughout childhood and to provide a strong skeletal foundation for adult life.

The particularity of this case consisted in the presence of a pediatric osteoporosis induced by osteogenesis imperfecta and other causes arise from cerebral palsy deficiencies, responsible for the production of atraumatic fractures.

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MANUSCRIPT REQUIREMENTS

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.