CONTENTS

1. ANATOMICAL AND BIOMECHANICAL CONSIDERATIONS IN AXIAL DEVIATIONS OF LOWER LIMB
   R Alagha, DG Goţia..................................................................................................................3

2. THERAPEUTICAL PERSPECTIVES IN OSTEOGENESIS IMPERFECTA
   Dorina Stoicanescu, Valerica Belengeanu, Monica Stoian,
   Otilia Marginean, C Popoiu, Maria Puiu..................................................................................6

3. ORDER IN CHAOS: A CONDENSED REVIEW OF THE LITERATURE ON INFLAMMATORY BOWEL DISEASE
   R Mejdi, H Osakwe..................................................................................................................9

4. TRISOMY 13 WITH CYCLOPIA AND PROBOSCIS-A CASE PRESENTATION
   D. Socolov, G. Iliev, D. Scripcaru, V. Gorduza, R.V. Socolov, M. Puiu........................................16

5. NIJMEGEN BREAKAGE SYNDROME – CLINICO-CYTOGENETIC PATTERN
   Eli Ormerod, Valerica Belengeanu, Monica Stoian, Nicoleta Andreescu,
   Simona Farcas, Cristina Popa, Mariana Banateanu, Alina Belengeanu..................................19

6. TRISOMY 21, CHOLELITHIASIS AND POSITIVE SWEAT TEST AT INFANT - DIAGNOSTIC DIFFICULTY
   Pop L, Popa I, Popa Zagorca, Ciucu Ioana, Nicolicea Cerasella, Lacatusu A, Gug Cristina, Tamas L..............................25

7. RENAL CONSEQUENCES IN HIV INFECTED CHILDREN
   K.R. Nilima, Mihai Gafencu, Gabriela Doros, C.N. Thanki, M. Lesovici, Margit Serban........................27

8. THE INFLUENCE OF MATERNAL VAGINAL AEROBIC FLORA ON NEWBORN EARLY INFECTIONS
   Camelia Budisan, Constantin Ilie..............................................................................................33

9. ACUTE APPENDICITIS IN INFANTS AND TODDLERS: RARE BUT CHALLENGING
   J.John, S.Hanini, C.M.Popoiu......................................................................................................36

10. NEPHROLOGICAL APPROACH OF 5 CASES WITH NEURAL TUBE DEFECTS
    Daescu Camelia, Sabau I, Mariş Ioana, Simedrea I, Marcovici Tamara, Craciun A, Belei Oana,
    Militaru Andreia, Duncescu C, Cernica M, Chirita-Emandi A, Constantin T..................................40

11. CONSIDERATIONS UPON METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS
    Mirela Poiac, Daniela Brega, I. Popa..........................................................................................45

12. EPIDEMIOLOGICAL STUDY ON UNDESCENDED TESTIS
    RE Iacob, Z Moldovan, M Soiu, Hl Osakwe, Maria Trailescu....................................................52

13. URINARY COMPLEX CONGENITAL MALFORMATION
    NH Jidveianu, OC Vonica........................................................................................................56

14. RARE CAUSES OF ACUTE SURGICAL ABDOMEN IN CHILD
    E.S. Boia, Camelia Popescu, Maria Trailescu, A. Pavel, C.M. Popoiu, O. Adam, V. David..................58

MANUSCRIPT REQUIREMENTS.........................................................................................................65
ANATOMICAL AND BIOMECHANICAL CONSIDERATIONS IN AXIAL DEVIATIONS OF LOWER LIMB

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Abstract
Planning for surgical correction of lower-limb deformity requires assessment of character and extent of the deformity. Angular deformities of tibia or femur in frontal plane lead to mechanical axis deviation of the lower limb and malorientation of the joints above and below the level of deformity. Accurate correction of the malalignment and of the joint orientation is important for function and to prevent joint degeneration. An awareness of the three dimensional nature of deformity is essential if correction is to be achieved. This applies to all aspects of orthopaedics, from total joint arthroplasty (the knee in particular) to fracture management. Mechanical axis deviations in the lower extremity are commonly seen in both paediatric and adult orthopaedic practice. This paper describes, for the trainee, the consequences of such deformity and the methods by which they are quantified.

Keywords: axial deviation, lower limb, children, deformities

Introduction.
Deformities in the lower limb comprise static and dynamic components and may occur in any plane, not just the "anatomical" sagittal or frontal planes. The concept of the weight bearing or "mechanical" axis was described by Pauwels in 1980 (1). It is a static weight bearing axis which can be drawn on a radiographic image of the limb. The mechanical axis of the lower limb in the frontal plane is defined as a line drawn from the centre of the femoral head to the centre of the ankle joint. In the sagittal plane the normal mechanical axis runs from the centre of gravity (in front of S2), to the centre of the ankle joint (1, 2, 3). The common situation is for deformity to occur between these anatomical planes, that are in an oblique plane (4, 5). Rotational deformity (internal or external) and translational deformity may coexist (1, 4, 6).

Development
On clinical examination most newborn infants present an external rotation tendency of the hips and mild internal tibial torsion. The hips rotate externally approximately 30° more than they rotate internally. This is known to be associated with approximately 35° to 40° of anteverision of the neck of the femur. This "physiologic" deformity is felt to be secondary to the marked knee-chest position which is present in the later months of pregnancy. If the intra-uterine positioning is severe or asymmetric, or if there is a congenital tendency for a rotational deformity, the usual physiologic rotation may be increased or decreased. In the course of normal development, most of these attitudes will correct themselves spontaneously so that in the adult the average rotation at the hips is approximately 40° internal and 45° external; the average ante torsion of the neck of the femur is 15° and the tibial torsion has changed to be approximately 20° of external rotation (1, 5, 7).

Types of deformities
Rotational deformities may be simple or mixed. By a simple deformity is meant that the several segments of the extremity are rotated in the same direction. By a mixed deformity is meant that there is an abnormal rotation in one segment in a given direction with an abnormal rotation in another segment in the opposite direction, such as increased anteverision of the femur with external tibial torsion or external rotation of the femur with internal tibial torsion. These deformities may be unilateral or bilateral. Also, the deformity may be located in only one segment-such as isolated internal torsion or isolated anteverision (8).

Internal rotation deformities
May be categorized broadly into congenital and acquired. The congenital form may be due to hereditary factors or intra-uterine positioning (table I). The acquired forms are usually due to abnormal postures (1). Such problems as tibia vara, dyschondroplasia, infantile or vitamin D resistant rickets, cerebral palsy and poliomyelitis may be etiologic factors in the production of these anatomic deformities. Frequently, as is the case with anteverision, as the patient matures, a compensatory external tibial torsion develops which gives him a superficial appearance of a normal gait. These children have a relatively high incidence of true or apparent bowleg and a certain amount of genu recurvatum which increases the apparent bowleg (4, 6, 7).

External rotation deformities
May be congenital, either on the basis of intra-uterine positioning or hereditary factors or they may be acquired (9). The most common cause of external rotation deformity in the lower extremity in the infant is at the hip, and this appears to be due to a constant frog-leg position, seen especially in the hypotonic infant.
This deformity is not uncommon and deserves treatment in infancy to avoid the persistent objectionable deformity of adulthood. These deformities may also be combined with internal tibial rotation deformity. Secondary internal tibial torsion is often seen as a compensatory deformity, which develops following attempt to walk with the toes pointed straight forward. Thus, a simple deformity may become a mixed deformity with growth (2, 5, 6).

### Table I. Causes of Rotation Deformities

<table>
<thead>
<tr>
<th>Causes of Internal Rotation Deformities</th>
<th>Causes of External Rotation Deformities</th>
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</thead>
<tbody>
<tr>
<td>Soft-tissue contracture</td>
<td>Soft-tissue contracture</td>
</tr>
<tr>
<td>Antversion of the femur</td>
<td>Loss of the normal femoral anteverision</td>
</tr>
<tr>
<td>Spastic internal rotators of the femora</td>
<td>Paralysis of internal rotators</td>
</tr>
<tr>
<td>Genu varus</td>
<td>Genu valgus</td>
</tr>
<tr>
<td>Internal tibial torsion</td>
<td>External tibial torsion</td>
</tr>
<tr>
<td>Metatarsus varus</td>
<td>Calcaneo valgus feet or pes planus</td>
</tr>
<tr>
<td>Pes planus or pes equinus</td>
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</tbody>
</table>

There is a relatively high incidence of knock knees with patients who have external rotation deformities of the hips. This is explained by the Heuter-Volkmann Law, which in turn is invoked by an abnormal foot strike and, to some degree, by a tight iliobibial band. These children have an abnormal foot strike, in that the pressure is distributed over the lateral calcaneal tubercle, thereby transmitting more pressure to the lateral knee epiphyses which are thus inhibited and result in a knock knee deformity (3, 7).

### Mechanics of Deformities

A rationale of diagnosis and treatment is based on the understanding of forces which modify epiphyseal growth.

Epiphyseal growth: The direction of growth of an epiphysis is modified by many factors: gravity, muscle imbalance, joint contractures, hereditary factors, nutrition, blood supply, disuse, infection and trauma. The Heuter-Volkmann Law of epiphyseal pressure states that increase in pressure across an epiphysis will decrease its growth; conversely, decreasing the pressure will increase the rate of growth.

Angular deformities which originate in the epiphyses result from asymmetric pressures applied parallel with the plane of epiphyseal growth, that is, perpendicular to the epiphyseal plate. Torsional deformities result from torque forces applied perpendicular to the plane of epiphyseal growth, that is, parallel with the plane of the epiphyseal plate (1, 2).

**Nature of forces:** The force required to produce or correct rotational or angular deformities is directly proportional to the width of the bone, and this is related to the age of the patient. Total force must be considered in regard to magnitude of force and duration of force. Thus, the same energy on the epiphyseal plate can be expended by a large force for a short time as can be expended by a small force for a longer time. The force needed for correction is equal and opposite to the deforming force, but since this cannot be calculated in magnitude or duration, the end point of anatomic alignment must be the criterion for correction (1, 2).

Diaphyseal changes: The thickened cortices which are noted in the diaphysis of long bones are the result of changes in the internal architecture secondary to stress (Wolff's Law). With the correction of these abnormal stresses, the diaphyseal changes can be observed to revert to normal. These diaphyseal deformities are the result of stresses imposed by rotational or angular deformities which originate in the epiphyseal areas (8).

**Clinical examination in children with rotational deformities.**

When a child is presented for examination, it is of the greatest importance that the entire extremity be examined, regardless of the initial complaint. One should observe gait patterns with and without shoes and examine all segments of the extremity in the standing, the sitting and the lying positions (fig. 1) (6).

![Fig. 1. Antetorsion of the neck of the femur – clinical aspect.](image)
HIPS: The extended position is the best method for determining the torsional deformity of the femur. The range of motion of the hip joint is examined thoroughly, and careful attention is paid to the ability to rotate internally and externally. The extended limbs are supported in the hands of the examiner over the end of the table, and the extremities are rotated simultaneously, internally and externally, measuring the degree of rotation. An alternate method of measuring hip rotation is with the patient prone and the knees flexed 90°. An internal rotation deformity of the hip is diagnosed when internal rotation exceeds external rotation by 30° or more. Conversely, if external rotation exceeds internal rotation by 30° or more, external rotation deformity is diagnosed (6, 7).

TIBIA: Tibial torsion should be measured while the patient sits on the edge of a table. The knee joint is flexed 90° and, with the foot supported passively, and with 90° of flexion at the ankle, the axis of the knee joint is compared with the axis of the ankle joint. A simple method is to relate the tibial tubercle to the malleoli. Normally, there is from 0 to 40° of external tibial torsion, the higher numbers occurring in adults (6, 7).

FOOT: The lateral border of the foot is noted to determine whether or not it is convex or straight. Also, the relationship of the plane of the metatarsals to the plane of the ankle joint is noted both while walking and on passive examination. The structure of the longitudinal arch of the foot is also noted (2, 6).

Conclusions
Deformities of the lower extremity in children are most frequently the result of intra-uterine positioning and congenital deformities. Sleeping, sitting and play habits of infancy have a great effect on the persistence of these deformities. It is not possible to predict which deformity will correct spontaneously; therefore, consideration should be given to treatment of the objectionable deformities and to prevention of the development of secondary deformities. Rotation deformities of the hips in older age groups are associated with actual change of normal femoral torsion. Treatment of soft-tissue contractures and deformities in infants may prevent skeletal deformities later in life. Rotation deformities may cause secondary angular deformities or may prevent the spontaneous correction of angular deformities by the Heuter-Volkmann or Wolff's Law. External rotation deformity of the hips in infants deserves recognition and treatment to prevent a cause for later knock knee and objectionable gait patterns in the adult. The early recognition and treatment of these deformities is better than a wait-and-see policy.

References

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THERAPEUTICAL PERSPECTIVES IN OSTEOGENESIS IMPERFECTA

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Abstract

Osteogenesis imperfecta is a genetic disease for which no cure is yet known. It is one of the most common skeletal dysplasias. It causes the osteoblasts to grow poorly, slowing the growth of children with the disease and causing their bones to break easily. The skeletal fragility is explained by the mutations in the genes for type I collagen, but the clinical range is wide and the relation between genotype and phenotype is complex. Some forms of osteogenesis imperfecta may cause severe disability and even death. Management of the disease includes focusing on preventing or minimizing deformities, and maximizing the individual's functional ability. With the more recent understanding of the molecular mechanisms of the disease, bone marrow transplantation is considered a potential future therapeutic modality. The young skeleton, normal or abnormal, is constantly changing, being formed and resorbed, modelled and remodelled. In theory blocking osteoclastic resorption or encouraging osteoblastic bone formation could produce useful increases in bone tissue even when the primary event is defective osteogenesis. Treatment with isolated allogeneic mesenchymal cells has the potential to enhance the therapeutic effects of conventional bone marrow transplantation in patients with genetic disorders affecting mesenchymal tissues. Thus, allogeneic mesenchymal cells offer feasible posttransplantation therapy for osteogenesis imperfecta.

Key words: osteogenesis imperfecta, therapy, bone marrow transplantation.

It is estimated that OI occurs in approximately 1 in 20,000 individuals; however, the mild form is underdiagnosed, and the actual prevalence may be higher. OI occurs with equal frequency among males and females and among different ethnic groups. Life expectancy varies depending on the severity of the disorder.

There are several types of OI, distinguished mostly by fracture frequency, severity and by some characteristic features (2). It is estimated that the vast majority (90 %) of OI is caused by a single dominant mutation in one of two type I collagen genes: COL1A1 or COL1A2. These genes provide instructions for making proteins that are used to create type I collagen, which is the most common protein in bone, skin and connective tissues. Type I collagen fibers are composed of a left-handed helix formed by intertwining of pro-alpha 1 and pro-alpha 2 chains. The COL1A gene on chromosome 17 encodes the pro-alpha1 chain, and the COL2A gene on chromosome 2 encodes the pro-alpha2 chain. Mutations in the loci that encode these chains cause the disease. Cartilage-associated protein (CRTAP) is a protein required for prolyl 3-hydroxylation. mutations of this gene cause excess posttranslational modification of collagen, and may be associated with syndromes resembling osteogenesis imperfecta, including recessive forms of lethal syndromes resembling the disorder (3). OI type VII is caused by recessive mutations in the CRTAP gene and type VIII by mutations of gene LEPRE1 (4).

Type I is the mildest form. Affected persons have bone fractures during childhood and adolescence often due to minor trauma, but during adulthood they have fewer fractures.

Type II is the most severe form. Infants with type II have shortarms and legs, bones that appear fractured before birth, narrow chest, fractured and misshapen ribs and underdeveloped lungs, unusually soft skull bones. Most infants are stillborn or die shortly after birth, usually from breathing failure.

Type III also has relatively severe signs and symptoms. Infants have very soft and fragile bones that may begin to fracture before birth or in early infancy. Bone abnormalities tend to get worse over time, being considered a progressive form.
Type IV is the most variable form of OI. Symptoms of OI type IV can range from mild to severe. Scleras are normal.

Type V has severity similar to that of type IV disease but with a predisposition to hyperplastic callus formation.

Type VI is clinically similar to types II and IV, but it has distinctive histology.

Type VII is clinically similar to osteogenesis imperfecta types II and IV but with rhizomelia as a distinctive feature.

Type VIII is associated with protein leprecan.

Precise typing is often difficult. Severity ranges from mild forms to lethal forms in the perinatal period. In addition, several syndromes resemble OI, with congenital bone fragility in association with other distinctive clinical or histologic features. In severe cases, prenatal screening ultrasonography performed during the second trimester may show bowing of long bones, fractures, limb shortening, and decreased skull echogenicity. Lethal OI cannot be diagnosed with certainty in utero (5).

Osteogenesis imperfecta is often inherited from an affected parent. Most types are inherited in an autosomal dominant pattern. The diagnosis is made on the basis of family history, clinical presentation, bone density measurements (6), X-ray findings that include fractures that are at different stages of healing, an unexpected skull bone pattern called Wormian bones and bones in the spine called "codfish vertebrae." Laboratory testing may include either biochemical testing involving studying collagens or DNA-based sequencing of COL1A1 and COL1A2. DNA sequencing of COL1A1 and COL1A2 is used to identify the type I collagen gene mutation responsible for the altered collagen protein. Normal biochemical and molecular testing in a child with OI warrants additional testing of less common collagen genes (CRTAP and LEPRE1) responsible for the rare recessive forms of OI 25-30 % of cases occur as a result of new mutations.

Osteogenesis imperfecta is a genetic disease for which no cure is yet known. Treatment requires a coordinated multidisciplinary team approach, and consists of physical therapy, surgical interventions, medications, and in some cases, experimental therapies (7, 8). Osteogenesis imperfecta treatment is typically focused on preventing or controlling symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Treatment involves supportive therapy to decrease the number of fractures and disabilities, help with independent living and maintain overall health. Medical and surgical care are completed by physical and occupational therapies that will help improving the ability to move, to prevent fractures and to increase muscle strength (9).

A newer treatment with medication called biophosphonates is being used to help with bone formation and to decrease the need for surgery (10). A surgical procedure called "rodding" is frequently considered for individuals with OI. This osteogenesis treatment involves inserting metal rods through the length of the long bones to strengthen them and prevent or correct deformities (11). Patients are encouraged to exercise as much as possible to promote muscle and bone strength, which can help prevent fractures. Swimming and water therapy are common exercise choices for people with osteogenesis imperfecta, as water allows independent movement with little risk of fracture. For those who are able, walking is excellent exercise. Children and adults with osteogenesis imperfecta will also benefit from maintaining a healthy weight. To date, no drug or vitamin therapy regimen has been effective as a treatment for this disorder. Research scientists continue to make progress with these issues.

Osteogenesis imperfecta causes the osteoblasts to grow poorly, which slows the growth of children with the disease and causes their bones to bend and break easily. In previous research studies it was found that children treated with bone marrow transplant began to grow faster, had more minerals in their bones, and broke their bones less often than before the bone marrow transplant (12). Several months after the bone marrow transplant however, body growth once again began to slow down (13). Chamberlain et al. designed a gene construct that targets exon 1 of the gene for collagen type Iα1 (COL1A1), which encodes one of the two collagen subunits. They predicted that, on insertion, the construct would both inactivate COL1A1 and confer resistance to the antibiotic neomycin. To insert the gene construct efficiently they used an adenoassociated virus as a vector, which, unlike adenoviruses, is integrated into chromosomal sites.

The results obtained with mesenchymal stem cells from two patients with osteogenesis imperfecta were extremely encouraging. In 31 to 90 % of the cells that became resistant to neomycin, the gene construct had inserted itself into either the wild-type or the mutated COL1A1 allele. In all cultures of the neomycin-resistant cells, most signs of the dominant negative protein defect were corrected — apparently because the cells in which the mutated allele was inactivated began to produce an adequate amount of wild-type collagen. Most important, the quality of bone synthesized by the altered mesenchymal stem cells was improved (14). Adult stem cells offer the potential to treat many diseases through a combination of ex vivo genetic manipulation and autologous transplantation. Mesenchymal stem cells, also referred to as marrow stromal cells are adult stem cells that can be isolated as proliferating, adherent cells from bone. Mesenchymal stem cells can differentiate into multiple cell types present in several tissues, including bone, fat, cartilage, and muscle, making them ideal candidates for a variety of cell-based therapies (15). The present findings suggest that long-term cultured bone marrow stromal cells from osteogenesis imperfecta (OI) animals have the potential to traffic through the circulatory system, home to bone, form bone and continue to express exogenous genes. These findings open the possibility of using these cells as vehicles to deliver normal genes to bone as an alternative approach for the treatment of some forms of OI and certain other bone acquired and genetic diseases.
References


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ORDER IN CHAOS: A CONDENSED REVIEW OF THE LITERATURE ON INFLAMMATORY BOWEL DISEASE

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Abstract

This article intends to be a condensed and simplified review of the literature on inflammatory bowel disease. The chaos of prolific and nonetheless controversial genetic, immunologic and epidemiologic studies has been conscientiously evaded in favor of issues of direct interest to the pediatric surgeon.

Keywords: inflammatory bowel disease, Crohn disease, ulcerative colitis, terminal ileitis, backwash ileitis, colorectal carcinoma, extraintestinal manifestations, ASA, pouchitis, endoscopic surveillance.

Introduction

Inflammatory bowel disease (IBD) is a set of chronic non-specific inflammatory disorders of the GI tract comprising primarily Crohn disease (CD) and Ulcerative colitis (UC); and additionally microscopic ulcerative colitis, microscopic lymphocytic and collagenous colitides. The intuitive clinical impression of CD and UC being variations on the same theme rather than distinct entities is corroborated by the overlap of their pathogenesis, clinical presentations, radiological and histopathological findings. Moreover, in 10-20% of colitides a definitive diagnosis cannot be established, hence the label of “indeterminate IBD”.

Alternative denominations- present and obsolete.

<table>
<thead>
<tr>
<th>Crohn disease</th>
<th>Ulcerative colitis</th>
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<tbody>
<tr>
<td>Regional enteritis</td>
<td>Colitis ulcerosa</td>
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<tr>
<td>Terminal ileitis</td>
<td>Proctocolitis</td>
</tr>
<tr>
<td>Granulomatous ileocolitis</td>
<td>Ulcero-hemorrhagic rectocolitis</td>
</tr>
<tr>
<td>Chronic granulomatous enterocolitis</td>
<td>Bloody flux</td>
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Epidemiology

There is a marked discrepancy in the distribution of IBD with north-to-south and urban-to-rural gradients. IBD being most prevalent in Caucasians from northern industrialized countries including the US, UK and Scandinavia; and less prevalent in South America, Asia and Africa.

Interestingly, IBD is 2-4 times more common in Ashkenazi Jews.

Recently, several studies tend to mitigate such clear-cut epidemiological data and demonstrate the closing of the racial, ethnic and socio-economic gap, probably due to “westernization” of lifestyle.

IBD has a bimodal age distribution with a first peak [15-30 y.o.] and a later smaller peak [60-80 y.o.]. 10% of patients are younger than 18 years.

IBD in the pediatric population must be regarded differently from the disease in adults for four major reasons: (1) IBD is relatively more severe in children, (2) Failure to thrive in infants and young children, and delayed growth during prepuberty are issues to be addressed, (3) Chronic disease and a toilet-centered life accentuate the usual emotional problems of the adolescent, and last but not least
The malignisation potential of the colonic lesions is amplified after long-standing colitis in childhood.

Etiopathogenesis

A positive family history is considered to be the most important risk factor for developing IBD. The risk of CD in first-degree relatives of a CD patient is 10-14 times higher than in the general population, with the risk of UC being 8 times higher. In CD, but not UC, affected patients are more likely to be siblings than first-degree relatives.

Based on studies of monozygotic twins, the coefficient of hereditability of CD is high (equivalent to that in type 1 diabetes mellitus). In UC, it is much lower, which argues for a stronger environmental component in susceptibility.

Oral contraceptives and isotretinoin (Accutane) have been identified as risk factors for CD and UC respectively. Patients with CD are more likely to be smokers, whereas smoking and appendectomies have a negative association with UC.

The etiopathogenic contribution of ethnicity, dietary, microbial, immunologic, environmental, vascular, and even psychosocial factors is still a subject of speculative debate and controversy.

Macroscopic and microscopic pathology

Crohn Disease is a chronic inflammatory condition that may potentially affect any segment of the GI tract from the mouth to the anus, but has a particular tendency to affect the terminal ileum and ascending colon (ileocolonic disease). The small intestine is involved in 90% of patients younger than 20 years old, whereas colonic involvement is more common in patients older than 40 years old. A useful mnemonic aphorism to remember is that the caliber of the intestine involved grows with the patient.

Microscopically, the initial lesion starts as a focal inflammatory infiltrate around the crypts followed by ulceration of the superficial mucosa. Later, the inflammatory process involves deep layers and begins to organize into non-caseating granulomas. These granulomas are transmural and extend into the mesentery and the regional lymph nodes. Although granuloma formation is pathognomonic of Crohn disease, absence does not exclude the diagnosis.

Macroscopically, the involved mucosa suffers hyperemia and edema. Later, discrete superficial ulcers form, which become deep serpiginous ulcers located transversally and longitudinally over an inflamed mucosa, giving it the appearance of a cobblestone. Aphthous ulcers are characteristic for CD and are most frequently sited in the mesenteric border of the terminal ileum. The lesions in CD are often segmental, being separated by normal intervening mucosa, and are often referred to as skip lesions.

Ulcerative Colitis can manifest as proctitis in 25% of cases (lesion confined to the rectum), as proctosigmoiditis (involvement of rectum and sigmoid colon), as left-sided colitis (lesion distal to splenic flexure) and as pancolitis, which occurs in 10% of patients (lesion extends proximal to splenic flexure or involves the entire colonic frame). The small intestine is never involved, except when the distal terminal ileum is subjected to a superficial non-ulcerating inflammation; in the presence of a severely incompetent ileocecal valve, a condition referred to as backwash ileitis and arising in 10% of patients with pancolitis.

Ulcerative colitis is characterized by a uniform neutrophilic infiltrate along with crypt abscesses and crypt distortion (cryptitis). These lesions are confined to the mucosa, with no intervening normal segments. Granulomas do not occur in ulcerative colitis.

Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As the disease becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on barium enema.

<table>
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<tr>
<td>Rectal involvement</td>
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<td>“Skip lesions”</td>
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<tr>
<td>Transmural</td>
</tr>
<tr>
<td>involvement</td>
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<tr>
<td>Granulomas</td>
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<tr>
<td>Goblet cells</td>
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<tr>
<td>Crypt abscesses</td>
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<tr>
<td>Perianal disease</td>
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<td>“Cobblestone” mucosa</td>
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Clinical presentation

Crohn disease presents with diarrhea, abdominal pain and tenderness in the RLQ, fever, weight loss and asthenia. Intestinal obstruction is a frequent complication. Initial ileus is caused by edema and mucosal spasm. It is intermittent and often reversible with conservative measures and anti-inflammatory agents. As the disease progresses, the obstruction becomes chronic and intractable due to fibrosis, luminal narrowing and stricture formation leading to less diarrhea and more constipation.

 Fistula formation is also a frequent complication of colonic CD. Fistulae are classified into: benign, nuisance and intractable. Benign fistulae include ileoileal, ileocecual and ileosigmoid fistulae, which might produce only mild or moderate diarrhea or even remain asymptomatic for years. Nuisance fistulae include cologastric (feculent vomiting),
colododenal, enterovesical (recurrent UTI, pneumaturia), enterovaginal (feculent vaginal discharge) and enterocutaneous fistulae (feculent soiling of the skin). Such fistulae must be sealed to eliminate their symptomatic nuisance and pathophysiologic consequences, but neither the complications nor the underlying bowel disease is severe enough to require surgery.

A last set of frequent complications of CD is comprised by anal and perianal lesions. These include fissures in ano (multiple and indolent), hemorrhoids, skin tags, perianal abscesses, ischiorectal abscesses, fistula in ano (may be multiple) and anorectal fistulae.

Ulcerative colitis presents with rectal bleeding and diarrhea with frequent discharges of watery stool mixed with blood, pus and mucus associated with tenesmus and rectal urgency, and even anal incontinence. 2/3 of patients experience abdominal cramping and variable degrees of fever, vomiting, weight loss and dehydration. Mild disease may be manifested only by an increase in the frequency or the decrease in the consistency of stools, and few patients complain of paradoxical constipation. The abdomen is tender in the hypogastrum or LLQ.

Several disease activity indices and scoring systems have been designed for the evaluation of the severity and progression of IBD. Truelove and Witt devised a simple classification to assess UC severity based on six criteria. The Crohn’s disease Activity Index (CDAI) was developed for the American National Cooperative Crohn’s Disease Study and has been subsequently used in the majority of subsequent clinical trials, before it evolved into the Severity-Activity Index (SI) of Goebell et al. Other popular and less popular scoring systems include the Vienna classification for CD and its modified successor; the Montreal classification, IBD Quality of Life Questionnaire (IBDQ) and the Lloyd-Still and Green clinical scoring system for patients with CD and UC.

### Vienna and Montreal classification for Crohn disease.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>A1 &lt; 40 yrs</th>
<th>A1 &lt; 16 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A2 &gt; 40 yrs</td>
<td>A2 [17-40 yrs]</td>
</tr>
<tr>
<td></td>
<td>A3 &gt;40 yrs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>L1 ileal</th>
<th>L1 ileal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L2 colonic</td>
<td>L2 colonic</td>
</tr>
<tr>
<td></td>
<td>L3 ileocolonic</td>
<td>L3 ileocolonic</td>
</tr>
<tr>
<td></td>
<td>L4 upper</td>
<td>L4 isolated upper disease&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>B1 non-stricturing, non-penetrating</th>
<th>B1 non-stricturing, non-penetrating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B2 stricturing</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td></td>
<td>B3 penetrating</td>
<td>B3 penetrating</td>
</tr>
<tr>
<td></td>
<td>p perianal disease modifier&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> L4 is a modifier that can be added to L1-L3 when concomitant upper GI disease is present.

<sup>2</sup> “p” is added to B1-B3 when concomitant perianal disease is present.

### Ulcerative colitis disease severity based on the Truelove and Witt classification.

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>MILD</th>
<th>SEVERE</th>
<th>FULMINANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stools (per day)</td>
<td>&lt;4</td>
<td>&gt;6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>Intermittent</td>
<td>Frequent</td>
<td>Continuous</td>
</tr>
<tr>
<td>Temperature</td>
<td>Normal</td>
<td>&gt;37.5 °C</td>
<td></td>
</tr>
<tr>
<td>Pulse (b/min)</td>
<td>Normal</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>Normal</td>
<td>&lt;75% of normal</td>
<td>Requires transfusion</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>&lt;30</td>
<td>&gt;30</td>
<td></td>
</tr>
</tbody>
</table>

### Extraintestinal manifestations of IBD

Extraintestinal manifestations occur in approximately 20% of patients with IBD, and include:

- Episcleritis + uveitis + conjunctivitis
- Skin lesions: there are 2 main skin lesions associated with IBD: Erythema nodosum and Pyoderma gangrenosum. Infectious skin lesions such as herpetic lesions induced by immune suppression are also observed.

Erythema nodosum is a painful, tender, raised, purplish lesion on the anterior surface of the tibia, correlates well with IBD activity and dissipates with treatment.

In contrast, Pyoderma gangrenosum is typically not associated with disease activity, starts as an inflammed patch ranging from 1 to several cms in diameter and then progresses towards ulceration; persisting for months. It shows no amelioration with IBD treatment.

- Urinary complications are most common in Crohn disease, and consist of oxalate nephrolithiasis and fistulous formations involving the ureters and bladder.

- Sclerosing cholangitis is most common in UC. When sclerosing cholangitis has been diagnosed first, perform colonoscopy. If colitis is present, clinical evidence of UC
should be expected within 2 yrs. 5-15% of patients with PSC tend to develop cholangiocarcinoma.

-Gallstones are common in CD and are usually asymptomatic.
- Liver diseases: hepatic steatosis is common, chronic hepatitis and cirrhosis are uncommon
- Venous thrombosis is more common in UC.
- IBD –associated anemia: Fe deficiency anemia due to chronic blood loss + anemia of chronic disease.
- Arthritis: the clinician should differentiate medication induced arthropaties from IBD-associated arthritis. IBD-associated arthritis is classified into: (1) axial or central arthritis (5% IBD), consists of ankylosing spondilitis and sacroiliitis, independent of disease activity, often associated with CD, and (2) peripheral arthritis (10% IBD), characterized by non-destructive lesions affecting large joints and seronegative RF, it is further subclassified into: pauciarticular (also known as type 1 arthritis – acute self-limiting attacks < 10 weeks, occur with IBD relapses, associated with other extra-intestinal manifestations), and polyarticular asymmetric (also known as type 2 arthritis – lasts for months-years, independent of IBD activity, usually associated with uveitis.)

**Differential diagnosis**
- Acute appendicitis
- Diverticular disease
- Gastroenteritis (bacterial, viral, eosinophilic)
- Endometriosis
- Pelvic inflammatory disease
- AIDS (Kaposi sarcoma with chronic diarrhea and colonic involvement)
- Antibiotic-associated colitis
- Arteriovenous malformations
- Colorectal carcinoma
- Infectious colitis (proctitis in “gay bowel syndrome”)
- Intestinal lymphoma (occasionally involves caecum)
- Intestinal TB
- IBS
- Ischemic colitis
- Pseudomembranous colitis
- Radiation-induced colitis
- Intestinal motility disorder
- Sarcoïdosis
- Food poisoning
- Celiac sprue
- CI esterase deficiency
- Giardiasis
- Lactose intolerance
- Psychiatric disorders (depression, bulimia, anorexia nervosa)
- Miscellaneous conditions presenting with diarrhea

**Lab studies**
- CBC with differential
- Anemia as a consequence of acute or chronic blood loss or malabsorption (Fe, folic acid, vitamin B12) or anemia of chronic disease.

- Leucocytosis, mild in active disease, markedly elevated in the instance of a suppurative inflammation.
- Thrombocytosis.
- ESR and CRP are frequently elevated during active disease.
- Serum Fe, ferritin and total binding capacity are used to assess the iron status of the child.
- Serum folate, B12, Schilling test – terminal ileum function
- Xylose absorption test is sensitive for assessing upper intestinal function.
- 72h-fecal fat excretion to document the severity of steatorrhea.

- Hypokalemia reflects the severity of diarrhea.
- Abnormal LFT in sclerosing cholangitis or pericholangitis.
- Protein-losing enteropathy
  - Hypoalbunemia
  - Hypocalcemia.
- Stool exam: fecal leucocytes, ova and parasites studies, bacterial pathogens culture.
- Fecal Calprotectin increase is useful to differentiate active disease from other causes of abdominal pain or diarrhea.

- Salmononella, Shigela, Campylobacter jejuni, Yersinia enterocolitica (50-80% of cases of acute terminal ileitis are due to pseudomembranous Yersinia enterocolitica infections).
- Positive Blood cultures if peritonitis or fulminant colitis is present.
- Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are positive in UC, and anti-Saccharomyces cerevisiae antibodies (ASCA) positive in CD.

**Imaging studies**
- Plain radiographs of the chest and abdomen are used to demonstrate pneumoperitoneum, pneumatosis coli, toxic megacolon, nephrolithiasis, cholelithiasis, osteopenia, arthritis of the spine or sacroiliitis.

- Barium enema was the first investigative tool to characterize the typical findings in IBD with the use of an extensive descriptive terminology which includes: “stove-pipe” or “lead-pipe” appearance (suggests chronic colitis that has resulted in the loss of colonic haustrae), “rectal sparing” (suggests Crohn colitis in the presence of inflammatory changes in other portions of the colon), “thumbprinting” (indicates mucosal inflammation), and “skip lesions” (suggest areas of inflammation alternating with normal intervening mucosa, again suggesting Crohn colitis). Barium can be refluxed into the terminal ileum in many cases, which can assist in the diagnosis of CD. Barium enema is contraindicated in patients with moderate-to-severe colitis because it risks perforation or precipitation of a toxic megacolon.

- Small bowel series, small bowel follow-through and small bowel enteroclysis are used to assess the severity and length of strictures if present (string sign) and often demonstrate fistulae even in the absence of clinical...
A fistulogram might be obtained by direct insertion of contrast into an enterocutaneous fistula in order to help determine the course of the fistula in anticipation of surgical correction and to assist in guiding the surgical approach.

- CT scan of the abdomen and pelvis has limited use in the diagnosis of IBD. CT is ideal in identifying an intraabdominal abscess, mesenteric inflammation and fistulae, and can be used to guide percutaneous drainage of an abscess.

- Ultrasonography can be an alternative to CT in the evaluation of the intraluminal and extraluminal manifestations of CD.

- Imaging procedures include:
  - Colonoscopy
  - Flexible sigmoidoscopy
  - Esophagoduodenoscopy
  - Small bowel enteroscopy
  - Capsule enteroscopy, is mainly used to locate the source of GI bleeding.

### Crohn disease vs. Ulcerative colitis - contrasted findings of conventional radiology and endoscopy.

<table>
<thead>
<tr>
<th></th>
<th>Crohn disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Radiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Collar button&quot; ulcers</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Small intestinal involvement</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Discontinuous involvement</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Fistulas</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Strictures</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Endoscopy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Discontinuous involvement</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Rectal sparing</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Linear/serpiginous/stellate ulcers</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Ulcers in terminal ileum</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

### Medical management

**CROHN DISEASE**

- Induction of remission: Oral / i.v. glucocorticosteroids, oral glucocorticosteroids + azathioprine (AZA)/ mercaptopurine (6MP), or enteral nutrition.
- Maintenance of remission: Aminosalicylates, or AZA + 6MP + mycophenolate mofetil.
- Treatment of glucocorticosteroid/immunosuppressive therapy-resistant disease: Methotrexate, i.v. cyclosporin or Infliximab (TNFα antibody)
- Perianal disease: Ciprofloxacin and metronidazole.

**ULCERATIVE COLITIS**

- Proctitis: Oral aminosalicylates and a local rectal steroid preparation are the first-line treatment. Mesalazine and budesonide enemas can be tried. In resistant proctitis, oral corticosteroids alone or in combination with azathioprine are used.
- Left-sided proctocolitis: Oral aminosalicylates and a local rectal steroid preparation in mild disease. In moderate to severe attacks, oral prednisolone will be required.
- Total colitis (moderate to severe attacks): Oral salicylates, i.v. hydrocortisone and full supportive therapy (i.v. fluids, nutritional support via the enteral and not parenteral route if required) +/- azathioprine. In patients responding to i.v. hydrocortisone treatment, oral prednisolone therapy should be substituted and doses slowly tapered.
- Maintenance of remission is with aminosalicylates. When it is not possible to taper the dose of prednisolone without flare-up, azathioprine is used.

### ASA compounds available for UC.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preparation</th>
<th>Mechanism of release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphasalazine</td>
<td>5- ASA linked to sulpyryridine</td>
<td>Bacterial cleavage in colon</td>
</tr>
<tr>
<td>Asacol</td>
<td>(enteric-coated mesalazine)</td>
<td>5-ASA pH-dependent coating</td>
</tr>
<tr>
<td>Salofalk</td>
<td>(enteric-coated mesalazine)</td>
<td>Dissolves at pH 7 or higher</td>
</tr>
<tr>
<td>Pentasa</td>
<td>(modified-release mesalazine)</td>
<td>5-ASA pH-dependent coating</td>
</tr>
<tr>
<td>Dipentum</td>
<td>(olsalazine)</td>
<td>Dissolves at pH 6 or higher</td>
</tr>
<tr>
<td>Colazide</td>
<td>(balsalazide)</td>
<td>5-ASA semipermeable membrane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Timed release of drug at luminal pH 6 or higher</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic bacteria cleave azo bond</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic bacterial cleavage</td>
</tr>
</tbody>
</table>
**Surgical management**

Table: Indications of surgery in CD and UC.

<table>
<thead>
<tr>
<th>Crohn disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of medical treatment</td>
<td>Failure of medical treatment</td>
</tr>
<tr>
<td>Complications:</td>
<td></td>
</tr>
<tr>
<td>Toxic dilatation</td>
<td>Toxic dilatation</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Perforation</td>
<td>Perforation</td>
</tr>
<tr>
<td>Abscesses</td>
<td></td>
</tr>
<tr>
<td>Entero-cutaneous fistulae</td>
<td>Chronic disease</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Incomplete response to med-</td>
</tr>
<tr>
<td></td>
<td>ical treatment</td>
</tr>
<tr>
<td></td>
<td>Excessive steroid require-</td>
</tr>
<tr>
<td></td>
<td>ment</td>
</tr>
<tr>
<td></td>
<td>Non-compliance with medica-</td>
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<tr>
<td></td>
<td>tion</td>
</tr>
<tr>
<td></td>
<td>Risk of colorectal carcino-</td>
</tr>
<tr>
<td></td>
<td>ma</td>
</tr>
</tbody>
</table>

**Indications of surgery in CD and UC.**

- Fulminant acute attack
- Failure of medical treatment
- Toxic dilatation
- Hemorrhage
- Perforation
- Chronic disease
- Incomplete response to medical treatment
- Excessive steroid requirement
- Non-compliance with medication
- Risk of colorectal carcinoma

Within 20 years of diagnosis, 80% of patients with Crohn disease require surgery, and many require multiple procedures. The surgical management of CD should be considered as a last resort and resections performed parsimoniously, since recurrence is inevitable (15% per year) with 20-30% of patients concerned within the first postoperative year.

In patients with ileal disease, some strictures are treated conservatively with stricturoplasty, however long or multiple strictures require resection and end-to-end anastomosis.

In total colonic involvement with rectal sparing/minimal rectal involvement, a subtotal colectomy and ileorectal anastomosis is performed. 2/3 of these patients are expected to experience recurrent ileal and/or rectal disease. 2/3 of these patients preserve a functional rectum for 10 years. In total colonic and rectal involvement, a panproctocolectomy with an end ileostomy is an obligate procedure.

While the treatment of UC remains primarily medical, its surgical management when needed is governed by the same conservative philosophy with which CD is approached.

Within 20 years of diagnosis, 1/3 of patients with UC will undergo colectomy and about 2/3 will require a second surgery.

In acute disease, subtotal colectomy with end ileostomy and preservation of the rectum is the procedure of choice. Later, either proctectomy with a permanent ileostomy or ileorectal anastomosis is performed. It is true that the latter procedure avoids a permanent ileostostomy and preserves the rectum, but perseverant surveillance of the rectal mucosa through annual biopsies must be achieved to exclude dysplasia, a precursor lesion for rectal stump carcinoma. An other alternative procedure is ileal pouch anal anastomosis (IPAA) with endoanal mucosectomy of the distal rectum and anal canal. While continence is usually achieved with this procedure, 1/3 of patients will experience pouchitis which presents with diarrhea, bleeding, fever and eventually exacerbation of extracolonic manifestations. In an attempt to ameliorate night-time continence, some surgeons advocate stapling the ileal reservoir to the distal rectum or proximal anal mucosa (ileal pouch-distal rectal anastomosis). The disadvantage of this technique is the cancer risk associated with diseased mucosa.

**Colorectal carcinoma and IBD**

The risk of development of colon carcinoma is estimated to be 20 percent/decade, after the first 10 years of UC. It is true that the incidence of carcinoma complicating CD is less than in UC, however the risk of colorectal carcinoma is still 20 times higher than in the general population. Many centers recommend that colonoscopy should be performed during the remission periods (to avoid iatrogenic perforation) at 1-3 - year intervals in patients with extensive UC of more than 10 years’ duration, and multiple biopsies (2-4 biopsies/10cm, even more specimens are harvested from the left colon, and elevated, stenotic and ulcerated segments). There is insufficient evidence to support the use of a surveillance program in patients with CD.

**References**

16. Valusek PA, Bhatia AM, MD Holcomb III GW, Crohn disease: surgical perspective, emedicine, Updated: Jul 6, 2006

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TRISOMY 13 WITH CYCLOPIA AND PROBOSCIS
A CASE PRESENTATION

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²“Cuza Voda“ Hospital, Iasi
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Abstract
The 3-rd of the “common trisomies”, the trisomy 13, is less frequent than trisomy 21 or 18 and its usually fatal in the 1-st year of life. We present a case of a trisomy 13 with a “normal” triple screen at 16 weeks and a “normal” first trimester US, who was referred at 27 weeks for a US examination. The fetus had a severe growth restriction and some of the malformations which even rarely encountered in the routine US practice, they are classically associated with this kind of disease. The amniocentesis revealed a trisomy 13. The parents asked for the termination of the pregnancy. A female 600g fetus was born and died immediately after delivery, by the impossibility of breathing.

Key words: trisomy 13, malformation, ultrasound.

Introduction
The 3-rd of the “common trisomies”, the trisomy 13, is less frequent than trisomy 21 or 18, occurring in 1/12000 live births [1]. It is usually fatal in the 1-st year of life, with only 8.6% survival rate after 1 year of life, because infants with trisomy 13 have numerous malformations, some of them incompatible with life. The ultrasound (US) examination is important in the detection of these abnormalities and of the severe growth restriction that accompanies this genetic disease.

We present a case of a trisomy 13 with a “normal” triple screen at 16 weeks and a “normal” first trimester US, who was referred at 27 weeks for a US examination. The fetus had a severe growth restriction and some of the malformations which even rarely encountered in the routine US practice, they are classically associated with this kind of disease.

Case report
A pregnant woman of 33 years old, IV G, I P (1 spontaneous abortion, 1 abortion by request, and 1 natural delivery of a normal 3800g baby), was referred at 27 weeks gestation for an ultrasound (US).

She has no significant past medical history, no history of any congenital defects in either her or her husband’s family.

She declared a “normal” US 1-st trimester scan at 13 weeks, a normal triple screen at 16 weeks. The patient had no IgM positive test for TORCH infections, but Ig G was positive for Toxoplasmosis and Rubella, and negative for syphilis and HIV.

The US scan revealed:
-a female fetus with 25 weeks biometry, of 560g weight
-a fetal growth restriction with biparietal diameter and head circumference at 23 weeks (<2%) and abdominal circumference and femoral length at 26 weeks.
-microcephaly with difficulties of the examination of cerebral structures
-semi lobar holoprosencephaly
-severe midline facial defects: cyclopia, absence of the nose, proboscis
-postaxial polydactyly at the right hand

The amniocentesis revealed a trisomy 13.

The parents asked for the termination of the pregnancy.

A female 600g fetus was born and died immediately after delivery, by the impossibility of breathing.

The malformations mentioned at the US scan were confirmed at the necropsy.

Discussions
History: Thomas Bartholin described in 1656 the clinical picture of a patient that may with certainty be classified as trisomy 13[2]. Later clinical descriptions were reported by Feichtiger in 1943 and Otto Ullrich in 1951. In 1960, Klaus Patau made the first cytogenetic description in one patient[3].

Mechanism of pathogenesis:
Trisomy 13 occurs when extra DNA from chromosome 13 appears in some or all of the body’s cells.

- Trisomy 13 - the presence of an extra (third) chromosome 13 in all of the cells.
- Trisomy 13 mosaicism - the presence of an extra chromosome 13 in some of the cells.
Partial trisomy - the presence of a part of an extra chromosome 13 in the cells. The extra material interferes with normal development.

Chromosome studies show trisomy 13, trisomy 13 mosaicism, or partial trisomy.

**Symptoms:**
- Infants with trisomy 13 are small for gestational age and microcephalic and have numerous malformations:
  - midline facial defects such as: cyclopia (single orbit), with microophthalmia or anophthalmia, cebcephaly (single nostril) and cleft lip and palate (60-70%)
  - midline CNS anomalies such as: alobar holoprosencephaly
  - ears are often small and malformed
  - a punched out scalp lesion over the left or right occiput called “aplasia cutis congenita”.
  - malformations of the limbs: postaxial polydactyly of the hands (75%), club feet, rocker bottom feet
  - abnormalities of the genitalia: hypospadias, cryptorchidism are common in boys whereas girls generally have hypoplasia of the labia minor
  - congenital heart disease (>80%).[4,5]
  - severe mental retardation
  - decreased muscle tone

Because fetuses with trisomy 13 have severe abnormalities, the sensitivity of prenatal sonography for the detection of this aneuploidy is very high, most studies reporting sensitivities greater than 90%[6,7,8]. Some of the most common findings included: central nervous system anomalies (58%), cardiac defects (48%), facial anomalies(48%), growth restriction (48%), holoprosencephaly(39%), renal abnormalities(33%)[6]

On the other hand, a study performed via routine scanning reported a sensitivity of only 68.2% for the detection of trisomy 13 [9] and the authors believed than when detailed scanning is undertaken, the performance would be better.

**Paraclinical exams and tests:**
- Gastrointestinal x-rays or ultrasound may show rotation of the internal organs.
- MRI or CT scans of the head may reveal a problem with the structure of the brain. The problem is called holoprosencephaly. It is the joining together of the two sides of the brain.

**References**
11. De R. J. M. Gardner, Grant R. Sutherland, Chromosome abnormalities and genetic counseling, third edition, 262

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NIJMEGEN BREAKAGE SYNDROME
CLINICO-CYTOGENETIC PATTERN

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Abstract

Here we report an 8 years old girl who had post natal growth deficiency, microcephaly, facial dysmorphism, partial syndactyly of the second and third toes, susceptibility to infections, leukocytosis, immunodeficiency, adenopathy, but now sign of telangiectasia, ataxia and in evolution developed malignancy. Chromosomal analysis showed anomalies. By combining clinical manifestations and laboratory findings including cytogenetic findings and taking in account the evolution of the patient, we sustain the diagnosis of Nijmegen Breakage Syndrome.

Key words: Nijmegen breakage syndrome, chromosome aberrations, Burkitt lymphoma

Introduction

Nijmegen breakage syndrome (NBS) is a rare genetic disease with an estimated incidence of 1:100,000 live births. This condition is characterized by chromosomal instability and it is considered to be related with Fanconi anemia (Schroeder et al., 1964), ataxia-telangiectasia (A-T) (Hecht et al., 1966) and Bloom syndrome (Bloom, 1966). NBS has an autosomal recessive inheritance pattern. Heterozygotes are usually asymptomatic. The cardinal symptoms of NBS are: microcephaly, growth retardation and immunodeficiency.

NBS was just recently accepted as a distinct clinical entity, Weemaes et al. in 1981 described this syndrome in 2 patients. In 1985, Seemanova et al. found the chromosomal instability sensitivity to ionizing radiation, and radioresistant DNA synthesis in a group of patients. These manifestations were similar to the characteristic chromosomal anomalies observed in ataxia-telangiectasia (A-T) but the clinical manifestations did not fit the pattern of A-T. NBS was considered a variant of A-T at that time. Two independent groups, one coordinated by Matsuura et al. and the other one by Varon et al., identified the mutation of NBS1 gene in 1998. NBS1 gene is located on chromosome 8q21 and is encoding a protein called nibrin. This protein is a member of the hMre11/hRad50 protein complex, and has an important role in DNA repair.

Nijmegen Syndrome is characterized by microcephaly, bird-like facies, growth retardation, IQ scores normal or borderline intelligence to mild mental retardation, despite severe microcephaly, irregular skin pigmentation as hyperpigmentation or hypopigmentation, congenital manifestations including clinodactyly, syndactyly, recurrent infections, chromosomal instability, immunodeficiency, predisposition to malignancies as non-Hodgkin lymphomas, leukemia, solid tumors like glioma, rhabdomyosarcoma, and medulloblastoma. The risk of developing malignancies is 60-150 times higher in patients with NBS, due to the chromosomal rearrangements encoding T-cell receptor (Bridges and Harnden, 1982; Gatti and Swift, 1985, Lehmann et al., 1989).

In Poland, Czech Republic, Slovakia, Germany and Ukraine there have been reported an increased number of patients with Nijmegen Syndrome. They seem to have a Slavic origin and carry a major founder mutation, 657del5, in the NBS1 gene. The heterozygote incidence is approximately 1 in 177 in Eastern European populations predominantly among persons from Poland, the Czech Republic and Ukraine (Varon et al. 2000).

Case report

We report an 8 years old female patient. She is the first-born child of a healthy young couple (mother’s age 25, father’s age 30) residing from a small Romanian community that is an isolate of people with Slavic origins (Ukraine). Affirmative the parents declared that they are not relatives. Somatic parameters at birth were: weight - 3200 g, length - 50 cm, head circumference - 30 cm (<3rd centile). There was no family history of short stature, congenital malformation and malignancy.

Clinical aspects initial and in evolution

The patient was first admitted to hospital for long lasting fever, microcephaly and was under suspicion for a urinary infection. The somatic parameters were below the normal values for her age: she was 115 cm tall (<3rd centile), 18 kg weight (<3rd centile), had a cephalic circumference of 42 cm (<3rd centile). The phenotypic appearance was suggestive of a genetic syndrome: microcephaly, receding forehead, prominent mid-face, upward slanting palpebral fissures, prominent nose, facial lentigines, micrognathia and large ears (Fig.1, 2). Limb anomalies were also present, shorter second finger phalanx and partial syndactyly of second and third toes of both feet (Fig. 3).
The second admitting to hospital was 6 months later when the patient presented with fever, cough, acute abdominal pain and difficulty in breathing. Clinical, imagistic and laboratory investigation were done. Clinical inspection and examination underlined submandibular adenopathy and an area of dullness during percussion of the right lung fields, fine crackles and dimmed vesicular sound.

The patient was admitted again to hospital 10 days after release because the general condition was aggravating although the treatment was continued at home.

**Complementary investigations**

The first time the patient was evaluated, thoracic X-ray, abdominal ultrasonographies were performed and no worrying signs were noticed. A very detailed neurological evaluation also showed no pathological signs.

At the second admitting the thoracic X-ray revealed right lung pneumonia, but there was no sign of mediastinal lymphadenopathy. Laboratory analyses were done. Complete blood count was performed and white blood cells (WBC) were high (32,000/mm³), hemoglobin and hematocrit values were low. C-reactive protein was found to have high values 15.7 mg/L (normal values: 0-3 mg/L). Immunoglobulins levels were tested and IgA was low (0.224 g/l) (normal range: 0.7-4 g/l), but IgE, IgG, IgM had normal values.

When readmitted, the patient was reevaluated and pulmonary CT was performed showing pneumonia. Abdominal and pelvic CT were done and the findings rouse the suspicion of malignancy. The abdominal CT (Fig. 4) showed an abdominal mass with dimensions of 5/4 cm that was suppressing inferior vena cava, and was extended upwards to inferior duodenal flexure and downwards to aortic bifurcation, retroperitoneal adenopathy at renal hilum in celiac ganglion group. Pelvic CT revealed adenopathy masses with dimensions between 1 and 4 cm at internal and external iliac lymph nodes on both sides (Fig. 5).
Laboratory analyses were repeated and leukocytosis was found, and also C-reactive protein was elevated, serum α-fetoprotein being in normal range. Biopsy samples were taken from abdominal mass, appendix and retroperitoneal ganglion. Pathologic examination of the biopsy pieces established the diagnosis of Burkitt lymphoma and the patient was referred to an Oncology Clinic for chemotherapy.

**Cytogenetic analysis**

The first attempt to reveal the patient karyotype failed. Cytogenetic analysis was difficult to perform due to the poor proliferation capacity of lymphocytes that was encountered. A second chromosomal analysis was done at the second admission to hospital. Two PHA stimulated peripheral blood lymphocytes cultures from the patient were performed. In the first culture, 9 mitosis could be analyzed, 6 metaphases had a normal 46,XX karyotype, while 3 revealed chromosomal anomalies. The second culture was supplemented with 2mmol/l L-glutamine and 26 mitoses were obtained, including 19 abnormal metaphases. The slides that were made were examined in Department of Genetics at Ulleval as well as in Timisoara. Cytogenetic findings included preferentially aberrations of chromosomes 7 and 14, as other cases of NBS reported in the literature (t(7;14)(q22;q32)). Other chromosomal anomalies found were translocations (t(2;6)(q33;q27), isochromosomes (11q) and aneuploidies such as monosomies, trisomies of chromosome 19 and 8, marker chromosomes and also chromosomal breakages, del(22)(q11) (Fig. 6, Fig. 7).

![Figure 4. Abdominal CT Abdominal mass suppressing inferior vena cava.](image1)

![Figure 5. Pelvic CT - adenopathy masses.](image2)

![Figure 6. Partial karyotypes with chromosomal anomalies: translocations, isochromosome and deletion. Arrows indicate chromosomal aberrations.](image3)
Discussions and conclusions

Associating the hallmark clinical findings, the recurrent respiratory infection, the paraclinical investigations (leukocytosis, fever, low levels of IgA), the imagistic investigations (echography, CT and histological exam), the cytogenetic findings and the evolution to Burkitt lymphoma, we can sustain the diagnosis of Nijmegen Syndrome. From the manifestation more rarely found we identified syndactyly (Table I).

Table I. NBS clinical manifestations

<table>
<thead>
<tr>
<th>Clinical manifestations in NBS:</th>
<th>Present patient</th>
<th>Others clinical manifestations in NBS:</th>
<th>Present patient</th>
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</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>+</td>
<td>Clinodactyly</td>
<td>-</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>Polydactyly (preaxial)</td>
<td>-</td>
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<tr>
<td>Peculiar face (“bird-like” appearance)</td>
<td>+</td>
<td>Transverse palmar crease</td>
<td>-</td>
</tr>
<tr>
<td>Receding forehead</td>
<td>+</td>
<td>Wide gap toes</td>
<td>-</td>
</tr>
<tr>
<td>Prominent mid-face</td>
<td>+</td>
<td>Syndactyly of the toes</td>
<td>+</td>
</tr>
<tr>
<td>Prominent philtrum</td>
<td>+</td>
<td>Renal abnormality</td>
<td>-</td>
</tr>
<tr>
<td>Receding mandible</td>
<td>+</td>
<td>Eye fundus with pigment deposits (“salt and pepper” type)</td>
<td>-</td>
</tr>
<tr>
<td>Upward slant of palpebral fissures</td>
<td>+</td>
<td>Recurring infections</td>
<td>+</td>
</tr>
<tr>
<td>Epicanthic folds</td>
<td>-</td>
<td>Respiratory tract: pneumonia, bronchitis</td>
<td>+</td>
</tr>
<tr>
<td>Large ears with dysplastic helices</td>
<td>+</td>
<td>Respiratory tract: bronchiectasis</td>
<td>-</td>
</tr>
<tr>
<td>Areas of hyperpigmentation</td>
<td>-</td>
<td>Urinary tract infections</td>
<td>+</td>
</tr>
<tr>
<td>Areas of hypopigmentation</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun-sensitivity of palpebrae</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abnormalities</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telangiectasia (conjunctival)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freckles (mainly in butterfly distribution in face)</td>
<td>+</td>
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</tbody>
</table>

The combination of immunodeficiency and chromosomal instability as seen in the girl we described is present in both ataxia-telangiectasia and Nijmegen breakage syndrome. Ataxia telangiectasia is excluded because the girl did not have progressive cerebellar ataxia, oculo-cutaneous telangiectasia or elevated serum α-fetoprotein typical for the disorder. Differential diagnosis also included: primary microcephaly, Fanconi anemia, Xeroderma pigmentosum, Bloom Syndrome, Immunodeficiency with proportionate short stature, A-T–like disease, X-linked.
agammaglobulinemia, Ligase IV (LIG4) syndrome (Ming et al. 1999). The clinical findings and the paraclinical investigations ruled out these syndromes.

The constitutional karyotypes of patients with NBS are usually normal (46,XX or 46,XY). However in literature, the typical cytogenetic anomalies reported are: spontaneous chromatin and/or chromosomal breakage (7p13, 7q35, 14q11, and 14q32), rearrangements involving mainly chromosomes 7 and 14: inv(7)(p13q35), translocations 7/14, 7/7 and 14/14 and acentric fragments. There have also been reported other chromosomal anomalies such as: dup(4)(q28q35.2), t(1;8), t(14;20).

It is important to mention that the first lymphocytes culture from this patient was unsuccessful. This is concordant with the other reports from literature (Vazken M. Der Kaloustian, 1996). It is also known that is difficult to perform cytogenetic analysis due to the poor proliferation capacity of lymphocytes (The International Nijmegen Breakage Syndrome Study Group conducted by J. A. Hiel, C. M. Weemaes and L. P. van den Heuvel). The cytogenetic anomalies found for the patient were in high proportion (62.8%). According to Hiel et al (2001), cytogenetic aberrations are present in all cases varying usually from 10 to 45% of the metaphase, but higher percentages have been reported. Translocations of chromosomes 7 and 14, 2 and 6 were clonal. The frequency of chromosomal breakage was low, possible due to the fact that the cytogenetic analysis was performed at the time the malignant process was identified. A high number of supernumerary marker chromosomes were also found.

Due to the fact that this is an autosomal recessive condition, the parents must be heterozygotes, carriers of a single copy a mutation in the NBS1 gene. It is important to monitor the genitors due to the fact that some reports have suggested an increased risk of malignancy in carriers of the common Slavic mutation, 657del5 (Chrzanowska, 2007). They have a risk of 25% of giving birth to another affected offspring. For prenatal genetic diagnosis might be useful the molecular genetic analysis and there are also available biochemical assay. Unfortunately, in Romania there is not possible to perform prenatal diagnosis for Nijmegen Syndrome.

No specific therapy is yet available for NBS. For this patient it is necessary a therapeutic strategy for Burkitt lymphoma. It also may be useful the antibiotic prophylaxis, vitamin E supplementation and substitution hormone therapy to support the development of secondary sex characteristics when the patient reaches the appropriate age.

The prognosis for the patients with Nijmegen Syndrome is poor; usually the premature death occurs due to the infection complications or the malignancy. Our patient had developed malignancy in a relative short period of time after she was first investigated and the prognosis is estimated to be low.

Although the clinical manifestations and investigations of the patient, and also the evolution of the disease allowed us to establish the diagnosis of Nijmegen Syndrome, for an accurate diagnosis, molecular genetic investigation for the mutations of the NBS1 gene is to be performed.

References

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TRISOMY 21, CHOLELITHIASIS AND POSITIVE SWEAT TEST AT INFANT - DIAGNOSTIC DIFFICULTY

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Abstract
A 5 month old female infant was admitted to hospital for evaluation of a particular phenotype. The particular phenotype was assimilated to a Langdon-Down syndrome. The karyotype has confirmed a structural chromosomal abnormality of robertsonian translocation type between acrocentric chromosomes 21 and 22, and a numerical chromosomal abnormality consistent with a total trisomy 21 type, the cytopenic formula being: 46, XX, -22, +21, trob (21;22). The echocardiography, revealed a common atrioventricular canal in its complete form. An abdominal ultrasonographic scan was also performing, showing the gallbladder, which exhibited three hyper echoic image. The sweat test was positive. The genetic test for cystic fibrosis was negative. The conclusion is, if it is about comorbidity trisomy 21 and cystic fibrosis, or sweat test could be false positive in trisomy 21.

Key words: trisomy 21, cystic fibrosis, cholelisthiasis

Case presentation
In October 2008, a 5 month old female infant was admitted to the II Pediatric Clinic for evaluation of a particular phenotype. The particular phenotype was observed at birth, and also a cardiac murmur was noted, labeled initially as a ventricular septal defect. The parents were reticent about medical problems evidenced and did not follow the recommendations linked to the med of additional evaluation. About 10 days prior to current admission, at an ultrasonographic examination, the presence of a cholelisthiasis is evidenced, and this prompted the admission to our clinic for evaluation. The clinical examination at admission revealed an average general status, a weight of 5000g, a length of 59 cm, a cranial perimeter of 40 cm, a thoracic perimeter of 38 cm a particular phenotype (Mongolian epicanthic skin folds, eyelid slit, small, low-seat ears, hypertelorism, epicanthus, a slightly open mouth with tongue protrusion, a single palmar flexion crease = simian crease, a groove between the great toe and the second toe = the sandal sign), pale integuments, a globally reduced subcutaneous tissue, a generalized muscle hypotonia, more marked on axial groups, no pathological change in lungs at auscultation, a telemid systolic murmur of III-IV/VI degrees on the entire cardiac area, with interscapulovertebral and axillary irradiation, a normal time of capillary re-coloring, a well-beating peripheral pulse, abdominal hypotonia with right abdominis diastasis, liver and spleen within normal limits, spontaneous miction with no signs of meningeal irritation.

We were facing an infant with a particular phenotype, with clinical characteristics of Langdon–Down syndrome, with a cardiac murmur attributable to the malformative complex, usually accompanying this syndrome. Associated to this is the diagnosis of cholelisthiasis.

Lung X-ray evidenced a global cardiomegaly and a paramediastinal opacity in the upper right area, relatively homogenous and well circumscribed (a possible condensation process, or an adenopathy), with a bilateral paramediastinal alveolar interstitial infiltrate (fig 1). The sweat test was positive; initially the concentration of NaCl was 86 mmol/l, later 98 mmol/l (normal values: < 40 mmol/l-negative; < 40/60 mmol/l-inconclusive; > 60 mmol/l-positive). An echocardiography, revealed a common atrioventricular canal in its complete form and a mild/moderate pulmonary hypertension; an abdominal ultrasonographic scan was also performing, showing normal results except for the gallbladder, which exhibited three hyper echoic image which a maximum diameter of 0,5 mm, a result confirmed also by a magnetic resonance cholangiography, where several millimetric images were seen, very likely due to a biliary microlithiasis. The karyotype has evidenced a structural chromosomal abnormality of robertsonian translocation type between acrocentric chromosomes 21 and 22, and a numerical chromosomal abnormality consistent with a total trisomy 21 type, the cytopenic formula being: 46, XX, -22, +21, trob (21;22) – fig 2.

The subsequent positive diagnosis was as follows: Trisomy 21 (Langdon-Down syndrome), common atrioventricular canal in complete form, cystic fibrosis, and cholelisthiasis.
In favor of cystic fibrosis diagnosis are pleading two markedly positive sweat test the failure to thrive, and the likelihood that mutations which make up the genotype could not be identified with the aid of the Elucigene CF 29 Kit, as well the presence of cholelithiasis (although the cholelithiasis usually is not a rapidly progressing developmental event beginning in infancy; as a matter of fact, it isn't mentioned in guides for the performance of sweat test).

The arguments against the diagnosis of cystic fibrosis are the following: a negative genetic test and a possibility of a false-positive sweat test. Among the disease in which the sweat tests may be false-positive one can mention: a severe malnutrition, celiac disease, mucopolysaccharitoses, hypothyroidism, pseudohypoaldosteronism, diabetes insipidus, HIV infection, as well as Down syndrome. In this regard, there are several European reports on cases, going up to 2001-2002, referring to isolated cases of Down syndrome with a positive sweat test, without statistical consideration though (the most extensive communication can be found in Pediatrics in 1968, reporting on 3 such cases).

Concerning the cholelithiasis, the following issues emerge: is it a developmental complication in the context of cystic fibrosis (the arguments against are presented above), is it a part of 6% of the cases of trisomy 21, appearing through hypotonia of excretory bile ductile or has it an independent cause). Among causes of biliary lithiasis in infants one cite the hemolytic anemia, parental nutrition, familial or anatomical cholestasis, and transiently, following ceptrixone administration.

The evaluation and the prognosis for this child depend on two major things: a surgical correction of congenital cardiac abnormality, and, if the suspicion of cystic fibrosis is confirmed, the development of respiratory disease influences the vital prognosis.

The particularity of this case consist, on one hand, in the rarity on the chromosomal abnormality involved, the robertsonian translocation representing a very small percentage (2,5-4%) of the integrality of abnormalities presented in the Down syndrome and, on the other hand, Down syndrome - cystic fibrosis - cholelithiasis, three independent or interconnected clinical situations.

References


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RENAL CONSEQUENCES IN HIV INFECTED CHILDREN

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Abstract

Background and Aim: Renal dysfunction is seen after years of HIV infection in adults but the true prevalence of childhood HIV nephropathy is unknown. HAART has been beneficial not only for long term patient survival but also to slow down the process of renal involvement and rapid progression to end stage renal disease. HIV infection can have a renal impact conditioned by the induced immunodeficiency (autoimmunity, infection) or by its highly aggressive therapeutical approach. The aim was to study the renal involvement of long term HIV infection in 91 children and adolescents. Materials and Methods: The study lot comprised 91 HIV patients (6 weeks-19 years old) admitted in the period of September 2008 - February 2009. All were previously diagnosed cases in different HIV stages. 70.32% of patients have been on HAART (2 NRTI + 1 PI) and rest on double or single anti retroviral drugs. Results: 32.96% of patients were hypertensive (16.66% borderline, 66.66% stage 1, 10.12% stage 2, and 6.66% stage 3). Hematuria in Addis cell count was present in 8.79% and proteinuria was found in 5.49% patients all in stage C2 and C3. On 24 hr urine samples we found 25.57% having high chloride levels, 6.59 with natriuria. Urinary levels of potassium and calcium were within normal range. Metabolic acidosis was found in 31.86%. 8.79% had hyperkalemia and 5.49% had hypernatremia in stage C2 and C3. 2.19% had low creatinine clearance (in stage C2). Urinary tract infection (UTI) was diagnosed in 13.18% (91.66% with E.Coli & 8.33% with Proteus); associated mild hydronephrosis in 5.49% and renal calculi in 3.29% of patients have been identified. 27.47% had a high viral load at the time of study. Conclusion: Renal involvement in HIV positive children is a frequent finding. Hence, measuring early urinary biomarkers can help in early detection of kidney disease and to prevent ESRD in HIV-infected children. Metabolic acidosis and hyperkalemia were positive findings without any evidence of kidney damage seen in our patients. The presence of proteinuria in only 5.49% patients was suggestive of none having severe glomerular lesions. There is evidence that HAART treatment has a beneficial effect on kidney disease progression as the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow velocity. Key words: HIV, nephropathy, children.

Introduction

HIV infection/AIDS is a global pandemic, with cases reported virtually from every country. In Romania we were confronted HIV/AIDS being one of the world’s most devastating diseases; nearly 25 million people have died worldwide, since 5th June 1981, since the first case was diagnosed by Dr. M. Gottlieb (from UCLA). The current estimates of the number of persons living with HIV infection worldwide are over 42 million. Though children represent only 6% out of it, they accounted for 18% of the 3 million AIDS deaths approximately every year. Only 4% out of the one million people now on antiretroviral treatment are children. Unlike adults where more than 90% of the time HIV infection occurs through sexual route, in children 95% of cases occur due to Vertical Transmission from their infected parents. Among the various organs which are involved with the progression of HIV infection, kidney is also a part of it. Hence, HIV-associated nephropathy (HIVAN) is a type of kidney disease that occurs in patients who are infected with the human immunodeficiency virus (HIV). In 1984, clinicians in New York and Miami reported HIV-infected patients with heavy proteinuria (often > 10 gm/day) and rapid progression to end-stage renal disease (ESRD) occurring within 1-2 years. Nephropathy associated with human immunodeficiency virus type 1 (HIV-1), is generally seen after years of HIV-1 infection, although in few cases early onset have been described (1). Associated AIDS is found in majority of patients with early-onset HIV associated nephropathy (2). Nearly 5 to 15 % of patients having well-controlled HIV-1 infection and an undetectable viral load in blood may have histologic stigmata of HIV-associated nephropathy (5). However, in these patients, actual AIDS had occurred in the course of the disease, which was not the same in our study group. A paper from NEJM 2005 suggested that HIV-associated nephropathy (HIVAN) can occur at any stage of HIV-1 infection (4). Attempts to estimate the number of HIV-infected or AIDS patients who have developed the HIV nephropathy are hindered by the fact that diagnosis of nephropathy in an HIV-infected patient does not lead to the diagnosis of AIDS; this diagnosis is made only when the HIV antibodies plus certain unusual infections occur. Appropriate accurate diagnosis based on HIV antibody detection until the age of 15 months is generally difficult and hence needs special additional parameters. (6) Striking similarities are encountered between patients having HIV associated or
AIDS associated nephropathy. These nephropathies are labeled as HIVAN, HIVN, AIDSN, AIDSAN, HAN, etc., but HIVAN and HIVN (7) are most frequently used. Varying components are described and the most significant include: proteinuria with nephrotic syndrome (NS), azotemia, normal blood pressure, enlarged kidneys, rapid progression to end-stage renal disease (ESRD), and not do not clearly respond to any treatment (8).

The virus
HIV1 is a retrovirus, which carries RNA as their genetic material and hence reverses the usual flow of genetic information within the host cells in order to reproduce (4, 20). Studying the infected Tcell has helped us in understanding the association between HIV-1 and host factors. The HIV1 virus induces a productive infection of the Tcells mainly by the process of membrane fusion (mediated by its envelope protein gp120, gp41 or Env) (26). The fusion of HIV-1 to the cell membranes is usually triggered by the interaction of gp120 with two cellular components: CD4 and a coreceptor belonging to the chemokine receptor family. Once inside the cells, the retrovirus RNA is copied using a reverse transcriptase enzyme into a complementary single strand of DNA. In the cytoplasm, this single-stranded retroviral DNA is then copied into double-stranded retroviral DNA and the retroviral DNA migrates into the host cell nucleus and becomes inserted into the host cell DNA as a provirus. At this stage, HIV-1 can remain in a latent form without producing any viral protein or may start to produce new copies of HIV RNA immediately. The process of HIV-1 replication starts when the cell’s RNA polymerase becomes activated by DNA sequences located in two DNA regions near the ends of the provirus, named long terminal repeats. Within the host cell, proviral DNA, when activated, produces new strands of HIV RNA. Some of the RNA strands behave like mRNA producing proteins essential for the production of HIV-1, while others become encased within the viral core proteins to become the new viruses. The HIV genome contains at least nine recognizable genes within the viral core proteins to become the new viruses. The epidemicological data
Despite HIVAN being a known complication of HIV infection in children, information on the prevalence, patient characteristics, and course of HIVAN with ESRD has not been reported for the United State ESRD population. Soon after HIVAN was described in adults, children with perinatal HIV infection were reported to develop collapsing FSGS similar to adults. Ahuja et al in 2004 analyzed data from the standard analysis files as of October 2001 of the United States Renal Data System (USRDS). (21) The incidence and prognosis of HIVAN in children with HIV infection was expected to be similar to adults, but from the 7,732 patients with HIVAN who received dialysis in the United States, only 0.78% was younger than 21 years. The fact that HIVAN occurs in end-stage AIDS could have attenuated the effect of HIV stage of infection on survival showed in Ahuja analysis (24, 25).

Under-reporting of cases of HIVAN could be an important factor contributing to the low prevalence seen in children, as routine screening of all ESRD patients for HIV infection is not a practice. In recent years the lower number of children with HIVAN who have ESRD is more likely due to a decrease in perinatal transmission due to an increase in the number of cesarean sections in HIV-infected mothers and the use of antiretroviral drugs during pregnancy, in US. (23) We tried to search in our patients the underlying etiology whether it is due to primary renal disease or it is due to HIV infection induced or it is an outcome of HIV treatment. While information on antiretroviral therapy in children with HIVAN and ESRD was not available, improved survival after 1996 is consistent with the initial researcher’s observations that HAART improves survival of ESRD patients with HIV. (24) The rate of biopsy in HIV-infected children is different from that of adults, which could have potentially underestimated the prevalence of HIVAN in children. So, the HIVAN and ESRD in children predominantly occur in blacks and the survival of the children is better than that of adults with HIVAN. Obviously, future studies are required to determine changing trends of incidence and prevalence of HIVAN in children in the HAART era.

Essential findings in HIV nephropathy - proteinuria and enlarged kidneys
HIVAN is caused by direct infection of the renal cells with the HIV-1 virus and leads to renal damage through the viral gene products. It could also be caused by changes in the release of cytokines during HIV infection. An up-regulation of renal heparan sulfate proteoglycans seemed to play a relevant role in this process, by increasing the recruitment of heparin-binding growth factors, chemokines, HIV-infected cells, and viral proteins. These changes enhance the infectivity of HIV-1 in the kidney and induce injury and proliferation of intrinsic renal cells. HIVAN usually occurs only in advanced disease states and approximately 80% of patients with HIVAN have a CD4
count of less than 200. Despite being a cause of chronic renal failure, kidney sizes are usually normal or large. Proteinuria seems to be the earliest finding which should raise suspicion of HIVAN and initiate efforts to distinguish HIVAN-related signs/symptoms from those of idiopathic NS. All the non-renal conditions associated with hypoprothrombinaemia and edema may be found in HIV-infected/AIDS patients: liver disease, intestinal protein losses, and malnutrition. For distinguishing HIVAN from other conditions, HIVAN requires identification of an excessive amount of total protein or albumin excreted in the urine per 24 h or determination of a high albumin to creatinine ratio in a spot sample (9, 10) with guidelines as follows: 24-h excretion of total protein >100 mg/m2 in a child. Gross proteinuria is defined as >1 g/m2 per 24 h in a child. (11) Urine albumin/creatinine ratio normally is <0.2 mg/mg in neonates and 0.1 in older children and in the NS usually exceed 5 mg/mg (12). Using Albustix - levels of > + found on more than one occasion are abnormal; persistent readings of > ++ are compatible with gross proteinuria (9). Although clearly present, levels of albuminuria have not been reported in patients with HIV infection/AIDS; thus, in these patients, abnormal albuminuria levels are defined less clearly than abnormal proteinuria levels.

In pediatrics a unique opportunity is available for prospective early identification of children born to HIV-positive mothers; this early identification by their group may account for the marked increase in our rate of identification of patients with HIVAN (12). Numerous technical difficulties get in the way of the accuracy of timed urine collections from infants and children, especially when they are ill. Although the random urine protein/creatinine ratio (Upr/UCr) has previously been shown to accurately reflect daily proteinuria in both adult and pediatric patients (9, 14, 15, 16), a primary concern was the possible overestimation of proteinuria by low creatinine excretion in malnourished patients with low muscle mass. Both Haycock (17) and Schwartz (18) have warned against the errors inbuilt in the assay for PCR. The preferable assessment of proteinuria in any population is the measurement of daily excretion. This may be facilitated by estimating daily urine volume. In the event that body measurements are unavailable, random Upr/UCr closely approximates daily proteinuria. An Upr/UCr <0.2 reflects normal proteinuria of <0.1 g/m2 per day and a ratio >2.0 is consistent with nephrotic proteinuria >1.0 g/m2 per day. (19)

Enlarged kidneys are also constantly found among patients with HIVN at both early and late stages; this characteristic may differentiate patients with HIVN from those with other proliferative renal disorders in which the kidneys are enlarged initially but shrink later on. It is important to remember that the finding of enlarged kidneys by ultrasound does not make the diagnosis of HIVAN. The enlargement may be the reason for requesting the determination of anti-HIV antibodies but the diagnosis of HIV infection must not be made until the other usual criteria are fulfilled (13, 20). The abnormal anatomical findings in the kidneys have consisted of engorged and enlarged organs which can be recognized on the outer and on the cut surfaces; weight and other measurements (width, length, etc.) have confirmed these findings. For all ages, normal tables for weight and size should be consulted for greater accuracy.

The histology

The true prevalence of childhood HIVAN is unknown, since in many pediatric centers renal biopsies have not been performed regularly in all HIV-infected patients with proteinuria [7, 28-33]. In the early years of the AIDS epidemic, based on histology and/or clinical criteria, Strauss et al. and others [30,31,32,33] reported a prevalence of childhood HIVAN of approximately 10%–15%, in populations with a majority of HIV-infected African American children (95%). The following clinical findings not typical of HIVAN were used to suspect the presence of other renal diseases: macroscopic hematuria; microscopic hematuria without proteinuria; high blood urea nitrogen and serum creatinine levels without significant proteinuria; hematuria and/or proteinuria in Caucasian or Hispanic HIV-infected children. Nevertheless, a renal biopsy is the only definitive way of making the diagnosis of HIVAN. One of the features considered characteristic of HIVAN is the presence of focal collapsing glomerulopathy associated with renal enlargement. These changes contrast with the small fibrotic kidneys typically seen in patients with chronic renal diseases of other etiology. In 1994, using the HIV-Tg26 mouse line, they (41) provided the first evidence that: the characteristic renal enlargement of HIVAN was due to an increased proliferation of RTEc; the expression of HIV-1 genes in RTEc was associated with the development of multicystic lesions; the renal accumulation of bFGF/FGF-2 was at least partially responsible for these changes. Subsequent studies confirmed and expanded their initial findings, both in HIV-Tg mice and children with HIVAN [34-38]. In 1999, a landmark paper by Barisoni et al. (38) reported that a dysregulated podocyte phenotype was associated with the proliferation of podocytes and development of HIV-collapsing glomerulopathy and other forms of collapsing FSGS. Under these circumstances, podocytes lose markers of cell differentiation, such as synaptopodin, podocalyxin, and Wilms tumor antigen (WT-1), and proliferate. Synaptopodin, normally found only in mature podocytes, is lost in HIV-associated nephropathy, (1,3) and the podocytes undergo proliferation. The combination of collapsing FSGS and extensive renal tubular injury was initially thought to be specific to HIVAN. However, today we know that under certain circumstances both adults and children not infected with HIV-1 can develop similar lesions. Thus, it is tempting to speculate that other infectious agents may be involved in the pathogenesis of collapsing FSGS. Several studies have investigated the role of Mycoplasma fermentans, the polymavirius simian virus 40, and parvovirus B19 with inconclusive results (39, 40, 41). Several reviews have been written describing the progress made in the treatment of HIVAN during the last 20 years [42-47]. Most previous studies were performed before the HAART era and excluded children. It should be noted that HIVAN is a typical late manifestation of AIDS and, as
such, the outcome of the renal disease will be affected by the presence of other AIDS-related illnesses (encephalopathy etc). Secondly, it is known that HIV-infected children who are not properly treated with anti-retroviral drugs or do not respond to HAART usually die of other reasons before developing ESRD. Thus, the treatment of childhood HIVAN should be planned in close collaboration with other physicians with experience in the treatment of pediatric AIDS, and the treatment of the HIV-1 infection should be a priority over the treatment of the renal disease.

The prognosis of childhood HIVAN depends on the presence of other AIDS-related conditions more than the nature of the primary renal diagnosis. These factors include the response of the child to anti-retroviral therapy, the stage of HIV-1 infection/AIDS, the nutritional status, and the severity of other AIDS-associated illnesses at the time of diagnosis. The mean duration from the onset of proteinuria to the development of ESRD in children with HIVAN varied from 8 months to up to 3 years, depending on the geographical location and the presence of other AIDS-associated illness. The prognosis of HIVAN in children on dialysis prior to the introduction of HAART was very poor, and depended on the overall clinical status of the HIV infection.

Our study

We started our study assuming whether the HIV infection can have a renal impact conditioned by the induced immunodeficiency (autoimmunity, infection) or by its highly aggressive therapeutical approach. The main aim was to study the renal involvement of long term HIV infection. Our cohort is 91 children and adolescents having age between 6 weeks and 19 years. (48 females and 43 males) admitted in the period of September 2008 to February 2009 in our HIV department were analyzed. All were previously diagnosed and registered cases of our hospital. The HIV stages noted were as follows: B1-23.07%, B2-8.79%, C1-38.46%, C2-21.97% & C3-4.39%; 70.32% of patients have been on HAART (2 NRTI + 1 PI) and rest on double or single anti retroviral drugs. No mortality was seen in our study period. All of them were from are from Timis, Arad and Caras-Severin counties, all three from the Western part of Romania. Monitoring the blood pressure, measuring the serum and urine electrolytes, analyzing the 24 hour urine specimens and taking into account the blood gas analysis were our main concerns. Results obtained were as follows: 32.96% of patients were hypertensive. Out of which 16.66% were having border line, and the majority 66.66% were in stage 1 of hypertension. 10.12% were in stage 2, and the rest 6.66% were having stage 3. Hematuria in Addis cell count was present in 8.79% and proteinuria was found in 5.49% patients all in stage C2 and C3 of HIV. On 24 hr urine samples we found 25.57% having high chloride levels, 6.59 with natriuria. Urinary levels of potassium and calcium were within normal range. Metabolic acidosis was found in 31.86%. 8.79% had hyperkalemia and 5.49% had hypernatremia in stage C2 and C3 of the disease. 2.19% had low creatinine clearance (in stage C2). Urinary tract infection (UTI) was diagnosed in 13.18%, among these majority i.e. 91.66%, E.Coli was the culprit found and in rest 8.33% Proteus was the causative bacteria. Abdominal ultrasound revealed associated mild hydronephrosis in 5.49% children and renal calculi in 3.29%. From all, 27.47% had a high viral load during the study period. Among these 91 children 48 were adolescents suffering from HIV infection for more than 10 year. The above mentioned laboratory picture was found more frequently in these 48 patients, then in children having less than 10 years since diagnosis, which leads us to understand that renal changes appear generally after a long term HIV infection. Hence from our study we were able to conclude that renal involvement in HIV positive children is a frequent finding. Therefore, measuring urinary biomarkers can help in early detection of kidney disease and also in preventing ESRD in HIV-infected children. Metabolic acidosis and hyperkalemia were positive findings without any evidence of kidney damage seen in our patients. The presence of proteinuria in only 5.49% patients was suggestive of none having severe glomerular lesions. Since UTI is present in similar percentage of normal sexually active adolescent population it cannot be concluded that presence of UTI found in our study lot is due to HIV associated decreased immunity. There is evidence that HAART treatment has proved to have beneficial effect not only in HIV treatment but also on kidney disease prevention and the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow pace. Early detection and careful clinical follow-up of children with HIVAN may reduce the incidence of renal complications and improve their quality of life.

Conclusions

Renal involvement in HIV positive children is a frequent finding. Hence, measuring early urinary biomarkers can help in early detection of kidney disease and to prevent ESRD in HIV-infected children. There is evidence that HAART treatment has a beneficial effect on kidney disease progression as the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow velocity. The prevention of HIVAN should be our first priority. The early identification of HIV-1-infected pregnant women and prevention of the vertical transmission of HIV-1 continues to be a health challenge throughout the world. Almost 20 years after the first cases of HIVAN were described; we continue to see children who are newly diagnosed with AIDS and HIVAN in the emergency room. Highly active anti-retroviral therapy (HAART) appears to be the most promising treatment to prevent the progression of childhood HIVAN. Moreover, the diagnosis of HIV-1 infection/AIDS in a child could be the first indication of the HIV-1-positive status of the mother. We are hopeful that during the next years, better education, prevention, and treatment programs will lead to the eradication of this fatal childhood disease.
References
33. in HIV-1 infected children. Pediatri Nephrol 11:161–163
42. Pediatr Nephrol 14:132–137
THE INFLUENCE OF MATERNAL VAGINAL AEROBIC FLORA ON NEWBORN EARLY INFECTIONS

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Abstract

Objectives: To study cervical colonization in women with premature rupture of membranes and the influence of infection on preterm newborns.

Methods: Prospective analysis.

Results: 167 (38.66%) from 432 preterm deliveries were complicated with premature prelabour rupture of the membranes (PPROM). Organisms which induce chorioamnionitis and newborn infections mostly belong to group B streptococci (GBS), E. Coli and Staphylococcus aureus. In most cases of congenital neonatal sepsis cases bacteriological cultures from the mother had been negative. Documented sepsis during 72 hours of life was detected in 13.17% of our patients and 55.8% of women received antibiotics. The risk of neonatal mortality rises proportionally and significantly in relation to low birth weight in PRM cases.

Conclusions: Further randomised trials with more sensitive methods of bacterial investigation should be conducted in order to reduce the incidence of preterm deliveries and newborn early infection.

Key words: premature rupture of membranes, neonatal complications.

Introduction

Premature rupture of fetal chorioamnionitic membranes by definition occurs before the onset of labor. Premature rupture of fetal membranes (PROM) occurs in approximately 10% of all pregnancies (1). When this event occurs before 37 weeks of gestation, it is deemed preterm premature rupture of membranes (PPROM) that has been estimated to affect 3% to 4.5% of all deliveries (2). Premature delivery is still a major medical problem as about 50% of cases are presumably due to infection. Preterm PROM increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death.

Potential pathogens arise largely from the ascending route of the genital tract and from the endogenous vaginal flora, causing chorioamnionitis. Organisms which induce chorioamnionitis and newborns infections mostly belong to group B streptococci (GBS), E. Coli, Staphylococcus aureus, Klebsiella spp, while respiratory tract organisms like Haemophilus influenzae, Streptococcus pneumoniae occur more rarely. The incidence of preterm deliveries is 8-11% in Romania.

Objective

The purpose of the study was to explore the vaginal aerobic flora and the influence of infection on preterm deliveries in Clinic of Obstetrics and Gynecology „Bega” Timisoara in 2004-2006.

Methods:

Prospective analysis.

Study design

There were 432 preterm deliveries in Clinic of Obstetrics and Gynecology „Bega” during the 3 year period. Although in general in good clinical practice, in the case of all spontaneous preterm deliveries, bacteriological analyses are taken from the cervix and vagina, only 68 bacteriological samples were taken from the cervix and 50 from the vagina during 3 years. In 120 cases bacteriological samples were taken from the preterm newborn’s blood.

Results

- 167 (38.66%) from 432 preterm deliveries were complicated with premature prelabour rupture of the membranes (PPROM).
- Route of delivery in 280 (64.8%) women was cesarean section. 51% of women received antibiotic before labor and corticosteroid were used in 187 (43.2 %) of cases to induce fetal lung maturity.
- Acute chorioamnionitis was diagnosed in 34 cases (7.88%). The incidence of chorioamnionitis increased significantly with decreasing gestational age.
- Most of the bacteriological samples taken from the cervix and the vagina were negative (Table 1).
Table 1. Relationship between gestational age and presence of pathogens in the cervix and the vagina before threatened or during preterm delivery.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>E. coli</th>
<th>Staphylococcus aureus</th>
<th>GBS</th>
<th>Other aerobic pathogens *</th>
<th>Number of negative samples</th>
<th>Number of investigated samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>30-34</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>34-37</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>14</td>
<td>86</td>
<td>118</td>
</tr>
</tbody>
</table>

*other aerobic pathogens (Klebsiella spp, Haemophilus influenzae, Streptococcus pneumoniae)

- Neonatal sepsis was diagnosed by positive blood or cerebrospinal fluid cultures. Possible neonatal sepsis was diagnosed when two or more of the following criteria were present: white blood cell count less than 5000/mm³, polymorphonuclear counts less than 1800/mm³, ratio of bands to total neutrophil counts greater than 0.2.
- In most cases of congenital neonatal sepsis cases bacteriological cultures from the mother had been negative, or the samples had not been taken (Table 2).

Table 2. Relationship between presence of pathogens isolated from the mother’s cervix during pregnancy and preterm newborn’s perinatal infection.

<table>
<thead>
<tr>
<th>Organism from cervix</th>
<th>Perinatal death</th>
<th>Congenital sepsis</th>
<th>Congenital pneumonia</th>
<th>Omphalitis</th>
<th>Conjunctivitis</th>
<th>Infectio nonspecific</th>
<th>Without infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>GBS</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Other aerobic pathogens</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Sample negative</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>28</td>
<td>70</td>
</tr>
<tr>
<td>Sample was not taken</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>22</td>
<td>9</td>
<td>16</td>
<td>37</td>
<td>16</td>
<td>55</td>
<td>167</td>
</tr>
</tbody>
</table>

- In 8 of 22 congenital sepsis cases pathogens were isolated from the newborn’s blood (E. Coli, group B streptococci (GBS), Staphylococcus aureus, Klebsiella pneumoniae, Haemophilus influenzae).
- Mother and newborn did not share the same pathogens in 13% cases.
- PPROM is associated with 30% to 40% of premature births and it is also responsible for the neonatal problems resulting from prematurity (3). PPROM by itself is not an independent risk factor for producing neonatal morbidities (Table 3).
- Preecocious neonatal mortality at preterm babies with PPROM represents 11.16%. The risk of mortality rises proportionally and significantly in relation to low birth weight in PRM cases.

Table 3. Neonatal morbidity after PPROM.

<table>
<thead>
<tr>
<th>Comorbid Conditions</th>
<th>Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal early sepsis</td>
<td>22</td>
<td>13.17</td>
</tr>
<tr>
<td>Moderate/severe intraventricular hemorrhage</td>
<td>42</td>
<td>25.14</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>72</td>
<td>80.83</td>
</tr>
<tr>
<td>Apnea of prematurity</td>
<td>78</td>
<td>46.70</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>2</td>
<td>1.19</td>
</tr>
<tr>
<td>Anemia of prematurity</td>
<td>123</td>
<td>73.65</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6</td>
<td>3.59</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>26</td>
<td>15.56</td>
</tr>
<tr>
<td>Secondary spontaneous pneumothorax</td>
<td>5</td>
<td>2.99</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>5.38</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>6</td>
<td>3.59</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>2</td>
<td>1.19</td>
</tr>
<tr>
<td>Skeletal deformities</td>
<td>11</td>
<td>6.58</td>
</tr>
</tbody>
</table>

* Surviving preterm babies had multiple comorbid conditions. Therefore, the percentages presented do not equal 100%.
Discussion

Rupture of membranes before 37 weeks of gestation accounts for 20% to 40% of PROM (4). Prematurity is the most significant factor in the increased perinatal morbidity and mortality associated with PROM because delivery occurs within 7 days of PROM in over 80% cases. So PROM is not an independent risk factor for neonatal morbidity in preterm births. Neonatal morbidity is affected mainly by prematurity itself, rather than by the occurrence of PROM (5). 84.66% of our infants were preterm which is more than two fold in other reported cases.

The neonatal pulmonary consequences of PPROM include congenital pneumonia which often is associated with maternal chorioamnionitis and surfactant deficiency (RDS) following preterm delivery, and pulmonary hypoplasia and pulmonary hypertension are secondary to interruption of fetal lung growth associated with loss of amniotic fluid. These three conditions may occur simultaneously in the same patient, and presenting signs of each may overlap with other confounding bedside diagnosis. The frequency of pulmonary hypoplasia following midtrimester PPROM has been reported as 0% to 24%. Kilbride et al. identified the risk of pulmonary hypoplasia as nearly 80% with early rupture of the membranes (<25 weeks gestation) combined with duration of severe oligohydramnios greater than 14 days (3). In our study there was 2 cases of pulmonary hypoplasia.

Although previous reports have suggested that prolonged PROM might accelerate pulmonary maturity, this effect has not consistently been recognized. For infants with respiratory distress, surfactant should be given as soon as possible after birth. A recent study suggests that complicated RDS cases, including those with superimposed asphyxia or infection following PROM, may benefit from earlier surfactant retreatment. In addition to RDS, severe preterm infants are at risk for other major morbidities, including intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and chronic lung disease. Limited outcome data suggest that these complications occur at similar rates for PROM survivors as for infants born without PROM (1). In our study 43.1% of infants had RDS.

In PROM cases deformities are significantly related to the duration and severity of oligohydramnios. The reported incidence of skeletal abnormalities in PROM series ranged from 0% to 35%. Commonly, the newborn’s feet or hands are broad and spade-like and may be somewhat edematous. In vertex presentation, the skull is elongated with molding, often with Potter facies. Breech positioning, which is two to three times more frequent following oligohydramnios in midtrimester, may result in marked fetal hip flexion contractures and hyperextension of the lower extremities with an increased risk of hip dislocation. In our study 6.5% of infants had skeletal deformities with club foot being the most common.

Incidence of documented sepsis in the premature born from mothers with rupture of membranes greater than 24 hours is approximately 4%. When signs and symptoms of chorioamnionitis are present the risk of proven sepsis increases to 6%. When prolonged rupture of membranes accompanied with prematurity, the incidence of proven sepsis is 6-7% and in highly suspected and proven sepsis the rate is 7-13% (6). Although the risk of neonatal sepsis is reduced after intrapartum prophylaxis, of a 5% to 9% risk remains (1).

Documented sepsis during 72 hours of life was detected in 13.17% of our patients and 55.8% of women received antibiotics. Sign of infection may be difficult to assess, particularly when the newborn has been partially treated. For preterm infants it is recommended that a sepsis work-up and empiric antimicrobial therapy is started shortly after birth. Depending on the antibiotic used for maternal prophylaxis, resistant or unusual organisms may predominate as etiologic agents for neonatal sepsis.

References


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ACUTE APPENDICITIS IN INFANTS AND TODDLERS: RARE BUT CHALLENGING

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Abstract
The diagnosis of appendicitis in infancy is very difficult to make and is thus usually delayed causing complications such as perforation and abscess formation as well as prolonged hospital stays. Though appendicitis in infants and toddlers is a rare happening, it should nevertheless be overseen in children presenting with colicky pain, vomiting (and/or diarrhea), and fever. Delayed diagnosis is common, particularly in young children, with perforation correlating strongly with delayed diagnosis. WBC and CRP have been demonstrated to be well correlated to the diagnosis of appendicitis in infants and toddlers. Rate of appendiceal perforation is extremely high in infants. Hospitals should develop clinical and imaging protocols that they can use effectively. In countries with limited resources, these protocols should be adapted to the cost effectiveness of the diagnosis and duration of hospital stay. Reducing the morbidity depends largely on increasing the rate of surgical diagnosis at the first presentation to a medical clinic.

Key words: appendicitis, infants, toddlers, management

Introduction
Acute appendicitis is the most common cause of abdominal pain requiring surgery in children. But it is an uncommon entity in young children and rare in infants. The diagnosis of appendicitis in infancy is very difficult to make and is thus usually delayed. This delay is often associated with complications such as perforation and abscess formation as well as prolonged hospital stays. Younger children can be particularly difficult to diagnose because the presentation may be nonspecific, and the child is often apprehensive and uncomfortable, making the evaluation challenging. This study and review of the literature is intended to call attention to the general practitioner that while appendicitis occurs rarely in infants and toddlers, it should be considered as part of the differential diagnosis in the evaluation of an infant or toddler with vomiting, diarrhea, or a simple colicky pain.

Methods
The study was conducted in compliance with the guidelines and after approval of the local ethics board. Records of 19 children less than 4 years of age operated for acute appendicitis at the Pediatric Surgery Clinic of Timisoara from January 2005 till December 2008 were reviewed. History, clinical examination and CBC were used as the primary diagnostic tools. Information reviewed included demographic data, laboratory data, imaging studies, operative reports and physicians’ notes. Descriptive analysis of the pertinent data was performed. Correlation between clinical signs, laboratory analysis and the likelihood of developing appendicitis was performed using basic statistical tools.

Results
19 children less than 4 years old (mean 33.5 months) comprised the study lot, with a male preponderance of 73% (14/19) while female children accounting for only 27% of the operated cases. The most common presenting symptoms were abdominal pain (16), vomiting (15) and fever (14). Diarrhea and anorexia were noticed in 3 cases each. The average duration of symptoms was 2.4 days, with 3 or more days in 7 children. 14 children were seen by a physician before the correct diagnosis was made; 6 were initially treated for an upper respiratory tract infection or otitis media. Leukocytosis was seen in 17 of the patients with an average WBC count of 17423/mm³. ESR was reported high in 47% of the patients while C-reactive protein was positive in 77% of them. 9 patients were subjected to plain abdominal radiography revealing in all of them air-fluid level. Intraoperative findings revealed perforation with peritonitis (19) and intestinal occlusion (7). Culture of the peritoneal fluid was positive for E-coli (6) and Klebsiella (1). Postoperative antibiotics were administered to 17 children for an average of 7 days. The average hospital stay was 10 days including an average of 3 days ICU stay.

Discussions
Appendicitis is the most common indication for emergent abdominal surgery in childhood and has been diagnosed in 1 to 8 percent of children evaluated in urgent care settings for abdominal pain [1,2]. The incidence increases from an annual rate of one to two per 10,000 children between birth and four years of age to 19 to 28 per 10,000 children younger than 14 years [3,4]. During the neonatal, infant and toddler period of life the diagnoses of acute appendicitis can be quite challenging due to the lack of specific signs and symptoms. Delayed diagnosis leads to
higher incidence of perforation and subsequently high morbidity and mortality rates.

**History and physical examination** of a child should consider the following age specific characteristics and should raise the suspicion of an acute appendicitis.

Neonates (birth to 30 days) - Abdominal distention and vomiting are frequently noted. Irritability and lethargy have been reported. A palpable abdominal mass and abdominal wall cellulitis have been noted. Hypothermia, hypotension, and respiratory distress may also occur.

Infants (less than two years) - Vomiting, pain, and fever are present in most patients. Diarrhea is not uncommon [5]. Irritability, grunting respirations, and right hip complaints have also been described.

Preschool (two to five years) - Vomiting and abdominal pain are present in most patients in this age group. Vomiting is often the first symptom noted and frequently precedes pain [6]. Fever and right lower quadrant tenderness are reported frequently in this age group. Anorexia occurs frequently. Most children have symptoms for at least two days prior to diagnosis [7].

Abdominal pain, vomiting and fever were observed to be the most significant classical triad in our study lot. Ninety-five percent (18/19) of patients with appendicitis had at least two of these three signs and symptoms. Presence of diarrhea can be misleading and is usually diagnosed as gastroenteritis.

The laboratory findings are non-specific, thus demanding the diagnosis of acute appendicitis to be an operative one during the infancy period. Elevations in the peripheral white blood cell count (WBC) and C-reactive protein (CRP) levels have been noted in children with appendicitis. The urinalysis is abnormal in some cases. However, these findings are variable and non-specific. Consistent to the findings in literature, we observed high WBC count the percentage of neutrophils elevated in 90% of children in our study lot. This finding, however, is nonspecific [8]. In an observational report describing children with nontraumatic abdominal pain who were evaluated in an emergency department, for those who had either increased WBC or elevated neutrophil count, the sensitivity and specificity for appendicitis were 79 and 80 percent respectively [9]. Infectious disorders that may cause abdominal pain with an increased WBC include gastroenteritis, streptococcal pharyngitis, pneumonia, and pelvic inflammatory disease [10,11]. Elevation of CRP has been reported in children with appendicitis, but sensitivities and specificities range widely [10]. The test appears to be less sensitive in patients who have had symptoms for less than 12 hours [12]. Limited studies suggest that CRP may be more sensitive than WBC in identifying both a gangrenous appendix and appendiceal perforation [12,13]. We noticed elevated ESR in 47% and CRP in 36% of the children. Increased CRP was highly suggestive of appendiceal perforation.

**Imaging techniques** like plain abdominal radiographs showing the presence of caecum and small intestine dilatations in the right lower quadrant (sentinel loop sign) in association with air-fluid level which increase in time are indicative for appendicitis. Free abdominal air is a negative prognostic sign indicating intestinal perforation. Ultrasonography (US) is available in most institutions, is relatively inexpensive, and is safe. US improves diagnostic accuracy in children with suspected appendicitis [14]. Sensitivities have been more variable, ranging from 74 to 100 percent [14,17]. Specificities from 88 to 99 percent have been reported. The diagnosis of appendicitis cannot be reliably excluded unless a normal appendix is seen. Reported visualization rates vary from 22 percent to 98 percent [15,16]. Factors that affect this variability include the experience and technique of the sonographer. Increased utilization of Computed Tomography (CT) and improved accuracy of imaging for acute appendicitis have not contributed substantially to lower rates of negative appendectomy since the mid 1990s, and the perforation rate remains as high as 33 percent [18]. This has raised concerns regarding increased exposure to ionizing radiation, health care costs, and delay in surgical treatment [19]. Limited evidence suggests that protocols emphasizing early surgical evaluation, selective imaging that emphasizes ultrasonography, and careful serial examination (for patients with equivocal radiographic and/or clinical findings) lower rates for negative appendectomy and perforation [20].

**Avoiding complications:** Most children with acute appendicitis have had a period of poor oral intake with increased fluid losses related to fever and vomiting prior to diagnosis. Evaluation of their fluid and electrolyte status is therefore important preparation for surgery. Intravenous hydration and analgesia should be provided. Electrolyte abnormalities should be corrected. Pain control is an important component of preoperative care of children with acute appendicitis, both before and after the diagnosis is made. Antibiotic prophylaxis is routinely used for patients with early appendicitis to reduce the incidence of wound infection and intraabdominal abscess formation. The effectiveness of this practice is supported by a systematic review that noted a significant reduction in wound infections and intraabdominal abscesses among adults and children undergoing appendectomy who received antibiotic prophylaxis [21]. Piperacillin/Tazobactam was the antibiotic of choice in 64% of the children (11/17), while culture sensitive antibiotics were introduced following positive results and included Ceftriaxone, Metronidazole, Ertapenam (all with or without the primary antibiotic). Evidence regarding the optimum duration of antibiotic therapy is limited. Many pediatric surgeons use normalization of white blood cells (WBC) and absence of fever as indications to discontinue intravenous antibiotics [22]. It is common practice among pediatric surgeons, however, to treat for up to seven days or longer, consistent with our findings [22]. We continue intravenous antibiotics in children with advanced appendicitis until they are afebrile, tolerating a regular diet, and have a normal WBC.
Conclusions

Though appendicitis in infants and toddlers is a rare happening, it should nevertheless be overseen in children presenting with colicky pain, vomiting, (+/- diarrhea) and fever. Delayed diagnosis is common, particularly in young children, with perforation correlating strongly with delayed diagnosis. A reliable abdominal examination is the key to demonstrating the physical findings associated with appendicitis and requires that the child be quiet and cooperative. Localized right lower quadrant pain develops more reliably in preschool age children and older. Early diagnosis of appendicitis in infants and children can prevent perforation, abscess formation, and postoperative complications, and can decrease cost by shortening hospitalizations. WBC and CRP have been demonstrated to be well correlated to the diagnosis of appendicitis in infants and toddlers. All children presenting with acute localized abdominal pain, vomiting and fever should be referred for surgical consultation. In children with a typical clinical presentation for acute appendicitis, clinicians should consult a surgeon with experience caring for children prior to obtaining imaging studies. Close observation and follow up without imaging is recommended in children who are unlikely to have appendicitis based upon the clinical examination and laboratory studies (absolute neutrophil count less than 6750/mm³; absence of nausea or vomiting; absence of maximal tenderness in the right lower quadrant). When an apparently normal appendix is found, it should be removed. A careful search for other causes of abdominal pain should be performed. Careful preoperative preparation is necessary to ensure the best outcome for patients with perforating or gangrenous appendicitis. Preoperative management includes replacement and maintenance fluid therapy and preoperative antibiotics. The choice of imaging study in any given clinical situation should consider patient characteristics and institutional resources, such as the availability of US and CT and the expertise of the staff. CT has led to modest improvements in reducing the rate of negative surgery. CT is costly and carries a risk due to radiation exposure. Hospitals should develop clinical and imaging protocols that they can use effectively. In countries with limited resources, these protocols should be adapted to the cost effectiveness of the diagnosis and duration of hospital stay. Reducing the morbidity depends largely on increasing the rate of surgical diagnosis at the first presentation to a medical clinic. The prognosis is reserved and severe in infants and toddlers with acute appendicitis as compared to older children and therefore warrants rapid diagnosis and treatment.

References


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NEPHROLOGICAL APPROACH OF 5 CASES WITH NEURAL TUBE DEFECTS

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Abstract

Introduction: Neural tube defects result from the failed closure of the neural tube between the 3rd and 4th week of in utero development. Myelomeningocele represents the most severe form of dysraphism involving the vertebral column. Objective: The evaluation of prognosis and renal-urinary complications in children with myelomeningocele. Material and method: Authors present 5 cases with myelomeningocele and neuropathic bladder admitted in “Louis Turcanu” Pediatric Emergency Hospital Timisoara. We evaluated clinical aspects, pathogenesis, evolution, complications and the treatment of these cases. Results: In all cases the defect was surgically corrected. In two cases shunting procedure for hydrocephalus followed, while the other cases present spontaneous stabilization of hydrocephalus. Mental retardation was severe (1 patient), moderate (1 patient) and mild (3 patients). Urinary anomalies consisted of neuropathic bladder (5 cases), massive bilateral hydronephrosis (4 patients) and horseshoe kidney (1 patient). The patients presented urinary incontinence, urinary infections (1 case deceased from sepsis) and renal failure. The immobilization, urinary and fecal incontinence represent a severe handicap for these patients and their family. Social integration is difficult. Patients’ prognosis is unfavorable: 1 case deceased at six years of age, two cases already with renal failure and the recurrence of urinary tract infections followed, probably, by renal failure for the other two patients. Conclusions: The association of genitourinary system pathology determined an unfavorable evolution and a negative prognosis for these cases. Folic acid supplementation should be initiated before conception and continued until at least 12th wk of gestation in order to prevent the neural tube defects.

Key words: myelomeningocele, neuropathic bladder, prognostic

Introduction

Neural tube defects result from the failed closure of the neural tube between the 3rd and 4th week of in utero development. Myelomeningocele represents the most severe form of dysraphism involving the vertebral column. The pattern of inheritance of these malformations is multifactorial, rendering the identification of the underlying causes. Essential signaling pathways of the development of the central nervous system include the planar cell polarity pathway, which is important for the initiation of neural tube closure as well as sonic hedgehog pathway, which regulates the neural plate bending.1

Recent findings suggested a link between cilia and the planar cell polarity signaling cascade. In particular, on focus on how this interaction may influence the process of neural tube closure and how these results may be relevant to our understanding of common human birth defects in which neural tube closure is compromised.2

Genetic studies in NTDs have focused mainly on folate-related genes based on the finding that perinatal folic acid supplementation reduces the risk of NTDs by 60-70%.3

Risk factors for renal injury in patients with meningomyelocele are: increasing age, evidence of hydrourteronephrosis and vesicoureteric reflux, high leak pressures and low bladder volume.4

Objective

The authors evaluated prognosis and renal-urinary complications in children with myelomeningocele.

Material and methods

Authors present 5 cases admitted in “Louis Turcanu” Pediatric Emergency Hospital Timisoara with diagnosis:

- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus
- Cerebral palsy
- Neuropathic bladder
- Urinary incontinence
- Renal-urinary anatomic or functional anomalies

We evaluated clinical aspects, pathogenesis, evolution, complications and the treatment of these cases.

Results

I Patriciu, 2 years

- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus
- Arnold Chiari II malformation
- Cerebral palsy
- Neuropathic bladder
- Urinary and fecal incontinence
- Ureterohydronephrosis
- Right vesico-ureteral reflux - ureterostomy
- Recurrent urinary tract infections
- Growth retardation
Table 1 Recurrent urinary tract infections of I Patriciu

<table>
<thead>
<tr>
<th>Days</th>
<th>198</th>
<th>275</th>
<th>379</th>
<th>645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td>E coli</td>
<td>Klebsiella</td>
<td>E coli</td>
<td>Contamination</td>
</tr>
</tbody>
</table>

N Iulia, f, deceased at 6 years of age from sepsis with MSOF
- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus – ventriculoperitoneal shunt
- Cerebral palsy
- Neuropathic bladder
- Urinary and fecal incontinence
- Horseshoe kidney with secondary hydronephrosis
- Vesico-ureteral reflux
- Recurrent urinary tract infections
- Growth retardation

Table 2 Recurrent urinary tract infections of N Iulia

<table>
<thead>
<tr>
<th>Days</th>
<th>1001</th>
<th>1082</th>
<th>1105</th>
<th>1198</th>
<th>1342</th>
<th>1507</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td>Proteus</td>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonas aeruginosa + E coli</td>
<td>Pseudomonas aeruginosa</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Figure 1a, b N Iulia’s Tc-DMSA planar renal scintigraphy show bilateral impairment of renal function.

I Dragana, f, 14 years
- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus
- Cerebral palsy
- Neuropathic bladder
- Urinary and fecal incontinence
- Ureterohydronephrosis
- Recurrent urinary tract infections
S Ionut, m, 15 years
- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus
- Cerebral palsy
- Neuropathic bladder
- Urinary and fecal incontinence
- Ureterohydronephrosis
- Recurrent urinary tract infections
- Chronic renal failure - diagnosed at 15 years of age
No compliance treatment and follow up.

C Adina, f, 14 years
- Neural tube defects
- Myelomeningocele
- Stabilized hydrocephalus – ventriculoperitoneal shunt
- Cerebral palsy
- Neuropathic bladder
- Urinary and fecal incontinence
- Ureterohydronephrosis
- Recurrent urinary tract infections
- Chronic renal failure - discovered at 4 years of age
- Renal anemia – treated with Erythropoetin
No compliance to treatment and follow up – 10 years without medical follow up.
Discussions

In all cases the defect was surgically corrected. In two cases shunting procedure for hydrocephalus followed, while the other cases presented spontaneous stabilization of hydrocephalus. Mental retardation was severe (1 patient), moderate (1 patient) and mild (3 patients).

Uroneurological assessment of these patients must be performed repetitive. Urinary anomalies consisted of neuropathic bladder (5 cases), massive bilateral hydronephrosis (4 patients) and horseshoe kidney (1 patient).

The patients presented urinary incontinence, urinary infections (1 case deceased from sepsis) and renal failure (2 patients).

The common goal in caring for these patients must be the prevention of progressive renal damage. However, once kidney failure has occurred, good and safe techniques for renal replacement therapy are available to bridge the time to transplantation, which is undoubtedly the best treatment for these patients.

The immobilization, urinary and fecal incontinence represent a severe handicap for these patients and their family. Social integration is difficult. The pubertal development of this patient may lead to improving there urodynamics.

Patients’ prognosis is unfavorable: 1 case deceased at six years of age, two cases already with renal failure and the recurrence of urinary tract infections followed, probably, by renal failure for the other two patients.

Conclusions

The association of genitourinary system pathology determined an unfavorable evolution and a negative prognosis for these cases.

Folic acid supplementation should be initiated before conception and continued until at least 12th wk of gestation in order to prevent the neural tube defects.
References


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CONSIDERATIONS UPON METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

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²MedLife Hyperclinic Timișoara

Abstract
The presence of cardiovasculary risk factors in childhood and adolescence is beginning to attract a growing interest in the medical world and in research.

Obesity plays an important role in the increased prevalence of its comorbid conditions. One of these, the metabolic syndrome (MS), includes a cluster of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), including insulin resistance, obesity, hypertension, and dyslipidemia.

MS appeared at an early age will surely have repercussions in adulthood. The early detection of MS and its major complications – early atherosclerosis – would allow prophylactic interventions that aim to decrease the precocious morbidity and mortality due to atherosclerotic cardiovascular diseases, to be as efficient as possible and targeted on the issue of interest.

Key words: child, adolescent, obesity, metabolic syndrome

Background
The metabolic complications associated with childhood obesity have been extensively studied over the last 10 years. Childhood obesity is a major risk factor for the development of chronic diseases and mortality in adult life.¹,²,³

MS includes a cluster of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), including abdominal obesity, insulin resistance, hypertension, and dyslipidemia.⁴ Obesity in children and adolescents has reached epidemic proportions, with the prevalence tripling in the past 3 decades. MS and type 2 diabetes have paralleled this obesity epidemic in children.⁵

MS continues to challenge the experts but both insulin resistance and central obesity are considered significant factors. Genetics, physical inactivity, ageing, a proinflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.

There is now evidence to suggest that features of the MS commonly found in abdominally obese patients with an excess of visceral adipose tissue increase coronary heart diseases risk. Childhood obesity, with concomitant hypertension, impaired carbohydrate metabolism, hyperlipidemia – included or not included in MS, are linked to CVD in adulthood. The atherosclerotic process develops silently for decades during childhood and adolescence before cardiovascular complications such as myocardial infarction and stroke occur in adulthood.⁴

With the MS driving the twin global epidemics of T2DM and CVD there is an overwhelming moral, medical and economic imperative to identify those individuals with MS early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or CVD disease.⁶

Aim of study
The authors target the evaluation of MS frequency in children and adolescents obesity, as well as the study of clinical manifestations and biological aspects.

Material and Methods
We have incorporated in the study a number of 247 obese between the ages of 5 months and 18 years, 135 girls and 112 boys who were in the care of the 2nd Clinic of Pediatrics Timișoara. 85 of these showed mild obesity, 106 had moderate obesity and 56 severe obesity.

According to the new definition of pediatric MS, for a child or adolescent to be defined as having the MS they must have: obesity plus any two of the following factors: fasting hyperglycemia / impaired glucose tolerance (IGT) / T2DM, low HDL cholesterol serum levels, high triglycerides serum levels and hypertension (table 1).

- The diagnosis of obesity was established:
  * for the infant and the child up to the age of two with a PI bigger than 1,1.
  * for the toddler over 2 years of age:
    - with a weight excess larger than 20%, or over 2 standard deviations, or greater than the 95th percentile, according to the normal weight for age, height and sex.
    - with a BMI greater than the 95th percentile.
- The degree of severity of obesity has been interpreted taking into account the size of the weight excess in the following way:
  - *Mild* obesity when the excess weight is between 20 and 30%.
  - *Moderate (medium)* obesity, at a weight excess of 30-50%.
  - *Severe* obesity, when the excess weight is greater then 50% of the normal weight.

In all cases a full clinical examination has been performed (including the repeated measurement of the blood pressure).
In order to identify MS, the glucidic and lipidic metabolism have been studied. Evaluation of the glucidic metabolism

*Fasting glycaemia* has been determined after a minimum of 8 hours of fasting. The glycaemia was determined from venous blood through the glucose-oxidase method. The value of fasting glycaemia was interpreted as follows:

- **Normal values** - for a glycaemia over 60mg% and under 100mg%;
- **Abnormal values** - when glycaemia is < 50mg% (low) or > 100mg% (high).

*OGTT*

According to WHO recommendations, this means (in conformity with the fasting rules and physical activity stated before) the administration of a 1,75g dose of glucose pulvis/kg of the body, without exceeding 75g - regardless of the bodyweight of the child. The glucose dissolved in 250-300 ml water, maybe flavoured, is drank in a short time interval (under 5 minutes), after a sample of blood has been taken to determine the fasting glycaemia. The test has been done for obese patients with a glycaemia à jeun under 126mg%.

Evaluation of the lipidic metabolism:

- the dosage of triglycerides – through the enzyme method using GPO-PAP peroxidase;
- the dosage of HDLc – through the precipitation method.

The determinations have been made with the help of a Hitachi 717.

### Table 1: Elements of new definition of pediatric MS.

<table>
<thead>
<tr>
<th>MS factor</th>
<th>Age (years)</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fasting glycaemia (mg%)</td>
<td>-</td>
<td>≥ 100</td>
<td>≥ 100</td>
</tr>
<tr>
<td>2. 2&lt;sub&gt;th&lt;/sub&gt; glycaemia (mg%)</td>
<td>-</td>
<td>≥ 140</td>
<td>≥ 140</td>
</tr>
<tr>
<td>at oral glucose tolerance test (OGTT)</td>
<td>8</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>125</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>135</td>
<td>125</td>
</tr>
<tr>
<td>3. Sistolic blood pressure (SBT) (mmHg)</td>
<td>112</td>
<td>119</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>125</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>135</td>
<td>125</td>
</tr>
<tr>
<td>Diastolic blood pressure DBT (mmHg)</td>
<td>8</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>4. Triglycerides TG (mg%)</td>
<td>12-16</td>
<td>135</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>16-19</td>
<td>≥ 150</td>
<td>≥ 150</td>
</tr>
<tr>
<td>5. HDLc (mg%)</td>
<td>6-8</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>9-11</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>12-15</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>16-19</td>
<td>≤ 35</td>
<td>≤ 35</td>
</tr>
<tr>
<td>6. Ponderal Index (PI) Body mass Index (BMI) (G kg/T² cm)</td>
<td>&lt; 2</td>
<td>&gt; 1,1</td>
<td>&gt; 1,1</td>
</tr>
<tr>
<td></td>
<td>&gt; 2</td>
<td>According to CDC tables</td>
<td>According to CDC tables</td>
</tr>
</tbody>
</table>
Results and Discussion
We have identified 32 cases of MS (12.92% of the total) with ages between 7 months – 18 years, 17 girls (53%) and 15 boys (47%) (figure 1).

All the cases of MS had a duration of obesity of over 5 years and/or collaterals to obesity, T2DM, CVD, dyslipidemias.

In our study, up to puberty the distribution according to sex is similar. At the age of puberty the percentage is higher for boys, and in adolescence the figures show higher percentage for girls.

As the degree of obesity increases, the prevalence of MS increases, with obesity occurring in 2.35% of mildly obese, 16% of moderately obese and 23.2% of severely obese children and adolescents. So the prevalence of MS in our cases has increased with the degree of obesity, therefore parallel with the BMI, as is emphasized in the recent medical literature.7

Fig. 1. The distribution of cases of MS according to age and sex.

Fig. 2. Distribution of cases according to the degree of obesity.
Obesity is strongly associated with insulin resistance, T2DM, and atherosclerotic CVD. Data from the Framingham Study have established an increased incidence of cardiovascular events in both men and women with increasing weight; Obesity tracks from childhood to adulthood, and childhood adiposity is a strong predictor of insulin resistance, and abnormal lipids in adulthood. Moreover, the rate of increase in adiposity during childhood was significantly related to the development of cardiovascular risk in young adults.

17 of the cases with MS (53%) had a clinical symptomatology, and 15 have been asymptomatic, which proves once again that MS can become a "silent killer" in a significant number of cases (fig.3).

The obese child's cephalalgia represented frequently the reason for coming to the hospital, this being the symptomatic manifestation of high blood pressure. Hypertension is an integral component of the MS. Increased sympathetic tone has been associated with obesity in adolescents, and both insulin and leptin appear to have a direct effect on sympathetic nervous system activity. Insulin infusions stimulate sodium retention by the kidney, and insulin stimulates vascular smooth muscle growth. Fasting insulin, used as an estimate of insulin resistance, has been significantly correlated with blood pressure in children and adolescents. The Cardiovascular Risk in Young Finns study showed a significant correlation between fasting insulin and blood pressure in children and adolescents and also showed that the level of fasting insulin predicted the level of blood pressure 6 years later. Similarly, leptin has direct central effects that increase sympathetic outflow to the kidney. It has been hypothesized that selective leptin resistance maintains leptin-induced sympathetic activation in obesity, which permits leptin to play an important role in the pathogenesis of obesity-related hypertension and MS. Studies in 11- to 15-year-olds showed a lack of significant correlations for blood pressure with fasting insulin (adjusted for BMI), insulin resistance, triglycerides, HDL-C, and low-density lipoprotein (LDL) cholesterol. However, when the MS factors (triglycerides, HDL-C, fasting insulin, and BMI) were considered together as a cluster and comparisons made between children with high and low blood pressure, the cluster score was significantly higher in the high blood pressure group. Thus, despite the lack of a significant relation between blood pressure and the individual risk factors, its relation with the cluster of risk factors is consistent with a clinical association of blood pressure and the MS before adulthood. Most recently, the Fels Longitudinal Study showed a strong association between childhood hypertension and adult MS.

With the current obesity epidemic and its metabolic consequences, the identification of children with impaired fasting glucose, that is, fasting glucose 100 to 126 mg/dL is very important, because appropriate management may decrease the progression to T2DM. Diabetes mellitus is associated with accelerated development of vascular disease. Nevertheless, not all children with impaired carbohydrate metabolism develop T2DM. In a study of children with impaired glucose tolerance followed up over a period of 1 year, one third became euglycemic, one third developed T2DM, and one third maintained impaired glucose tolerance.

We have observed metabolic disturbances in 24 of the MS cases (75%) (fig.4).

One or more defining modifications of the lipidic metabolism have been present in 30 of the MS cases (94%) (fig.5).

Lipid abnormalities, particularly high triglycerides and low HDLc serum levels, are strongly associated with insulin resistance and are criteria for the MS. Studies in rats have shown that hyperinsulinemia stimulates the synthesis of fatty acids by increasing the transcription of genes for lipogenic enzymes in the liver. Fatty acids in turn stimulate increased production of very-low-density lipoprotein. It is currently unknown whether insulin resistance induces dyslipidemia or whether insulin resistance and dyslipidemia are associated via an underlying cause.
Abnormal lipid profiles also are found in children with obesity and insulin resistance.\(^{18,19}\) Data from the Bogalusa Heart Study have shown that overweight children have significantly higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower HDL-C levels than normal-weight children.\(^{20}\) The hypertriglyceridemic waist phenotype has been proposed in adults as a predictor of the MS.\(^{21}\) A recent study in more than 3000 adolescents that used the modified ATP III cut points for serum triglycerides (≥110 mg/dL) and waist circumference (≥90th percentile for age and sex) has shown that the concomitant presence of these criteria was significantly associated with a clustering of metabolic abnormalities, which is characteristic of the MS.\(^{22}\)

A third of the cases analyzed associated more than three defining factors for MS (table2), which means that the risk for developing cardiovascular diseases in adulthood is very high: 7 patients presented an association of 4 factors (21.8%) and 4 cases presented 5 factors (12.5%).

Obese individuals develop different degrees of insulin resistance, but not all those with obesity develop glucose intolerance. The factors that make some individuals more likely to progress to T2DM are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment. Patients with T2DM often have other risk factors for cardiovascular disease; hypertriglyceridemia has been reported in 4% to 32% of children with T2DM.\(^ {23}\) Essential hypertension is known to be associated with diabetes in adults,\(^ {24}\) and it is estimated that cardiovascular risk doubles when hypertension and diabetes mellitus coexist; however, population-based prevalence data on hypertension in children with diabetes are not available.
Indeed, although the majority of children with MS tend to be overweight or obese, not all overweight or obese children develop MS, T2DM, or cardiovascular disease. In view of the increasing prevalence of and adverse trends in obesity and its comorbidities in children, the question is whether tools can be developed to identify children who are most at risk metabolically.

Conclusions
1. Pediatric MS is a complex pathological problem.
2. Althought scarce, the clinical sympthomatology can be very valuable for the monitoring of complications/comorbidities present in the obese patients.
3. The metabolic modifications represent the most frequent morbid states for the child affected by MS, observed even at very early ages.
4. Detecting and treating obesity and the present complications/comorbidities from childhood must be included in the health programmes - as rational means of decreasing the morbidity and mortality of the adult due to atherogenic cardiovascular diseases.

References


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EPIDEMIOLOGICAL STUDY ON UNDESCENDED TESTIS

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Abstract
Although half a century ago doctors believed undescended testis could descend in the scrotum anytime during the childhood up to the beginning of puberty, today it is accepted that both testes should be in the bursae at the time of birth (in 3 – 4% of cases this is not the situation). Otherwise, according to the most authors, one can wait at most one year (incidence drops to 1%), and then, during the second year of life, the testicular descent must be performed, as pathological changes in the undescended testis are visible as early as from the age of two thanks to the improvement of optical microscopy. However, an important number of cases are still diagnosed as late as around puberty, the purpose of this study being to evidence some of the possible causes that lead to this delayed diagnosis, which results in the modification of condition prognosis.

Key words: undescended testis, epidemiological aspects

Introduction
Half a century ago doctors believed undescended testis could descend in the scrotum anytime during the childhood up to the beginning of puberty. There are still many authors who await the spontaneous descend of the testis until the puberty, and they indicate no medical or surgical treatment during this period of time¹.

At a later time, the optical microscopy shows the presence of lesions in the undescended testis around the age of seven – ten years; as a result, initiation of cryptorchidism treatment between seven and ten years of age (beginning of puberty) has been required.

By constant improvement of optical instruments, objectification of several pathological changes at the age of two has been made, electronic microscopy studies revealing anatomic-pathological changes in undescended testis as early as from the age of one².

Today it is accepted that both testes should be in the bursae at the time of birth (in 3 – 4% of cases this is not the situation). Otherwise, according to the most authors, one can wait at most one year (incidence drops to 1%), and then, during the second year of life, the testicular descent must be performed³.

On the contrary, there are many studies in the literature that reveal the performance of many orchidopexies around puberty, which may be explained either through the belief of some authors that the spontaneous descent can be waited to this age, or through the existence of acquired undescended testis cases (this situation is more and more often described in the recent studies) or by neglecting the diagnosis of this affection to this age, not many references trying to explain the causes of this last situation⁴.

The need to identify the causes that delay the early diagnosis of undescended testis were the basic arguments for choosing this particular research theme.

Objectives
During this study I have constantly tried to find answers to a series of epidemiological aspects. This is why I have elaborated a list of objectives to be followed during the study:

1. to establish the incidence of undescended testis in the apparently healthy infantile population, as compared with the frequency of surgical pathology in children.
2. to establish the diagnosis age in the undescended testis.
3. to establish the degree in which the patients with undescended testis attend the dedicated medical services in relation to:
   - environment of origin
   - social-economical conditions

Material and method
The clinical-statistical study has been performed within the Pediatric Surgery and Orthopedics Clinic of the County Emergency Clinical Hospital Arad. 77 children, aged between 0 and 17 years, with undescended testis were here examined, hospitalised, investigated and treated medically and/or surgically between 2006, January 1st and 2008, December, 31st.

In order to acquire the useful data for our study, the detailed analysis of examination and hospitalisation registers, and clinical observation forms was required. We took out a series of epidemiological data that were later processed following a standardised protocol in order to clarify both the circumstances that lead to the diagnosis of this condition, and the further implication over the therapeutic approach.

Within the Pediatric Surgery and Orthopedics Clinic and the specialty Ambulatory were also performed the periodic clinical re-examinations of the operated patients.

Results and discussions
Within 2006, January 1st and 2008, December, 31st, 77 children with undescended testis were treated in the Pediatric Surgery and Orthopedics Clinic of the County Emergency Clinical Hospital Arad.
Although this study focuses on a time interval of only three years, given the number of analysed cases (77), I consider that the lot is statistically representative, as we find in the literature many very valuable papers performed on even less numerous groups of patients than the present one.

1. Annual incidence of undescended testis cases

Out of the 77 cases of undescended testis, 28 were recorded in 2006, 24 in 2007 and 25 in 2008 (Table 1, Figure 1).

A relatively equal distribution of the number of cases is seen, in each of the three years being recorded approximately 1/3 out of 77 total cases, with a insignificant peak of cases in 2006, as compared with the 2007 and 2008 years.

Therefore, we can say that 25 cases of undescended testis are diagnosed and treated annually.

2. Incidence of cases in relation to the number of hospitalisations

When relating the number of cases to the total number of hospitalisations in the respective years, the following results were obtained:
- 2006: 28 cases of undescended testis out of 2247 hospitalisations, which represents 1.24 % of cases;
- 2007: 24 cases of undescended testis out of 2199 hospitalisations, which represents 1.09 % of cases;
- 2008: 25 cases of undescended testis out of 2490 hospitalisations, which represents 1 % of cases (Table 1).

We can see the constancy of the relation between the undescended testis cases as compared to the total number of cases of surgical conditions of the patients hospitalised in the respective year in a graphic illustration.

3. Distribution of cases depending on urbanisation degree

Distribution of cases based on urbanisation degree is a way in which we are able to indirectly estimate the level of population’s medical education and the degree of parents responsibility to the children.

Following this criterion, most of the cases came from the urban environment (43, compared with 34 cases from the rural environment), which is most probably the result of a better patients’ attendance of the specialty medical services (Table 2).

4. Distribution of cases depending on age

Considering that, during the growth and development period, the child undergoes medical examinations when entering different collectivities (nurseries, kindergartens, schools, camps etc.), situations in which the possibility of random diagnosis of undescended testis cases occurs, we have considered useful and interesting the study of cases distribution in relation to the growth and development stages, as they are defined within the puerculture notions:

- 0-1 year – age of newborn and infant;
- 1-3 years – toddler;
- 3-7 years – preschool child;
- 7-11 years – school child;
- 11-14 years – pubescent;
- 14-17 years – teenager.

The number of cases based on age and origin environment for the studied interval are synthesised in the following table:
When synthesising these results, we noticed a delay in the diagnosis of the condition for the cases coming from the rural environment, most probably explained by a decreased access to the specialty medical services, and also a lower medical education level.

Part of the undescended testis cases diagnosed between 11 and 17 years of age may not be congenital, but acquired. There are more and more studies today that indicate a part of testes present initially in the scrotum may later ascend in the inguinal channel due to cremasteric muscle hypertonicity. The situation is frequently met in children with neurologic conditions experiencing muscle spasms.

By follow-up studies, as Villumsen study, it has been shown that in the spontaneously cured congenital cryptorchidism, ascension of testes requiring surgery may reoccur later in the childhood. Description of acquired cryptorchidism is related to the observation that a great number of older children undergo orchidopexies, in spite of recommendations for treatment during the early childhood. In a study regarding boys with undescended testis performed by Hack in 2003, the acquired cryptorchidism ratio was almost three times greater than that of congenital cryptorchidism. The same author shows in 2007 that, due to the high ratio of spontaneous descent in the acquired cryptorchidism, it has been proven that delaying the orchidopexy in the pre-puberty period decreases the number of delayed orchidopexies, but the consequences of delaying orchidopexy on health can be highlighted only after follow-up studies are performed. In a recent study, acquired cryptorchidism prevalence was of up to 2.2% in boys aged between 6 and 13 years3,6.

Within this context, there is the possibility that in the rural environment to be more cases of acquired undescended testis, given the increased muscle tonicity in children coming from this environment, due to the more intense physical activity3.

**Table 3. The number of cases based on age group and origin environment.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1-3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>3-7</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>7-11</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>11-14</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>14-17</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Conclusions**

1. As regards the frequency of undescended testis within the infantile population, 25 new cases are diagnosed and treated annually.

2. Global incidence of this condition within the studied interval, calculated by relating the total number of cases to the total number of hospitalisations, was of 1.11% (with an annual variation between 1-1.24%). In other words, in every 1000 children with surgical conditions, 11 cases of undescended testis are discovered.

3. As regards the urbanisation degree, most of the cases came from the urban area; (43, as compared with the 34 cases from rural environment), which is most probably due to a better patient attendance of the specialty medical services.

4. Weighing the balance in the favour of urban area is done considering the age groups of 0-1 year, 1-3 years and 3-7 years, where the number of cases coming from this environment exceeds the number of cases coming from the rural area.

5. For age groups of 7-11 years and 11-14 years, we have recorded an alternation of the environment of origin of undescended testis cases so that, totalling the cases from age groups of 7-11 years and 11-14 years, we have come to an urban/rural report of 1:1.

6. The delayed diagnosis of undescended testis for the cases coming from the rural area is most probably explained by a more limited access to the specialty medical services, but also through a lower medical education level.

7. It has to be mentioned that a part of undescended testis cases diagnosed between 11-17 years might be acquired, and not congenital; there are more and more studies today indicating that a part of testes initially present in the scrotum may later ascend in the inguinal channel due to a hypertonicity of the cremasteric muscle.
References


2. Butenandt O. Cryptorchism. Treatment should be finished by age 2. MMW Fortschr Med. 2007 Nov 29;149(48):14


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URINARY COMPLEX
CONGENITAL MALFORMATION

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Abstract
The urinary congenital anomalies are frequent in pediatric pathology and their presence is often pointed out early by an acute symptoms. We present a case report of a 3 month girl hospitalized with severe hydronephrosis and urinary infection, who present ureteral segmental stenosis and ureterocel. The prenatal diagnosis was unknown, because mother did not make an ultrasound exam during pregnancy. By endourologically approach we found a left ureterocel and a close narrowing of superior half of the left ureter. We removed the ureterocel by electroresection. By open approach we removed the stenotic ureteral segment. From a pelvic flap we obtained a new superior ureteral segment and we make an anastomosis between the 2 ureteral segments. After 10 months a follow up revealed a narrowing of inferior segment of the left ureter. By the endourologic approach we inserted into ureter an 3 CH JJ stent for a long term. It is a good long term evolution. The follow up evaluation (by clinical examination, ultrasound exam and laboratory investigations) reveal no clinical signs and the urine sterility.

Key words: hydronephrosis, congenital urinary anomalies, early diagnosis, surgical treatment.

Introduction
Hydronephrosis is a dilation of the inside or collecting part of the kidney. It often results from a blockage in the ureter where it joins the kidney that prevents urine from draining into the bladder. Urine is trapped in the kidney and causes the kidney to stretch. Hydronephrosis may also be due to abnormal backwash or reflux of urine from the bladder. It is often detected on an ultrasound test during pregnancy (prenatal ultrasound). The blockage that produces hydronephrosis is usually the result of a narrowing at the top of the ureter near the kidney. The severity of hydronephrosis depends on the extent of the blockage and the amount of stretching of the kidney. It may range from mild to severe. Children with mild and moderate hydronephrosis usually do not have symptoms, the kidneys are minimally affected and the problems may disappear in the first year of life. In extremely severe cases of hydronephrosis, damage to normal kidney function may occur. In addition to affecting the child's kidney function, this condition may also cause infections, pain and bleeding. These effects may take months or even years to occur or may never occur. To determine the amount of hydronephrosis present, nuclear medicine and radiologic tests to measure kidney function and structure may be recommended. In children with mild hydronephrosis, observational therapy has been shown to be safe and has become the accepted method of treatment. However, in children with moderate to severe hydronephrosis, the answer is not as clear. The surgical procedure (pyeloplasty) involves removing the obstructed part of the ureter and then reattaching the healthy ureter to the collecting part of the kidney. The success rate of the surgical therapy in infants is 90-95%. Prenatal testing for hydronephrosis has permitted early detection and treatment. In the past most children were found to have hydronephrosis at the time of urinary infection or pain. Surgery was almost always performed in many children after 3-4 years of age. Those children that improved by itself without ever causing infection or pain, were probably never diagnosed or treated for hydronephrosis. Children who are diagnosed prenatally with moderate to severe hydronephrosis are now being seen at such an early age that they have not had a chance to improve on their own. Current testing cannot accurately predict which patients might or might not get better on their own. Therefore, today there is no standard treatment for all children. Many centers are choosing to watch and carefully monitor children with moderate to severe hydronephrosis while others continue to use surgery as treatment.

Case report
A three month girl presented in our clinic with urinary tract infection. She presented fever, vomiting, increasing urinary frequency and a general bad condition. Laboratory exam of the urine reveal the infection with E.colli. Antibioterapy was started and we obtained a short remission of the clinic symptoms. The abdominal ultrasound exam and the intravenous urography reveal a left severe hydronephrosis and an left ureterocel. By a 7 CH cystoscope we explored the urinary blader and found the left ureterocel. We removed this ureterocel by electroresection. The left ureter exploration reveals a strong stenosis in its superior half. In this situation we decided the open surgery is necessary and we found an important pelvic dilation, a partial kidney rotation with a fetal aspect, a reduced renal mass and a strong stenosis of the superior segment of the left ureter. We removed the narrowed segment of the ureter (3 cm length). We created a new superior ureteral tube from a flap obtained from the stretched pelvic wall. We performed an anastomosis between the two ureteral segments (fig. 1). For 10 days, a 3 CH tube protected the anasthomosis. We used 6-0 monofil resorbable sutures (Surgicryl). Antibiotherapy continued for three months.
The evolution was good after operation. A follow up evaluation consisted in clinic, ultrasound exam and urine exam in every month in the first 6 months, and at three months after this period, and no problems reveal. In the second year we found an ureterohydronephrosis (by ultrasound examination). By cystoscopy we found the narrowing of the anastomosis between the two ureteral segments. We performed to incise this stenosis and inserted a 3 CH JJ stent for long term. Antibiotics used for three months. After this operation follow up evaluation continued (at every three months) and no clinical problems reveal and urine is sterile.

Discussions

In the absence of maternal ultrasound exam, the diagnosis delayed since the severe urinary infection occurs. The early diagnosis is essential (better during pregnancy) and it permit to adopt a correct therapy. The associated urinary malformations needs a complex therapeutical approach (endourologicaly tehnics and open surgery tehnics). Short term prognosis is good in the presented case because the urine flow is good and no functional troubles of kidney occurs. Long term prognosis depend by the urinary flow and the development of the affected kidney.

References

1. Jidveianu NH, Teodorescu O, Chirurgie Pediatrică, Ed. ULB Sibiu, 2005

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RARE CAUSES OF ACUTE SURGICAL ABDOMEN IN CHILD

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Abstract:
Acute surgical abdomen has one or more of the following syndromes as clinical manifestation: occlusive, peritonitis or hemorrhage. We present here 9 children who were admitted to our hospital in Pediatric Surgery Department with rare causes of acute surgical abdomen.

Key words: acute surgical abdomen, rare causes.

Introduction
The acute surgical abdomen is one of the most common cause for addressing to a Emergency Room of Pediatric Surgery Department. It is defined as an intraabdominal process causing severe pain and requiring surgical intervention. There are four causes for acute surgical abdomen: inflammatory, mechanical, vascular and congenital defects. The main cause for acute inflammatory surgical abdomen is acute appendicitis. Mechanical causes like intussusception or strangulated hernia are more common in newborn and small child. In older children intrabdominal tumors and postoperative peritoneal adhesions are the main cause for mechanical acute surgical abdomen. Congenital defects like intestinal atresia, omphalocele or diaphragmatic hernia, malrotation of the intestine can be causes for acute surgical abdomen in the first day of life[1].

Clinical findings include various symptoms according to the etiology, but the central symptoms is abdominal pain. Clinical exam gives informations about the type and degree of intraabdominal process and the indication for surgical intervention.

Laboratory Tests
Urine and blood should be examined in all cases. Complete blood cell counts may reveal pancytopenia if the bone marrow is involved in malignant tumors or high number of leucocytes with high acute phase reactants in acute inflammatory abdomen. The other laboratory findings as nutritional disturbances, iron deficiency anemia, acute dehydration helps in pre-and postoperative care.

Imaging Studies
X-ray Examination
Plain x-ray films of the abdomen in the upright positions can showed air below the diaphragm, this sign being pathognomonic for perforation of hollow viscera. Dilated distended loops of intestine with air-fluid levels are specifically in small bowel obstruction. Barium enema is used as diagnostic and therapeutic mean in intussusception of infants and children. Barium enema may also be helpful in diverticulosis or polyposis of the colon and in large bowel neoplasms. In these cases colonoscopy and biopsy are helpful.

The ultrasonography and CT scan of the abdomen and pelvis is useful in abdominal trauma. Abdominal MRI and CT scan also can be used to evaluate abdominal and pelvic lymphadenopathy, masses and visceral involvement in neoplastic tumors[2]. This helps in determining the extent of the disease and may aid in determining the most suitable site for biopsy. If neurologic signs are present CT scan or MRI of the brain or spinal cord is indicated. CT scan of chest may be also useful for discovered intratoracic metastasis in abdominal tumors.

The endoscopy of the GI tract is the diagnostic tool of choice for confirming the diagnosis in gastrointestinal bleeding[3, 4] and in mechanical obstruction due to tumors or foreign bodies[5].

The positive diagnosis is then established based on clinical findings, lab studies and imaging studies.

We present here 9 children who were admitted to our hospital in Pediatric Surgery Department with rare causes of acute surgical abdomen. The preoperative diagnosis was acute surgical abdomen in all these cases and the etiology was established intraoperatory.

Patient 1: B.E. is a girl, 2 years and 10 months old, 9 kilograms in weight.
She was admitted in Pediatric Surgery Clinic with the following symptoms: colic-like abdominal pain in the right hemi abdomen and abdominal distension, bilious vomiting, fever, nocturnal sweats, change in bowel habits with present intestinal transit.

Objective exam at admission: altered general state, deficitary nutritional state (G=11 kg, Hight=84 cm), anorexia, pouches eyes, pale teguments and mucosa, abdominal painful tumor in the middle right quadrant, with a diameter of about 4/5 cm, firm consistency, with not-well limited borders, fixed on the subjacent plains.

Laboratory data reveals: high number of leucocytes and thrombocytes, high acute phase reactants, high serum lactate dehydrogenase, nutritional disturbances (decreased proteins and albumins), feriprive anemia, acute dehydration with hyponatremia.The other laboratory findings were
within normal limits (alpha-fetoprotein, alkaline phosphatase, serum aminotransferase, gamma-GT, urea, creatinine, glycaemia, urine brief exam).

*Imagistic data:*

Chest and abdominal X-ray did not offer useful diagnostic information.

Barium enema showed the barium column stopped below the hepatic angle of colon which is more dilated (Fig. 1).

Abdominal MRI: revealed displacement of pancreas posteriorly, dilated ascendant part of the large intestine with enlarged and dualised wall, much thicker than normal, with ileum displacement to the right, small quantities of liquid in the interhepato-diaphragmatic and parietocolic right space; normal findings for liver, kidneys, spleen; (Fig. 2)

*Treatment:* After all these investigations we decided to do exploratory laparotomy in order to establish the diagnosis and the treatment. After a short period of preoperative preparation we performed a median laparotomy. We found moderate ascitic liquid, endoluminal tumor of the caecum and ascendant colon extended to about 10-15 cm in length, with stenosis of the lumen, infiltrating the terminal part of the ileum with extension to the mesenter and the retroperitoneum. (Fig. 3)
We practiced right hemicolectomy with ileotransversoanastomosis termino-terminalis, with biopsy of the mesenteric and epiploonal ganglia and peritoneal drainage. The evolution was favorable and the child was transferred in Oncology Department for chemotherapy.

Histopathology findings confirmed the diagnosis: Burkitt lymphoma, (abdominal beginning) with high grade of malignancy.

**Patient 2**: R.A., is a girl, 11 years old, normal weight.

She had a history of two weeks of colicky abdominal pain, nausea, bilious vomiting, lack of stools.

**Physical examination**: at admission in the hospital she presented altered general state, pouched eyes, pale teguments, bilious vomiting and constipation. The distended abdomen was diffusely sensitive to palpation, with signs of peritoneal irritation in the left hemi abdomen. Abdominal auscultation revealed static intestinal sounds (borbormism). Digital rectal examination revealed empty rectal ampulla, and absence of any pathological material on the hand gloves.

**Laboratory data** The blood count showed a marked leucocytosis, high number of thrombocytes, high acute phase reactants, increased level of urea, and signs of acute dehydration with hyponatremia.

**Imagistic data**: Abdominal X-ray showed multiple air-fluid levels without presence of air under the diaphragm, while the ultrasound examination was negative for any abnormality. A positive diagnosis of intestinal obstruction was established based on the previous examinations.

**Preoperative diagnosis** was acute peritonitis with inflammatory mechanical occlusion.

**Treatment**: we performed exploratory laparotomy and we found inflammatory intestinal adhesions, small perforation of first jejunal loop and intraluminal moveable tumor of splenico-colonic arch. Surgical treatment consisted in lysis of intestinal adhesions, jejunoraphy in double layer; lavage of the abdominal cavity using NaCl 0.9%; double drainage of the abdominal cavity, suture of the abdominal wall, anal dilatation and pull-out the tumor which was a trichobezoar (Fig. 4).

![Fig. 3: Intraoperative details.](image)

![Fig. 4: The trichobezoar.](image)
Patient 3: T.A., is a girl, 10 years old, weighting 26 kg. She was admitted in Pediatric Surgery Clinic with the following symptoms: diffuse colicky abdominal pain and abdominal distension, bilious vomiting, lack of intestinal transit.

**Objective exam:**
- Auscultation of the abdomen: struggle bowel sounds.
- Digital examination of rectum revealed a painful tumoral mass, well defined borders, oval in shape with longitudinal diameter of about 15 cm, firm consistency.

**Laboratory data:** The blood count documented eosinophilia.

**Imagistic data:** Abdominal X-ray revealed multiple air-fluids levels for colon and small bowel and lack of air in pelvis.

*The preoperatory diagnosis* was intestinal occlusion and the intraoperative diagnosis was hidatic cyst of subperitoneal pelvic space.

**Surgical treatment** consisted in subtotal pericystectomy (F.Lagrot) and antiparasitic treatment with Albendazole.

Patient 4: J.A., is a boy, six years old, normal weight. Clinical signs at admission to the hospital were colicky abdominal pain in left inferior quadrant, bilious vomiting and fever 38.8 °C.

**Objective exam** of the abdomen showed signs of peritoneal irritation in left hemiabdomen. Two weeks ago the child presented a functional constipation with hard stools which were painful and difficult to expel.

**Laboratory data:**
- Total and differential blood count documented leucocytosis with increased eosinophils percentage.
- Radiological examination of the abdomen revealed 2-3 air-fluids levels on the left colon, lack of air in pelvis.

*Imagistic data:* Radiological examination of the abdomen revealed a peritoneal irritant.

**Treatment:**
- Treatment consisted of solution of parenteral nutrition (glucose, amino acids), antibiotics (piperacillin tazobactam), electrolytes and enemas with NaCl 0.9%.
- Because the objective exam suggested peritoneal irritation we decided to perform exploratory laparotomy. The diagnosis was small blocked perforation of the colon-sigmoid junction due to ischemia (cause being constipation). Surgical treatment consisted of suture of sigmoid perforation and peritoneal drainage.

Patient 5: O.N., is a boy, 13 years old, normal weight. He presented to the hospital for diffuse abdominal pain, diarrhea and rectal bleeding.

**Objective exam** of the abdomen showed no signs of peritoneal irritation. Rectal examination revealed a lot of sessile polyps, not painful, 5-7 mm in diameter, with fresh blood on hand-gloves.

**Laboratory data:** revealed posthaemorrhage anemia, serum proteins and alpha-phetoprotein were in normal range.

**Histological findings:** biopic polypectomy of 2 lesions was performed during colonoscopy. The first fragment was described as being a hyperplastic adenomatous tubular polyp with minimal dysplasia, and moderate fibrosis with lymphoplasmocytic infiltrate of the chorion. The second fragment turned out to be an adenomatous tubulo-villous polyp with minimal dysplasia.

**Imagistic data:**
- Colonoscopy (Fig. 5) detected hundreds of sessile polyps involving the entire colon extending from the rectum up to the cecum and hence establishing the diagnosis of familial adenomatous polyposis.

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**Fig. 5. Colonoscopy.**
Upper G.I. tract endoscopy revealed no gastric or duodenal tumors. Abdominal CT scan detected no extracolonic involvement and no desmoid tumors.

Barium study of the abdomen showed multiple polyps disseminated throughout the colon. (Fig. 6)

Treatment
A prophylactic subtotal colectomy and ileoproctostomy with intraoperative diathermy of the residual polyps seemed to be the ideal procedure for this case. Avoiding to sacrifice the rectum was a satisfactory option because the patient had few rectal polyps and the concern about keeping a near-normal bowel movement pattern. (Fig. 7,8)

Fig. 6 Barium enema.

Patient 6: C. G., five years old, normal weight. Objective exam of the abdomen showed signs of peritoneal irritation (generalized tenderness). The patient presented abdominal pain, bilious vomiting, fever 38-39 °C.

Laboratory data:
The total blood count showed an increased number of leukocytes, increased acute phase reactants and acute dehydration.

Fig. 7 and 8 – Colon sub totally resected was sectioned longitudinally to reveal multiple adenomatous tubulo-villous polyps involving the entire length of the colon.
The positive diagnosis was generalized peritonitis. Treatment was surgical: we performed the great median laparotomy and diagnosed generalized peritonitis caused by traumatic perforation of duodeno-jejunal angle through ingested foreign body (pen). We pulled-out the pen, then we performed jejunoraphy in double layer; lavage of the abdominal cavity using NaCl 0.9%; double drainage of the abdominal cavity.

**Patient 7:** T.B., 4 years old, 15 kilograms in weight. At admission to the hospital he presented hemorrhagic shock with dyspnoea, tachypnoea, hypotension, pale teguments and cold extremities. Objective exam of the abdomen revealed abdominal distension, signs of peritoneal irritation, absence of bowel sounds. Treatment consisted in median laparotomy and we diagnosed massive retroperitoneal haematoma caused by spontaneously rupture of Wilm’s tumor. We performed nephrectomy, but haemostasis was difficult and the patient died in Intensive Care Unit, few hours later.

**Patient 8:** G.E., preterm baby, 4 days old, 2.3 kg weight, APGAR score = 7. He was admitted in Pediatric Surgery Clinic with the following symptoms: fecaloide vomiting, absence of bowel sounds, lethargy, and altered general state with respiratory failure. He presented normal passage for meconium. Objective exam revealed abdominal distension and tenderness with hypogastric parietal oedema. Laboratory data: showed anemia (Hb=6.1g%, RBC=1,820,000/ ml), acute dehydration, high values for serum aminotransferase, total bilirubin, direct and indirect bilirubin. Imagistic data: Plain radiographs of the abdomen in orthostatic position showed air-fluid levels in right inferior quadrant, absence of the air in pelvis, oedema of abdominal wall (Fig 9).

We diagnosed neonatal peritonitis. Treatment consisted in median laparotomy and we diagnosed intestinal volvulus with complete gangrene of the midgut, malrotation and neonatal peritonitis. We performed volvulus correction, peritoneal drainage. We had no signs of improved blood supply for midgut so we closed the abdomen. The patient died 5 weeks later with cardio-respiratory shock.

**Patient 9:** R.R, preterm baby, 9 days old, 1680 grams in weight. At admission to our clinic she presented altered general state, jaundice and pale teguments, bilious vomiting with gastric bleeding and absence of passage for stools. Objective exam of the abdomen revealed abdominal distension, tenderness at superficial palpation, hypogastric parietal oedema. Digital examination of rectum revealed meelenic stools in small quantities. Laboratory data: showed anemia, high levels of total bilirubin, direct and indirect bilirubin, hypoproteinemia and hypopotasemia. Imagistic data: Plain radiographs of the abdomen in orthostatic position showed sketches of air-fluid levels, marked distension of bowel and pneumoperitoneum(Fig. 10). The diagnosis was generalized peritonitis.
Treatment consisted in median laparotomy and we diagnosed generalized peritonitis with 2 perforation of ascendant and descendant colon due to preterm baby hypoxemia. We performed right colostomy, left coloraphy and peritoneal drainage. Six weeks later we decided to reestablish digestive continuity. During the second surgical intervention we diagnosed intestinal adhesions, many intrinsic stenosis of ascending colon and 2 intrinsic stenosis of descendin colon. The etiology of this stenosis probably was intrauterine hypoxia. We practiced right hemicolecctomy, coloraphies and end to end ileocoloanastomosis and peritoneal drainage.

Conclusions

The causes of acute abdomen in these 9 cases were as it follows:
- intestinal occlusion due to Burkitt lymphoma of the caecum and ascendant colon (1 case), trichobezoar presented in the left angle of transverse colon (1 case), hidatic cyst of pelvisubperitoneal space (1 case);
- acute peritonitis with sigmoid perforation due to presence of fecal mass with decubitus lesions (1 case), traumatic duodenal perforation in incidental ingestion of foreign body (1 case);
- hemorrhage syndrome in intraperitoneal rupture of Wilm’s tumor (1 case), familial adenomatous polyposis with rectal bleeding (1 case);
- congenital malformations in one case of intestinal volvulus with malrotation and one case with multiple colonic atresias with small bowel occlusion and diastases perforation in neonates.

All these children have had surgical treatment immediately. Outcomes were goods, except in child having Wilm’s tumor diseases who died immediately after surgery. Mortality was found after 5 weeks of operation in the child with intestinal volvulus having complete midgut necrosis. And unfortunately the child with Burkitt lymphoma survived just 3 months postoperatively. The other 6 children have a good evolution till date.

References

1. www.ece.ncsu.edu/imaging/MedImg/SIMS/Module2/GE2-4.

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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 – 1,7 cm. 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.