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CONTENTS

ETIOPATHOGENY OF CONGENITAL CARDIAC MALFORMATIONS

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Abstract

The prevention of congenital cardiac malformations has long been hampered by a lack of information regarding the modifiable risk factors. Over the last century there has been a major progress on understanding the genetic causes of congenital cardiac diseases, but also on identifying the genetic anomalies specific for certain types of malformations. The percentage of cases that could be prevented through changes in the fetal environment is unknown at the moment. A study suggests that the fraction of identifiable imputable causes and which could be modified can reach 30% for certain types of defects. The purpose of this paper is to analyze the present situation of knowledge regarding the teratogenetic, genetic and risk factors, of cardiac structural anomalies, in order to establish guidelines for the change of the future parents' lifestyle and for a better monitoring of pregnancies. The study of teratogenetic factors has focused on those which can influence the cardiac development during the gestation weeks, taking into account also the limitation of the period of exposure before pregnancy (3 months) and during the first quarter of pregnancy.

Keywords: etiopathogeny, congenital cardiac malformations, child

Introduction

The epidemiology of noninfectious diseases establishes the prevalence and association between certain diseases and the factors involved in etiology and pathogeny. Information obtained, represents a solid argument for the introduction of surveillance measures for monitoring both the population's health status and the national programs of public health.

On the basis of epidemiologic data, in the developed countries there has been established that congenital cardiac malformations (CCM) represent a priority problem for the public health, since they represent 25% of the total of malformations.

Congenital cardiac malformations, according to a definition by Mitchell and el, represent "structural anomalies of the heart or of the major vessels at the base of the heart, present at birth, having or which will be having a functional echo"(1,2). Most of them originate in the abnormal morphogenesis of the primitive cardiac tube in the first 50 days of embryonic life.

Recognized associations are consigned in Down, Noonan, Turner, Williams, Marfan or Holt-Oram syndromes. 40% of the children with Down's syndrome present an atrio-ventricular channel, while most of those with Turner's syndrome present obstructive lesions of the left heart (3).

Approximately 0.8 % of the viable births are complicated by a cardiovascular malformation. This aspect doesn't take into account the most frequent two cardiac anomalies: the bicuspid aortic valve disease and the valvular anomaly associated with the mitral valve prolapse. Recent studies indicate greater incidences than those that are known regarding VSD, the persistence of both the left superior vena cava and the atrial septal aneurysm. Hence, it is revealed very clearly that the old statistical analyses have underestimated a lot the incidence of the congenital cardiopathies, the recent studies forecasting an incidence of 50 to 1000 live newborns (4).

The huge progress achieved with respect to diagnosis and treatment of congenital cardiac malformations will be followed by the prolongation of these persons' life, with the possibility to come to maturity and reproduce.

On the other hand, despite the advanced therapies available at present, the morbidity and mortality associated with some types of congenital cardiac malformations are still significant (for instance the hypoplastic left heart syndrome).

ETIOPATHOGENY

GENETIC FACTORS

For the clinician whose job is to look after children with congenital cardiac malformations, it is very important to know if these defects are due to genetic modifications, for the following reasons:

- other system of organs might be affected too;
- he can establish a diagnosis for the clinical evolution;
- the family should be informed about the risk of recurrence in phratria which is higher than that of the general population;
- establishing a genetic cause imposes the genetic testing also of the other members of the family.

GENETIC TESTS USED IN THE EVALUATION OF CONGENITAL CARDIAC MALFORMATIONS

The genetic tests used to establish the genetic modifications in children with congenital cardiac malformations include cytogenetic techniques, fluorescence in situ hybridization (FISH) and the analysis of the DNA mutations.

Before using the cytogenetic techniques, the standard analysis of chromosomes established the presence of

chromosomal aberrations between 8-13% in newborns with congenital cardiac malformations. This percentage has increased since the molecular techniques were used (5).

The standard analysis of the metaphase karyotype is useful especially for the diagnosis of chromosomal affections which involve the modification of the number of chromosomes. A more sensitive test and the high-resolution stripes define better the structural chromosomal anomalies.

The FISH cytogenetic technique diagnoses the microdeletions, small overlaps and subtle translocations. The Williams, Alagille and DiGeorge syndromes can be diagnosed only by using this FISH technology.

If the karyotype is normal in a patient suffering from facial dimorphism, congenital anomalies (including heart anomalies) and mental and physical development retardation, the subtelomeric FISH studies are indicated as well as additional examinations of the other members of the family.

The families in which a subtelomeric malformation is identified should receive medical advice from a genetician who is able to offer them the adequate criteria of evaluation.

Other genetic techniques involve methods of discovery of the genes which have caused the disease (by cloning the gene) and analysis of the DNA mutations. The scope and heterogeneity of the genes and mutations identified so far, suggest that they are associated with a variety of pathogenetic mechanisms, including the loss of expression and inactivation, or the loss or gain in a function through allelic mutation.

The challenge of the future is to define the pathogenesis that causes mutations and which in its turn, will offer the opportunity to develop diagnosis and treatment strategies, as alternatives to those used so far.

CYTOGENETIC TESTING

It is necessary in the following situations:

- *any infant or child with a phenotype of known chromosomal syndrome;*
- *any infant or child with congenital cardiac malformations associated with:*
  1. *facial dimorphism;*
  2. *statural retardation that cannot be attributed to cardiac malformation;*
  3. *mental retardation;*
  4. *other congenital anomalies.*
- *infants or children with a family background in multiple abortions and/or brothers with congenital malformations;*
- *prenatal ecographic diagnosis of a major cardiac malformation and/or of visceral malformations.*

The identification of the genetic cause is beneficial because it allows for an examination of the other members of the family, the genotyping being very useful. The persons with negative genotype have a low risk for cardiovascular malformations and their clinical examination is not necessary. The persons with positive genotype will be periodically examined, to monitor the development of the phenotype.

ETHICAL CONSIDERATIONS

The genetic predictive testing of children and adolescents must not take place as a direct result of the testing before the patient has reached the age of 18, except when there are clinical benefits.

The genetic testing can establish a genetic mechanism of the disease which offers an important opportunity for the genetic counseling of the whole family.

TERATOGENETIC FACTORS

Teratogenetic factors are responsible only for a minor part of congenital cardiac malformations, but they have a great "quality"- they are "modifiable".

The environmental or exposure conditions during pregnancy have been classified into 5 categories:

1. factors which can be associated with a low risk for congenital cardiac malformations;
2. factors which can be associated with a high risk for congenital cardiac malformations;
3. factors for which information regarding the risk for congenital cardiac malformations are unconvincing;
4. factors that have been studied, but for which there haven't been found associations with congenital cardiac malformations up to the present;
5. factors which have been studied, but for which there is too little available information to determine the risk (6).

Up to the present, there have not been published prospective comprehensive studies that would examine environmental exposures or exposures of other nature, associated with congenital cardiac malformations.

The best information available is from large populations, extracted from case-control studies specially conceived to investigate possible risk factors for congenital cardiac malformations.

Two studies deserve to be mentioned - Baltimore-Washington Infant (BWI) (prospective study) (7), and The Study of the National Institute for Public Health, in Helsinki (8).

MULTIVITAMINS AND FOLIC ACID

Recent discoveries state that the use of additional multivitamins before pregnancy, that contain folic acid, can reduce the risk for congenital cardiac malformations, that is similar to that for neural tube defects. This result was obtained for the fist time following the analysis of the data from a random study. The supplement of folic acid was associated with a global reduction of 60% of the risk for congenital cardiac malformations (9), and of 25% in another case-control study conducted in Atlanta (10). Other studies showed a drop in a one congenital cardiac malformation, and not in all. For SDV two studies showed a reduction in the risk by 40%, and respectively 85%. (10).

The studies conducted on high-risk groups bring justifiable evidence in correspondence with the protective effect of the supplements of folic acid multivitamins:

- in women who have used medications that contain folic acid antagonists (11);
- in maternal febrile diseases (12);

Similar conclusions have been reported also for other malformations (13).

MATERNAL DISEASES

Maternal fenilcetonuria

If untreated, it is associated with a 6-time increase in the risk for congenital cardiac malformations (14). The most frequent are tetralogy of Fallot, VSD, CPA and single ventricle defect. The control of diet before pregnancy and during pregnancy reduces this risk (15).

Maternal diabetes

Congenital cardiac diseases have been constantly associated with pregestational diabetes and less with the gestational one (7,16). The associated specific types are: transposition of great vessels, atrial septal and nonchromosal ventricular defects, left heart hypoplasia, outflow tract defects and CPA (7,17). Malformations appear before the seventh week of pregnancy (18), with a direct relation between their appearance and the glycemic control during organogenesis (19). The strict control of glycaemia before and during pregnancy reduces the risk at levels comparable with those of the general population (20).

Taking into account the increase in the prevalence of risk factors for diabetes mellitus, it is important to obtain a better understanding of the present impact of both types of diabetes in congenital cardiac malformations (21).

The mechanisms suspected to be involved are:

- the high level of glycaemia would perturb the expression of a regulatory gene leading to embriotoxic apoptosis (22);
- the oxidative stress which results form the metabolic disorders and free radicals (23).

Rubella, febrile diseases, flue

Maternal infection with rubella during pregnancy is associated with congenital rubella syndrome. Of the cardiac malformations the most frequently associated are: CPA, pulmonary valve anomalies, peripheral pulmonary stenosis, VSD (24). The risk for rubellic embriopathy can be eliminated by guaranteeing that women of fertile age received their anti-rubella vaccine (25).

Several recent studies have pointed out that any febrile disease, including flue, during the first quarter of pregnancy increases twice the risk for congenital cardiac malformations, (pulmonary stenosis, tricuspid atresia, aortic coarctation, conotruncal defects, VSD) (7,12).

One of the possible mechanisms is the change in apoptosis which is involved in cardiac morphogenesis (26). Changes can be due to fever, infection itself, or use of medications to combat the fever or infection.

Obesity

Conclusions were not constant regarding the contribution of obesity as a teratogenetic factor in the appearance of congenital cardiac malformations. A study reported an association between an index of corporal mass > 26 Kg/m^2 with a group of malformations of the great vessels (27). Other studies reported an increase between 2 and 6 times in the risk for congenital cardiac malformations (28).

This infection seems to be rather a predisposing factor than a teratogenetic one. Nevertheless, obesity is a complex condition which should be studied carefully, because it can be associated with other nutritive factors or type 2 diabetes mellitus.

HIV infection

This infection can be transmitted vertically from mother to fetus. Children infected through in utero HIV1 transmission are subject to an increased risk of dilatative cardiomyopathy and left ventricular hypertrophy (29), but at the moment not to cardiovascular congenital structural malformations.

Epilepsy

The risk for children born by epileptic mother is high. However, it has been quite difficult to establish whether maternal convulsions are independently responsible for this fact or it should be taken into consideration only the treatment through the direct action of anticonvulsants or their indirect action through the interference of the folic acid metabolism (30).

MATERNAL EXPOSURE TO THERAPEUTIC DRUGS

U.S. Food and Drug Administration have classified a series of medications depending on their risk for causing congenital malformations, if used during pregnancy.

Thalidomide

It is known to be a cardiac teratogen, malformations caused by it varying from **atrial and ventricular septal defects** to **complex conotruncal defects**.

Vitamin A congeners/retinoids

The maternal contribution of isotretinoin causes congenital cardiac malformations. **The characteristics** of embriopathy caused by the isotretinoin are: central nervous system malformations, micrognathia, palatoschizis, thymus malformations, ocular, cardiac and great vessels malformations. The frequency of malformations does not seem to be high in persons having interrupted the treatment before conception (31). These medications are contraindicated during pregnancy and among women who are on the verge of receiving in vitro fertilization. Etretinate persists for a long time inside the body after the treatment has been stopped, while congenital malformations can be observed also 45 months later since stopping the treatment (32). The length during which Acitretin can cause congenital cardiac malformations is between 50 and 60 hours since stopping the treatment.

It's very unlikely that the tretinoin topical treatment, in usual doses, should present a teratogen substantial risk. Data is however insufficient to state there is no risk.

Antibiotics

Many studies' results have shown that there is no association between the use of treatment with ampicillin or penicillin during pregnancy and a high risk for congenital cardiac malformations (33).

Epidemiologic data regarding maternal treatment with metronidazole in the form of ovules brings controversial results in the first quarter of pregnancy. Two meta-analyses state that the risk for congenital malformations has not increased (34). One of the studies conducted at BWI, states that the maternal use of metronidazole during pregnancy proved to be associated with a high risk for malformations of great vessels and for membranous VSD (35).

Two ample studies support the association between the sulfamethoxazole-trimethroprim treatment in the first quarter of pregnancy and the increase in the risk for congenital cardiac malformations (11). The risk was reduced when the mother received folic acid supplements.

Antiretroviral treatment

An analysis by the Antiretroviral Pregnancy Registry did not show an increase in congenital malformations in women who receive treatment in the second or third quarter of pregnancy.

Antifungal treatment

Two studies, a cohort one conducted in Great Britain and a Danish one analyzed the association between the administration of fluconazole, one oral dose, in the first quarter of pregnancy, and the increase in the risk for congenital cardiac malformations. In both cases the risk did not increase. Four cases, in which mothers had been treated since the first quarter of pregnancy and in a larger dose, were followed by the appearance of cardiac malformations. These observations suggest that it is necessary for the research to go on (36).

Anticonvulsant treatment

Even though there are many epidemiologic studies, the present available data is insufficient to solve controversies regarding the fact that malformations are due to epilepsy or anticonvulsant treatment. This treatment involves many times the association of several anticonvulsant medications, in series or simultaneously, while a witness group is out of the question (37). In other words there are characteristic anomalies associated with some of the anticonvulsants (hydantoin, phenytoin, valproic acid).

Lithium- several recent retrospectives suggest that lithium is not a teratogen (38).

Benzodiazepines, barbiturates, tranquilizers

The treatment with diazepam during the first quarter of pregnancy was not associated with a risk for congenital cardiac malformations (39) and neither was the occasional treatment with amobarbital (40).

The treatment with sympathomimetics was not associated with malformations (40).

Corticosteroids were not associated with congenital cardiovascular malformations.

Folate antagonists

The maternal treatment with sulfasalazine or with other inhibitor of dihydrofolate reductase during the second and third quarter of pregnancy was associated with congenital cardiac malformations. Folic acid supplements prevented this association.

Non-steroidal anti-inflammatory treatments

There have been reports of persistent pulmonary hypertension and premature closing of the arterial channel, in children whose mothers used non-steroidal anti-inflammatories (naproxen, diclofenac, ketoprofen, indomethacin) (41) during pregnancy.

Feminine hormones

Not until recently it was considered that the maternal use of oral contraceptives presented a risk factor (42), but recent studies have not found any association with congenital cardiac malformations.

The treatment with clomiphene has been analyzed in several case-control studies and it has been proved that it increased the risk for aortic coarctation, conotruncal defects and tetralogy of Fallot.

Narcotics – two case-control studies reported the association of the use of codeine during the first quarter of pregnancy with congenital cardiac malformations, but the methodology used raises questions about the validity of these results (43);
-other two studies did not find any association (44).

MATERNAL EXPOSURE TO NON-THERAPEUTIC DRUGS

Caffeine- a case-control study included 277 infants with congenital cardiac malformations, evaluating the ingestion of caffeine, tea and cola, at the end, not a single risk was identified for any of these drinks (40).

Alcohol

Since 1973, when the fetus was diagnosed with the syndrome due to the consumption of alcohol during pregnancy, many studies have described a wide range of teratogenetic effects including cardiovascular malformations (45). In BWI, the association between alcohol and congenital cardiac malformations was limited with a high risk only for small, muscular VSD. A similar study conducted in Finland reported a double risk for ASD, in children whose mothers had consumed alcohol during pregnancy (46).

Cocaine and marijuana

A meta-analysis carried out from other 6 studies, pointed out there is no significant association between the consumption of cocaine during pregnancy and fetal cardiovascular malformations (47). Marijuana, evaluated in BWI, was associated with a small increase in the risk for Ebstein disease (48).

Smoking

Some recent studies have reported associations between maternal smoking during pregnancy and combined cardiac malformations, but these associations have not been corroborated with comprehensive studies.

ENVIRONMENTAL FACTORS

Organic solvents

- exposure to degreasing substances was associated with a high risk for: hypoplastic left heart syndrome, aortic coarctation, pulmonary stenosis, transposition of the great vessels with intact ventricular septum , tetralogy of Fallot, total anomalous pulmonary venous return, Ebstein disease;
- professional exposure to organic solvents was associated with a high risk for VSD (49);

- exposure to paint and shellac was associated with conotruncal malformations;
- products from mineral oils, was associated with aortic coarctation (50).

Herbicides, pesticides, rodenticides

In BWI, the exposure to herbicides and pesticides was associated with a high risk for the transposition of the great vessels, while the exposure to pesticides was associated with pulmonary venous return and VSD (51).

Contamination of underground waters

There was reported a high risk for congenital cardiac malformations among children whose parents had come into contact with waters contaminated with trichloretyne (52).

MATERNAL SOCIO-DEMOGRAPHIC CHARACTERISTICS

Age

In BWI, the mother's age:

> 30 years, was associated with a high risk for the transposition of the great vessels and Ebstein disease;

> 34 years, was associated with a high risk for bicuspid aortic valve and ASD;

< 20 years, was associated with a high risk for tricuspid atresia;

A study in Atlanta associated the advanced maternal age (35-40) with a high risk for all congenital cardiac malformations (53).

Race

In comparison with black infants, white infants proved to have a high prevalence of Ebstein disease, aortic stenosis, VSD, ASD, aortic coarctation, common arterial trunk, transposition of the great vessels, tetralogy of Fallot, CAP, pulmonary stenosis, hypoplastic left heart syndrome (54).

History of Obstetrics

A maternal history of: *spontaneous abortions*- was associated with a high risk for tetralogy of Fallot and Ebstein disease; *birth of dead children in antecedents* – non-chromosomal septal defects; *premature births in antecedents* - ASD;

These pathological antecedents can actually be translated into concern for teratogenetic exposures or for an inherent, increased sensitivity to congenital cardiac malformations.

Stress

Seen as maternal reference to loss of job, divorce, separation or death of a close relative or fiend, stress proved to be associated with an increased risk for conotruncal cardiac malformations, especially in mothers with university education (55).

PATERNAL SOCIO-DEMOGRAPHIC CHARACTERISTICS

Paternal factors can play an important part in the origin of general congenital defects and cardiac defects in particular. New mutations are more frequent among elder parents than among people in general. A general model for the increase in the risk simultaneously with the ageing of the father was found for: ASD, VSD, and CPA (56).

BWI reported an association of the consumption of paternal cocaine with an increased risk for any of congenital cardiac malformations, and first of all DSV and tricuspid atresia. A statistically significant relation between smoking and paternal consumption of alcohol could not be demonstrated.

Conclusions

1. Because congenital cardiac malformations represent some of the most prevalent congenital malformations, with a significant morbidity throughout life, and an important cause of mortality attributed to congenital malformations, the development of efficient prevention measures is essential from the perspective of public health.
2. A lot of the recent evidence is preliminary, and not always proves to be of causality. Nevertheless, some reasonable recommendations can be offered to future parents and medical staff to reduce the risk of having a child with congenial malformations.
3. Future parents should discuss with the family doctor or obstetrician about the factors that can affect pregnancy, such as alimentation, physical activity, lifestyle and way of working.
4. Women who are at the fertile age should receive daily multivitamins containing folic acid during the period before pregnancy and avoid certain types of behaviors, such as exposure to organic solvents. Also, they should be tested for diabetes and precedent exposure to rubella, and if they are to use any type of medication it is better for them to ask for the obstetrician's advice.
5. Depending on the anamnestic data of each family, genetic tests should be done for children with congenital cardiac malformations.
6. The scope and heterogeneity of the genes and mutations identified so far as being responsible for some of congenital cardiac malformations, suggest that they are associated with a variety of pathogenetic mechanisms. The challenge of the future is to define the pathogenesis that causes mutations and which in its turn, will offer the opportunity to develop diagnosis and treatment strategies, as alternatives to those used so far.

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EMPIRIC ANTIBACTERIAL THERAPY DURING GRANULOCITOPENIA IN FEBRILE CHILD, INDUCED BY ACUTE LIMPHOBLASTIC LEUKEMIA (ALL)

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Abstract

In this article is discussed the empirical use of antibacterial therapy and addresses the basis of modifications in therapy. Empiric therapy with broad-spectrum antibiotics against Gram-negative bacteremia is necessary in febrile granulocytopenic ALL patients. The level and dynamics of granulocyte count are extremely important in determining the outcome of bacteremia. Most empiric regimens will require therapeutic modifications which contribute to a high overall success rate. Only microbiologically documented infections and especially bacteremias are useful for comparison of initial response to antimicrobial regimens. Gram-positive pathogens have become a common cause of bacteremia in granulocytopenic ALL patients. The response rate to empiric treatment may be suboptimal, but the associated mortality is low. The rational use of antibiotic therapy in children at risk for severe, live-threatening infection represents one of the major advances in the supportive care of children undergoing antineoplastic therapy.

Key words: antibacterial therapy, neutropenia, fever

Introduction

Infection is the most frequent complication of granulocytopenia and when left untreated is often fatal. Since fever is commonly the only symptom of infection in neutropenic patients, the empiric administration of antimicrobials to febrile granulocytopenic patients has become accepted practice. [1] Dramatic progress has been made in the management of febrile children with neutropenia (absolute neutrophile count < 500 neutrophils/μL^3), the single most important risk factor for infection. [2, 3] Today, it is decreasing the chance for children to die from infectious complications during therapy, primarily because of the evolution of supportive care afforded children with neutropenia. [4, 5] These advances in the management of infectious complications have permitted oncologists to treat with higher doses of therapy and to treat more patients on re-induction schema. This, in turn, translates into an expanding number of children with ALL undergoing aggressive therapy who are at risk for infection. [6] The presence of neutropenia is the most important factor associated with infection in the febrile child with cancer.[3, 7] The early institution of empirical antibiotics in the febrile, neutropenic patient has resulted in a marked decrease in morbidity and mortality, even in the absence of either a microbiologic or a clinical diagnosis. [1, 2, 8, 9] Accordingly, the depth and duration of neutropenia are important determinants in assessing the relative risk of a serious infection, guiding decisions to initiate, modify or terminate empirical antibiotic therapy. In the 1990s, the mortality associated with a febrile, neutropenic event is approximately 5%. [3] A number of advances in supportive care are responsible for this trend, including early intervention with new broad-spectrum antibiotics, earlier detection of pathogens, recombinant haematopoietic growth factors, and the recognition of specific clinical syndromes.[6] Still, the fact that mortality has not been completely eliminated underscores the gravity of fever and neutropenia in children with ALL. Because the majority of febrile, neutropenic events do not have a source of infection identified, treatment is administered to many who may not have needed therapy. [5, 9, 10] However, the consequences of observing but not treating can be devastating. [7, 11] The algorithms for treating febrile, neutropenic patients have been based on cancer patients with therapy-induced neutropenia. It is important to recognize that other factors, such as mucositis, suppression of other arms of host defense, specifically, cell-mediated immunity and the presence of indwelling catheters, also contribute to the overall risk of infection. [6]

GENERAL ISSUES OF ANTIBIOTIC CHOICE

Initial empirical therapy:

The choice of antibiotic therapy in febrile neutropenic children should be designed to provide broad coverage for a range of pathogens. Historically, the emphasis has been on providing adequate coverage for treating Gram-negative enteric bacteria and *Pseudomonas aeruginosa*. Because of the significant morbidity and mortality associated with these bacteria, coverage has been directed at these devastating pathogens, even though they may not be the most common. Beginning in the late 1970s, at the same time that long-term indwelling catheters were introduced, a gradual shift of microbiologically determined infections took place. [13] A preponderance of Gram-negative bacteria has given way to Gram-positive organisms. [14-16] Recently, an increase in Gram-negative organisms has been noted, but it is too early to determine if this is a long term shift. Until recently, the standard empirical antibiotic regimen consisted in combination of antibiotics designed to

provide broad coverage and discourage the emergence of resistant organisms. [17] Synergy, improved killing with two antibiotics, provided a rational basis for combination therapy. [18, 19] Many different combinations have been tested, but no particular combination has shown superior efficacy. [20, 21] Nonetheless, partly because of familiarity and partly because of pharmacokinetic considerations, successful combinations that has gained universal acceptance include a β-lactam agent, either an ureidopenicillin or third-generation cephalosporin, and an aminoglycoside. Use of ceftazidime as monotherapy has been substantiated in numerous studies and was recently reviewed in a meta-analysis. [22] The introduction of carbapenams (which include imipenam) offers slightly increase coverage of Gram-positive organisms (e.g. enterococci) and anaerobes. Studies with this agent have confirmed equivalency in overall efficacy compared to either combination therapy of ceftazidime monotherapy. Some authors have raised concerns regarding the use of monotherapy for fever and neutropenia, especially in children, but the theoretical basis of these concerns have been answered by extensive clinical experience. [18, 23] Still, the choice of monotherapy must be made in the context of the unique experiences of the local hospital epidemiology and resistance patterns. However, it cannot be overstated that it is necessary to maintain a flexible approach with regard to selection and modification of an empirical regimen. This mandates frequent and meticulous clinical evaluation of patients daily. Furthermore, the choice of agents for empirical coverage should take into account trends in antibiotic usage and susceptibility patterns of recently isolated pathogens. The success of initial therapy has been predicated on the administration of one or more antimicrobial agents that achieve high serum concentrations. In this regard, the ability to achieve effective bactericidal activity, even in the absence of neutrophils, is critical to the success of therapy. The choice of initial antibiotics should include agents for which the risk of encountering and selecting for resistance is low. For example, one of the motivations for developing third-generations cephalosporins was to counter the emergence of lactamase activity in enteric Gram-negative organisms. However, selected pathogens, such as *Enterobacter* and *Citrobacter spp.*, have emerged which quickly develop resistance during therapy. [24] The choice of antibiotics must also take into account the toxicity profile and the potential for drug interactions. Lastly, the decision to choose antibiotics should also be based upon a demonstrated clinical efficacy. The standard approach has been to continue administering intravenous antibiotics until both the fever and the neutropenia resolve, if neutropenia resist for at least one week. [3, 17, 30] In selected circumstances, fever may be short-lived and yet the neutropenia persists. The recommendation is a minimum of 5 to 7 days of parenteral antibiotics be administered after resolution of fever in patients with protracted neutropenia. [17] Several preliminary studies have attempted to shorten the duration of empirical antibiotics in children with prolonged neutropenia. [31-33] In fact, children were discharged from the hospital with no antibiotic therapy, if they became afebrile quickly and had no microbiologic or clinical diagnosis made. However, the studies are small and the numbers insufficient to establish this approach for all patients. The application of early discharge does have its proponents who argue that the determination of low- and high-risk patients should be adequate for tailoring continuation therapy or discontinuing therapy. [34] They suggest that "low-risk" patients should be discharged early if all cultures are unremarkable, fever has abated, a short period of neutropenia is anticipated and easy access to care is available. [31-33, 35, 36] Ongoing studies with oral antibiotics may lead to more cost-effective strategies, but this approach, too, is investigational. If a microbiologically or clinically diagnosis is made, the duration of therapy should err on the longer side. In other words, if *Klepsiella pneumoniae* sepsis is diagnosed in neutropenic child, therapy for at least two weeks with intravenous antibiotics or until neutrophils recover is indicated, whichever is longer. If clinically indicated, oral antibiotics can be successfully used to complete therapy, once neutropenia has resolved.

Modification of initial coverage:

Independent of the initial choice of empirical antibiotics for management of the febrile, neutropenic child, it is important to recognize that modifications of the primary agents will be necessary, particularly the longer a patients remains neutropenic, This is especially true in patients with a clinical or microbiologic diagnosis. Generally, during the first 5 to 7 days, modifications are made in response to the susceptibility pattern of an isolated pathogen or a clinically identified problem, such as a perirectal focus of infection. The decision to add anaerobic coverage for severe mucositis should be predicated on severity of lesions. Generally, the addition of clindamycin or metronidazole should be reserved for serious lesions with necrosis or foul-smelling odor. On occasion, a breakthrough or a resistant organism will require modification of the initial empiric antibiotic therapy. Still, the persistence of fever is not necessarily an indication to alter coverage. In patients with protracted neutropenia, fever is commonplace, in spite of broad-spectrum antibacterial coverage. However, the presence of persistent fever is an important warning sign that necessitates careful and continual investigation; yet in a substantial majority of patients, no new etiology will be identified. The likelihood of a documented infection is greatest at the time of presentation. In roughly one-third of patients a specific clinical syndrome or a microbiologically isolated pathogen will be diagnosed within days of presentation with fever and neutropenia. [9] However, the recurrence of fever after several days or the persistence of fever for 5 or more days is an indicator of increased risk. [7]

Preventive strategies:

Over the past 25 years, a number of preventive strategies have been investigated in patients with cancer. Some have been designed to protect the neutropenic patients from acquiring new pathogenic bacteria. The basic principle

underlying this approach is to isolate the patient from new potential pathogens. This strategy has had many proponents who have used such measures as complete isolation and a sterile room with filtered air and protective barriers including masks, gloves and gowns. Variations of this theme include neutropenic diets, avoidance of public places during both of neutropenia, reverse precautions or single rooms. Above all, the most important measure includes good handwashing before and after examining neutropenic children. Another parallel approach has been to administer prophylactic or preventive antibiotics to reduce or eliminate endogenous bacteria, considered to be dangerous opportunistic pathogens in the immuno-compromised host. This approach referred to as selective gut decontamination, is based on the principle of affecting colonization resistance patterns. [38, 39] Over time, successive studies with non-absorbable agents trimethoprim / sulfamethoxazole, and recently fluoroquinolones have been conducted. [40, 41] Unfortunately, the success of each of these strategies has not been impressive, especially when one considers the cost, toxicity and selection of resistant organisms. Furthermore, delays in recovery of bone marrow, skin rashes and selection of fungal and multiply-resistant bacteria are major side effects. It is noteworthy that trimethoprim / sulfamethoxazole is an excellent choice for prophylaxis against *Pneumocystis carinii* pneumonia, especially in children with leukemia receiving consolidation or maintenance therapy. [42] Trends have shifted from the use of total protective precautions to the use of prophylactic antibiotics but with little impact on the incidence or severity of infection. The use of prophylactic fluoroquinolones reached its limits in the early 1990s but with the emergence of resistant organisms the trend has been to shy away from this strategy. For the most part, fluoroquinolone prophylaxis should be reserved for special circumstances and not used routinely in all neutropenic patients at risk for infection.

SPECIFIC ANTIMICROBIAL AGENTS

Third-generation cephalosporins:

By the early 1990s, extensive experience with ceftazidime alone established the efficacy of monotherapy in the febrile, neutropenic patients. Ceftazidime is well suited for this purpose, primarily on account of its broad spectrum of activity, including excellent minimum inhibitory concentrations against *P. aeruginosa* as well as enteric Gram-negative organisms. Cefaperazone, the other commercially available third-generation cephalosporin with comparable activity has been shown to be effective in combination therapy. Its use as monotherapy has been limited. Both drugs have excellent tissue penetration, including the cerebrospinal fluid (which is rarely the site of infection in neutropenic patients but when present can be devastating). The toxicity profiles for both drugs are favorable and unlike other third-generation cephalosporins, it does not interfere with the coagulation pathways. The decision to use ceftriaxone in pediatric cancer patients is complex and is not recommended at this time. Despite the advantage of once a day administration, the lack of activity against *P. aeruginosa* and other Gram-negative enteric bacteria prevents the recommendation of ceftriaxone as first-line therapy. Ceftazidime has attained the designation of "standard of therapy" for monotherapy. [3, 9, 23] A large, prospective randomized controlled study established efficacy comparable to combination therapy. [9] If ceftazidime is chosen as monotherapy, the clinician must be willing to modify therapy quickly when indicated by either microbiologic results or clinical changes in the febrile, neutropenic child. [37] The ability to administer a single agent offers a number of advantages but also requires close observation during the course of therapy. In this regard, it is not appropriate to use ceftazidime as an outpatient or home infusion antibiotic for a febrile neutropenic event. One attractive advantage of ceftazidime monotherapy is that it eliminates the risks, cost and need to monitor serum levels of aminoglycosides.

Carbapenem:

Imipenem is a member of Carbapenem class of antibiotics, offering a second comparable choice for empirical monotherapy. [37, 43] Its spectrum of activity extends beyond the range of ceftazidime and includes improved coverage for enterococci and many anaerobes. It has favorable pharmacokinetics, shows excellent activity against the primary pathogens and is relatively well-tolerated. It has been used successfully in febrile, neutropenic children with cancer. [37, 44] compared to ceftazidime, it has more gastro-intestinal toxicity, specifically, nausea, diarrhea and *Clostridium difficile* colitis and did not significantly decrease the overall need for antibiotic modification. [37] A number of individual studies have established its efficacy, showing that it is equivalent to either ceftazidime monotherapy or combination therapy. [37, 43] The problem of gastrointestinal toxicity associated with imipenem is an important factor for choosing between ceftazidime and imipenem. For this reason alone, it may be prudent to start with ceftazidime for monotherapy and use imipenem for patients who show signs of cardiovascular instability or breakthrough / resistant infection. Meropenem is a new agent with great potential. Preliminary data suggest it is safe and probably equivalent wipenem but with less toxicity. Studies in children are ongoing at this time.

Aminoglycosides:

Aminoglycosides were once considered essential agents in the empirical management of febrile, neutropenic patients, primarily because of their excellent activity against Gram-negative enteric bacteria and Pseudomonas spp. At one time, it was inconceivable to start therapy without an aminoglycoside. This approach arose from both clinical experience and was justified by the *in vitro* observation that the combination of a β-lactam agent and an aminoglycoside resulted in a synergistic microbicidal effect. Monotherapy with imipenem or ceftazidime has been shown to be both safe and efficient and thus, aminoglycoside therapy has been

relegated to a secondary role. Even the use of a short course of aminoglycosides has been shown to provide only a marginal advantage for survival in patients with a documented Gram-negative bacteremia. [45] In the large randomized study that established the efficacy of ceftazidime monotherapy, an analysis of the modifications revealed a significant overuse of aminoglycosides. In the 1990s, aminoglycosides have marginal utility for initial therapy in the febrile, neutropenic patient. In truth, aminoglycoside therapy is best used for pathogen-specific indications. In this regard, the use of aminoglycosides in the initial management of the febrile, neutropenic child should be reserved for those children in whom combination therapy with either a ureidoor carboxypenicillin is required or an intravenous fluoroquinolone is indicated (because of a drug allergy to β-lactamase agents). The former may be necessary because of a high incidence of infections in the local institution with Gram-negative organisms that are resistant to β-lactams or develop resistance during monotherapy (e.g. Enterobacter spp., Acinetobacter spp. and Pseudomonas spp.). Aminoglycosides should be included in the initial therapy for neutropenic child who exhibits cardiac instability or hypertension. In a similar manner, use is indicated in patients already receiving therapy who suddenly develop signs and symptoms of sepsis.

Aztreonam:

Aztreonam is a monobactam antibiotic that is highly resistant to most β-lactams. Its spectrum of activity is comparable to that of the aminoglycosides, it is active against Gram-negative enteric bacteria but does not have significant renal toxicity and ototoxicity. Combined with vancomycin, it has been used successfully in the empirical treatment of febrile, neutropenic cancer patient in a small uncontrolled study. [46] However, aztreonam lacks synergy with β-lactams against Gram-negative enteric bacteria. Because of its poor activity against Gram-positive and anaerobic bacteria and its cost, its use is limited to substitution for an aminoglycoside in a child with renal disease / toxicity, a highly resistant organism or a severe penicillin allergy. [59]

Fluoroquinolones:

The fluoroquinolones offer excellent coverage for Gram-negative enteric bacteria and have favorable pharmacokinetics suitable for either oral or intravenous administration. [47] There is little compelling data to support monotherapy with a fluoroquinolone, especially in children. [48] This is based upon lack of efficacy and the emergence of resistant strains of Gram-negative enteric bacteria. On occasion, fluoroquinolones have been used to successfully treat multiply-resistant organisms for which few or no other antibiotics are available. [21] In addition the poor coverage for Gram-positive organisms, especially staphylococcal and streptococcal species, makes this class of agents unsuitable for monotherapy. Several outbreaks of pathogenic, resistant coagulase-negative staphylococci infection have been reported in oncology centers where fluoroquinolones are commonly administered for prophylaxis. [49] Moreover, breakthrough with life-threatening streptococcal infections has emerged as a major complication in patients receiving fluoroquinolones as a single prophylactic agent during prolonged neutropenia. For treatment of febrile, neutropenic patients, fluoroquinolones may be a suitable agent for use in β-lactam-allergic patients but in combination with an aminoglycoside. Excellent oral bioavailability is a distinct advantage for treatment of low-risk febrile, neutropenic patients as outpatients. Studies are ongoing to address whether this strategy is safe and efficient. Despite the paucity of published data, many practicing adult oncologists have adopted this practice for low-risk patients, usually in combination with other agent with extended Gram-positive coverage, such as ampicillin / sulbactam. At the same time, fluoroquinolone usage in children, originally discouraged by animal data suggesting an injurious effect on bone / cartilage development, is increasing. Recently, a subcommittee of the International Society of Chemotherapy endorsed the use of fluoroquinolones in children with severe infections, especially when an alternative safe therapy is not available. Until conclusive studies demonstrate that early discharge of febrile neutropenic patients treated with oral fluoroquinolones is safe, it is unlikely that fluoroquinolones will be considered the first-line choice for febrile, neutropenic children. Fluoroquinolones have been shown to be effective when administered as prophylactic antibiotics during periods of neutropenia. However, the selection of resistant organisms represents a powerful deterrent for this practice in all but selected circumstances. On a theoretical basis, one could argue that they may be useful for prophylaxis during the recovery phase from a bone marrow transplant. The distinct advantage in this setting is that the patient is not repeatedly exposed to fluoroquinolones and in this regard, selection of resistant organism is minimized. Repeated uses encourage not only the emergence of newly acquired resistance but also the selection of organisms, such as α-streptococci, which may be devastating in the intensively treated patient.

Vancomycin:

Because of the emergence of Gram-positive organisms as the most commonly encountered clinical isolate in febrile, neutropenic children, vancomycin usage is common in pediatric oncology. [13, 16] Since it is the most effective agent against non-aureus staphylococci, enterococci and α-streptococci, three important pathogens in the immuno-compromised child, it is a primary choice for documented infections with the above pathogens (pending sensitivities). Often, one or more of these pathogens cause a catheter-associated bacteremia, even in the non-neutropenic child. Vancomycin is administered as an intravenous bolus and levels are frequently measured to establish adequate dosage. Its spectrum is limited to Gram-positive organisms. Another glycopeptide, teicoplanin offers a similar spectrum of activity but the clinical experience with this agent is limited compared to vancomycin. Some have recommended

that vancomycin be added to the up-front empirical regimen and in fact, many centers have adopted this approach. [25, 26, 28] Conversely, it has been argued that vancomycin should be withheld until the Gram-positive isolate has been identified microbiologically since most of these organisms are of low virulence and inhibited by β-lactam antibiotics. [27] On the other hand, Karp et al. [26] showed that the incidence of the secondary Gram-positive infections was decreased in patients who received empirical vancomycin with initial therapy. The routine administration of empirical vancomycin would have over treated nearly 95% of patients. Out of concern for the burgeoning problem of vancomycin resistance in enterococci, one has to consider the importance of withholding this agent until a microbiologic diagnosis is made. In conclusion, the routine inclusion of vancomycin in initial empirical therapy is not indicated, but it should be held in reserve for pathogen-specific usage. Again, local institutional patterns of susceptibilities and isolated organisms may require reconsideration of this approach.

Conclusions

The judicious use of empirical antibacterial therapy in the pediatric patient with fever and neutropenia has contributed significantly to improvements in the management of infectious complications of antineoplastic therapy. Indeed, the use of new, broad-spectrum antibiotics as monotherapy has eliminated more troublesome combinations while providing comparable success of therapy. The goal of next decade will be to develop strategies using recombinant growth factors (for well-defined indications), molecular diagnostics and the selective use of available antibiotics to refine the approach to treating the febrile, neutropenic child. At the same time, it is imperative that we better define the pleiotropic effects of chemotherapy and other limbs of the immune system. The success of supportive care (especially of infectious complications) has permitted oncologists to push the limits of toxicity (e.g. risk of infection) and consequently created a larger number of children at risk. Present controversies include not only the choice of antibiotics, both at initiation and in response to either microbiologically isolated pathogens or clinical syndromes, but also the duration and mode of administration (intravenous versus oral). The optimal use of biologic modifiers and recombinant growth factors remains to be determined. [50] They should not be used indiscriminately in children, but when the risk of a serious infectious complication is well-defined, such as following ablative therapy and rescue with either bone marrow or peripheral stem cells. The crisis of resistant organisms is a sobering reality that challenges the specialist to assess the indication for using antibiotic therapy. Most experts would agree that the trend in the future will be to limit the use of antibiotics as a measure to minimize the emergence of resistant organisms but also as a cost-saving measure. For this strategy to be effective, we will need to develop algorithms to refining risk groups and basing treatment decisions accordingly. [11] Lastly, the controversies regarding the choice and modification schemes for antibiotic intervention need to be viewed in the context of the individual patient. In the end, the patient bears the consequences of the clinician's choice of therapy. The clinician must determine the acceptable risks and benefits of not only initiating therapy but also modifying and terminating therapy for infectious complications in the child receiving ALL therapy.

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THE NEONATE BORN BY CAESAREAN SECTION

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Abstract

This paper presents the risks for the neonate born by caesarean section versus normal birth. It is deemed that these risks cover a very wide range and, when associated with other maternal-foetal risks, may influence the morbidity and mortality during the neonatal period. Also, besides the fact that it is not a comfortable and painless solution, this way of giving birth becomes more and more *fashionable* and loads the caesarean percentage with more or less argued indications, as well as the percentage of planned caesareans without labour, from which newborns with many problems of immediate and tardive adaptation result.

The conclusions of the paper focus on highlighting the major risks of this way of birth for the child and warn at least prudentially about the decision for caesarean section.

Key words: neonate born, caesarean section, normal birth

One of the most controversial themes of modern obstetrics is whether pregnant women should choose caesarean delivery or caesareans should be performed only when the case.

In the past, the maternal mortality associated with this type of birth was very high, with caesarean section being the only way to save the child. First mentions of birth by caesarean section come form the 16th century, but only in the 18th and 19th centuries both mother and newborn survival were ensured as a result of this procedure.

Over the last three decades, important changes concerning the relationship between birth and perinatal prognosis have appeared, including the efforts to reduce the frequency of caesarean deliveries, concomitantly with the attempt to allow for the pregnant women to express their obstetrical options. The increase of caesarean ratio was not associated with any benefit for the child or mother, but with increase of morbidity in both categories. As caesarean delivery may be scheduled so as to be convenient both for the physician and for the patient, there is a risk for this procedure to be performed more frequently and earlier than needed. It is therefore necessary to inform pregnant women on the potential risks and benefits related to the caesarean delivery [1].

WHO recommends the ratio of caesarean deliveries to be of approximately 10-15% out of total births. All the studies show the real percentage is much more higher, in regard to total number of births:

- in Australia – 19.4% in 1994 → 29.15 in 2004,
- in USA – 30.2% in 2005,
- in Latin America– 33% in 2005,
- in Romania – currently, in some centres, the percentage exceeded 50%.

However, despite the increase of its supporters as alternative for vaginal birth, the caesarean section is not a benign intervention.

We shall present hereinafter evidences and proves arguing this aspect.

In 2007 BMJ published a study by Villar and colleagues [2] that highlights the increased risk for severe maternal morbidity in case of caesarean delivery compared with vaginal delivery, both in the case of *intrapartum* and elective caesarean delivery. The authors defined the **elective caesarean** as the intervention decided by the physician before the onset of labour, without a medical indication, and the ***intrapartum* caesarean** as the intervention indicated during labour, regardless if the labour was spontaneous or induced. This **cohort** study, conducted in Latin America on 97,095 deliveries, showed the increased rate of caesarean deliveries does not necessarily lead to an improvement of maternal and neonatal prognosis.

Neonatal evolution has been tightly correlated with presentation at birth. Foetal mortality of 9.69% and neonatal mortality (before hospital discharge) of 8.55% in the case of vaginal delivery with breech presentation is significantly higher as compared to elective caesarean section with the same presentation (0.96% foetal mortality and 1.79% neonatal mortality). The authors concluded that caesarean delivery had a protective effect on this group of pregnant women in the case of breech presentation. The protective effect on the foetal mortality in cephalic presentation was less obvious, with a neonatal mortality significantly higher associated with elective or *intrapartum* caesarean delivery. As the neonatal morbidity concerns, study results show that either *intrapartum* or elective caesarean, in the case of cephalic presentation, increases the risk for admission to the neonatal intensive care unit for more than seven days and also enhances the neonatal mortality risk after hospital discharge (this remains high even after the exclusion of all the caesareans with indication of foetal distress).

Absence of labour was a risk factor for admission to the neonatal intensive care unit for seven or more days and for the neonatal mortality after hospital discharge in the newborns delivered by elective caesarean section. In these cases, premature and/or precocious rupture of amniotic membranes may be protective. As maternal morbidity regards, study results reveal a severe increase of it in the case of elective/*intrapartum* caesarean compared to vaginal delivery, the antibiotic treatment being five-fold higher in caesarean sections.

The study conclusion was that caesarean delivery reduces the risks in breech presentation and the *intrapartum* foetal mortality risk in cephalic presentation, but increases the neonatal and maternal morbidity and mortality risk in cephalic presentation.

In a recent study (2009) published by Tita and colleagues [3] in The New England Journal of Medicine, authors showed pregnant women choosing planned caesarean before 39 weeks of gestation are two times more exposed to the risk of having a newborn with severe complications, including the risk for respiratory pathology requiring mechanical ventilation and intensive care unit admission. Authors assert the reason of conducting this study was the increase of caesarean deliveries rate in USA from 20.7% in 1996 to 31% in 2oo6, one of the reasons being that vaginal delivery is not performed after a caesarean delivery. The study was performed on 13,258 elective repeat caesarean deliveries. The aim of the study was to assess if in children born at 37 weeks of gestation by elective there are more frequent caesarean complications such as:

- respiratory distress syndrome and transient tachypnea of the newborn,
- neonatal sepsis,
- neonatal seizures,
- ulcero-necrotising enterocolitis,
- perinatal hypoxic-ischemic encephalopathy,
- necessity of ate ventilator support within 24 hours after birth,
- umbilical artery sanguine pH < 7,
- 5-minute Apgar score ≤ 3,
- admission to the neonatal intensive care unit or prolonged hospitalisation.

The study conclusions confirmed that "**precocious**" caesarean delivery before 39 weeks of gestation may be unfavourable to the neonatal prognosis. Newborns by elective repeat caesarean at 37 weeks of gestation are four times more predisposed to above mentioned complications as compared to those born in the same way at 39 weeks of gestation. Those born at 38 weeks carry only a two times higher risk. Tita and colleagues [3] consider "**a narrow window between 39 and 40 weeks of gestation is optimal for the newborn and any deviation before or after this week increases the neonatal risk**" in elective caesarean delivery.

Comparable results were obtained in a study performed within a university hospital in Denmark during 1998-2006 on 2,687 infants born by elective caesarean section as compared to 31,771 infants born by vaginal delivery or by caesarean as a result of an emergency during the labour. It has been concluded that newborns by elective caesarean at 37-39 weeks of gestation bear a 2 - 4 times higher risk to develop respiratory pathology as compared to vaginally delivered newborns. A decrease in the respiratory pathology might be achieved by planning the elective caesarean sections only after 39 weeks of gestation [3].

There are studies in the literature evaluating the individual risk for certain respiratory diseases in the context of birth by caesarean section. Sonia Hernandez-Diaz and colleagues [4], in a study conducted between 1998-2003 within Boston University, on 377 mother-child pairs with persistent pulmonary hypertension (PPHT) and 836 control pairs. Results showed the risk to develop PPHT is higher in the neonates born by caesarean section as compared to the infants born naturally [4].

In a paper published by the American College of Obstetricians and Gynecologists, the conclusion has been that PPHT is 5 times more frequent in caesarean section births. The authors presented the hypothesis of labour having a beneficial effect on the lungs of the newborn, therefore close neonatal monitoring in newborns by caesarean section, as well as inclusion of neonatal risk in the informed consent before surgery is mandatory.

Some studies identify **the neonatal pneumotorax** in approximately one thirds of newborns with iatrogenic syndrome of respiratory distress. More recently, severe pneumotorax and/or PPHT were observed in newborns delivered by elective caesarean section. The study published by Zanardo and colleague [5], on a group of 66,961 newborns on a two-year period, concluded that full-term birth by elective caesarean associates an increased risk for neonatal pneumotorax as compared to the emergency caesarean or vaginal deliveries. Performing the elective caesarean after 39 weeks of gestation would be expected to reduce the risk of iatrogenic neonatal pneumotorax.

The relationship between caesarean section and onset of **bronchial asthma** has been assessed by a group of researchers within Public Health and Environment National Institute in The Netherlands. The aim of the study was to determine the probability that newborns delivered by caesarean section to carry an increased risk to develop bronchial asthma during childhood. 2,917 children were included in the study and followed-up from birth to the 8 years of age. The authors' conclusion was that children born by caesarean section bear a higher risk to develop bronchial asthma as compared to those born vaginally, especially in children from atopic parents. Caesarean increases the risk of sensitivity to common environmental allergens in children from non-allergic parents only.

A research by Queen's University in Belfast examined 20 studies from 16 countries in which 10,000 **type I diabetes mellitus** children were analysed. The researchers discovered a 20% higher risk in children born by caesarean section to develop type I diabetes mellitus during childhood. Increase of this risk could not be explained by other associated factors, such as: birth weight, mother age, gestational diabetes or breastfeeding. Type I diabetes occurs when the immune system destroys the insulin producing cells in the pancreas. According to the theory of researchers in Belfast, normal development of newborn's immune system is affected by caesarean section delivery, these children being firstly exposed to the bacteria in the hospital,

instead of being normally and naturally exposed to the maternal bacteria [6].

Summarising the above mentioned data and other recent results of researches focused on this theme, we may conclude the following risks are or become major for the neonate born by caesarean section.

Neonatal death. Although usually births by caesarean section need to be carried out in the benefit of the baby, there are major risks (often lethal) accompanying this type of birth. In a study conducted in California that included more than 580,000 births it has been ascertained that both children born by planned caesarean section and children born by unplanned caesarean section bear a four times higher risk of death before hospital discharge than children born vaginally (8 deaths per 10,000 birth for each planned or unplanned caesarean and 2 deaths per 10,000 births for vaginally born infants) [7].

Respiratory problems. The best described problems are the respiratory ones occurring in full-term newborns. These respiratory difficulties, known as transient tachypnea of the newborn (TTN), probably represent an outcome of the failure of foetal lung liquid reabsorption mechanism that starts automatically during vaginal birth. In a retrospective study performed on approximately 30,000 births results, TTN incidence is almost three-fold higher after birth by elective caesarean section then after vaginal birth (3.1% vs. 1.1%) [8].

Bronchial asthma. Several studies reported an association between birth by caesarean section and a subsequent development of bronchial asthma. One of these studies shows the risk to be hospitalised for bronchial asthma during childhood increases by 30% in the children born by caesarean section as compared to the children born vaginally [9].

Iatrogenic prematurity is related mainly to the cases of birth by planned caesarean section. It occasionally occurs even in full-term newborns, as stated in a study conducted on more than 170,000 births in UK.

Birth trauma. Children born by caesarean section are exposed to the risk for trauma, as a result of surgical lesions, chiefly in emergency deliveries. A recent study reports a traumatic lesions index after caesarean section of 3%.

Failure of breastfeeding. A meta-analysis of 9 studies shows that failure of breastfeeding in newborns by (mostly unplanned) caesarean section is significantly higher as compared with those naturally born. A study on 580,000 women in California showed that mothers who delivered by caesarean section, either planned or unplanned, presented two times more frequently noninitiation or insufficiency of breastfeeding during neonatal period as compared to those who delivered naturally.

Conclusions

1. There are currently sufficient arguments and evidences regarding the immediate or delayed risks for the neonates born by caesarean section vs. natural delivery.
2. The risks are variably, but significantly augmented when elective caesarean vs. *intrapartum* caesarean, elective caesarean at $\leq$ 37 weeks of gestation, as well as repeat caesarean is indicated.
3. Before deciding the type of delivery, the obstetrician has to carefully and judicially analyse the advantages of each type (natural vs. caesarean) and, if necessary, to advise with the neonatologist concerning the necessity to extract the newborn by caesarean section.

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NEUROBLASTOMA - A CONCISE REVIEW

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Abstract

Far from pretending to be an exhaustive ex-cathedra exposé on neuroblastoma, this article attempts to be a concise review of the literature. It focuses on clinical diagnostic reflexes and staging paradigms. Controversial and hair-splitting issues regarding risk stratification, treatment and prognosis have been discretely and carefully avoided.

Key words: neuroblastoma, peripheral neuroblastic tumors, ganglioneuroblastoma, ganglioneuroma, small blue round cell tumors, pathologic classification, paraneoplastic syndromes, tumor markers, clinical staging.

Introduction

Neuroblastoma (NB) is the fourth most common malignancy of childhood, accounting for roughly 8% of tumors – preceded by leukemia (30%), CNS tumors (22%) and lymphoma (15%). It is nonetheless the first intraabdominal and the first extracranial solid tumor to be encountered in the pediatric population[1,2].

NB is a neurocristopathy, arising from pluripotent primordial neural crest cells. Though the tumor predilectively involves the adrenal medulla, it may arise anywhere along the sympathetic axis, to involve the neck, posterior mediatinum, retroperitoneal (paraspinal) ganglia, adrenal medulla or pelvis[3]. Figure 1 – illustrates the anatomic distribution of neuroblastoma primary sites.

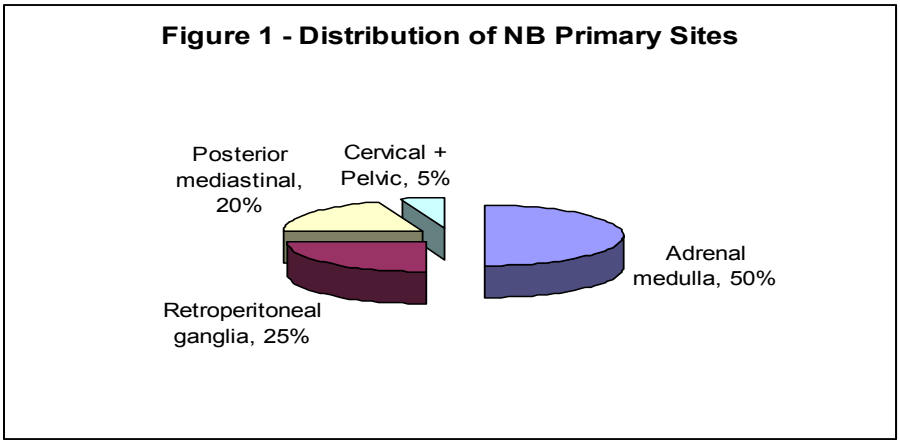

Figure 1 – The anatomic distribution of neuroblastoma primary sites.

Epidemiology

The incidence of NB is approximately 1 case per 10.000 live births/yr. It has a bimodal distribution with a first peak during infancy and a later peak at the age of 2-4 yrs. It is more common in whites, with a slight male predisposition to develop the tumor (M:F = 1.3:1).

Several epidemiologic studies with conflicting results investigated the contribution of a multitude of risk factors, including maternal obstetric and gynecologic history, preterm birth and low birth weight, breastfeeding, drug and lifestyle exposure during pregnancy, parental occupation and environmental exposures[4,5].

Histopathology

NB is a part of a histopathologic continuum, namely Peripheral Neuroblastic Tumors (pNTs) which include neuroblastoma, ganglioneuroblastoma and ganglioneuroma[6].

Undifferentiated NB consists of small round blue uniform cell tumors with dense hyperchromatic nuclei and reduced cytoplasm. Neuropils or neuritic processes are pathognomic for neuroblastoma. Eosinophilic neuritic processes are surrounded by neuroblasts to form Homer-Wright pseudorosettes, present in 15-50% of bioptic samples. Ganglioneuroma which lies at the differentiated extreme of the spectrum is associated with a benign tumoral behavior. It is composed of mature ganglia, schwann cells and neuritic processes[7,8].

Shimada et al. devised a histopathological system in 1984, adopting the original concept of age-linked morphological evaluation. It was later modified in 1999 as the International Neuroblastoma Pathology Classification with a strong reliability in predicting tumoral behavior and prognosis[9,10]. Table 1 – summarizes the modified Shimada system of neuroblastic tumors.

The Shimada classification considers age, neuroblast differentiation, Schwanian stromal density, mitosis–karyorrhexis index (MKI) and nodular pattern, to sort out patients into a favorable and unfavorable histology groups.

Joshi et al. introduced an alternate classification system in 1992, based on mitotic rate and calcifications combined patient age at diagnosis. It was later updated in 1996 by substituting MKI for mitotic rate.

Table 1 - Modified Shimada Pathologic Classification of Neuroblastic Tumors.

Morphology		**Favorable Histology**	**Unfavorable Histology**
Stroma rich		Well differentiated (ganglioneuroma) Ganglioneuroblastoma, intermixed	Ganglioneuroblastoma, nodular
Stroma poor (neuroblastoma)	**Age <18 mo**	MKI < 4%	MKI > 4% or undifferentiated
	Age 18-60 mo	MKI < 2% and differentiating	MKI > 2% or Undifferentiated or Poorly differentiated
	Age > 60 mo	None	All

Clinical presentation:

NB diagnosis continues to be a challenging enterprise due to the multitude of variables involved in its clinical presentation (primary site, presence of metastatic disease, vasoactive tumoral by-products.)

An intraabdominal primary site is reported in up to 75% of patients. Therefore, it is of paramount importance to elicit a history of recurrent abdominal pain and identifying a palpable, nontender, firm, irregular mass crossing the midline (nephroblastoma in contrast is a smooth mobile flank mass which does not cross the midline.)

Whereas localized disease is hard to pinpoint upon history taking and physical examination, metastatic dissemination (encountered in 50% of children presenting with NB) is associated with malaise, fatigue, irritability, anorexia, weight loss or failure to thrive, fever of unknown etiology and bone pain.

Characteristic paraneoplastic telltale presentations are rare, but they may prove invaluable in clinical practice since they may offer a shortcut to an otherwise evasive diagnosis. Such peculiar clinical presentations include:

1. Kinsbourne syndrome (Opsomyoclonus-ataxia syndrome, OMA), an autoimmune cerebellar disorder, classically described as "dancing eyes and dancing feet" consists of involuntary rapid erratic eye movements and/ or ataxia and polymyoclonus of the palpebrae, the trunk and the limbs, often with behavioral, motor and cognitive developmental deficits.

2. Transverse myelopathy, dumbbell lesions with intraspinal extradural extensions, resulting in motor and sensory deficits, radicular or back pain, and sphincter disturbances.

3. Kerner-Morrison syndrome, a tetrad (affecting serendipitously 4% of cases) associating neuroblastoma, intractable treatment-resistant secretory diarrhea, dehydration and hypokalemia. This sequence is believed to be initiated by VIP (vasoactive intestinal peptide) oversecreted by maturating neuroblasts.

4. Horner Syndrome, characterized by enophtalmia, ptosis, miosis, heterochromia and anhydrosis. The recruitment of locoregional ganglia by the tumoral process is a plausible explanation of the association with neuroblastoma.

5. Hypertensive syndrome, usually implicates the activation of the renin-angiotensin system by tumor pressure on the renal artery rather than the intuitive mechanism of catecholamine metabolites secretion by the tumor.

6. Pepper syndrome, associated with 4S neuroblastoma, involves infants (<1 yr.) suffering extensive metastatic dissemination, but still limited to skin, liver and bone marrow. Spontaneous regression is the rule. However, massive hepatomegaly, respiratory insufficiency and severe sepsis may pose a fatal threat.

7. "Blueberry muffin" metastatic subcutaneous nodules, associated with 4S neuroblastoma. It is essential to distinguish such nodules from leukemic infiltrates.

8. Hutchinson syndrome, caused by massive metastasis to bone with consequent osteodynia, limping and pathologic fractures.

9. "Raccoon eyes", or *"panda eyes"*, reminiscent to bilateral periorbital echymoses consecutive to skull base fracture implicating the anterior fossa, expression of metastasis of an intraorbital tumor.

Diagnosis:

It is an undisputable fact that histopathological studies remain the ultimate tool in ascertaining a definitive diagnosis. Nonetheless, it is not a rigid dogma to be used as a pretext to hinder the clinical thinking process. Indeed the convergence of characteristic clinical presentation, mediastinal, intraabdominal or pelvic mass, elevated urinary catecholamines [vanillylmandelic acid (VMA)/

homovanillic acid (HVA)], plain radiographs, ultrasonography, contrast-enhanced CT , MRI, radiolabeled metaiodobenzylguanidine (MIBG), technetium 99 – methylene diphosphonate bone scan and bone marrow biopsy offer invaluable complementary diagnostic and clinical staging data.

Differential diagnosis:

-Small Blue Round Cell Tumors:
  -Ewing's sarcoma
  -Peripheral neuroectodermal tumors (PNET)
  -Rhabdomyosarcoma (RMS)
  -Desmoplastic small round cell tumor (DSRCT)
  -Non-Hodgkin Lymphoma (NHL)
-Neonatal adrenal hemorrhage
-Nephroblastoma
-Esthesioneuroblastoma (= Olfactory neuroblastoma)
-Pheochromocytoma
-Paraganglioma
-Ganglioneuroblastoma
-Ganglioneuroma

Tumor markers:

-VMA, HVA and VMA/HVA ratio in urine or serum
-Neuron specific enolase (NSE)
-Ferritin
-Lactate dehydrogenase (LDH)
-Chromogranin A
-Neuropeptide Y
-Chromosomal and molecular markers:
  -N-myc amplification, triploidy, del.1p, TrkB, telomerase RNA correlate with a poor prognosis.
  - diploidy/ tetraploidy, TrkA, TrkC, CD44 correlate with a favorable prognosis.

Staging:

A minimal evaluation for clinical staging of NB will necessarily include:

(1) History and physical examination
(2) Laboratory studies:
  -CBC, differential, platelets
  -Liver and kidney function studies
  -24h-urinary metanephrines excretion
(3) Diagnostic imaging:
  -Chest radiograph
  -Skeletal survey with orbital views
  -Bone scan
  -CT scan of abdomen and pelvis (neck or thorax if primary in these areas)
(4) Bone marrow aspirate +/- biopsy.

Table 2 - The International Neuroblastoma Staging System (INSS), based on the Evans staging system.

Stage		Definition
1		Localized tumor with complete gross excision, with or without microscopic residual disease; negative ipsilateral lymph node.
2	**2A**	Localized tumor with incomplete gross excision; negative ipsilateral nonadherent lymph nodes.
	2B	Localized tumor with or without complete gross excision; positive ipsilateral nonadherent lymph nodes; negative contralateral lymph nodes.
3		Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement, or Localized unilateral tumor with contralateral regional lymph node involvement, or Midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4		Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin or other organs (except as defined for stage 4S.)
4S		Localized primary tumor (as defined for stage 1, 2A, or 2B) with dissemination limited to skin, liver and bone marrow [<10% involvement] (limited to infants < 1 year old.)

Treatment - Basic guidlines

The treatment of neuroblastoma is based on a multimodal, pluridisciplinary approach uniting the efforts of surgeon, pediatrician, pathologist, chemotherapist, radiation therapist and intensive therapist.

Age plays a pivotal role in clinical decision making, therapeutic management and risk stratification of children with neuroblastoma. Infants < 1yr. usually present with tumors of favorable histology. Spontaneous regression (with no therapeutic intervention) of 4S tumors is the rule; if no major organ function is compromised. This is illustrated by Pepper syndrome where massive hepatomegaly, respiratory failure and severe sepsis could be fatal.

Complete resection remains an ideal desideratum of surgical treatment since it is curative in 90% of cases. Nevertheless, incomplete excision and tactical debulking enhance the responsiveness to adjunctive therapy.

Popular chemotherapeutic regimens used in NB include: vincristine + cyclophosphamide + doxorubicin, etoposide in combination with carboplatin, cisplatin or ifosfamide. Consolidation regimens include: carboplatin + etoposide + melphalan or cyclophosphamide,

thiotepa + cyclophosphamide, and ifosfamide with total body irradiation (TBI).

Innovative chemotherapeutic strategies are subjected to extensive investigation. These include the use of tumor-targeted biologic agents such as retinoids, tyrosine kinase inhibitors, modulators of apoptotic pathway and angiogenesis, anti-angiogenic agents, arsenic trioxide, demethylating agents, histone deacetylase inhibitors, and immunologic agents such as anti-GD2, IL-2, tumor necrosis factor, INF and vaccines.

The advent of effective chemotherapeutic regimens eclipsed the role of radiotherapy in the management of neuroblastoma. Nonetheless, it is still useful in 3 therapeutic scenarios: (1) amelioration of outcome in stage III patients > 1 yr., (2) palliative therapy in bone metastasis and persistent primary disease, and (3) TBI in massive chemoradiation therapy prior to bone marrow transplantation.

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PARTICULAR MORPHOPATHOLOGICAL ASPECTS OF THE NEW-BORN'S CEREBRAL HEMORRHAGE

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Abstract

Introduction: Cerebral hemorrhage represents the main cause of death of the premature new-born and a rare one for the new-born in term.

Aim: This study pinpoint that the neuronal damages are present long time before the labour, to a important cohort of neonatal death, especially premature.

Material and method: Study group includes 153 new-borns deceased to our Children Hospital, during 2002-2007, wich main cause of death was the cerebral hemorrhage.To all studied cases we performed a complet morphopathological examination of the brain.We proceeded to a inventory of the brain injuries, for every cases

Results: The analysis of the casuistry guided us to elaborate the following observations:

• a meaningful ratio of neonatal mortalityt hrough cerebral hemorrhage, is 31.35%;
• an meaningful incidence of the fulminating form with decease in the first 7 days of life;
• a diffuse localization of the injuries to premature borns, proportionate with the degree of the immaturity;
• a constant harm of the undercortical structures, in the periventriculer, basilar, and cerebellar zones;
• the coexistence of some old injuries(ante-natal) with others recent (post-natal) is a frequente situation to the dominant group, with small weight at birth,(63.4%);
• a lesional association to the 60% of the cases, involving, in the next order : hemorrhage of the cerebral artery, ventricular inundation, vascular thrombosis

Conclusions:

1. Cerebral hemorrhage represents the main reason of the decease of the premature new-born;
2. The impact of the ante-natal time on the immature fetal brain generates a stronglesional potential;
3. The multiple sites in the territory of the cerebral artery is prevalent in the morphopatho-logical aspects of the cerebral hemorrhage.

Key words: cerebral hemorrhage, new-borns

Introduction

Newborn's cerebral hemorrhage occurs in hypoxic-ischemic complex brain injuries and not as an obstetric mismanagement of term birth anoxia[2,3,6]. We consider that most cases of neonatal hypoxic-ischemic encephalopathy have antenatal insults, difficult to pinpoint[2,8,9,]. We already can be sure about a great number of vasculopathy alteration, such as :

- changes in the blood flow direction in circle of Willis[8];
- decreased blood-flow velocity in the veins;
- changes in the flow of the right vertebral artery, with isolated hemorrhagic lesions;
- neonatal thrombotic vessels;
- vessels occlusion by an embolus with obstruction of the middle cerebral artery.

Aim

This study pinpoint that the neuronal damages are present long time before the labour, to a important cohort of neonatal death, especially premature.

Material and methods

Study group includes 153 new-borns deceased to our Children Hospital , during 2002-2007, wich main cause of death was the cerebral hemorrhage.To all studied cases we performed a complet morphopathological examination of the brain.We proceeded to a inventory of the brain injuries, for every cases.

Specimens Samples were obtained from the brains in the time of autopsy, from all 153 newborns who died with cerebral hemorrhage.After fixation in 4% buffered formalin, for 24-48 hours, we procedeed sections (4 μm thick), and embedded in paraffin.We used routinely technique Hematoxylin–Eosin(HE), for microscopic analyses.

Immunohistochemistry Samples sections were rehydrated, washed and then rinsed in PBS (pH 7.2).Sections were incubated with 3% hydrogen peroxide solution for 5 minutes, then washed with PBS. After endogenous peroxidase inhibition and antigen retrieval, the sections were incubated with the primary antibodies.

Formalin-fixed, paraffin-embedded tissues were incubated so the slides could react with a labelled avidin-biotin complex, peroxidase-labelling detection system(Vector Universal Elite kit) and then treated with 3,3'-diaminobenzidine-peroxidase substrate solution, as chromogen (DAB Tablets, S3000-Dakopatts, Glostrup Denmark) until color was visualized.It was done using the method EmVision Dual Link-HRP.All reagents and supplied for the technique were from Dako, Denmark.

The primary antibodyies, which were: the monoclonal rabbit anti-GAFP (Dakopatts, Glostrup Denmark) mouse anti-S-100 (Dako, polyclonal, code

N1573, ready-to-use), anti-CD68 (Dako, PG-M1) and the monoclonal mouse antivimentin (Dako, clone V9).The negative control reagent used for LSAB2 was Universal Negative Control, Rabbit (code N1699).

Sections were washed twice in distilled water to stop the reaction, then counterstained in hematoxylin, washed, dehydrated, cleared in xylene, mounted with DPX, and glass cover-slipped.

Sections were examined under oil immersion with a ×100 objective on a Nikon Eclipse E–400 microscope, and images were captured using a Coolpix 995 digital camera and a DN–100 digital imaging system. Histological sections were reviewed independently by two pathologists, and then discussed for consensus.

Results

The analysis of the casuistry guided us to elaborate the following observations:

- a meaningful ratio of neonatal mortality through cerebral hemorrhage, is 31.35%(Table 1);
- a meaningful incidence of the fulminating form with decease in the first 7 days of life (Table 1);
- a diffuse localization of the injuries to premature borns, proportionate with the degree of the immaturity (Table 2);
- a constant harm of the undercortical structures, in the periventricular, basilar, and cerebellar zones (Fig.1, 2 and Table 3);
- the coexistence of some old injuries (ante-natal) with others recent (post-natal) is a frequente situation to the dominant group, with small weight at birth,(63.4%) (Fig. 3,8 and Table 3) ;
- a lesional association to the 60% of the cases, involving, in the next order : hemorrhage of the cerebral artery , ventricular inundation, vascular thrombosis (Table 3);
- immunohistolabeling for the brain and the choroid plexus, revealed intens positivity for:

  - **G.F.A.P. -** glial fibrillary acidic protein – that is thought to help to maintain astrocyte mechanical strength; it is also involved in many cellular functioning processes, such as cell structure and movement, cell communication, and the functioning of the blood brain barrier (Table 2, Fig. 5, 9);
  - **CD 68** has also intes positivity, especially in the brain lesions (Table 2, Fig. 4, 10); CD68 is a glycoprotein which binds to low density lipoprotein, predominantly a late endosomal protein but is expressed also on the cell surface . It is predominately expressed in cytoplasmic granules of monocytes/macrophages, dendritic cells, and granulocytes.
  - **Protein S100** – we saw intens positivity in the brain, (Table 2, Fig.6); protein S100 is secreted by cultured astroglial cells and functions as a trophic factor for a number of neuronal cell types, stimulating the differentiation of immature neurons. It promotes the survival of these cells in vitro and induces the outgrowth of neurites.
  - **Vimentin –** shows negativity, for the brain and choroid plexus, (Table 2, Fig. 7, 12). Vimentin plays a significant role in supporting and anchoring the position of the organelles in the cytosol. Vimentin is attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally.In general, it is accepted that vimentin is the cytoskeletal component responsible for maintaining cell integrity.

Table 1 – Prematures and age at death (in days) of the newborns with cerebral hemorrhage.

STUDY YEARS	PREMATURES (from all newborns)	AGE AT DEATH (days)			
		1 -7	8 -14	15 - 21	22 - 30
2002	16	19	4	1	1
2003	22	21	5	3	1
2005	19	14	4	5	
2006	15	16	4	2	1
2007	12	12	3	3	3
TOTAL	105	106	28	14	5

Table 2 - Particular macroscopical aspects of neonatal cerebro-vascular injuries are often associated and variable.

MARKER STUDY	CASES / YEAR	BRAIN						CHOROID PLEXUS & EPENDIMA					
		ASTROCITE		MICROGLIA		NEURAL DEATH		ASTROCITE		MICROGLIA		NEURAL DEATH	
		YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
H&E	2/2002	+		+		+		+		+		+	
GFAP	4/2003	+		+			+	+		+			+
prot. S100	4/2005	+			+		+	+			+	+	
CD68	10/2006	+		+		+		+		+		+	
Vimentine	11/2007		+		+		+		+		+		+
TOTAL	31	4	1	3	2	2	3	4	1	3	2	3	2

Table 3 - Immunohistolabeling for brain, choroid plexus and ependima.

STUDY YEARS	Cortical infarcts and petechial white-matter hemorrhage	Multifocal hemorrhagic white-matter infarcts	Choroid plexus and subependymal thrombosis	Germinal matrix and intraventricular hemorrhage
2002	14	5	15	12
2003	17	8	18	15
2005	16	8	14	9
2006	15	3	16	11
2007	10	3	10	6
TOTAL	91	38	86	78

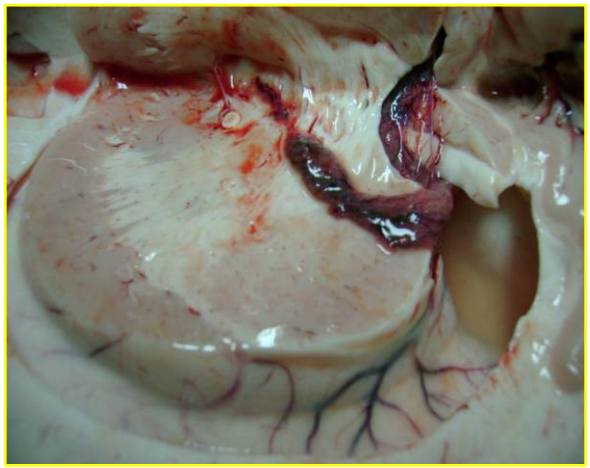

Fig. 1 Brain – Thrombotic choroid plexus with vessels thrombosis subependimal.

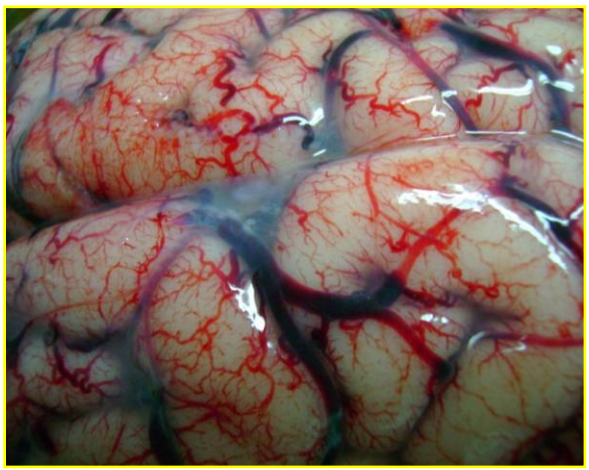

Fig. 2 Brain - Thrombotic generalized.

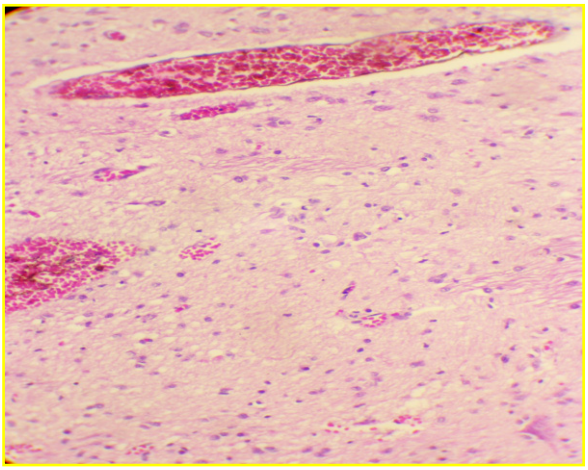

Fig. 3 Brain - H.E.

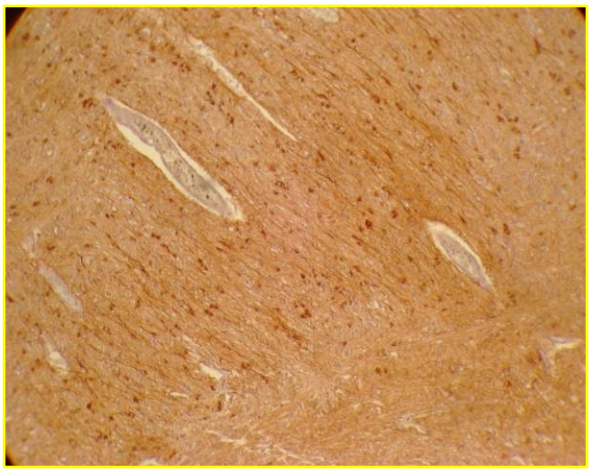

Fig. 4 Brain - CD 68.

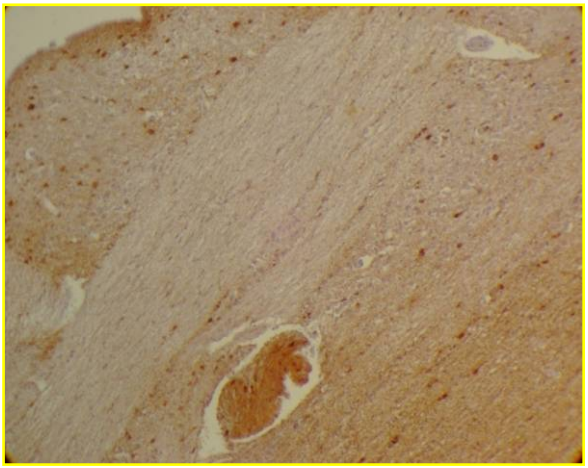

Fig. 5 Brain - G.F.A.P.

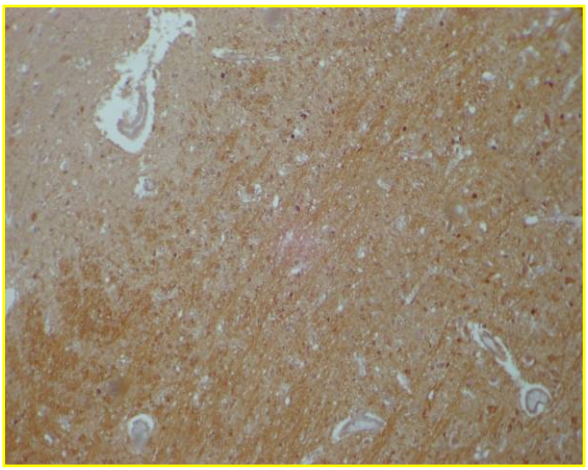

Fig. 6 Brain - Protein S 100.

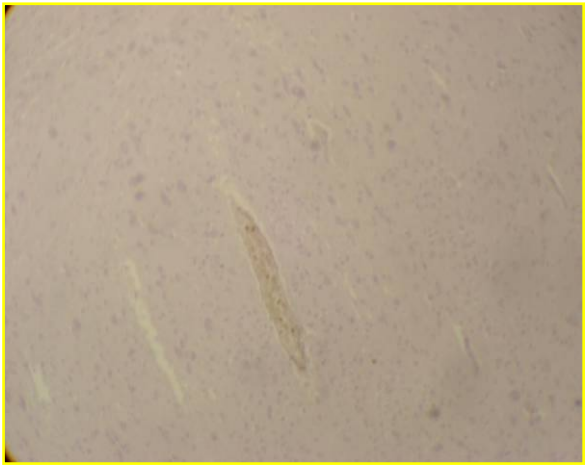

Fig. 7 Brain – Vimentin.

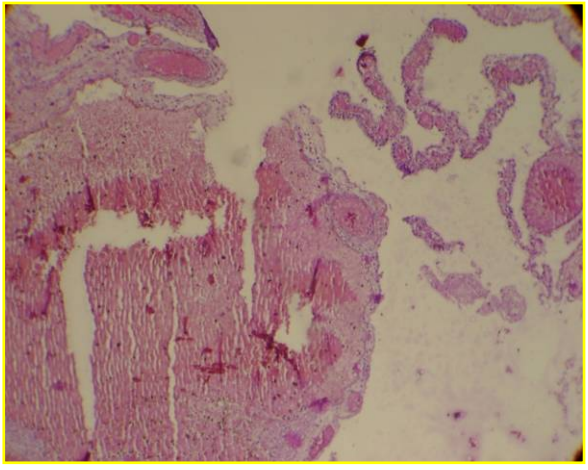

Fig. 8 Choroid plexus - H.E.

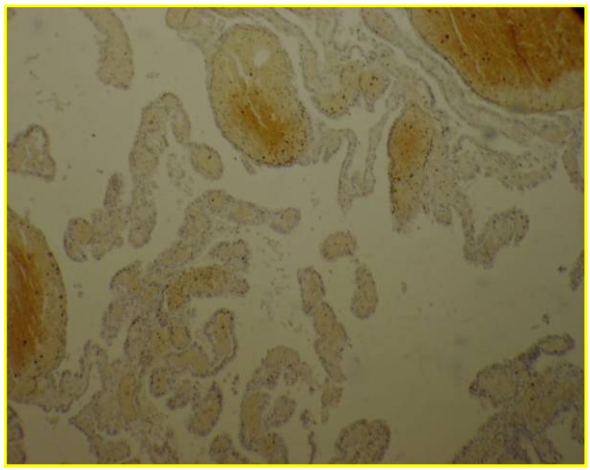

Fig. 9 Choroid plexus - G.F.A.P.

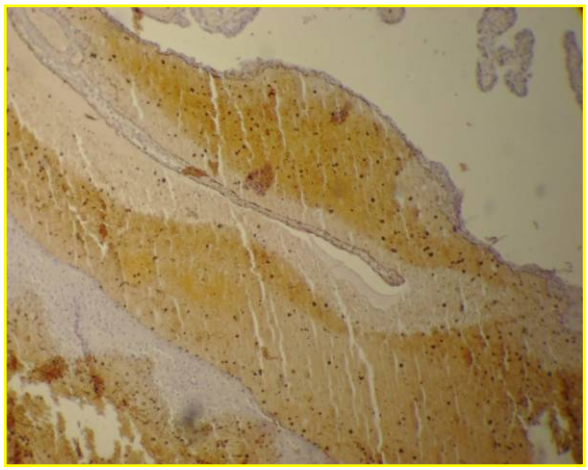

Fig. 10 Choroid plexus - CD 68.

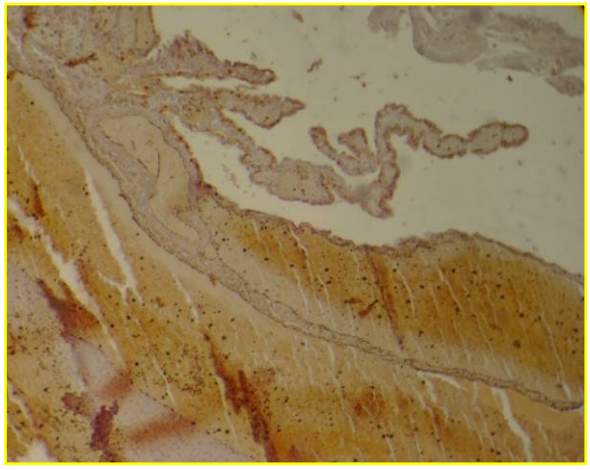

Fig. 11 Choroid plexus - Protein S 100.

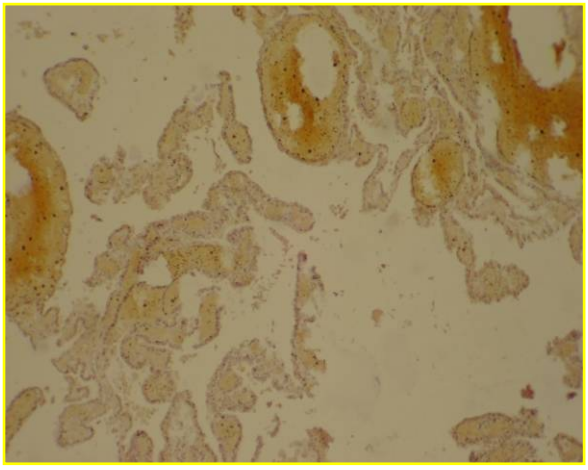

Fig. 12 Choroid plexus – Vimentin.

Discussion

Very few studies are correlating the pathological findings in neonatal brains with detailed pathological clinical systematical based[7].

Usually related with the reactions to signs of birth asphyxia, in the present study we try to explane which are the neuronal and axonal injury in these infants, and find the basis for neurological deficits[2]. We intend also to investigate these brains for specifical markers of neuronal injuries in neonates(precursors of protein detected in future by noninvasive methods).Usually located in the cerebral white matter and internal capsule, positivity were significantly correlated with the features of birth asphyxia, particularly a history of neonatal hemorrhage.Immunocytochemistry for GFAP is not difficult to be labeled, systematically, because it is very important to help us to select the presence together, of recent and older damages, particularly in preterm infants[9,10].

Conlusions

1. Cerebral hemorrhage represents the main reason of the decease of the premature new-born[4];
2. The impact of the ante-natal time on the immature fetal brain generates a strong lesional potential[5.11,12];
3. The multiple sites in the territory of the cerebral artery is prevalent in the morphopathological aspects of the cerebral hemorrhage[10].
4. In the absence of trauma, the mechanism of hypoxia/ischaemia remains the main cause[1,8].

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CEREBRAL MALFORMATIONS ASSOCIATED WITH MACROCRANIA – CLINICAL AND PARACLINIC DIAGNOSIS

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Abstract

Precocious determination of positive diagnosis in the presence of macrocrania, confirmed by the increase of the cranial perimeter with more than 2 percentiles and by the dilation of the ventricular system, visualized with the help of ultrasounds.

The study was carried out retrospectively on a one year period (2008) in the Newborn and Infant care Clinique from "Louis Turcanu" Children Hospital, on a number of 11 hospitalized premature newborn children, selected based on clinical and imagistic criteria.

The incidence of the cerebral malformations was of 1.21 percent, the most frequent malformative types being the craniovertebral dysraphisms: five cases.

Rapid-evolving hydrocephalia was the death cause for the associated cerebral malformations. The most frequent malformative types were the craniovertebral dysraphisms, which presented a complete clinical and imagistic picture.

Key words: macrocrania, the craniovertebral dysraphisms, hydrocephalia, premature.

Introduction

Myelomeningocele represents the most severe form of dysraphism involving the vertebral column and occurs with an incidence of 1/4000 live birts.

The cause of myelomeningocele is unknown, but as with all neural tube closure defects, a genetic predisposition exists; the risk of recurrence after one affected child increases to 3-4% and increases to 10% with two previous abnormal pregnancies. Nutritional and environmental factors undoubtedly have a role in the etiology of myelomeningocele as well. Folate is intricately involved in the prevention and etiology of neural tube defects(dysraphism).

This condition produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the central nervous system. A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele, as well as the associated lesions. Newborns with a defect in the midlumbar region typically have a saclike cystic structure covered by a thin layer of partially epithelialized tissue.

Remnants of neural tissue are visible beneath the membrane, which may occasionally rupture and leak cerebrospinal fluid.

Material and method

The positive diagnosis was confirmed by the increase of the cranial perimeter and by the imagistic methods. The cranial ultrasonography was used as a method for diagnosis and the estimation of prognosis. The MRI was used for diagnosis confirmation and determination of the time of the surgical intervention.

The study was carried out retrospectively on a one year period (2008) in the Newborn and Infant care Clinique from "Louis Turcanu" Children Hospital, on a number of 11 hospitalized premature newborn children, selected based on clinical and imagistic criteria.

Out of the group of 11 premature newborns with frequent cerebral malformations, 5 cases presented craniovertebral dysraphism, 4 cases presented hydrocephalia secondary to intraventricular hemorrhage, and 2 cases deceased due to hydrocephalia secondary to intraventricular hemorrhage and meningoencephalitis.

The following parameters were observed: gestational age, weight at birth, antepartum and perinatal pathology, increase of the cranial perimeter, dilation of the ventricular system, observed by ultrasonography and MRI.

Results

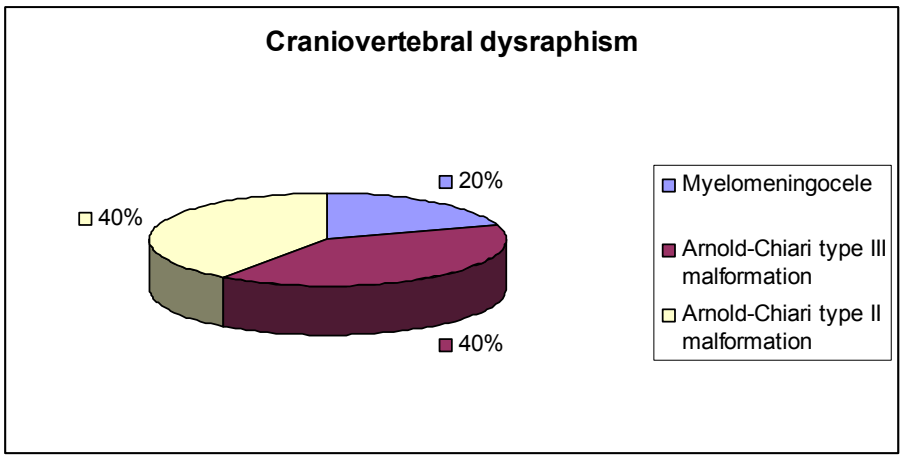
The incidence of the cerebral malformations was of 1,21 percent, the most frequent malformative types being the craniovertebral dysraphisms: five cases (45.45 percent). Thus the following were associated: the myelomeningocele – one case (20 percent), Arnold-Chiari type III malformation – two cases (40 percent), Arnold-Chiari type II malformation – two cases (40 percent) (Graphic 1, fig 1, fig 2.). The corpus callosum agenesia was observed in three of these cases (fig 3.). One case of these presented meningoencephalocele, holoprosencephaly and the Arnold-Chiari type III malformation.

In all of these cases the gestational age varied between 36 and 37 weeks of gestation.

The weight at birth varied between 2470 and 3100 grams.

Antepartum and perinatal pathologies were present in all cases.

The increase of the cranial perimeter was observed in all cases (Graphic 2).



Graphic 1. Craniovertebral dysraphism.

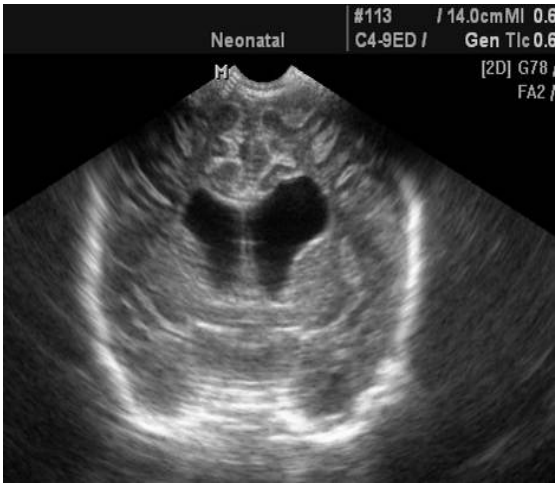


Fig.1. Median coronal scan. Mild hydrocephalus in association with a type II Chiari.

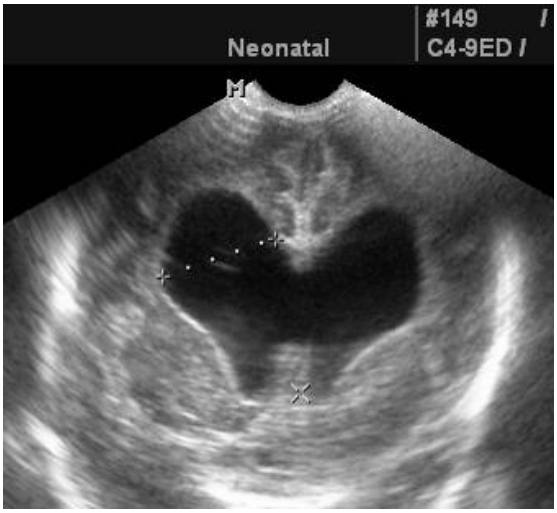


Fig.2. Median coronal scan. Severe hydrocephalus in association with a type II Chiari.

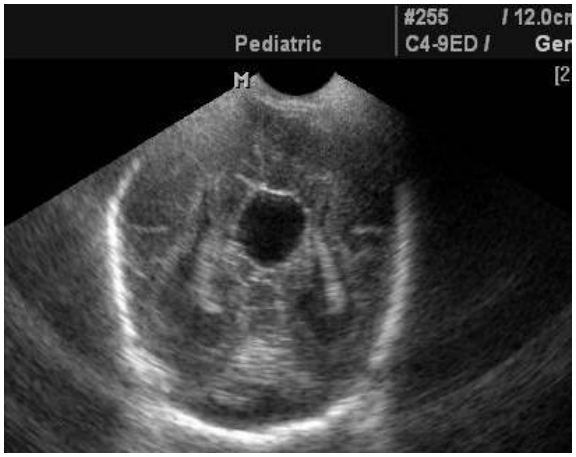
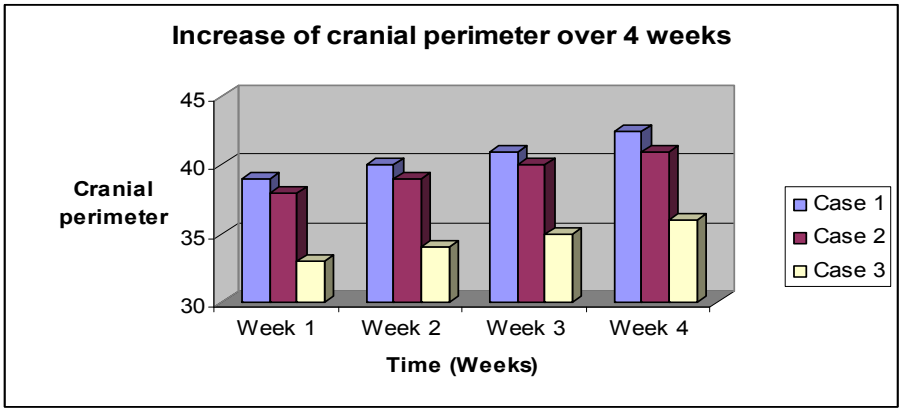


Fig.3 Posterior coronal scan. The corpus callosum agenesia. Hypertrofia of cavum septum pellucidi.



Graphic 2. Increase of Cranial perimeter over 4 weeks.

The clinical signs were the classic ones of hydrocephalia to which the following were associated: neonatal seizures, paresis, inferior member paralysis, respiratory and cardiac rhythm disturbances.

Cerebral imagistics was utilized for the assessment of ventricular dilatation and the degree of compression of the cerebral tissue (fig3).

Although the therapeutic intervention was fast, the ventricular-peritoneal drainage valve was mounted in five cases (fig.4) and the specific anticonvulsive and ethiopathogenic medication was administered, the mortality rate was still high 18,18 percent). Four cases presented a favorable evolution, with the ventricular dimensions stabilized.

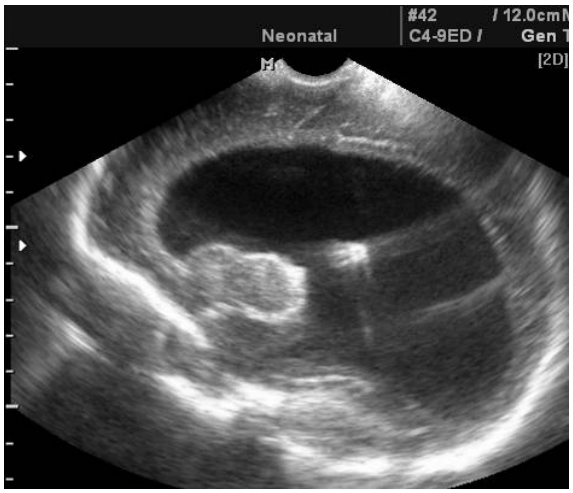


Fig.4. Sagital scan. Severe hydrocephalus. The ventricular-peritoneal drainage valve.

Disscussions

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower extremity deformities (clubfeet, subluxation of the hips).

Infants with myelomeningocele typically have an increasing neurologic deficit as the myelomeningocele

extends higher into the thoracic region. Patients with a myelomeningocele in the upper thoracic or the cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus.

Hydrocephalus in association with a type II Chiari defect develops in at least 80% of patients with myelomeningocele. The possibility of hydrocephalus developing should always be considered, no matter what the spinal level. Ventricular enlargement may be indolent and slow growing or may be rapid, causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting associated with an increased head circumference. About 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This Chiari crisis is due to downward herniation of the medulla and cerebellar tonsils through the foramen magnum.

Surgery is often done within a day or so of birth but can be delayed for several days (except when there is a cerebrospinal fluid leak). Evaluation of other congenital anomalies and renal function can also be initiated before surgery. After repair of a myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the medulla and cervical cord is indicated.

In utero surgical closure of a spinal lesion has been successful in a few centers. Preliminary reports suggest that there may be preservation of motor function with better motor outcomes as well as a lower incidence of hindbrain abnormalities and hydrocephalus. This suggests that the defects may be progressive in utero and that prenatal closure may prevent the development of further loss of function. In utero diagnosis is facilitated by maternal serum alfa-fetoprotein screening and by fetal ultrasonography.

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10-15%. At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population. Because myelomeningocele is a chronic handicapping condition, periodic multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

Holoprosencephaly is a developmental disorder of the brain which results from defective cleavage of the prosencephalon and inadequate induction of the forebrain structures. The abnormality, which represents a spectrum of severity, is classified into three groups: alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality.

Facial abnormalities including cyclopia, cebocephaly, single central incisor tooth, and premaxillary agenesis are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. A lobar holoprosencephaly is characterized by a single ventricle, an absent falx, and fused basal ganglia. Care must be taken not to overdiagnose based on ventricular abnormalities alone. Evidence of noncleaved midline brain structures is the critical element.

Affected infants have high mortality rates; some live for years. The incidence of holoprosencephaly ranges from 1/5000 to 1/16000. A prenatal diagnosis can be confirmed by ultrasonography after the 10^{th} week of gestation for more severe types. The cause for holoprosencephaly is usually not identified, although there appears to be an association with maternal diabetes.

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that vary in expression from severe intellectual and neurologic abnormalities to the asymptomatic and normally intelligent individual. The corpus callosum develops from the commissural plate that lies in proximity to the anterior neuropore. An insult to the commissural plate during early embryogenesis causes agenesis of the corpus callosum. When agenesis of the corpus callosum is an isolated phenomenon, the patient may be normal, whereas individuals with neurologic symptoms, including mental retardation, microcephaly, hemiparesis, diplegia and seizures, have associated brain anomalies due to cell migration defects, such as heterotopias, microgyria, and pachygyria (broad, wide gyri) in addition to the absence of the corpus callosum. The anatomic features are best depicted on MRI or CT scan and show widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect. Absence of the corpus callosum may be inherited as an X-linked recessive trait or as an autosomal dominant trait. The condition may be associated with specific chrosomal disorders, particularly 8-trisomy and 18-trisomy.

Hydrocephalus is not a specific disease; rather, it represents a diverse group of conditions that result from impaired circulation and absorption of cerebrospinal fluid or, in the rare circumstance, from increased production by a choroids plexus papilloma.

Causes of hydrocephalus:

1. Communicating: achondroplasia, basilar impression, benign enlargement of subarachnoid space, choroid plexus papilloma, meningeal malignancy, meningitis and posthemorrhagic.
2. Noncommunicating: aqueductal stenosis (infectious, X-linked), Chiari malformation, Dandy-Walker malformation, Klippel-Feil syndrome, mass lesions (abscess, hematoma, tumors and neurocutaneous disorders, vein of Galen malformation, Walker-Warburg syndrome).
3. Hydranencephaly: holoprosencephaly, massive hydrocephalus and porencephaly.

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct or a lesion in the 4^{th} ventricle.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant.

The clinical presentation of hydrocephalus is variable and depends of many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure. In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and the scalp veins are dilated. The forehead is broad, and the eyes may deviate downward because of the impingement of the dilated suprapineal recess on the tectum, producing the setting-sun eye sign. Long-tract signs including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign are common owing to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. Irritability, lethargy, poor appetite, and vomiting are common manifestations. Serial measurements of the head circumference indicate an increased velocity of growth. A foreshortened occiput suggests Chiari malformation.

Chiari malformation consists of two major subgroups. Type I typically produces symptoms during adolescence or adult life and is usually not associated with hydrocephalus. Patients complain of recurrent headache, neck pain, urinary frequency and progressive lower extremity spasticity. The deformity consists of displacement of the cerebellar tonsils into the cervical canal. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the 4th ventricle during fetal development is responsible. The type II Chiari malformation is characterized by progressive hydrocephalus with a myelomeningocele. This lesion represents an anomaly of the hindbrain, probably due to a failure of pontine flexure during embryogenesis, and results in elongation of the 4th ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal. Approximately 10 % of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by posterior fossa decompression. Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression.

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamida and furosemide, may provide temporary relief by reducing the rate of cerebrospinal fluid production, but long-term results have been disappointing. Most cases o f hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt (occasionally a ventriculostomy suffices). The major complications of shunting are occlusions (characterized by headache, papilledema, emesis, mental status changes) and bacterial infections (fever, headache, meningismus), usually due to Staphylococcus epidermidis. With meticulous preparation, the shunt infection rate can be reduced to less than 5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor, possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus.

Prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced, particularly for performance tasks, as compared with verbal abilities. Many children have abnormalities in memory function. Visual problems are common (strabismus, visual field defects, optic atrophy with decreased acuity secondary to increased intracranial pressure).

Conclusions

Rapid-evolving hydrocephalia was the death cause for the associated cerebral malformations. The most frequent malformative types were the craniovertebral dysraphisms, which presented a complete clinical and imagistic picture.

The incidence of the cerebral malformation was 1.21 percent, out of which 45.45 percent were craniovertebral dysraphisms and 36.36 percent were hydrocephalia secondary to intraventricular hemorrhage.

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TRISOMY 8 MOSAICISM WITH ATYPICAL PHENOTYPIC FEATURES

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Abstract

Mosaic trisomy 8 is a relatively common chromosomal abnormality, which shows a great variability in clinical expression, however cases with phenotypic abnormalities tend to present with a distinct, recognizable clinical syndrome with a characteristic facial appearance, a long, slender trunk, limitation of movement in multiple joints, and mild-to-moderate mental retardation; the deep plantar furrows are a typical finding, the agenesis of the corpus callosum occurs frequently. We report a case, which in addition to certain characteristic features of mosaic trisomy 8, presented with craniofacial midline defects, including notched nasal tip, cleft maxillary alveolar ridge, bifid tip of tongue, grooved uvula and left choanal atresia, previously not described in this chromosomal disorder and a severe delay in psychomotor development, uncommon in trisomy 8 mosaicism.

Keywords: mosaic trisomy 8, atypical findings, midline defects

Introduction

Mosaic trisomy 8 is a relatively common chromosomal abnormality, with a distinct, recognizable phenotype in most cases. Characteristic of the clinical picture are: normal birth weight, normal or advanced growth, mild-to-moderate mental retardation, dysmorphic facies with a myopathic appearance, with prominent forehead, down slanted palpebral fissures, a coarse, pear-shaped nose, everted lower lip and low-set, large ears with a protruding lower segment; a long, slender trunk, limitation of movement in multiple joints [1, 2]. Particularly typical are the deep plantar furrows; agenesis of the corpus callosum is a frequent finding, internal organ malformations are uncommon. We report a case, which in addition to certain characteristic features of mosaic trisomy 8, presented with several signs including craniofacial midline defects, previously not described in this chromosomal disorder.

Case report

The proposita is the first child of an unrelated, healthy couple, a 21-year-old mother and 28-year-old father. Fetal ultrasounds scan at 20 week of gestation revealed ventriculomegaly. The baby was delivered by cesarean section at 37 weeks of gestation with a birth weight of 3010 g, length 50 cm and head circumference of 34 cm. At birth she was noted to have a particular facial appearance (Fig.1A) with telecanthus, upslanting palpebral fissures, notched nasal tip, cleft upper alveolar ridge, bifid tip of tongue, grooved uvula and low-set, dysplastic ears.

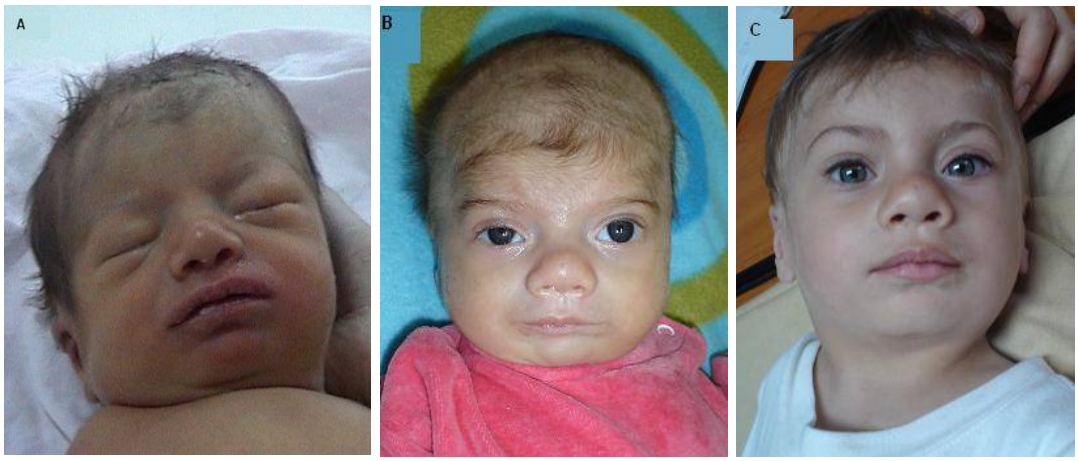

Fig. 1: Facial appearance of the patient: (A) the neonatal period, (B) at the age of six weeks, (C) age of 14 months.

On both hands deep palmar creases were observed (Fig. 2 A), a single transverse palmar crease and a single flexion crease on the fifth fingers; the thumbs were proximally inserted bilaterally (Fig. 2 B). The feet were in equinovarus position, with a wide space between the first and second toes and deep plantar grooves bilaterally. The perinatal period was complicated with seizures and apneic episodes.

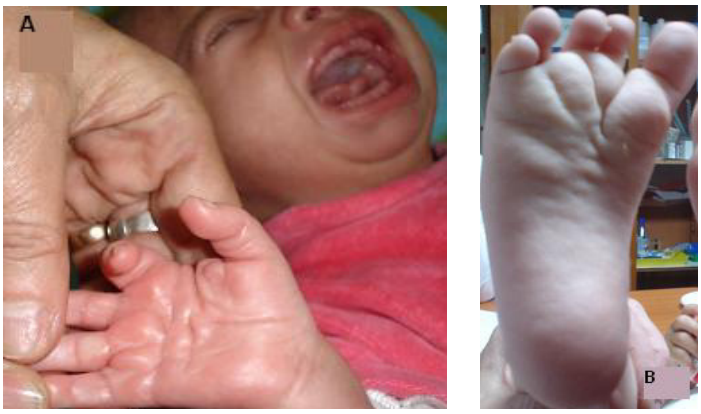

Fig. 2 (A) Bifid tip of tongue and grooved uvula, deep palmar creases, single flexion crease on the fifth finger. (B) Foot image - "hallmark " sign of the syndrome.

Transfontanellar ultrasound revealed absence of corpus callosum and enlargement of the occipital horns of lateral ventricles. MRI imaging confirmed the agenesis of corpus callosum and mild enlargement of lateral ventricles, on the other hand excluded associated cerebral malformations (Fig. 3 A, B). Cardiac ultrasonography showed an atrial septal defect. On oto-rhino-laryngologic examination left choanal atresia was found.

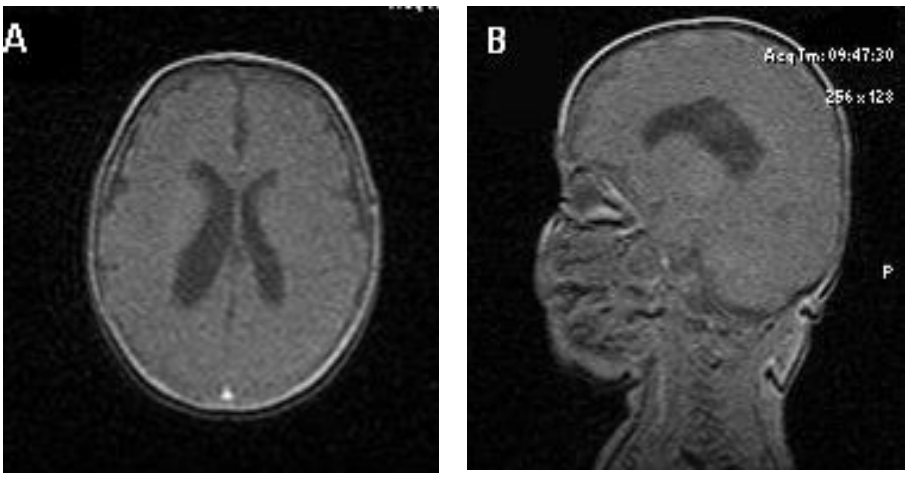

Fig. 3 (A) Mild enlargement of lateral ventricles (B) Agenesis of corpus callosum.

On clinical examination at six weeks of age, she had telecanthus, broad nasal bridge, bulbous nasal tip with a small pit in the midline and micrognathia (Fig. 1B). A small midline cleft of the maxillary alveolar ridge, a bifid tip of tongue and grooved uvula were noted. The ears were low-set, abnormally shaped with thickened cartilage. She had soft dark hair on the forehead extending to the eyebrows. The neck was short with redundant skin folds and the chest was narrow with widely spaced nipples.

The deep palmar and plantar creases in association with corpus callosum agenesis were highly suggestive of trisomy 8. Chromosome analysis on peripheral blood lymphocyte culture revealed trisomy 8 (Fig. 4) in 12 metaphases of a total of 50 examined metaphases. FISH analysis on cultured blood lymphocytes with a centromeric probe of chromosome 8 (CEP8-Spectrum Orange, Abbott-Vysis) showed 3 hybridization signals in 25 % of cells (120/ 492 nuclei) (Fig. 5).

Fig. 4: Metaphase showing three copies of chromosome 8.

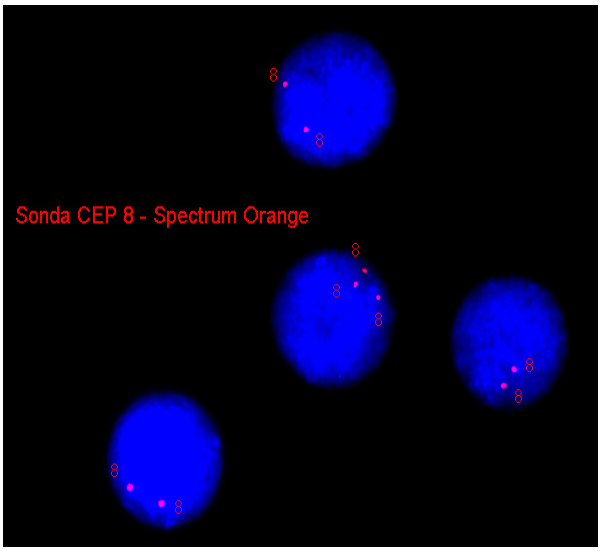

Fig. 5: Interphase FISH with a centromeric probe for chromosome 8 (CEP 8-Spectrum Orange) 1/4 of nuclei with three hybridization signals.

In view of the patient's facial appearance not typical of mosaic trisomy 8 and especially the midline defects previously not reported in trisomy 8 mosaicism, an array-CGH was performed to investigate the possibility of cryptic unbalanced rearrangements. The commercially available array (GenoSensor Array 300, Abbott) contains 287 genomic targets that include telomere, microdeletion, oncogenes, tumor suppressor genes and other selected loci scattered along each chromosome arm. No genomic imbalance could be detected.

We reassessed the patient at the age of 14 months: length was 84 cm (> 95 %), head circumference was 46 cm (50 %); she had a slender body habitus, broad face (Fig. 1C), short webbed neck and funnel-shaped chest. Except for mild limitation of movement in the right ankle, no restriction of movement at any joints could be detected. Developmental milestones were grossly delayed: she can sit alone briefly, cannot stand or crawl, she started to babble recently, using single syllables, does not recognize her name or respond to simple commands.

Discussions

Trisomy 8 mosaicism is characterized by a great variability in clinical expression due to the variation in tissular repartition of normal and trisomic clones [3, 4], therefore reported patients show a highly variable combination of clinical findings. Mental retardation is variable from mild-to-severe, but individuals with normal intellect and even with entirely normal phenotype have been described. However, cases with phenotypic abnormalities tend to present with a distinct clinical picture. Our case has many of the characteristic features of mosaic trisomy 8, including the long and slender body habitus, the deep plantar creases and the agenesis of corpus callosum. However, the facial appearance is not typical of trisomy 8 mosaicism, and the midline clefts and choanal atresia have not been described to date in patients with mosaic trisomy 8.

Corpus callosum agenesis generally prolonged latencies of interhemispheric stimulus-response paradigms, but not with unilateral stimulation paradigms to be processed. Peru et al. [5] found in patients with traumatic lesion of the corpus callosum, both temporary and permanent impairment such as dyspraxia, dyslexia and dysnomie firmly. Lassonde et al. [6] thought that different morphological and functional pathology of the corpus callosum, regularly lead to impairment in tasks that the integration visual and tactile information crosses the midline or the transfer of motor or visual-spatial skills required. Sauerwein et al. [7] discussed that the cognitive functions are not generally impaired in the absence of the corpus callosum, but it may appear a greater variability of these functions. For the clinicians is particularly important that the mosaic trisomy 8, may be associated with language impairment, respectively cognitive deficits. If language impairment is found cytogenetic investigation may be initiated. This is especially true when a combination with congenital malformations (kidney, skin, brain, heart, vertebrae among others) is present.

The diagnosis of mosaic trisomy 8 is not only for the assessment of development, but also has other significant consequences. Trisomy 8 is a frequently acquired cytogenetic abnormality in myeloid disorders. In patients with myeloid disorders the abnormal cells appeared to have developed from the trisomic clones. Patients with mosaic trisomy 8 may be at increased risk for the development of CML and MDS [8, 9, 10].

The additional anomalies might be part of the more severe manifestations within the phenotypic spectrum of

mosaic trisomy 8, due to a high proportion of trisomic cells in the developing facial structures. The array-CGH did not reveal further imbalances, however the array used is not pangenomic, and small gains or losses of genetic material may have escaped detection [11]. Trisomy 8 mosaicism, unlike the other common trisomies, in the majority of cases results from postzygotic mitotic nondisjunction [12, 13, 14], nevertheless, a proportion of cases are due to meiotic nondisjunction. Inasmuch as we could not investigate the parental origin of the three copies of chromosome 8, it cannot be excluded that uniparental disomy of chromosome 8 in the euploid cell lines might be responsible for the atypical phenotypic features, through either homozigosity for a mutation in a gene located on chromosome 8 or abnormal genomic imprinting. However, the latter seems improbable, since individuals reported with both maternal and paternal uniparental disomy of chromosome 8 had an entirely normal phenotype [15].

Conclusions

We described a case with mosaic trisomy 8, which in addition to certain characteristic features of this syndrome presented with craniofacial midline defects, previously not described in this chromosomal disorder. We consider the clinical findings in our patient may contribute to the extension of the phenotypic spectrum of trisomy 8 syndrome.

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DEPRESSION IN MEDIASTINAL COMPRESSION SYNDROME

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Abstract

Psychological disorders like depression, anxiety or insomnia are common in children's diagnosed with mediastinal compression syndrome and predict worse quality of life. The aim of the study is to highlight the main aspects regarding the psychological disorders found in the evolution of the mediastinal compression syndrome in children with Hodgkin or non-Hodgkin lymphoma.

50 subjects aged between 4 and 17 years, diagnosed with Hodgkin or non-Hodgkin lymphoma wore closely observed for a period of 5 years. The male gender and the patients lived in rural areas was dominant. The most frequent psychological disorders found in these patients were: depression, anxiety, pathological panic, insomnia, delirium, anorexia, nausea/sickness, pain, and a few cases of suicidal tendencies etc.

Key words: mediastinal compression syndrome, psychological disorders

Introduction

Symptoms of anxiety are common in children's diagnosed with mediastinal compression syndrome and predict worse quality of life. The mediastinal disorders that generate the mediastinal compression (the pulmonary, bronchial, and mediastinal located tumors and many other pulmonary, pleural, cardiac, esophageal and thyroidal diseases) can trigger the occurrence of neuropsychiatric manifestations accompanying the main disease (4). From these manifestations can "benefit" both the older child and the adult person that beside the main disease signs will show many other symptoms, psychiatric manifestations especially. The mediastinal syndrome represents the clinical expression of certain expansive processes located in the mediastinal structures. The main determining affections are:

- primary or metastatic mediastinal tumors: bronchi-pulmonary cancers, gastric cancers, esophageal cancers, the Hodgkin disease, thymus diseases, neurogenic tumors, embryonic tumors etc.
- mediastinal un-tumoral processes: intrathoracic goiter, hydatid mediastinal cist, inflammatory adenopathy, aneurisms of the aorta
- acute and chronic mediastinitis (1,3,5)
-

The aim of the study is to highlight the main aspects regarding the psychological disorders found in the evolution of the mediastinal compression syndrome in children with Hodgkin or non-Hodgkin lymphoma.

Material and method

The lot of study consisted of 50 children – that have been admitted as in-patients in the Hemato-Oncology department of Saint Mary Hospital, over a period of 5 years, having been diagnosed with Hodgkin Disease or malign non-Hodgkin Lymphoma. The ages of the children were between 4 and 17 years. 83% of them have been diagnosed with Hodgkin Disease and 17% with malign non-Hodgkin Lymphoma. The male gender was dominant, accounting for 35 cases, whereas the feminine gender was accounting for only 15 cases. The mentioned types of disease have been found mainly in children aged over 8 years (43 cases). 57% of the patients lived in rural areas and only 43% were raised in urban areas. The children have been psychologically monitored, the specific symptoms being also closely observed.

Results

The clinical manifestations were extremely varied depending on the characteristics and the extent of the process. All 50 children were displaying characteristic symptoms of the main disease but also various neuro-psychological ones, especially obvious in the case of the older children. The following symptoms have been noted among our patients: enlargement of one lymph nodes group, unilaterally (30%), enlargement of the mediastinum (58%), restrictive respiratory dysfunction, weight loss (68%), lymphadenopathy (63%), rash and collateral circulation in the neck and chest areas (7%), superior vena cava syndrome 30%, depression 60 % – in the older children in particular, anxiety 66% – in the younger children in particular, pathologic panic 6% (3 children), insomnia 22% (11 children), nausea, sickness 50% and anorexia 64% (32 children). 3 patients accused a memory deficit. Dyspnea (paroxystic, permanent or accentuated by effort) was present in 40% of the children, cough in 27% and tachypnea in 7%. Dysphagia was noted in 15 cases, intermittent at the beginning and only with solid food, sometimes accompanied by regurgitation and sialorrhea.

The diagnostic of Hodgkin disease was based on clinical, biological, histological criteria and also on the reading of the immunity deficit. 60% of children had the mixed cellularity subtype. The most frequent clinical manifestations were: unexplained fever lasting for longer than 8 days at 15 children; anorexia at 32 children; nocturnal perspiration 80%; pruritus 24%; weight loss 50%; depression 42% and anxiety 50%.

Feelings like uselessness and guilt, negative judgments regarding one self's qualities and value, or the

self blaming for being a person affected by disease and failing to deliver on professional and personal levels was found in 20 cases. Thoughts about death, suicidal ideas and even attempts ware also reported in 2 cases. The obsessive self-incrimination for being an ailing person and because of that a burden for the loved ones, the feels they have lost their ideals and self-esteem, the sense and purpose of their existence generated the idea that the only viable option for their situation is the act of suicide, death appearing as an escape route from a reality now strange and foreign to them, impossible to comprehend or live in.

Frequently, depression was caused by the communication of the diagnosis of the disease or the treatment side effects. In many cases, radiotherapy produced side effects like stomatitis, glossitis, esophagitis and taste alteration, generating the lack of pleasure of eating, appetite loss and anorexia.

The finding of the diagnostic in a random, unplanned way and improper circumstances generated stupefaction, loss of trust, disbelief and confusion. The affected child appeared as a sad, pessimistic, discouraged person. In some cases the patients reported feeling drained of energy, with no feelings or, on the contrary, restless, the presence of the depressive disposition being easily noticed in the physiognomy and behavior of the person. We noticed that children's diagnosed with mediastinal compression syndrome that wore excessively timid, generally humble, peaceful and well-behaved towards superiors and people perceived as more powerful, had an aggressive evolution than the persons less humble, timid, introverted and more likely to express negative emotions.

The main factors that influenced the state of mind of children diagnosed with syndrome of mediastinal compression ware:

1. the type and class of cancer and its responsiveness to therapy (benign tumors raised less problems regarding treatment compared with the malign tumors, which have rapid evolutions and will only allow for reserved prognoses)
2. the stage of the disease when diagnosed
3. the mental and physical state of the individual before the diagnostic
4. the attitude of the person regarding this type of disease, the acceptance of compromise, the will to get through the therapy and take advantage of the medical and support services available
5. the family's attitude towards the person diagnosed with mediastinal compression syndrome;
6. the extent of control available over the side effects of the treatment.(1,2,3)

Cancer patients have a series of common concerns, known in the medical practice as "6D": 1.death; 2.dependency on family, partner, doctor, care team; 3. disfiguration – changes in the physical appearance and personal image, diminishing or loss of sexual functions; 4.depreciation of work capabilities, of chances of professional, learning and free activities success; 5. destroying of personal relationships; 6. discomfort and pain in the terminal stages of the disease (1, 2)

The patient's capability to face these concerns depends on the quality of the medical team, psychological (emotional) help and the social aspects, including:

- the disease itself (location, symptoms, clinical aspects, necessary type of treatment)
- psychological and social status before the start of the disease
- the disease's threat level to the individual's goals and aspirations specific to age, profession, family status
- cultural and religious attitudes
- the existence around the patient of people capable of offering quality emotional support
- patient's potential for physical and psychological recovery, patient's personality and capacity of facing difficult situations (2,3)

Discussions and conclusions

The mediastinal tumors cases are on the rise regarding incidence and prevalence and represent an important segment of pathology. The increase in the number of cases has allowed a better understanding of this pathology, offering more and more complex and revealing data.

The tumoral pathology of the mediastinum is extremely complex, a relatively small anatomical area housing a vast variety of histological types. The mediastinum can be the stage for a large number of primitive tumors and a series of secondary lesions caused by vicinity or metastatic dissemination.

The mediastinal lymphomas of Hodgkin or non-Hodgkin types represent an important share of the mediastinal tumoral pathology. The Hodgkin lymphoma was the form most frequently appearing in the study lot. Among the non-Hodgkin lymphomas the most frequent are the big cells ones, of type B. An important segment of the mediastinal tumoral pathology is represented by the secondary tumors, they affecting the mediastinum by direct invasion or by metastatic dissemination.

The most frequent psychological disorders found in the patients diagnosed with mediastinal compression syndrome and cancer, in particular, was: depression, anxiety, pathological panic, insomnia, delirium, anorexia, nausea/sickness, pain, suicidal tendencies etc. The most common mental/psychiatric manifestation of those affected is depression, which can have serious consequences regarding both the evolution and the prognosis of the disease. When a sudden behavioral change is noted in a cancer patient the doctor should investigate all potential causes for delirium.

The acknowledging of the diagnostic in random, unsuitable circumstances can produce stupefaction, loss of trust, confusion and unnecessary additional suffering to the children patients. All these could be avoided if the mediastinal compression sufferers, previous to the revealing of the diagnostic, would be psychologically assessed (to establish their capability of facing the reality of their situation and more importantly, to understand it) and given a minimum of preparation to help them deal with the situation (emotional support, encouraging of attitudes of hope,

braveness, patience, active involvement in the fight against the disease etc.). Even if, understandably, in shock and traumatized, the family members must keep themselves together and, at very least in the presence of the affected person, should avoid lamenting, bewailing, pitying, reproaching; the patient needs his/her dignity and human qualities to be respected and that is being offered the best care and best available treatment in order to be brought back to normal health.

The cancer treatment can imply certain medical techniques that cause pain and discomfort. The lack of explaining of these techniques and quality family, friends and medical team support, can increase the patient's fear and anxiety. When the organism doesn't respond as expected to the treatment, the patient could lose hope. The side effects of chemotherapy (hair loss, nausea, sickness etc.), the surgery procedures (organ extirpation or amputations) will cause the cancer patient extensive psychological trauma.

A realistic perspective and a positive attitude towards the illness and life in general can help an individual fight the disease and can be a valuable supplement to the conventional treatment. Attitudes like optimism, courage, hope, active involvement can encourage a positive evolution of the disease, whereas pessimism, despair, impatience, the refuse to communicate with the specialists and to accept the medical care can cause the sufferer's situation to degenerate rapidly, with death the likely outcome

Depression following the disease's diagnosis, treatment and medication is a common occurrence, it is however difficult to determine with any degree of certainty whether depression in a mediastinal compression case is linked or not to a pre-existent disposition disorder.

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INTERCEPTIVE TREATMENT IN HYPODONTIA

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Abstract

The early treatment of nonskeletal orthodontic anomalies in early mixed dentition is intended to prevent the development of pronounced anomalies in the permanent dentition with the ultimate aim of reducing or even eliminating the need for later orthodontic treatment. Congenital missing teeth (tooth agenesis) is one of the most common developmental problems in children and hypodontia is the term most often applied to this situation.

The aim of the present paper is to report three cases of hypodontia and to review the literature regarding the etiology, the clinical implications and the management.

Key words: early treatment, interceptive therapy, malocclusion, hypodontia.

Introduction

One of the most significant and interesting aspects of orthodontics is certainly prevention and early treatment of malocclusions.

There has been a tendency over the years for us take an overall view of oral pathology in the child, bringing together paediatric dentistry and orthognathodontics to study the growth, psychological behaviour, oral habits, hereditary and congenital problems and the acquired problems of patients.

We tended to consider interceptive orthodontics as almost the exclusive domain of paediatric dentistry and thus a restricted field, born out by the greater part of our research, scientific papers and clinical practice.

Interceptive therapy should preferably be understood as early intervention, using simple means, and of brief duration, capable of totally or partially correcting a malocclusion or preventing it from becoming more serious.

The interceptive therapy should not be confused with prevention (prevention consists in not allowing a disease to start), since it carried out when a morphological anomaly is already present with the aim of reducing any disturbances to growth, function, aesthetics or, at times, to the emotional life of the child. There is often a strict correlation between these last two aspects, even the smallest children are able to feel needs in relation to their look.

However, interceptive therapy is an integral part of the overall orthodontic treatment, aiming to increase its effectiveness and reducing the treatment time.

To be able to deal with the questions of prevention and early treatment means above all having to be well acquainted with the etiopathogenesis, dental malocclusions and craniofacial dysmorfosis.

We have to be able to asses the patient in the first 3-5 years of life and see whether there is a good relationships between the different anatomical components that make up his craniofacial architecture as well as their size, shape and the functional relationships existing between them. Also, we have to be able to intervene as early as possible, if required, to re-establish their balance and harmony to obtain a good and stable occlusion. It may be the growth and early orthodontic treatment may not be enough to improve the situation, in which case the planning treatment will be necessary.

During the first few years of life, greatest growth implements take place. In the first 3 years the child double in height and at the age of 4 the skull has reached 60% of its adult dimensions. At the time that many orthodontists start the treatment, around 12 years, 90% of facial growth is complete. At the age of 7-8 years, there is clearly a great benefit from the patient's point of view to be gained from receiving facial orthopaedic treatment. At this age, it is still possible to influence the remaining 30% growth to improve the result from an orthopaedic and occlusions related point of view [1].

Alongside the genetical factors, all the environmental factors with influence the etiology of dentofacial anomalies need to be considered with a view to long-term prevention action. These includes gingivitis and mucosal infections, oral habits, atypical swallowing, accidental or intentional trauma, early tooth loss and the congenital missing teeth.

Hypodontia and oligodontia are classified as isolated or nonsyndromic hypodontia/oligodontia and syndromic hypodontia/oligodontia or hypodontia/oligodontia associated with syndromes. Anodontia is an extreme case, denoting complete absence of teeth [2].

In the literature, the clinical studies on the prevalence of hypodontia in the primary dentition range from 0.08% to 1.55%. In the permanent dentition, prevalence has been reported to range from 2.3% to 11.3% depending on the population investigated.

It is generally accepted that, excluding third permanent molars, the second mandibular premolar is the most frequently missing permanent tooth representing 40% to 50% of the total number of developing missing teeth. Hypodontia affecting the maxillary lateral incisor is next in terms of frequency (25%), followed by the maxillary second premolar (20%) and the mandibular central incisor (6.5%) [3].

Different authors have different theories on the etiology of dental agenesis. The most cited causes of hypodontia are: evolution of the species, hereditary transmission, congenital diseases and diseases affecting the fetus, chromosomal syndromes and local causes. Two

mutated genes in human, MSX1 and PAX are known to cause agenesis of permanent teeth [4].

Early detection of this type of anomaly is indispensable for interpreting the complications and dysfunctions such as malposition of the teeth next to the agenetic site, with consequent midline deviation or resorption of the alveolar bone. Dysfunctions generated by extended hypodontia and especially if it concerns the frontal segment affecting patient' smile contributes to the psychological problems.

In case of reduced hypodontia, especially of the teeth in the frontal region, early detection of teeth involved by the reduction process offers optimal conditions for closing the spaces through controlled mesial migration of the teeth.

E. Ionescu sustains the idea that, in hypodontia, every time it is possible to close the spaces through supervising and directing the natural process of eruption of permanent teeth, this version is to be preferred to other therapeutic solutions [5].

Hypodontia, be it reduced or extended, imposes emergency therapeutic intervention, in conditions as biological as possible, to stimulate the growth process adequate to the age specificity [6].

One of the main characteristics of the treatment is the duration, that may vary from case to case, although it is mostly short, have low costs, and it is extremely effective.

A great cooperation in all treatment phases from both, the young patient and the parents, can be easily required.

One of the most important things to have is the knowledge of the growth process and ability to predict growth patterns.

Aim and objectives

The purpose of this article is to describe the need for early examination and diagnosis of hypodontia in growing children and the necessity of the interceptive therapy in this malloclusion. Interdisciplinary teamwork between the pediatric dentist, orthodontist, and restorative dentist is very important when analyzing factors related to individual patients and establishing overall treatment plans.

Case reports

Case report 1

An 8-year-old male patient was reported for dental treatments. On clinical examination, retained deciduous mandibular both central incisors with no mobility were found (Figure 1). Suspecting permanent lower central incisors hypodontia, an orthopantomography was taken and confirmed the provisional diagnosis (Figure 2).

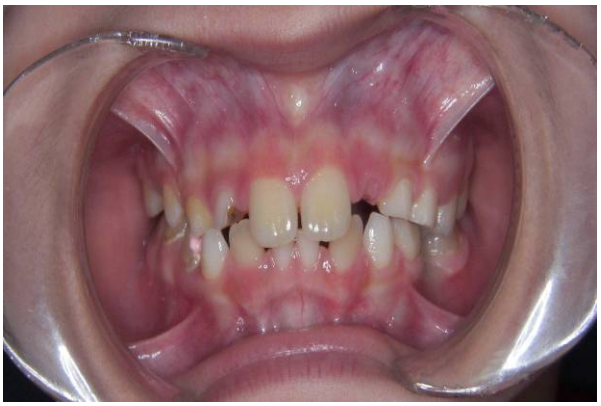

Figure 1. Clinical aspect.

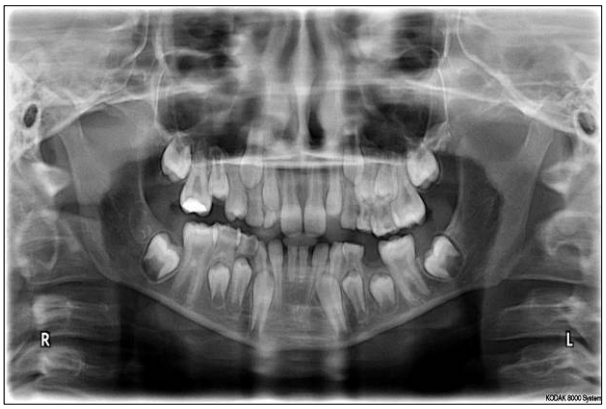

Figure 2. Radiological aspect.

Both permanent lateral incisors were abnormally angulated with crown deviating laterally and roots deviating medially. Along with agenesis of centrals, horizontal impaction of right canine was also evident on the radiograph (Figure 2). As the deciduous centrals were still firm without evidence of root resorption, no extractions was done at present. In this case the indication for space closure was reduced. If we would closed the space, the Class I cuspid relation would be lost due to a drifting of the cuspids to the lateral incisors positions, with the consequence of a group disoclusion.

Treatment was aimed at maintaining the primary incisors, with a view to their later replacement with a mix of implants and resin-bonded bridges planned to restore missing teeth and aesthetics.

Case report 2

A 7-year-old male patient reported to the orthodontist complaining of spacing in the lower anterior teeth. Intraoral examination showed the absence of first permanent mandibular central incisor (Figure 3). Radiographic examination revealed congenital agenesis of permanent right mandibular central incisor, but also, maxillary lateral incisors hypodontia (Figure 4).

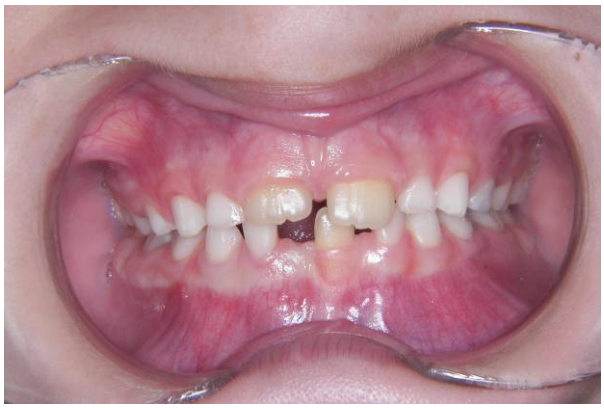

Figure 3. Clinical aspect.

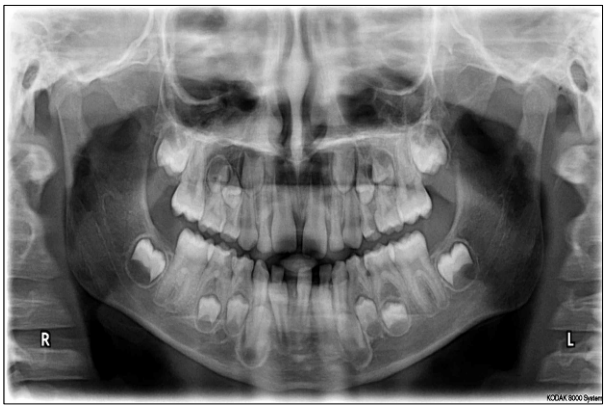

Figure 4. Radiological aspect.

For the maxillary lateral incisors the choice of closing the space involves mesial movement of the entire segment on the same side of agenesis, from canine to last molar. Thus, in this case, extraction of primary lateral incisors should be performed as urgently as possible in order to interrupt the dental arch and to allow the tangential forces to facilitate the generalized migration to the mesial of teeth. The attitude in relation with the primary canine will be determined by the mesial-distal report between its root and the crown of the permanent canine. When the primary canine is in a mesial position in relation to the permanent one, extraction will be performed sooner. The cuspid will take the place in the arch of the lateral incisors. Because the agenesis is bilateral, closure of the spaces usually poses less aesthetic problems as correct orthodontic treatment maintains the symmetry of the teeth in the upper arch.

In the lower arch extraction of the primary central incisor is indicated, as early as possible, followed by moving both permanent lateral incisors with orthodontic devices. After performing the extractions, mesial migrations of the teeth will be directed in close correlation with choosing the appropriate moment for extraction of the primary canine. Choosing this moment depends on the reciprocal reports between the primary canine and its successor, reports detected radiologically. Extraction of the primary canine can be correlated in time with a therapy of orthodontic closure of the first permanent canine. From this point of view, the favorable moment is towards the end of the period of active treatment or at the beginning of stabilizing the results, since there is a tendency of generalized mesialisation, stimulated by the action of the orthodontic device, which propagates at distance at the level of the dental arch. The treatment is easier by the limited distal dimensions of the lower incisors and by the natural tendency to crowding in this area.

Case report 3

A 10-year-old male patient was reported for dental treatments. Intraoral examination revealed mixted dentition with class III molar relation. Radiographic examination confirmed that 4 teeth, excluding third molars, were developmentally missing teeth: 15, 27, 37 and 47. Significant external root resorption was found in the retained primary teeth 55, so we decided to extract it and to open the space during the orthodontic treatment. The necessity of the orthodontic treatment was extreme because the second permanent molars were missing, as this would lead to a notable shortening of the hemiarch. In the left hemiarches, the therapy will be directed at positioning the third molar in the place of the second molar. But, where both the second and third molars are missing the treatment will be more difficult.

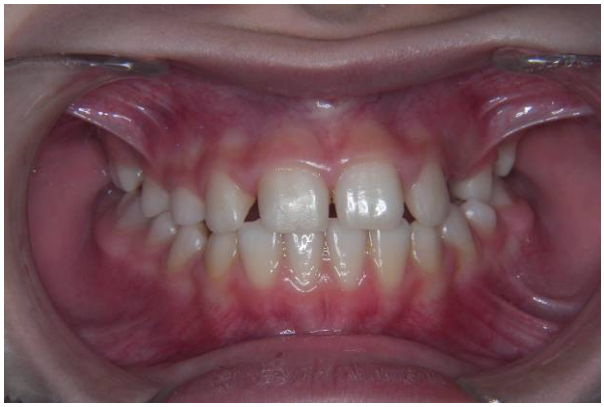

Figure 5. Clinical aspect.

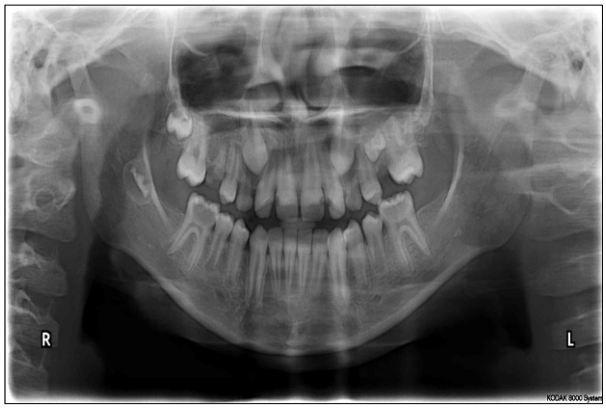

Figure 6. Radiological aspect.

Discussions and conclusions

Early diagnosis in case of hypodontia does not always imply an immediate orthodontic treatment; however, prevention of caries or appropriate treatment of the existent ones should be a priority. This priority resides in the fact that, in certain situations, the therapeutic solution is to preserve the primary teeth on the dental arch. Moreover, considering that the teeth represent secondary osteogenetic growth centers, under the circumstances of their numeric reduction, the state of health of the existent ones should be ensured, including of those in the primary dentition, in order to contribute to the formation of maxillary bones.

Agenesis of the anterior segment is generally prejudicial to the smile. In these cases, the primary aesthetic reasons guide therapy must not be overlooked particularly the cuspid guide where the space closure with mesial movement of the cuspid in to the missing lateral incisors space is considered.

A missing tooth in the lateral segment often causes a distal movement of the mesially located teeth. This has generally negative repercussions in the anterior segment due to mid line deviation towards the side of the agenesis.

The third molar is the tooth with the highest incidence of agenesis. If the tooth is missing no treatment is indicated. Problems may arise when both second and third molar are missing, as this may lead to a notable shortening of the hemiarch and overeruption of the antagonists.

In case of numeric dental modifications, hypodontia being one of them, one of the therapeutic conditions is the extraction of primary teeth.

In some cases the purpose of orthodontic treatment is to maintain space for a prosthetic replacement.

Pediatric dentists and orthodontists very frequently encounter patients with hypodontia. Because patients with hypodontia have other dental anomalies associated, it is necessary that they be supervised closely from an early age.

It is very important to make clinical and radiographic examination in every patient with a retained deciduous teeth or abnormal spacing, for early diagnosis and early intervention of hypodontia. If radiographic investigation is not carried out before exfoliation of the second primary molar, any diagnosis must necessarily be clinical and, as such, should be rather on the late side. Early diagnosis of hypodontia may allow a more favorable prognosis and minimal functional, aesthetical and psychological complications. Its importance cannot be over-emphasized. Thus it is the general dentist's responsibility and ability to identify hypodontia patients for early referral to receive multidisciplinary treatment before any complications can occur.

Interceptive orthodontic treatment is part of an overall orthodontic treatment plan. The aim of the treatment is not always to achieve complete correction. It is (at times) sufficient to obtain a partial result while establishing the prerequirements for normal growth.

Treatment plan must be made based on growth potential, eruption pattern, tooth position, and tooth health. In addition, excellent communication with patients and parents is necessary, as the treatment duration for patients with hypodontia may extend over many years.

The orthodontists should increase the interdisciplinary collaboration between them and the paediatric dentists, the orofacial surgeons, the paediatricians, the otolaryngologists, the psychologists and the speech therapists.

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CONGENITAL LOBAR EMPHYSEMA (CLE) RADIOLOGIC AND IMAGISTIC (CT) DIAGNOSTIC

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Abstract

A new born child, age: one month, sex: masculin, with acute respiratory distress syndrome, perioronasal cyanosis and hypoxemia has been diagnosed (radiological and imagical – CT) with congenital lobar emphysema (CLE) at the level of the right superior lobe.

One month after, the new born child has been diagnosed with the aforesaid syndrome, and, now two months old, he has been subjected to a surgical intervention consisting in lobectomy at the level of the right superior lobe.

His postsurgical evolution has proved satisfactory with pulmonary reexpansion.

Key words: congenital phatology, pneumophatology, congenital lobar emphysema

Introduction

Congenital malformations of the lung are rare and vary widely in their presentation and severity(4).

Congenital lobar Emphysema (CLE) is infrequent and usually present at birth(8).

The superior lobes are affected (5) and a single lobe usually is involved; however, patients can show multiple lobar involement (8). The rates of occurrence are: left upper lobe – 41%, right middle lobe – 34%; right upper lobe - 21%(5,8).

Frequently, cartilage plates in the bronchi are absent at the level where cartilage is expected (5,8). The abnormality is related to intrinsic bronchial narrowing. In these cases, there is weakened or absent bronchial cartilage, so that there is inspiratory air entry but collapse of the narrow bronchial lumen during expiration. This bronchial defect result in lobar air trapping (7,8).

Pulmonary arteries are normal in patients with CLE (8). Angiography shows slow and poor arterial filling (5).

Hipoxemia (in severely affected pacients) may occur (8).

CASE PRESENTATION

Anamnesis and clinic findings:

1 (one) month new – born child, male has been brought to Louis Turcanu Children Emergency Hospital from Timisoara on April 21, 2009 and has been hospitalized in the Pediatric Department.

Upon hospitalization, he presented a severe general state, perioronasal cyanosis, aerated secretions at the mouth level, mixed dispneea, continuous exhausting cough and disseminated subcrepitant rhonchi.

Paraclinic findings:

- Gases into the blood: ph=7,431; pCO2 (carbon dioxide pressure) = 44,2mmHg; reduced pO2 (oxygen pressure) = 38,1mmHg (normal: pO2 = 75,0 – 100,0mmHg).
- Blood exam: HGB = 11,5g/dL (normal: 12,0 – 16,5g/dL), lymphocytes ($11,25x10^3$/uL), monocytes ($1,87x10^3$/uL).
- Cardiac echograhic examination (conclusion): normal structured cord, moved to the left and down side, inclusive the aortic arch is moved 2 (two) inter – rib space down.
- ECG: RS – regulated, 160 beats per minute, QRS + 60^0 axis, left branch minor block, the rest presents a normal electric path.

Radiological and imagical aspects:

Standard Radiography:

Marked hyperaeration and overdistention of the right upper lobe with mediastinal shift to the left. Aer ation and left lung reduction (hypoventilated by means of compression) (Fig. 1, Fig. 2).

Computer Tomography:

Pronounced distention of the right superior lobe with lobar hypovascularisation in comparison with the left superior lobe. The hyperinflated LSD directs the medistine structures towards the left side, having a compressive effect on the LMD and LIED (Fig. 3, Fig. 4).

Virtual Bronchoscopy:

At the level of the right superior lobar bronchus, an anterior and inferior oriented tract can be noticed, with a permeable lumen extending up to the bifurcation level, where, due to the extremely reduced dimensions of the segmentary bronchi diameter, the endobronchial navigation can no longer continue. The diameter of the right superior lobar bronchus has diminished in comparison with the left superior lobar bronchus (1,4 mm at emergency, in comparison with a 1,8 mm diameter).

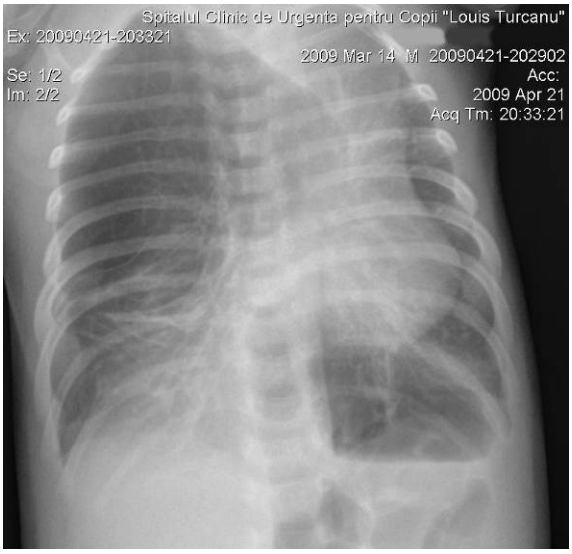

Fig. 1 Postero-anterior view. Marked hyperaeration and overdistention and mediastinal shift to the left.

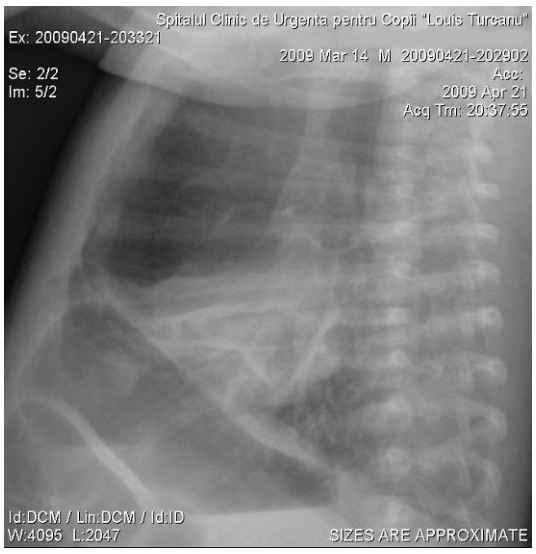

Fig. 2 Lateral view. Marked hyperaeration and overdistention of the retrosteranal space.

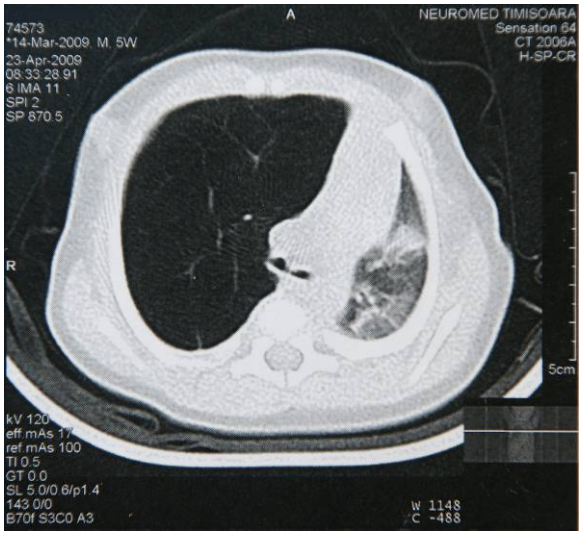

Fig. 3 Uper thorax sectioon. Marked hyperaeration and overdistention of the right superior pulmonar lobe with mediastinal shift and compresion with hypoventilation of the left superior pulmonar lobe.

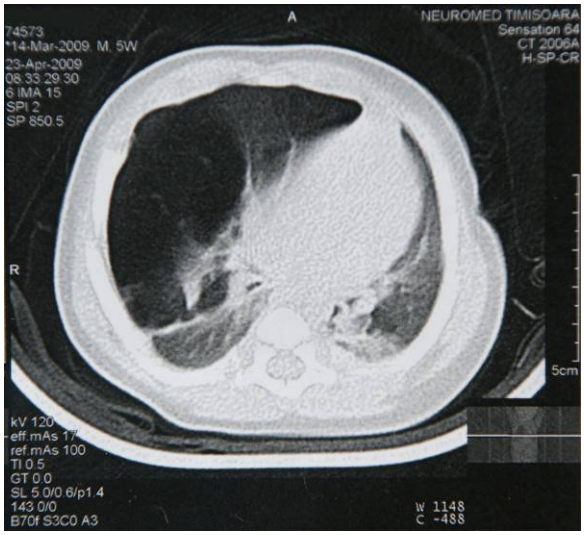

Fig.4 Midle thorax. Marked hyperaeration and overdistention of the right superior pulmonar lobe with mediastinal shift and compresion with hypoventilation of the left superior pulmonar lobe.

Discussions

The congenital lobar emphysema can be detected even from the prenatal period in the presence of a hyperechogenic pulmonary zone (2). The echographic semiology is not very clear, and that 's why, we shall resort to other medical imaging techniques, such as prenatal nuclear MRI and postnatal tomodensiometry (CT)(2).

As regards our medical investigation, the diagnosis established by us has been revealed by the postnatal tomodensiometry (CT).

The symptomatic form of the congenital lobar emphysema (CLE) must be immediately detected and operated because the subsequent diagnosis shall be conditioned by the patient 's age at the moment when the surgical intervention is performed (3).

The surgical intervention can be avoided only in case of incipient forms of the syndrome, with negligible distension and without apparent symptomatology (3,6).

Unfortunately, the patient into question has been diagnosed with a quite serious distension and apparent symptomatology so, in this case, the surgical intervention was absolutely compulsory. The surgery (right superior lobectomy) has been performed on May 18, 2009, more specifically, one month after the diagnosis has been established. The postsurgical evolution has proved satisfactory with the reexpansion of the left pulmonary and the segments left from the left lung (Fig. 5).

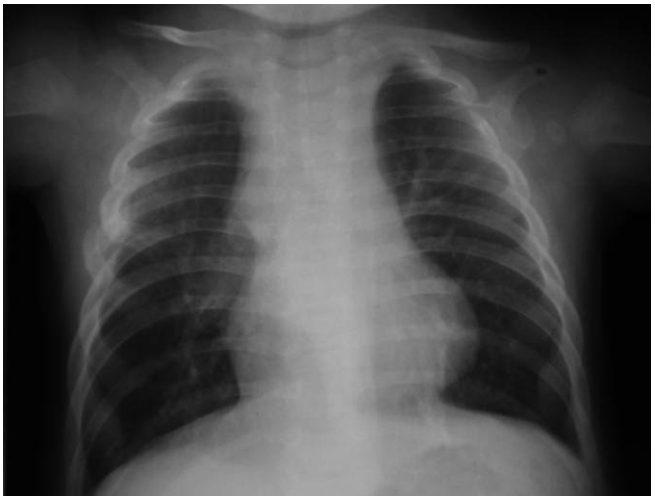

Fig. 5 Postoperative aspect. Re-expantion of the midle and inferior lobe of the right lung andre-expantion of the left lung.

As regard to the differential diagnosis (1) analysed by us after the standard cardiopulmonary radiography has been performed, the possibility of the left pulmonary hypoplasia with right pulmonary hyperinflation has been brought into discussion and analyzed.

Conclusions

1. The cardiopulmonary radiologic exam (standard radiography: front and profile) and the imagistic exam (CT or MRI) represents diagnosis elements in the cases of congenital lobar emphysema (CLE).
2. The surgery (lobectomy) represents the treatment indicated by the apparent symptomatic forms of the congenital lobar emphysema (CLE).

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THE VARIATION OF ANTIBIOSENSITIVITY FROM 1998 AND RESPECTIVELY 2008 IN CHILDREN'S SHIGELLA ACUTE DIARRHEA IN ARAD COUNTY

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[2]Arad County Hospital

Abstract

Aims: The authors aim to establish the variation of antibiosensitivity from1998 and, respectively 2008, in Shigella acute diarrhea and based on the results to elaborate a therapeutic local guide

Methods: The authors study the antibiosensitivity versus resistance models, in Shigella acute diarrhea of children from Arad County admitted in the hospital during 1998 and, respectively from 2008; Difussimetric antibiotic test are performed according to the existing standards and the antibiosensitivity of the 11th most frequently used antibacterial drugs in the antibiotic sensitivity tests was noted.

The data is introduced in an Excel database and analyzed with statistical methods in SPSS 10.

Results: A significant decrease of sensitivity ($p < 0.001$) in the last 10 years is noted for Ampicillin +Sulbactam(93,33% versus 48,31%), Amoxicilin+ Clavulanic Acid (91,11% versus 54,83%), Cephalosprins of 3rd generation(97,77% versus 70,36%), followed closely by Nitrofurantoin (55,55% versus19,35%)($p = 0.002$), Nalidixic Acid (80% versus 19,35%) ($p=0.01$) and Fluroquinolones (93,33% versus 77,41%)($p=0.05$). Comparing the results obtained from both groups, we can observe that the resistance has increased for all antibiotics, except for Chloramphenicol, Gentamicin and Co-Trimoxazole (not statistically significant).

Conclusions: The antibiosensitivity at Shigella in our region to the usual anti-microbial agents (Ampicillin, Tetracycline, Sulphametoxazole/ Trimethoprim, Nalidixic Acid, Nitrofurantoin), has importantly decreased, being demandatory to limit their use.

Fluoroquinolones (at children >12 years old) and cephalosporines (at children < 12 years old), remain the choice anti-bacterial agents in the eradication of Shigella infection.

Regional antibiotherapy guidelines, periodical up-dated by chimiosensitivity studies are needed.

Key words: antibiosensitivity, antibioresistance, Shigella, child

Background

Acute diarrhea with Shigella remains an important problem of morbidity in Romania. There are studies which consider this etiology to be the first in the digestive infections of children in Romania. A 5 year study realised in 2006 by our group, which involved 387 children admitted with acute diarrhea showed that the main etiology is represented by Shigella and Salmonella strains, followed by Escherichia Coli, Campylobacter, and in a low percentage by Proteus:

Table 1- The etiology in bacterial acute diarrhea in children from Western Romania - a 5 year study (387 children).

The etiological factor	Frequency	Percentage
Shigella	**182**	**47.1**
Salmonella	**155**	**40**
Pyocyanic	**4**	**1**
Escherichia Coli	**22**	**5.7**
Proteus	**1**	**0.3**
Campylobacter	**23**	**5.9**
Total	**387**	**100.0**

It's hard to say if this percentage represents a real incidence and that is not a bacteria more easily detected in Romania!

The resistance at antibiotics in our region is not well known due to: unicentral studies, realised on small groups of children (low number of strains), limited geographical areas, short periods of time.

The data are hardly accessible, lacunary, without

being assembled in one vision which would allow us to visualize the problem.

Aim

To detect if the pattern sensitivity/resistance at antibiotics in Shigella from our geographical area has suffered statistically significant changes in the last decade.

The results could help to create regional guidelines of antibiotherapy in Shigella's acute diarrhea in children.

Methods

73 children, age 1 month – 18 years old , admitted in the Department of Infectious Diseases, Clinic of Paediatrics, Arad, Romania between 1998, respectively 2008 with the diagnosis of acute diarrhea with Shigella were included. The children were divided into 2 groups: the 1998 group(42 strains with Shigella) and the 2008 group (31 strains with Shigella).

In both groups, the strains of Shigella flexneri were presented in the highest percentage, followed in a low percentage by Shigella sonnei, Shigella boydi. The strains of Shigella dysenteriae were identified only, in the 1998 study group:

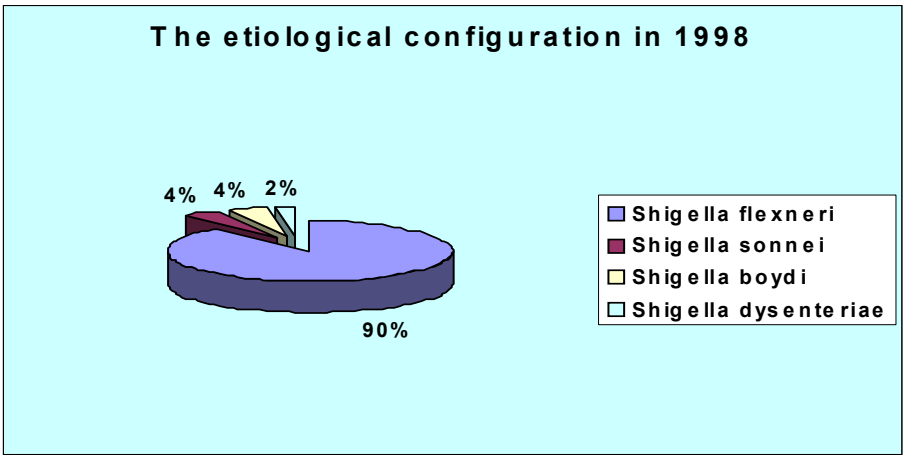

Figure 1 - The etiological configuration in 1998.

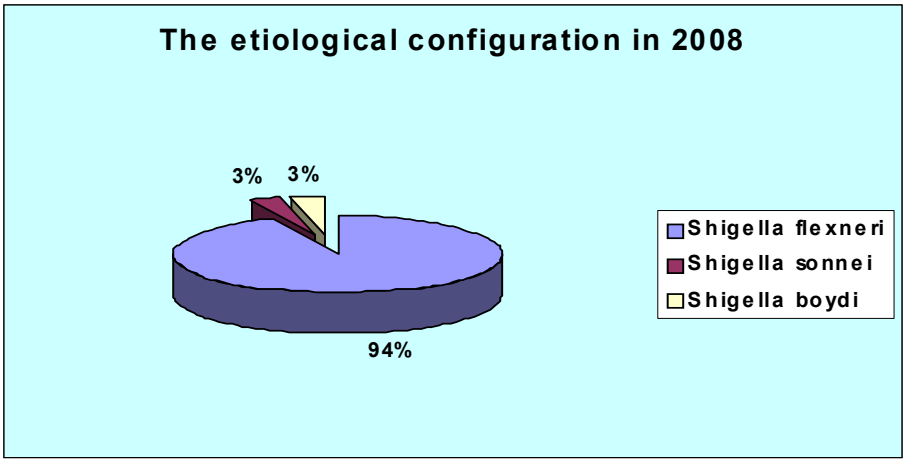

Figure 2 - The etiological configuration in 2008.

The following variables were monitored :

Antibiosensitivity – MIC (minimum inhibitory concentration) at least 2- 4 times < the level of antibiotic in serum or humours.

Antibiotic resistance - MIC > the level of antibiotic in serum or in humours.

The diffusimetric antibiotic test was performed according to the existing standards in the Laboratory of Microbiology, Clinical Emergency Hospital, Arad, Romania.

The data was introduced in an Excel database and analyzed with statistical methods in SPSS 10. The value of $p< 0.05$ was considered significant.

The variables were reported to the most frequently used antibacterial drugs in the antibiotic sensitivity tests: Ampicillin, Ampicillin + Sulbactam, Amoxicillin + Clavulanic Acid, Cephalosporins, Gentamicin, Chloramphenicol, Tetracycline, Co-trimoxazole, Nalidixic Acid, Fluoroquinolone and Nitrofurantoin.

Results and discussions

Table 2 - The comparison of antibiosensitivity 1998/2008.

	Sensitivity 1998		*Sensitivity 2008*		
	No	***%***	***No***	***%***	***P***
A	*9/45*	*20*	*2/31*	*6.45*	*insignificant*
A + S	*42/45*	*93.33*	*15/31*	***48.38***	***<0.001***
A+ C	*41/45*	*91.11*	*17/31*	***54.83***	***<0.001***
Ceph 3rd gen	*44/45*	*97.77*	*22/31*	***70.86***	***<0.001***
G	*15/45*	*33.33*	*13/31*	*41.83*	*insignificant*
C	*6/45*	*13.33*	*12/31*	*38.70*	***0.02***
T	*2/45*	*4.44*	*1/31*	*3.22*	*insignificant*
S/T	*16/45*	*35.5*	*12/31*	*38.7*	*insignificant*
Nx	*36/45*	*80*	*15/31*	*48.38*	*0.01*
Fluoroq	*42/45*	*93.33*	*27/31*	***77.41***	*0.05*
N	*35/45*	*55.55*	*6/31*	*19.35*	*0.002*

A-Ampicillin, ***A + S*** Ampicillin + Sulbactam, ***A+ C*** Amoxicillin + Clavulanic Acid, ***Ceph 3rd gen*** Cephalosporins, ***G*** Gentamicin, ***C*** Chloramphenicol, ***T*** Tetracycline, ***S/T*** Co-trimoxazole, ***Nx*** Nalidixic Acid, ***Fluoroq*** Fluoroquinolone and ***N*** Nitrofurantoin

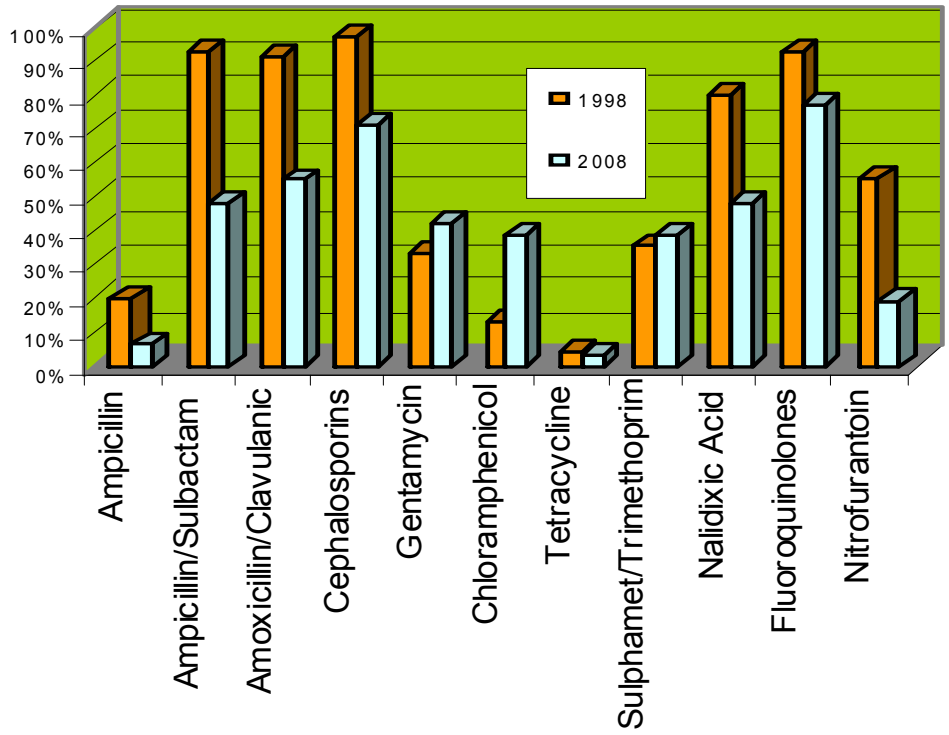

Figure 3 - The comparison of antibiosensitivity 1998/2008.

The comparative data analyse show that the highest sensitivity is for Cephalosporins, Fluoroquinolones, Amoxicillin and Clavulanic Acid, Nalidixic Acid.

A significant decrease of sensitivity ($p < 0.001$) in the last 10 years is noted for Ampicillin +Sulbactam, Amoxicilin+ Clavulanic Acid, Cephalosprins of 3rd generation, followed closely by Nitrofurantoin ($p = 0.002$), Nalidixic Acid ($p = 0.01$) and Fluroquinolones ($p = 0.05$).

For Ampicillin a percentage decrease is mantained without being significant statistically.

A statistically significant increase of Chloramphenicol's sensitivity is observed.

Table 3 -Antibiotic resistance 1998/2008.

	Resistance 1998		Resistance 2008		
	No	%	No	%	P
A	15/45	33.33	28/31	90.32	<0.001
A + S	1/45	2.22	7/31	22.58	<0.001
A+ C	2/45	4.44	6/31	18.35	0.05
Ceph 3rd gen	1/45	2.22	6/31	18.35	0.02
G	20/45	44.44	17/31	54.83	insignificant
C	30/45	66.66	15/31	48.38	insignificant
T	30/45	66.66	28/31	93.56	0.002
S/T	20/45	44.44	16/31	51.61	insignificant
Nx	6/45	13.33	10/31	72.25	0.05
Fluoroq	2/45	4.4	7/31	24.58	0.02
N	18/45	40	20/31	64.51	0.05

A-Ampicillin, ***A + S*** Ampicillin + Sulbactam, ***A+ C*** Amoxicillin + Clavulanic Acid, ***Ceph 3rd gen*** Cephalosporins, ***G*** Gentamicin, ***C*** Chloramphenicol, ***T*** Tetracycline, ***S/T*** Co-trimoxazole, ***Nx*** Nalidixic Acid, ***Fluoroq*** Fluoroquinolone and ***N*** Nitrofurantoin

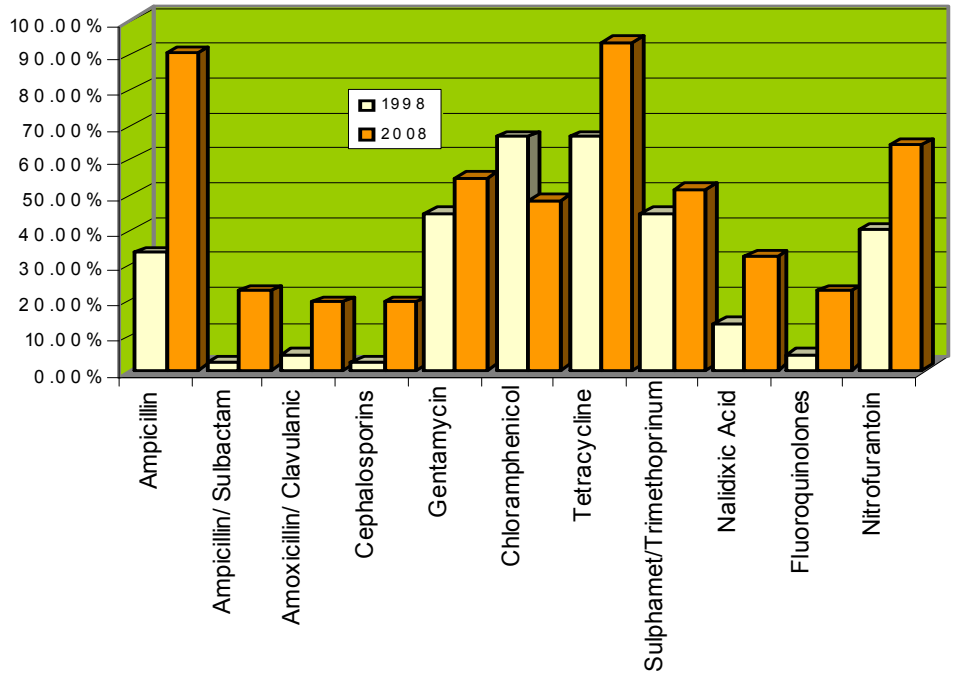

Figure 4 - Antibiotic resistance 1998/2008.

Comparing the results obtained from both groups, we can observe that the resistance has increased for all antibiotics, except for Chloramphenicol (is not statistically significant).The highest antibiotic resistance in 2008 is for Tetracycline, Ampicillin, Nalidixic Acid and Nitrofurantoin The increase of antibiotic resistance in the last decade is observed for Ampicillin, Tetracycline, Ampicillin+ Sulbactam, Cephalosporins 3rd generation, Fluoro-quinolones, Nitrofurantoin and Nalidixic Acid. Gentamycin and Sulphamethoxazole/ Trimethoprim don't show significant changes.

A decrease of sensitivity for all antibiotics is observed, except for Chloramphenicol; the decrease is statistically significant for 6 of them. An alarming phenomenon is the decrease for the antibiotics more recently introduced as therapy: Ampicillin/Sulbactam, Amoxicillin/ Clavulanic Acid, Cephalosporins of 3rd generation, Fluoroquinolones.The increase of resistance for all antibiotics is observed except for Chloramphenicol (not statistically significant)

The increase of resistance is significant for Ampicillin, Tetracycline, but alarming as well for

Ampicillin/Sulbactam, Cephalosporins of 3rd generation, Fluoroquinolones, Nitrofurantoin and Nalidixic Acid. Gentamycin and Sulphametoxazole/Trimethroprim don't show significant changes.

Based upon these findings we tried to create a local guideline for using antibiotics in Arad county in Shigella acute diarrhea in childhood. The first recommended antibiotic choice should be represented by fluoroquinolones (children >12 years old) and cephalosporins (children < 12 years old):

Table 4 - Local guidelines of antibiotic therapy in Shigella's infection.

First choice	To avoid
Fluoroquinolones **Cephalosporins**	**Ampicillin** **Tetracyclin** **Nitrofurantoin** **Sulphametoxazole/Trimetoprim**

Many international studies (1, 2, 4, 5, 7, 9, 10, 11, 12, 13, 14, 15) show that the antibiotic susceptibility patterns are variable for each geographical region.

The pattern of antibiotic susceptibility in Arad is characterised by the following features:

- increase of resistance to the classic antibiotics, as well as to the more recently introduced antibiotics, whose efficiency degraded progressively in the last decade.
- the resistance has increased compared to the previous studies performed in Romania Musta (7), Jugulete (9):
- the level of the antibiotic resistance is:
  - a little bit higher than the European one, showed by the studies of Vrints (16) Belgium, Haukka (6) - Finland, Samonis (12) Greece.
  - under the European one described by Karacan-Turkey (8).
  - similar to the ones described by Diniz Santos-Latin America (2), Peirano- Brasil(11), Fulla-Chile (4).
  - under the Asian one described by Uppal (15), Pazhani (10)– India and under the African one described by Asrat – Ethiopia (1) and Sire-Senegal (13).

The normal questions to be asked, after analysing these results are: What happened in the last decade to determin such an important decrease of antibiosensitivity of the usual anti-microbial agents at Shigella, in our region? What are the responsable factors which influenced this outcome?

An answer to these questions, could be, the increased unreasonable administration of antibiotics in the last decade due to various reasons: unreasonable prescriptions in simple or toxigene acute diarrhea; use of reserve antibiotics which determine a fast errosion of their efficacity; non -adequate dosage of therapy (low dosage, mistakes in the administration rhythm, medical interractions); lack of patient compliance; a large availability of antibiotics on the pharmaceutical market , allowing, also, an important self-medication of the patient.

A study on self-medication with antimicrobial drugs (5), realised in 19 European countries in 2006, showed that Romania has the 4th position in keeping an antibiotic storage at home after Italy, Spain and Lithuania, has the 2nd place in self-medication after Lithuania and occupies the 8th place, for prescribed antibiotic use after Slovakia, Italy, Croatia, Malta, Ireland, Israel and Spain.

The future solutions in controling this alarming phenomen, could be the beginning of a national programme to centralize all the important studies regarding the antibiotic resistance(ABR); creating regional guidelines of antibiotic therapy in acute diarrhea; continuous medical training for using the antibiotics with discrimination; involvement of creating opinion leaders in the field of child infectious pathology; mass-media involvement for informing the public opinion on the real danger of what antibiotic abuse means and restriction of self-medication and of access to antibiotics without prescription.

Conclusions

1. The antibiosensitivity at Shigella in our region to the usual anti-microbial agents (Ampicillin, Tetracycline, Sulphametoxazole/ Trimethoprim, Nalidixic Acid, Nitrofurantoin), has importantly decreased, being demandatory to limit their use.
2. Fluoroquinolones (at children >12 years old) and cephalosporines (at children < 12 years old), remain the choice anti-bacterial agents in the eradication of Shigella infection but start to develop significant resistance in the last decade.
3. Regional antibiotherapy guidelines, periodical up-dated by chimiosensitivity studies are needed.

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MULTIDRUG RESISTANT BACTERIA IN CHILDREN: OUR WORST NIGHTMARE

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Abstract

Background: Bacterial infections caused by multidrug resistant bacteria (MDR) are a constant challenge for physicians throughout the world. *Aims:* To identify and to phenotype MDR bacteria responsible for infections in children. *Material and methods:* MDR strains isolated from children (0-18 years) admitted at "Louis Turcanu" Children Hospital between April to September 2009 was phenotype at the Microbiology and Virusology Department of University of Medicine and Pharmacy Timisoara. Automated system Vitek ® 2 Compact 30 was used. Methicilino-Resistant Staphylococcus aureus (MRSA) and Methicilino-Resistant Coagulase-Negative (MRCN), extended-spectrum β-lactamase (ESBL)-producing E. coli and Klebsiella pneumoniae, carbapenems-resistance Pseudomonas aeruginosa and Acinetobacter baumanii were studied. *Results:* Out of the 815 bacterial strains isolated during the study period, 23 (2.82%) were MDRS. They were encountered in children admitted in Intensive Care Units (34.78%) and Newborns Departments (34.78%). These bacteria were isolated from bronchial aspirates (30.43%), wound secretions (21.74%), urine cultures (21.74%) and vascular catheters (8.69%) and other specimens. The following phenotypes were identified: PBP mutations in *S. aureus* (13.04%) and *S. coagulase-negative* (21.73%); ESBLs / acquired penicillinase + cephalosporinase, ESBLs or ESBLs (CTX-M) phenotype in *E. coli* (17.39%); ESBLs, ESBLs + Cephamycine impermeability / ESBLs or carbapenems resistance / carbapenemase secretion (metal or KPC) in *Klebsiella pneumoniae* (21.74%) and high-level carbapenems resistance phenotype in *Pseudomonas aeruginosa* (21.74%) and *Acinetobacter baumanii* (4.35%). 34.78% of isolated strains presented extensive drug resistance**.** *Conclusion:* The incidence of MDRS found was not so important. It is necessary to continue the determination of resistance phenotypes, in order to a proper use of antibiotics and to prevent further emergences of MDRS.

Key words: bacteria, drug resistance, infection, antibiotics.

Introduction

Antibiotics have long been considered the "magic bullet" as Paul Ehrlich described them in the 19th century that would end infectious disease. Although they have improved the health of countless numbers of persons, many antibiotics have also been losing their effectiveness since the beginning of the antibiotic era. Bacteria have adapted defenses against antibiotics. They will continue to develop new resistances, even as we develop new antibiotics. In recent years, much attention has been given to the increase of antibiotic resistance. As more bacterial strains become resistant, many infectious diseases have become difficult to treat, a phenomenon frequently ascribed to both excessive and inappropriate use of antibiotics. There is no doubt that the use of antibiotics provides selective pressure responsible for antibiotic resistant bacteria and resistance genes. These strains had a survival advantage, under the selective pressure of antibiotics propagated, and spread throughout the world, contributing to a web of resistance that includes humans, animals and environment.

Nowadays infections caused by multidrug-resistant (MDR) bacteria are daily challenges to physicians throughout the world. During the last decade, the efforts to combat MDR mainly focused on Gram-positive bacteria and drug companies have developed several novel antimicrobial agents to fight these bacteria (e.g. Linezolid or Daptomycin). Unfortunately, the growing problem of MDR in Gram-negative bacteria was not paralleled with the development of novel antibiotics. This explains the growing number of infections caused by Gram-negative bacteria for which no adequate therapeutic options exist. This return to the pre-antibiotic era has become a reality in many parts of the world.

In comparison with Gram-positive bacteria, for which resistance to a single antibiotic indicates the antibiotic resistance phenotype of interest (e.g. Vancomycin-resistant Enterococcus or Methicillin-resistant Staphylococcus aureus), MDR in Gram-negative bacilli are difficult to define. Paterson and Doi[1] introduced the universal definitions for the various degrees of antimicrobial resistance among Gram-negative bacilli. Isolates characterized as MDR are resistant to three or more classes of antibiotics. "Extensive drug resistance" (XDR) defined isolates that are not susceptible to antipseudomonal cephalosporins (Ceftazidime and Cefepime), antipseudomonal carbapenems (Imipenem and Meropenem), Piperacillin/Tazobactam and fluoroquinolones (Ciprofloxacin and Levofloxacin), except Colistin. According to Falagas[2,3] "pan-drug resistant" (PDR) exhibited resistant to all 7 antipseudomonal antimicrobial agents, including Tigecycline and Polypeptide (e.g., Polymyxin B and Colistin).

In order to detect if a bacteria is MDR, its phenotype need tested. A phenotype is defined as the expression of a

specific mechanism of susceptibility or resistance to a given drug class within a particular species[4]. The wild-type phenotype is defined as the phenotype for that species in the "wild," prior to any mutation of chromosomal genes or acquisition of new DNA that alters susceptibility to the drug class.

It is necessary to know the resistance phenotypes existing in your hospital, because they give important information regard to the mechanism of resistance, the emergence and spread of MDR strains. These help to take the correct decision concerning the proper antibiotic treatment.

Objectives

The aim of our study was to identify and to phenotype MDR bacteria responsible for severe infections in children admitted in our hospital.

Material and methods

Our study took place at Emergency Children's Hospital "Louis Turcanu" between Aprils to September 2009. Our lot comprised children (0-18 years) with severe bacterial infections caused by MDR bacteria. We took into consideration the following MDR strains:

- Methicillin-Resistant Staphylococcus aureus (MRSA) and Methicillin-Resistant Coagulase-Negative Staphylococci (MRSCN),
- Extended-spectrum beta-lactamase (ESBL) producing E. coli and Klebsiella pneumoniae,
- Carbapenems-resistance non-fermenting Gram-negative bacilli

After isolation from different specimens received in the Microbiology Laboratory, the strains were tested, in order to identify their antibiotics resistance. The disk-diffusion method was used. MRSA or MRCN defined S. aureus or Coagulase-Negative S. respectively, resistance to Oxacillin and Methicillin. E. coli and Klebsiella pneumoniae resistant to the last generations of Cephalosporins and Aztreonam were ESBL producing strains. Pseudomonas aeruginosa and Acinetobacter baumanii resistant to Carbapenems were also considered as being MDR isolates.

After the identification, all MDR isolates were sent to the Microbiology and Virusology Department of the University of Medicine and Pharmacy, Timisoara in order to phenotype them. Isolates were cultured 24 hours at 37ºC on Columbia agar containing 5% sheep blood and Mac Conkey agar. Suspensions of these cultures were made in 0.45% saline, adjusted to the turbidity of a 0.5 McFarland standard and used to load the cards of system Vitek ® 2 Compact 30. The manufacturer's directions (bio Merieux) were followed. The antibiotic susceptibility test cards were used depending on the type of tested strains. Briefly, for each antibiotic containing test, a turbidity signal was automatically measured at every 15 minutes for up to 18 hours. These data were used to generate growth curves and by comparison with a control, the minimum inhibitor concentration of each antibiotic was estimated. E. Coli ATCC 25922 and 35218, Pseudomonas aeruginosa ATCC 27853 and Staphylococcus aureus ATCC 29213 were used as control strains. These extended antibiograms allow us to fit the tested bacteria into a resistance phenotype.

Results and discussions

During the study period, 815 bacterial strains were isolated and tested in the hospital laboratory. Out of these, 23 isolates (2.82%) fulfilled our inclusion criteria and were considered as MDR bacteria. Gram-negative bacilli (73.81%) were more prevalent than Gram-positive isolates (Table 1). Medical literature showed that Gram-negative organisms have become MDR bacteria over the last two decades and remained to be the major threat all over the world[5].

Table 1: Distribution of isolated bacteria

SPECIES ISOLATED		
	No.	%
Staphylococcus aureus	3	13,04
Staphylococcus hemolyticus	2	8,69
Staphylococcus hominis	3	13,04
E. coli	4	17,39
Klebsiella pneumoniae	5	21,64
Acinetobacter baumannii	1	4,35
Pseudomonas aeruginosa	5	21,74
Total	**23**	**100**

The majority of MDR strains were isolated from bronchial aspirates (30.43%), wound secretions (21.74%), urine cultures (21.74%) and vascular catheters (8.69%) as presented in table 2.

Table 2 Distribution of specimens from which MDR bacteria were isolated.

SPECIMENS	No.	%
Bronchial aspirates	7	30,43
Wounds cultures	5	21,74
Urine cultures	5	21,74
Vascular catheters	2	8,69
Pus cultures	1	4,35
Peritoneal cultures	1	4,35
ETT tubes	1	4,35
Nasal swab	1	4,35
Total	**23**	**100**

As we can see in figure no. 1, the majority of MDR bacteria were encountered in children admitted in intensive care units (ICU) and neonatal departments (ND). Nephrology, Gastroenterology or Pediatric Surgery Department were also other wards in which children were suffering from different infections caused by MDR strains.

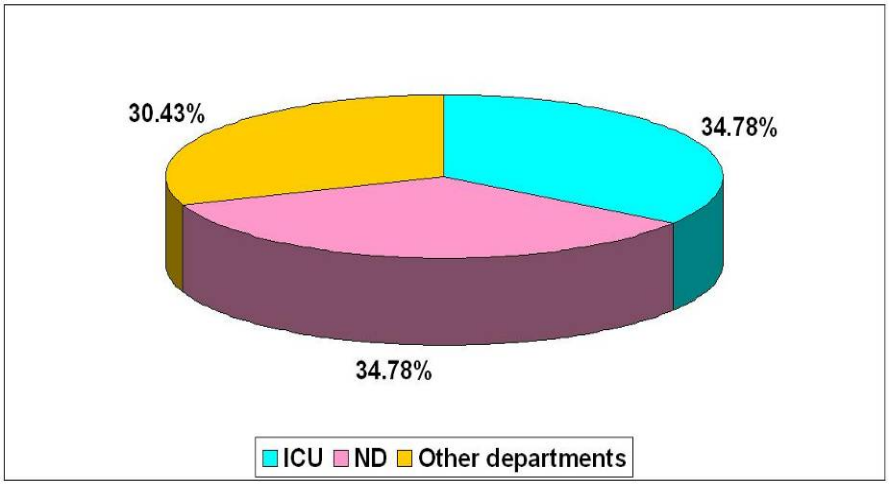

Figure no.1 Distributions of departments with MDR bacteria.

In both ICU and ND, children are exposed to several invasive procedures such as: tracheal intubations, mechanical ventilation, airway aspiration, indwelling vascular catheters in order to save their life. These invasive maneuvers alter their skin or mucous membrane barriers and represent an important pathway for bacteria to enter in the organism and to cause infections. Especially neonates are more susceptible to infections because of their weak immune system and inadequate development of mechanical barriers such as skin and gastrointestinal tract mucosa[6] . Compared with older children and adults, infants, particularly premature infants, are relatively immunocompromised. Small gestational age, low birth weight, mechanical ventilation therapy and prolonged hospitalization were found to be also important risk factors for MDR bacteria infections[7]. Widespread use of broad-spectrum antibiotic in IC and ND is a serious risk factor for the emergence and spread of MDR pathogens[8]. Antibiotic used interferes with colonization by normal flora, thereby facilitating colonization with more virulent pathogens. Studied demonstrated that the rise of E. coli and Klebsiella pneumoniae ESBL strains and Pseudomonas aeruginosa carbapenems-resistant was correlated with increased consumption of extended-spectrum cephalosporins, β-lactam/β-lactamase inhibitor combinations, carbapenems, quinolones and aminoglycosides. Carbapenems-resistant Acinetobacter spp. was significantly associated with the increased usage of extended-spectrum cephalosporins[9]. This flora is frequently MDR as it has developed under the selective pressure of antibiotics and can cause invasive disease. Transmission of pathogenic agents is by direct contact or indirectly either via contaminated equipments, intravenous fluids, medications, blood products or enteral feedings. Various studies have also reported length of stay in ICU or ND as a conditioning factor for the occurrence of infections with severe MDR bacteria. Mean time between ICU admission and acquired of infection with MDR bacteria was 12 +/- 9 days[10, 11].

Table 3 The Gram positive MDR bacteria phenotypes identified.

Species	MDR Gram positive bacteria		
	No. %	Identified phenotypes	No.%
Staphylococcus aureus	3 (13.04%)	**MRSA:**PBP mutations (penicillin-binding protein); Amg-resistant; Fq, glycopeptide, oxazolidinone, fosfomycin, fusidic acid, rifampicin, SXT, tetracycline- wild;	2 (66.66%)
		MRSA: PBP mutations (penicillin-binding protein); Amg-resistant; Fq -partial resistant/ wild; SXT-resistant; MLSB, glycopeptide, oxazolidinone, fosfomycin, fusidic acid, SXT, rifampicin, tetracycline-wild;	1 (33.33%)
Staphylococcus hominis	3 (13.04%)	**MRSCN:** PBP mutations (penicillin-binding protein); Amg-resistant; Fq-resistant /partial resistant ; Fosfomycin, SXT, tetracycline-resistant; MLSB – constitutive; Glycopeptide, fusidic acid, oxazolidinone, rifampicin-wild;	1 (33.33%)
		MRSCN: PBP mutations (penicillin-binding protein); Amg-heterogenous; Fq-partial resistant; Tetracycline- altered targed /partial resistant; Teicoplanin, fusidic acid, rifampicin-resistant; SXT - resistant/wild; Fosfomycin, oxazolidinone-wild;	1 (33.33%)
		MRSCN: PBP mutations; Amg- resistant; Fq- partial resistant; Tetracycline - altered targed/ partial resistant; Rifampicin, SXT-resistant; Fusidic acid, glycopeptide, oxazolidinone, fosfomycin-wild	1 (33.33%)
Staphylococcus haemolyticus	2 (8.69%)	**MRSCN:** PBP mutations (penicillin-binding protein) ; Amg-heterogenous; Fq resistant/partial resistant; MLSB-inductible/resistant; Tetracycline - altered targed/partial resistant; Fosfomicyn, fusidic acid, SXT -resistant; glycopeptide, oxazolidinone, rifampicin-wild;	1 (50%)
		MRSCN: PBP mutations (penicillin-binding protein) ; Amg-heterogenous; Fq resistant/partial resistant; MLSB-inductible/resistant; Tetracycline - altered targed /partial resistant; Teicoplanin, fosfomicyn, SXT- resistant; Oxazolidinone, fusidic acid, rifampicin-wild;	1 (50%)

Note: MRSA- Methicillin-Resistant Staphylococcus aureus; MRSCN- Methicillin-Resistant Coagulase-Negative Staphylococcus; MLS- Macrolide, Lincosamine, Streptomycine; Amg-Aminoglycosides; Fq-Fluoroquinolones; SXT-Trimethoprim/Sulfamethoxazole

Further, it is necessary to know the mechanisms involve in the emergence and spread of MDR strains for a better understanding of resistance phenotypes encountered in our hospital

S. aureus is a Gram-positive bacteria that colonizes the skin of about 30% of healthy humans. Although mainly a harmless colonizer, it can cause severe infection, due in part to its ability to acquire and express an extensive array of virulence factors and antimicrobial resistance determinants. Mobile genetic elements are involved in the dissemination of virulence and resistance genes in S. aureus and include plasmids, bacteriophages, pathogenicity islands, transposons and chromosomal cassettes [12,13]. Its oxacillin resistant form (MRSA) is one of the most important causes of antibiotic resistant worldwide. Moreover, infections with MRSA may result in prolonged hospital stay and higher mortality[14]. According to the European Antimicrobial Surveillance System[15], MRSA proportions varied from less than 1% in the north to over 50% in southern European countries. Romania showed a significant decrease in MRSA proportions in the last four years with an identified proportion of 33%. Although Coagulase-negative Staphylococci (CNS) are commensally bacteria of human skin and nasal mucosa, in the advent of increased invasive interventions and treatments, they have been frequently detected as a cause of opportunistic infections. Predominant CNS species associated with clinically relevant infections are Staphylococcus epidermidis and Staphylococcus haemolyticus. They are difficult to eradicate, as they possess the capacity to form biofilms on indwelling devices. Worldwide surveys revealed that 60 to 85% of clinical strains are resistant to Methicillin [16, 17]. Although there are three known mechanisms for which S. aureus and CNS becomes resistant to Methicillin- hyperproduction of β-lactamases[18], the presence of an acquired penicillin-binding protein and PBP2a[19], and modification of normal penicillin-binding proteins (PBPs)[20] - the last one was responsible for the emergence of resistant strains isolated in our study. The numbers of MRCNS isolates found were higher than MRSA, which was in agreement with other previous works[21]. All MRSA strains were also aminoglycoside-resistant Staphylococci contained at least one aminoglycoside modifying enzyme gene. Other antibiotic resistance phenotypes associated to MRSA and MRSCN are presented in the table 3. Fortunately, no Vancomycin Resistant Staphylococcus was encountered.

Table 4 The Gram negative MDR bacteria phenotypes identified.

Species	Gram-negative MDR bacteria		
	No. %	Identified phenotypes	No.%
E. coli	4 (17.39%)	**ESBL (acquired penicillinase + cephalosporinase);** Amg -heterogenousous; Fq-resistent-1/wild; SXT, Polypeptide- wild;	1 (25%)
		ESBL (acquired penicillinase + cephalosporinase); Amg-heterogenousous; Fq, SXT- resistant; Polypeptide- wild; *	1 (25%)
		ESBL (CTX-M); Amg, Fq, Tetracycline, SXT-resistant; Polypeptide-wild;	1 (25%)
		ESBL; Amg-heterogenous; Fq-resistant-1/wild; Tetracycline, Furan, SXT-resistant;	1 (25%)
Klebsiella pneumoniae	5 (21.64%)	**Carbapenems-Resistant** *(*KPC or metallo-β-lactamases); Amg-heterogenous; Fq, SXT-resistant; Polypeptide-wild; *	1 (25%)
		ESBL+ Cephamycine impermeability / ESBL; Amg-heterogenousous; Fq-wild/resistant-1; SXT-resistant; Polypeptide -wild;	1 (25%)
		ESBL; Amg-heterogenous /wild; Fq-resistant; Furan, Tetracycline-wild/resistant; SXT-wild;	1 (25%)
		ESBL; Amg-heterogenous/resistant; Fq, Tetracycline-resistant; Polypeptide -wild;*	1 (25%)
		ESBL; Amg-heterogenous; Fq-wild/resistant-1; Furan-wild/resistant; Tetracycline-resistant; SXT-wild;	1 (4.35%)
Acinetobacter baumannii	1 (4.35%)	**Carbapenems-Resistant *(*Carbapenemases)**; Fq, Amg, SXT-resistant; Polypeptide-wild;*	1 (100%)
Pseudomonas aeruginosa	5 (21.74%)	**Highly resistant to carbapenems;** Amg, Fq-resistant; SXT-Polypeptide-wild; *	4 (80%)
		Highly resistant to carbapenems/ESBL; Amg, Fq, Polypeptide- resistant; SXT-wild;	1 (20%)

Note: ESBL- extended-spectrum beta-lactamases; Amg-Aminoglycosides; Fq-Fluoroquinolones; SXT-Trimethoprim/Sulfamethoxazole;
*Strains considered as being XDR (N=8)

Nowadays MDR Gram-negative bacilli have become the most important cause of severe hospital and community acquired infections, as well as the consequences with respect to mortality, hospital length of stay and increased hospital costs[22].

ESBL strains have been increasingly reported in Europe since their first description in 1983. These strains confer bacterial resistance to all β-lactams except carbapenems and cephamycins, which are inhibited by other β-lactamase inhibitors such as clavulanic acid. A shift in the distribution of different ESBLs has recently occurred in Europe, with a dramatic increase of CTX-M enzymes over the classical TEM and SHV variants. Although ESBLs still constitute the first cause of resistance to β-lactams among Enterobacteriaceae, other "new beta-lactamases" conferring resistance to carbapenems, such as metallo- β -lactamases and KPC carbapenemases or to cephamycins, such as CMY enzymes[23].

Among the MDR Enterobacteriaceae isolated, 77.77% of isolated strains were ESBL strains. As we can observe in table 4, some strains possess also a penicillinase phenotype after they had acquired a plasmid-mediated penicillinase. Therefore, they are resistant to penicillins and perhaps to Cephalothin. If the strain acquires a plasmid-mediated AmpC β -lactamase from an organism such as Enterobacter spp. or Citrobacter freundii, the strain will have a cephalosporinase phenotype and will display resistance to virtually every β–lactam drug except the carbapenems. Resistance to fluoroquinolones, Tetracycline and Trimethoprim/Sulfamethoxazole were found among our isolates. Thus, the presence of an ESBL is a good marker of the MDR phenotype[24].

Reports of carbapenemases have been increasing over the last few years. This phenotypic grouping of enzymes is heterogeneous mixtures of β-lactamases belonging to molecular Ambler class A (penicillinases), class B (metalloenzymes) and class D (oxacillinases). These enzymes have the common property of hydrolyzing, at least partially, carbapenems together with other penicillin or cephalosporin antibiotics. Out of these, IMP and VIM series in Pseudomonas aeruginosa and Enterobacteriaceae and of the oxacillinase type in Acinetobacter baumannii are clinically worrying [25].

More than half of phenotypes of Gram-negative bacilli tested using Vitek® 2 Compact 30 were resistant to the antipseudomonal cephalosporins, antipseudomonal carbapenems, β-lactam/ β-lactamase inhibitor combinations, fluoroquinolones and aminoglycosides. According to

Falagas[3,4] these phenotypes are characteristic to XDR bacteria. These strains were isolated from children diagnosed with ventilator-associated pneumonia (VAP). Prior antibiotic exposure (3rd generation Cephalosporins), excess antibiotic use and durations of antibiotic administration beyond 7 or 8 days in mechanically ventilated children have been linked with severe infections caused by MDR bacteria[26]. Medical studies recommended the use of Colistin and Tigecycline as the optimal antibiotics in the treatment of XDR infections[27,28]. Tigecycline, the first representative of the glycylcycline class, was approved its use for complicated intraabdominal and skin infections. Regarding its mechanism of action, this antibiotic enters bacterial cells through energy dependent pathways or with passive diffusion[29], but unfortunately, it is not recommended for children use[30] . Colistin was used for about two decades after its discovery in 1950, but the reported nephrotoxicity and neurotoxicity led to gradual decrease of its use. However, this antibiotic recently regained some popularity in several countries as a salvage antimicrobial agent against MDR bacteria. Clinical studies showed the efficiently of inhaled Colistin in treating VAP caused by MDR bacteria[31,32], but unfortunately, a relationship between the increasing clinical use of Colistin and resistance in Gram negative bacilli has been reported. Colistin-resistant Pseudomonas aeruginosa, Acinetobacter baumannii have been described [33, 34, 35]. Hence, this antibiotic should be spread for serious cases in order to avoid the emergence of MDR or even PDR bacteria.

Conclusions

The purpose of this article was to present new information concerning the MDR bacteria and to underline the importance of knowing the resistance phenotype in a hospital. The resistance phenotype helps in choosing the best antibiotic treatment in order to cure the infection and to prevent the emergence and spread of new MDR strains. Although old pathogens continue to be a threat around, new and more powerful, MDR bacteria emerge under the selective antibiotics pressure.

The incidence of MDR isolates encountered in our hospital was not so important (2.82%). While approaching the "end of antibiotics era" new strategy need imposed. It is easy to prevent than to fight with MDR bacteria. Older preventive healthcare measures such as hand hygiene and vaccinations against the most common bacteria during childhood limit the spreading of MDR strains. Hand hygiene" is considered worldwide to be the cornerstone of MDR bacteria infection prevention. In addition, decrease antibiotic consumption is associated with decreased resistant rates of MDR bacteria. De-escalation of the administered antibiotics is required as soon as culture results are obtained.

At the beginning of the 21-century a new question appeared. Do antibiotics continue to be the "magic bullet" or become boomerangs?

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TOLERATED CONGENITAL MEGACOLON - CASE REPORT

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Abstract

In 1886, Harold Hirschsprung first described Hirschsprung disease as a cause of constipation in early infancy. Early recognition and surgical correction of Hirschsprung disease protects affected infants from enterocolitis and debilitating constipation[3]. Paper aim is to present the case of an eight months old baby, admitted in Clinic II Pediatrics for abdominal distention, vomiting and chronic constipation.

Key words: Hirschsprung disease, tolerated, delayed diagnose

Background

Congenital megacolon (Hirschsprung disease) results from the absence of enteric neurons within the myenteric (Auerbach) and submucosal (Meissner) plexus of the distal colon resulting in a functional obstruction. Enteric neurons are derived from the neural crest and migrate caudally with the vagal nerve fibers along the intestine. These ganglion cells arrive in the proximal colon by 8 weeks' gestation and in the rectum by 12 weeks' gestation. Multiple loci[8] appear to be involved, including chromosomes 13q22, 21q22, and 10q. Arrest in migration leads to an aganglionic segment. This results in clinical Hirschsprung disease. The exact worldwide frequency is unknown, although international studies have reported rates ranging from approximately 1 case per 1500 newborns to 1 case per 7000 newborns[1]; this disease occurs more often in males than in females, with a male-to-female ratio of approximately 4:1. Hirschsprung disease should be considered in any newborn who fails to pass meconium within 24-48 hours after birth[7]. Most cases are nowadays diagnosed in the newborn period.

Case presentation

A 8 months old baby boy was admitted in our clinic for : abdominal distention, vomiting, chronic constipation. The child was born at 39 weeks gestational age, 2750 g and 9 APGAR score. He received natural alimentation for 1 month,continued with NAN 1 till the admission. We don t have any specific data about the beginning of his symptoms. The mother was not informed about the passage of meconium. The child was sent home with severe abdominal distention and consulted by a paediatric surgeon at the age of 9 days being suspected of Hirschsprung disease. The diagnosis was not confirmed at that time.

Clinical examination revealed an infant with 7.6 kg weight, 70 cm, pale, marked abdominal distention with palpable dilated loops of colon, visible superficial vessels.

Rectal examination revealed an empty rectal vault.

Laboratory investigation revealed hypoproteinemia and mild anaemia.

Abdominal ultrasound showed a bowel filled up with gas and loops.

Sweat test for cystic fibrosis: negativ.

Surgical examination concluded significant suspicion of Hirschsprung disease.

The patient is transfered in the Paediatric Surgery Clinic, "Louis Turcanu " for further investigation.

Contrast enema demonstrates the transition zone in the rectosigmoid region from dilated, normally innervated bowel to normal caliber, noninnervated bowel (fig 1).

Pathology exam. There were harvested 2 biopsies at 3-5 cm from the dentate line. Hematoxilin-eosin stain reveals hypertrophied nerve trunks in the submucosal layer of the bowel (fig 2).

Imunochemistry (ENS, S-100, CD 117) improved the accuracy of the diagnosis (fig 3,4,5).

Based on these findings, the diagnosis of Hirschsprung disease could be sustained.

For differential diagnosis[4], many conditions were considered as follow:

1. Chronic constipation, clinically similar to Hirschsprung disease was excluded by rectal examination (rectal vault empty)
2. Abdominal tumors also manifested with abdominal distention, but abdominal ultrasound and exploratory laparatomy revealed no such findings.
3. Cystic fibrosis may associate distal obstruction syndrome. This condition is excluded by the negative sweat test and the absence of steatorrhea
4. Malformative pathology of the digestive tract (Anorectal malformations, Intestinal atresias or stenosis, Intestinal malrotation) excluded by rectal examination and contrast enema.
5. Intestinal motility disorders (Neuronal intestinal dysplasia, Chronic Intestinal Pseudo-obstruction) clinically and radiological similar to Hirschsprung disease. Exclusion: Positivity for ENS and S-100 .

6. Cow milk allergy. Recurrent constipation may occur at 6% of the children with cow milk allergy. Exclusion: Absence of clinical findings such as weight loss, rash, diarrhea. Rectal biopsy shows no specific alterration (eosinophilic infiltration) in the mucosal layer.

Surgical intervention[5]: median laparotomy, rectal amputation, rectosigmoidian resection, left diverting colostomy. After 6 months of favorable outcome, the descendent bowel segment is pulled trouh (Duhamel technique)[5].

Particularity of the case is the discrepancy between the pathology aspects and tolerated form of the disease for a relatively long time (8 months).

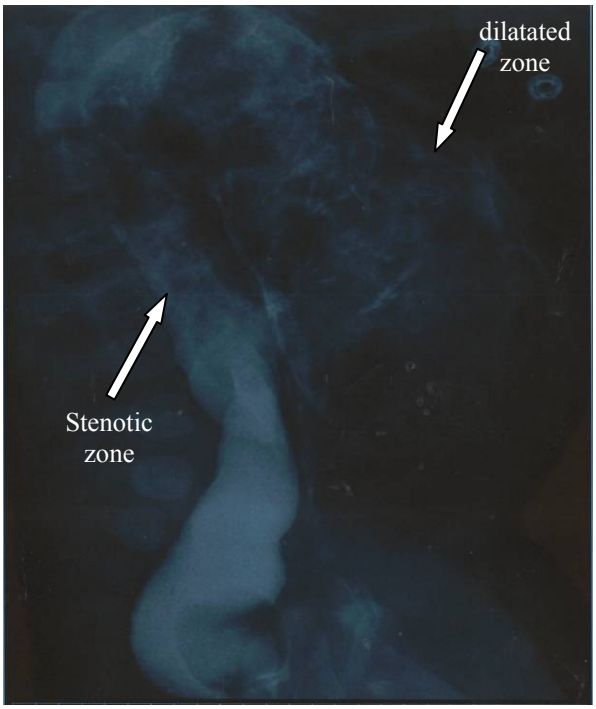

Fig.1 Contrast enema.

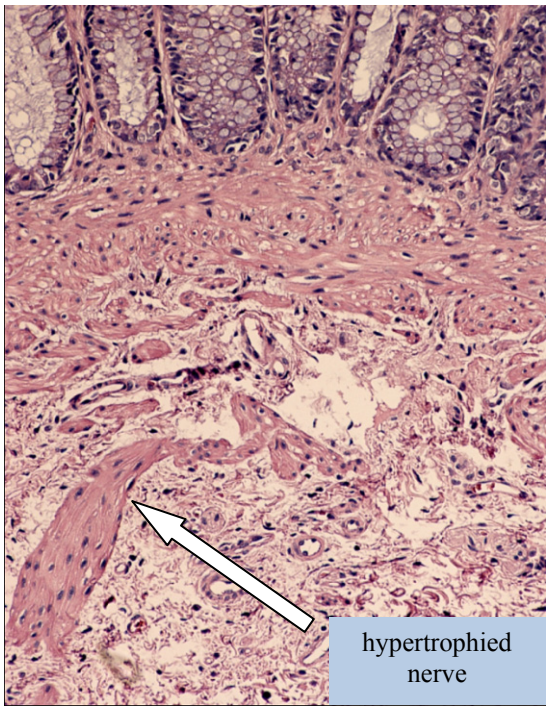

Fig.2. Bowel biopsy HE stain.

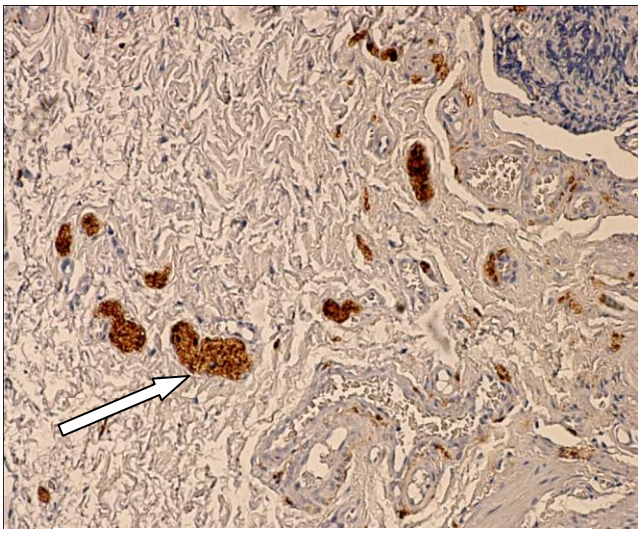

Fig.3 Imunochemistry ENS
(reveal hypertrophied nerve trunks).

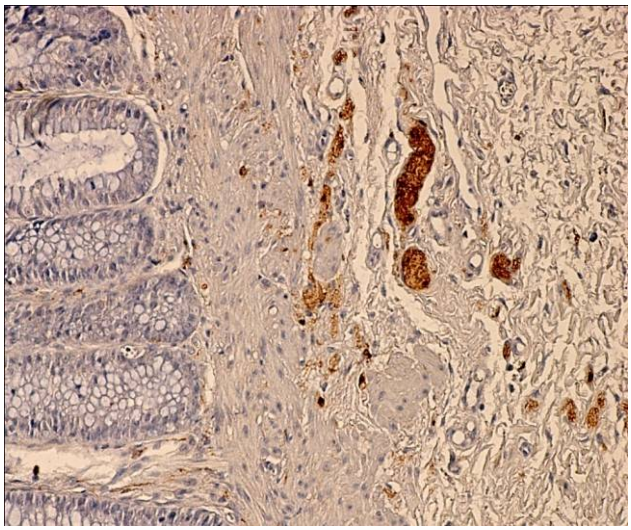

Fig.4. Fig.4 Imunochemistry for S-100
accentuates the absence of ganglionar cells

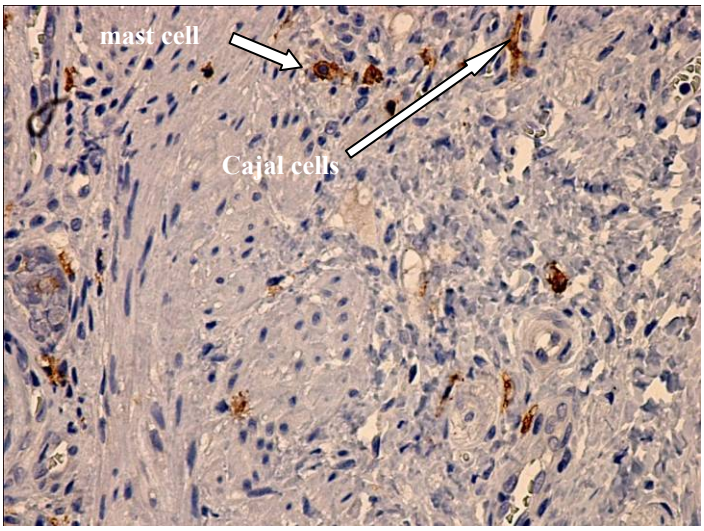

Fig.5 Imunochemitry for CD 117
(rare Cajal cells, frequent mast cells).

Conclusions

The diagnosis of this disease recquires multiple investigations. Early diagnosis is important to prevent complications (enterocolitis, colonic rupture)[6]. A rectal suction biopsy can detect hypertrophic nerve trunks and the absence of ganglion cells[5] in the colonic submucos, confirming the diagnosis.

Up to one third of patients develop Hirschsprung's-associated enterocolitis, a significant cause of mortality. Patients should be monitored closely for enterocolitis for years after surgical treatment[7] . With proper treatment, most patients will not have long-term adverse effects and can live normally.

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THE INFLUENCE OF THE TREATMENT WITH VALPROIC ACID IN THE THYROID FUNCTION IN CHILDREN AND ADOLESCENTS DIANGNOSTICATED WITH EPILEPSY

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Abstract

Some of the children who have been diagnosed with epilepsy and treated with valproic acid presented an alteration of the thyroid function (subclinical hypothyroidism).

Key words: epilepsy, valproic acid, thyroid function

Introduction

The hypothyroidism is the most frequent anomaly of the thyroid function in children, and in the majority of the times it is caused by the chronic autoimmune thyroiditis (1). Besides primary and central, the hypothyroidism can be subclinical (levels raised blood of thyrotropin [TSH] and normal levels of thyroxin [T4]) or clinical (TSH's high concentration in whey and fall of T4).

The thyroid function is regulated as much for retroaction negative (feedback) as for self regulation, being related intimately to the quantity of iodine of the organism. The biological action is not realized by the hormones tied to the proteins but only the free fraction.

The subclinical hypothyroidism can lead to an evident hypothyroidism. This disease cannot be identified on the basis of symptoms or specific signs and for this only it is possible to diagnose using the laboratory tests. Whatever the reason being, the hypothyroidism in children can have harmful effects on the growth, school yield and the pubertal development.

Clinically, it appears with decrease of the speed of the growth with a low resultant stature, alteration of the school yield, weakness and lethargy, intolerance to the cold, constipation, skin dries, fragile hair, facial inflammation and muscles pain, delay in the pubertal development. The secretion of hormone of the growth can be normal or diminished and the production of the factor of growth type insulin 1 is in general diminished (1).

The diagnosis puts in relation to the blood levels. The first one generally confirms the presence of hypothyroidism, whereas the second help to distinguishing between primary, secondary or tertiary disease. In case of hypothyroidism the treatment of election is the substitution for T4.

The valproate (VPA), sodium salt of the valproic acid or the dipropilacétic acid, is, together with the phenytoin, the phenobarbital and the carbamecepine, one of the 4 of anti-epileptic drugs called "classics" or "majors". It is a question of an anti-epileptic of very wide spectrum, assets opposite to practically all kinds of crisis, of remarkable efficiency and of excellent tolerance the majority of the times. The affectation on the cognitive functions has been demonstrated minim or practically void, which has been a point to favor for the utilization in children and teenagers. Unlike the medicaments mentioned above it behaves as an enzymatic inhibitor.

A more detailed description of its properties, indications and adverse effects they are available in the prospectus and in the technical sheet (2, 3).

There is not known with accuracy the mechanism of action of the valproic acid, but part of VPA effect is related to a direct or secondary increase of the concentrations of the inhibiting neurotransmitter GABA (gammaaminobutíric acid), caused possibly by a decrease of the metabolism or by a decrease in his recaptation.

The results of several works seem to suggest that the treatment with VPA can have an effect in the thyroid function fundamentally appearing like subclinical hypothyroidism. This effect seems to be related according to some works with the time of administration, according to others with the thyroid previous function of the patient. Other works think that this effect does not seem to be attributable directly to the VPA therapy, but this one would promote the effect of other medicaments on the thyroid function on having administered them in polytherapy. In any case, the majority of authors find reasonably to recommend the accomplishment of controls of thyroid function before and during the treatment at least in patients of risk. Nevertheless, the population of risk is far from being well definite.

Objectives

Today it is not yet known exactly with what frequency there happens the alteration of the thyroid function in patient children and epileptic teenagers in treatment with VPA, and what consequences this aspect could have. Of equal way, the magnitude of the problem is known but it can be important because the enormous prevalence of the epilepsy to this age and so frequent use of the VPA in this population (1).

Knowing this information is fundamental to know what type of controls could be indicated, in what population and in what moment. At present there are not existing clear recommendations. In the habitual practice the majority of neuropediatrics realizes an analytical blood exam before initiating the treatment and another control sometime after beginning the treatment with valproic acid, with the object fundamentally to discard an effect on the hepatic function. In view of the current condition of knowledge it brings over of the possible effect on the thyroid, we could question these recommendations.

The present work has as aim to analyze the influence of the treatment with VPA on the thyroid function in children and teenagers with epilepsy, describe which is the effect that takes place (is produced), with what frequency it happens and on what variables seems to depend, in order to be able to establish if it is possible a series of recommendations or indications of screening and of treatment.

Material and methods

The present work is an observational, retrospectively and descriptively study of a series of cases of children and teenagers with epilepsy who receive treatment with VPA and to which they have been done a determination of thyroid hormones.

The criteria of selection have been therefore a population with age included between 0 and 18 years, in anticonvulsive treatment with VPA during the previous year, to which there has been realized a determination of thyroid hormones. There have not been included in the study patient that were presenting before alterations of the thyroid function.

The source of information was the clinical histories gathered from the service of Pediatrics of the Clinical Hospital San Carlos of Madrid, concretely in Neuropediatrics consultation. The thyroid function is valued initially across the blood levels of the thyroid hormones (T3, T4, TSH), previous informed consent signed by the parents.

Some patients are included thanks to the serum levels of valproic acid registered in the computer system of clinical analyses of the Clinical Hospital San Carlos from January 1, 2006 until December 31, 2007, being established the contact with them after identification.

There have been gathered demographic information, indication of the anticonvulsive treatment, age at the beginning of the disease, age in the moment of the withdrawal of the information, the base disease, the dose of VPA (usually 15-45mg/kg/dia in two or three captures) and the blood levels of the medicine, the duration of the treatment, analytical information and concomitant diseases of the patient as well as the capture of other anticonvulsive drugs.

The analytical information that has been considered available has been the last found in the clinical history of the patients. The serum levels of valproic acid have been considered between 20 and 40 mg/kgc/day and in case of the TSH, according to the laboratory of clinical analyses of the Clinical Hospital San Carlos, between 0.34 and 5.6 mU/l.

In case of be confirming the presence of a biochemical hypothyroidism, they have been sent to the consultation of endocrinology to extend study. The clinical and analytical information suggesting of thyroid dysfunction was considered to be a complication of the treatment.

As for the statistical analysis, the qualitative variables appear with his distribution of frequencies. The quantitative variables are summarized with his average and standard diversion. The association between qualitative variables was evaluated with the test of *Chi – square Table or Fisher' test*, in case more than 25 % of the awaited ones were minor of 5. For all the tests there was accepted a value of significance of 5 %. The processing and analysis of the information was realized by means of the statistical package SPPS 12.0.

Results

The number of the patients included in the study was of 23 patients. The middle ages of the studied group are of 9.00 years, with a maximum of 18 and one minimum of 1 (standard deviation 5.931). They are women 52.2 % and men 47.8 %.

The majority of patients followed in the consultation were recounting history of some type of convulsions. The final indication of treatment with VPA has been epilepsy (without specifying type) in 21 patients (91.30 %) and neonatal convulsions in 2 (7.70 %).

The doses of VPA are comprehended between 17.2 and 35.7 mg/Kg/day (average 26.45 mg/kg/day) in 2 ó 3 doses oral way.

The valproic acid, according to the blood levels recounted above like therapeutic for this indication, is inside the therapeutic range in 20 of the patients (92 %) and is in subtherapeutic range in 3 (8.00 %). None of the patients was presenting overdose of dose of valproic acid.

It has been found an increase of the serum levels of TSH in 7 of 23 patients (30.43 %), between 5.85 and 9.24 mUI/L (1 appears). This relation seems to be present as much in the cases that receive polytherapy (figure 1) as in that they receive monotherapy with valproic acid (figure 3).

It has not been found statistically significant differences between the age and the sex regarding to the existence of TSH's level increase.

The children with hormonal alterations have been sent to endocrinology section for study. Actually it is depending on results.

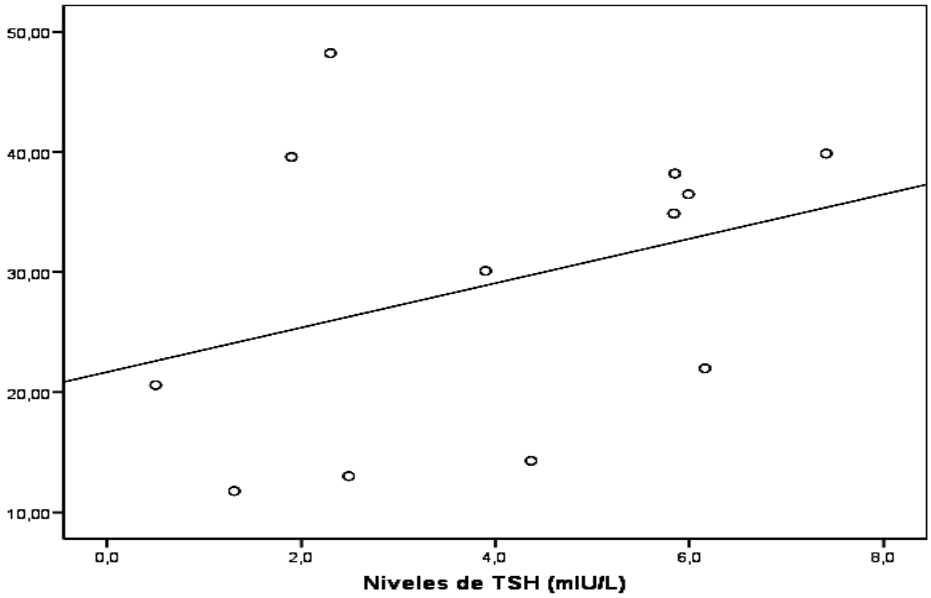

Fig 1. TSH levels in the cases that receive polytherapy.

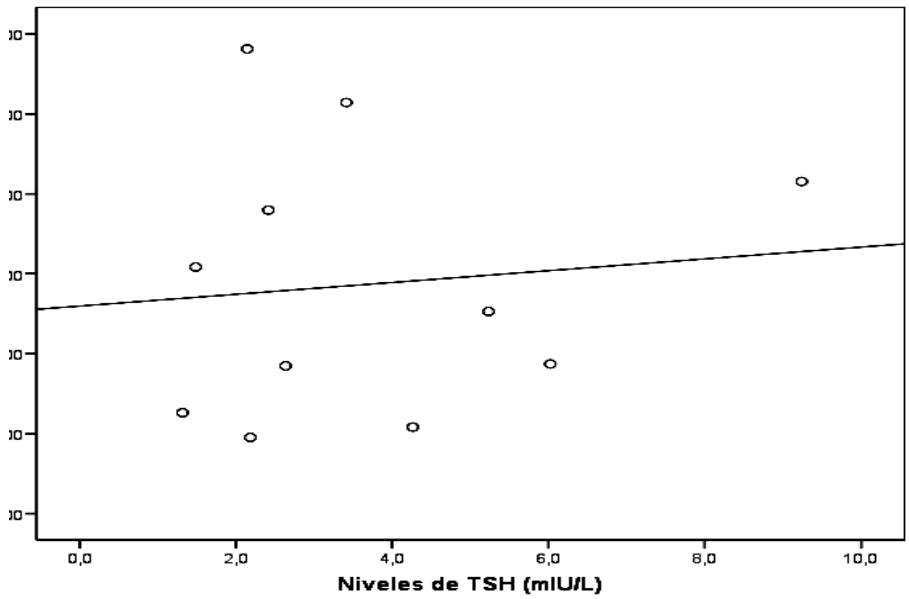

Fig 2. TSH levels in the cases that receive monotherapy with valproic acid.

Discussions

The use of the oral therapy (principally valproic acid) has improved the forecast of the patients with epileptic disease, besides offering a comfort in the daily life of these. A correct anti-epileptic therapy prepares the neurological deterioration, and this is furthermore importantly in the age of development.

The valproic acid is at present the anticonvulsivant more frequently used in children and teenagers in developed countries. To have it, there was contributing, as we already we´ve been commented, a lot of factors, as the efficiency, his wide spectrum, his availability in different forms and pharmaceutical presentations, his excellent tolerance, with practically absence of sedative action or effects on the cognition, and his safety.

As regards the safety and the appearance of adverse effects, such and so it comes recounted in the technical sheet and the prospectus of the medicament, classically it has given attention to the effects of the valproic acid on the hepatic function, especially in those patients of minor age. Having this intention, and in spite of the absence of clear recommendations, the neuropediatrics use to realize an analytical blood exam, the first before and another a little time after initiating the treatment, controlling also the platelets, the times of coagulation, the amylase and, in occasions, the amonio. Nevertheless, it is not habitual any type of control of the thyroid function in absence of symptoms.

According to the information of the present study, an intrinsic relation exists between the appearance of the hypothyroidism and the treatment with valproic, both in monotherapy and in polytherapy (valproic acid more than others antiepileptic drugs). This information rests those already aimed on other works.

It is not known any information about the magnitude of the possible problem, though having in our mind the distribution bimodal of the incidence/frequency of the epilepsy, with a peak in pediatric age, and the preferential indication of the valproic acid, as it has been explained, to these ages, is of supposing that it can be important.

Other authors have proposed that would be reasonable to realize controls of thyroid function before and during the treatment with VPA. Nevertheless, there is no information on in what patients' subgroups, in what moments and for what period of time would be necessary to realize the above mentioned controls.

In order to give response to all these questions, and in view of the results of this work and of others of the literature that show a relation between the treatment with valproic acid and the appearance of subclinical hypothyroidism in children and teenagers with epilepsy, it is necessary to realize prospective controlled studies that should allow to clarify, first, the presence of a causal relation and, secondly, to sit the bases to establish a few recommendations to detect and to treat precocious and adequately this condition in the clinical practice.

Conclusions

- There is observed a relation between the treatment with VPA in children and teenagers with epilepsy and the appearance of alterations of the thyroid function in the shape of subclinical hypothyroidism.
- The occurrence of these alterations is observed in this academic work in children and teenagers with epilepsy in treatment with valproic acid both in monotherapy and in polytherapy, independently of the age and of the sex.
- The frequency of these alterations, the variables on which depends as well as the causality of these observations show that in the next future should be necessary the accomplishment of other prospective controlled studies.
- At the moment there is no sufficient information to give us the ability to make some recommendations concerning the indication of a control of the hormonal function in children and teenagers with epilepsy in treatment with VPA neither what moment, in case it should be considered to be indicated, could be more ideal this accomplishment.

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SEPTIC SHOCK CAUSED BY KLEBSIELLA - CASE PRESENTATION

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Abstract

Septic shock is sepsis-induced hypotension despite adequate fluid resuscitation. Sepsis is characterized by the Systemic Inflammatory Response Syndrome (SIRS) induced by infection.

The authors present a case of a male newborn, S.A., 2 weeks old, term born and of normal weight, admitted in January 2009 in the 1st Paediatric Clinic of the Emergency Clinical Hospital of Craiova, due to fever, coughing and vomiting. At admission the child presented pale teguments, with petechial elements on the face, thorax and hands, marked cyanosis around the mouth and nose and cyanosis of the nails, cold and mottled extremities, with capillary refill more than 4 sec, signs of serious dehydration with persistent skin fold and depressed prior fontanelle, ringed face, tachypnea, crepitations at thorax auscultation, HR 160-180 b/min, systolic BP 56 mmHg, delayed reactivity at painful stimulus. The laboratory findings indicated anaemia, hyperleucocytosis and positive culture for Klebsiella from the tracheo-bronchial fluids; the chest x-ray showed broncho-pneumonia. Because the respiratory distress syndrome was severe, the new-born was intubated with assisted breathing for 5 days. He needed parenteral nutrition for 5 days and then he was nourished with breast milk through nose-gastric tubule. The treatment has been performed with isotonic sodium chloride solution intravenously, broad spectrum antimicrobial agents, corticotherapy, with favourable evolution. The whole period of hospitalization lasted for 20 days, the patient being released healed.

Key words: shock, sepsis, newborn

Introduction

The shock is a syndrome of important acute circulatory deficiency, which leads to a poor tissue perfusion inadequate for cellular needs, with disruption of homeostasis mechanisms. Septic shock is a pathogenic form having in substrate intricate mechanisms (vasogenic, hypovolemical, cardiogenical) (3,8).

Septic shock is also defined as a severe sepsis with persistent hypotension, despite sufficient intake of intravenous fluids (12).

Case presentation

The authors present the case of patient S.A., male newborn two weeks age, admitted during January-February 2009 in the 1st Paediatric Clinic of the Emergency Clinical Hospital Craiova (F.O. 2684).

The patient is the second child of healthy, young parents, from a physiological pregnancy, being born at 38 weeks with weight born (WB) = 3300 g, Apgar score = 9, birth naturally, in the cranial presentation. He had physiological jaundice 3 days, good adjustment period, with discharge at the age of 4 days of maternity.

At the age of 10 days has begun to produce fever, cough, 1-2 times daily vomiting. No treatment was given. In 4th day from the beginning the overall condition was rapidly altered, has repeated bilious vomiting, hypotonia with hypo reactivity, cyanosis initially around mouth and nose, and then of the extremities, sucking refusal, symptoms which lead to the emergency internment.

On objective examination at admission has been observed: newborn with weight 3000 g, with fever 38°C, the overall condition very influenced, pale ringed face, with around mouth, nose and periorbital cyanosis, lips and nails cyanosis, pale-grained teguments, with rash on face, neck, thorax above, hands and upper abdomen, abdominal skin fold persistent, depressed prior fontanelle, tachypnea, respiratory rate (RR) = 70 breathing/min, depression of the intercostals spaces, lung stetacustic auscultation: pulmonary garrulity decreased and crepitations, heart rate (HR) = 169-196 b/min, prolonged of capillary refill over 3 sec, systolic blood pressure (BP) = 56 mmHg, belly scoop, charged tongue, food refusal, without signs of meningeal irritation (Fig. 1).

Laboratory investigations

First day of admission : core venous pressure (CVP) = 0/min, Pulse = 30 b/min; heart rate (HR) = 168 b/min; Sat O_2 = 79%, after one hour 83%; pH = 7,2 (N = 7,35 – 7,45); pCO_2 = 63,7 mmHg (N = 35 – 45); pO_2 = 38,3 mmHg (N = 75 – 100); EB = 0,9 mmol/l; standard HCO_3 = 25 mmol/l; Hb = 12,5 g/dl (hemoconcentration). The decompensated respiratory acidosis had maintained itself until the fourth day. Na = 141,4 mmol/l; K^+ = 4,16 mmol/l; Ca^{++} = 1,01 mmol/l (N = 1,13 – 1,32); Cl = 99 mmol/l (N = 98 – 106).

In the second day after admission after the intake of isotonic sodium chloride solution intravenously and glucose solution 10%, with electrolytes, hypovolemy has been corrected. Complete blood count: Hb = 9,2 g%, Ht = 27%, L = 3400/mm^3, neutrophils (PMN) = 59%, LF = 30%, M = 11%, TQ = 70%, TH = 105 sec; blood sugar = 59% as the ENP with glucose.

On the third day of admission persists the decompensated respiratory acidosis: pH = 7,2, pCO_2 = 79 mmHg, pO_2 = 32,5 mmHg; standard HCO_3 = 27 mmol/l, BE = 3,6 mmol/l. The respiratory acidosis persisted until the 5th day after admission despite mechanical ventilation.

Electrolytes were in normal limits during the entire critical period, except of a mild hypocalcaemia (decreased ionized calcium). Complete blood count on 5th day of admission: Hb = 9 g%, platelets = 186000/mm^3, leucocytes = 22000/mm^3, PMNns = 8%, PMNs = 43%, lymphocytes = 40%, monocytes = 5%, Eo = 4%; blood smear: anisocitosis +, hypochromia +++; erytrocyte sedimentation rate (ESR) = 70/97 mm.

Through the tracheal probe adherent mucous-purulent secretions have been aspirated. Collected culture from tracheo-bronchial secretion in second day of admission, revealed Klebsiella - sensitive to Imipenem; resistant against Negram, Cefoperozone, Ampicillin.

Chest X-ray performed in 2nd day of admission showed "interstitial peribronchovascular opacities perihilar and infrahilar", and in 5th day "opacification at the left perihilar region level, caudal clearly delimited, having alveolar focus character with underlying hypertransparency".

The patient has been intubed and mechanically ventilated until the 5th day of hospitalization, and the intravenously infusion has been maintained 7 days, in the last 3 days being fed in the same time with breast milk through nose-gastric tubule.

Treatment was performed with Meronem - 10 days, Zyvoxid 7 days, then Cefuroxime; gastric protection, corticosteroid administration. Evolution was slowly favourable: he presented a second degree coma during the first 4 days of hospitalization, hypotension (under 60/40 mmHg), HR ranged between 160-190 b/min dissociated from pulse - imperceptible at admission, then low perceptible 4 days. He was febrile for 2 days, then his temperature varied between 37°-38°C the next 5 days. From the 5th day of internment he began to react at external stimulus crying, then he began to breathe spontaneously. Tachypnea (60-70 breaths/min) has maintained until the 15th day of hospitalization. After 3 weeks he was discharged clinically healed, with normal investigations.

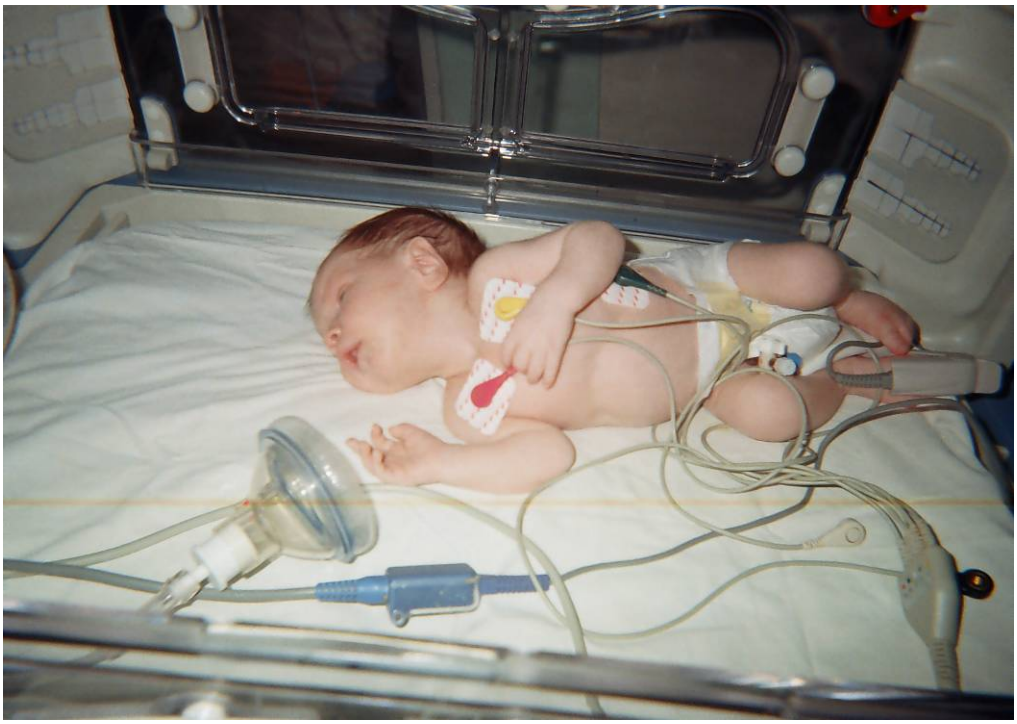

Figure 1 – Clinical aspect.

Discussion

Klebsiella is a Gram-negative bacillus, aerobic, Enterobacteriaceae group. It is an opportunistic microorganism in the digestive tract, behaving like a saprophyte germ or a conditionated pathogenic germ. It triggers pneumonia, often septic shock in newborns and infants, premature or with biological deficiencies (6).

In medical literature it is classified after streptococcus group B and Escherichia Colli, in neonatal sepsis etiology, but in a study performed by C. Popescu (2007) it is indicated on the 2nd place after E. Colli (11).

Infecting in newborn can occur both by airway, from the upper respiratory tract, and hemathogen (only in newborn), with the possibility of contamination by intubation.

The diagnosis of pneumonia caused by Klebsiella is established by: clinical examination (the presence of signs of bronchopneumonia), by lung x-ray (usually with trend to

fluid collection, then the appearance of a aeric or hydroaerical cavity) and by positive culture (6). In presented case, because the original image was interstitially pneumonia and only in the 5th day was revealed the aspect of localized bacterial pneumonia, we can presume that the lungs were infected by blood. The origin of infection was digestive (newborn initially presented vomiting). Infection was initially manifested as septic shock, then it had appearance of Klebsiella pneumonia, located in the left perihilar region as a alveolar focus radiologically visible.

Septic shock can result in any bacterial infection in newborn (and especially in infections with gram-negatives and with staphylococcus). The body reacts to infection by SIRS (systemic inflammatory response syndrome) that includes fever, leucocitosis (or leucopenia - in newborn and imunodepressed), tachypneea, tachycardia (13). Bacteria are destroyed by the fagocitar system, but also by the administration of a bactericide antimicrobial therapy and are released endotoxins (in gram-negative infections, like Klebsiella sepsis). Endotoxins produce activation of proinflammatory cytokins (especially TNFα, IL-1, IL-6), which discharged in bloodstream, producing vasodilators and damaging to the capillary endothelial cells (2).

Vasodilators lead to hypotension and hypoperfusion of abdominal viscera. At the same time, the capillaries can be obstructed by proliferation of leucocytes that have invaded the area to attack bacteria and will cause further cell damages, creating area of generalized tissue ischemia, with insufficient infusion of tissue that characterizes septic shock. It is also released from damaged vascular endothelial nitric oxide (NO) which was shown to reach high levels in sepsis, interposing the cardiovascular effects of septic shock, thus explaining generalized cyanosis in infected child. NO produces effect of vascular relaxation, resulting in so-called vasoplegia in septic shock (3).

In the analysed case, transient hypoglycaemia was present and a shift from leucopenia to leucocitosis was often recorded in neonatal sepsis. Initial hyperdynamic phase of septic shock took place at home. The patient was brought to hospital in hypodynamic stage.

Hypodynamic phase is the stage which generally characterizes shock, evidenced by hypotension, cold extremities, absent or low pulse and may occur at onset, when septic shock is accompanied by a marked decrease in effective circulating volume. It is the case of presented newborn, which issued bilious vomiting and was inapetent a few hours before admission.

Conclusions

Young age (newborn) with deficiency of humoral immunity (possessing only IgG and IgA transmitted from mother) is associated with poor response to infectious aggression, resulting high frequency of systemic infection and septic shock in this age.

Fortunately, described newborn presented favourable evolution and weight deficit recovered after healing.

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ANTIBIOTIC RESISTANCE IN URINARY TRACT INFECTIONS IN CHILDREN

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Abstract

Introduction: These days, urinary tract infections (UTIs) represent the third cause of infection in children. Their treatment can be a problem in near future due to increasing antibiotic resistance.

Objectives: The aim of our study was to determine the prevalence of antibiotic resistance amongst pathogens causing UTIs in children admitted in the 1st Pediatric Clinic, Children Emergency Hospital, "Louis Ţurcanu," Timişoara, between January-June 2008.

Materials and methods: Inclusion criteria were clinical symptoms and significant bacteriuria (at least 100,000 colony-forming units/ml urine). The antibiograms were made from the first morning urine sample, based on the principle of dilution in agar, using MicroScan® WalkAway-96 system.

Results: The majority isolates were Escherichia coli (58%), followed by Klebsiella pneumoniae (21%) and Proteus mirabilis (9%). Female: male ratio was 2.45: 1. Pseudomonas aeruginosa and Klebsiella pneumoniae were prevalent in infants, while E. coli was found more often in puberty age girls. The results of the antibiograms showed a high percent of resistance to Ampicillin (86%), Sulfamethoxazole/Trimethoprim (74%) and to Cephalosporins (42-72%). The lowest resistance was identified to Imipenem, Fluoroquinolones and to beta-lactam/beta-lactamase inhibitor combinations. We identified that 25% of strains were beta-lactamases producers (65% Escherichia coli strains and 35% Klebsiella pneumoniae strains), from which 80% were ESBL-producing organisms.

Conclusions: Ampicillin and Sulfamethoxazole/Trimethoprim should be avoided for the use as the empiric treatment of UTIs. The high percent of multidrug resistant bacteria is increasing, so a complex observation program of antibiotics resistance should be imposed.

Key words: children, urinary tract infection, resistance, ESBL-producing strains

Introduction

The urinary tract infections (UTIs) are the most frequent bacterial infections found in children and an important cause of morbidity. Community acquired UTIs cause significant illness in the first 2 years of life. This are considered as common health problem in school and pre-school aged children[1]. In adults, persisting UTIs can lead to arterial hypertension and renal failure. Etiologic agents of UTIs are variable and usually depend on time, geographical location and age of patients. Although UTIs can be caused by any pathogenic organism from the urinary tract, the most frequent are from the Enterobacteriaceae family (Gram-negative bacilli, facultative anaerobic germs)[1].

Antibiotics used in the treatment of UTIs play an important role. Choosing an antibiotic depends on various factors such as the patient past medical records, past hospital reports of other illnesses, their spontaneous cure rates and their antibiotic-resistance charts, the frequently identified etiological agent, its antimicrobial sensitivity testing, its pharmacokinetics and its toxicity, the patients' age etc.

Antibiotic resistance is highly increasing these days. The epidemiology and the resistant patterns show a regional variability and prove to have a continuous change of frequency, due to excessive use of antibiotics. Studies show that the risk factors play an important role, for the emergence of the antibiotics resistance. Some of them are due to the mal-administration of the antibiotics in the past history, renal malformations associated and the frequent use of antibiotics for the prophylaxis of recurrent infections. However, many reports have indicated the presence of multidrug resistance in organisms causing UTIs[1,2]. The Gram-negative bacteria have a plasmid or chromosome resistance mechanism such as the presence of beta lactamses or enzymes that change of antibiotic structure, impermeability of outer membrane, efflux pumps, altered tagged molecules. Extended spectrum beta-lactamases (ESBL) are responsible for the secretion of new enzymes (cephalosporinases), which are capable of hydrolyzing all beta lactams, especially the last generation cephalosporins and Aztreonam. Amp C beta-lactamases are of two types plasmid-mediated and chromosomal or inducible. Chromosomal Amp C enzymes are typically inducible by beta lactam antibiotics such as Cefoxitin and Imipenem, but poorly induced by the 3rd or 4th generation Cephalosporins. The transposition of Amp C gene (responsible for producing novel plasmid-mediated beta lactamas enzymes) in Escherichia coli and Klebsiella pneumoniae strains determine the emergences of antibiotic resistance[1,2,3,4].

Objectives

The objectives of this retrospective study were to determine the prevalence of antimicrobial resistance against urinary tract pathogens and to identify the patterns of resistance in children admitted in 1st Pediatric Clinic, "Louis Turcanu" Children Emergency Hospital, Timişoara, during

January-June 2008. Hence, the result of this study can help direct empirical therapy in UTIs for future.

Materials and methods

The study lot comprised of 356 urocultures from children less than 18 years old admitted in 1st Pediatric Clinic during January-July 2008. The identification of fermentative and non-fermentative Gram-negative bacteria was made from the first morning urine sample, after sowing on agar plate, based on conventional biochemistry and cromogenic tests.

Antibiograms were performed using the MicroScan® WalkAway-96 Dade Behring (Sacramento, California), computerized system that allows automatic determination of minimum inhibitory concentration (MIC) or qualitative susceptibility for the test organism (sensitive S, resistant R or intermediate I). This technique was based on the principle of agar dilution. MicroScan® Dried Gram Negative Panels containing antibiotics in increasing concentrations were used. Some well-isolated colonies from 18-24 hour non-inhibitory agar plate were emulsified with Inoculum water, so the final turbidity should be equivalent to that of a 0.5 McFarland Barium Sulfate turbidity standard. The suspension was subsequently transferred to Mueller Hinton broth enriched with calcium and magnesium. After incubation at 35°C for 16-18 hours in a CO_2 environment, the MIC is determined, by observing the lowest antimicrobial concentration showing inhibition of growth. For quality control, strains of Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853 and Klebsiella pneumonia ATCC 700603 were used. Reading and interpreting the results were made by the current NCCLS standards.

The antibiotics tested were Ampicillin, Cephalothin Cefuroxime, Ceftazidime, Cefepime, Ceftriaxone, Cefazolin, Gentamicin, Amikacin, Tobramycin, Trimethoprim/Sulfamethoxazole, Ampicillin/Sulbactam, Amoxicillin/ Clavulanate, Ticarcillin/Clavulanate, Piperacillin/Tazobactam, Imipenem, Ciprofloxacin, Levofloxacin.

The MIC of Ceftazidime, Cefotaxime, Ceftriaxone, Cefpodoxime and Aztreonam were used to identify beta lactams strains (ESBL and AmpC type) after comparison with the recommended NCCLS standards (Table 1). Cephamycin differentiates between ESBLs and AmpC beta lactams: it's an ESBL strain, if it is sensible to Cephamycin; and if the germ was resistant, it was an Amp C type.

Table 1 NCCLS standard for identification of ESBL and Amp C betalactamses[1]

Beta lactams	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefotaxime	Cefotetan	Cefoxitin
ESBL	≥2µl/ml	≥4 µl/ml	≥4 µl/ml	≥4 µl/ml	≤16 µl/ml	≤16 µl/ml
Amp C	≥2µl/m	≥4 µl/ml	≥4 µl/ml	≥4 µl/ml	>32 µl/ml	>32 µl/ml

Results

From the 356 urocultures made in the hospital laboratory in the first half of 2008, 55 children were diagnosed with urinary tract infections, verified both by the clinical symptoms (fever, dysuria, pain in the abdomen and pelvic area) and the laboratory data (leukocytosis, leukocyturia, significant bacteuria with growth of at least 100.000 colony-forming units/ml of urine).

The most identified germs were Escherichia coli (58%), followed by Klebsiella pneumoniae (21%), Proteus mirabilis (9%) and Pseudomonas aeruginosa (5%). Other rare bacteria found were Kluyvera ascorbata, Enterobacter aerogenes, Enterococcus faecium, Raoultella ornithinolytica**.** UTIs dominated in female children than males (70.90% versus 29.09%). There were 17 infants (30.90%), 13 (23.63%) children with age between 1-10 years and 25 (45.45%) teenagers. Pseudomonas and Klebsiella were seen in 71.42% of infants, while E. coli was found in 77.14% of puberty age girls.

The highest rate of resistance was seen to Ampicillin (86%), Trimethoprim/Sulfamethoxazole (74%), Cephalothin (72%) and Ampicillin/Sulbactam (70%). (Figure 1).

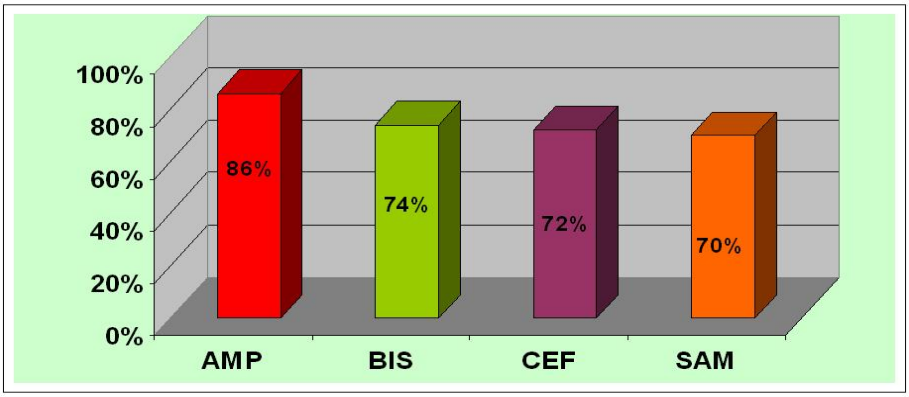

Figure 1 High rates of antibiotics resistance found in our study (AMP- Ampicillin, BIS- Trimethoprim/Sulfamethoxazole, CEF-Cephalothin, SAM-Ampicillin/Sulbactam).

From the Cephalosporins, the 1st generation was found to have more resistance (Cephalothin 72%, Cefazolin 58%). In addition, we observed that there were not significant differences between the Cephalosporins generations concerning resistance, the percentages being between 42-47%. The lowest resistance was identified to Imipenem 5%, followed by Fluoroquinolones (Ciprofloxacin and Levofloxacin) 14%, beta-lactam/beta-lactamase inhibitor combinations (Amoxicillin/Clavulanate, Ticarcillin/Clavulanate and Piperacillin/Tazobactam) 16% and Aminoglycoside (Amikacin) 24% (Figure 2).

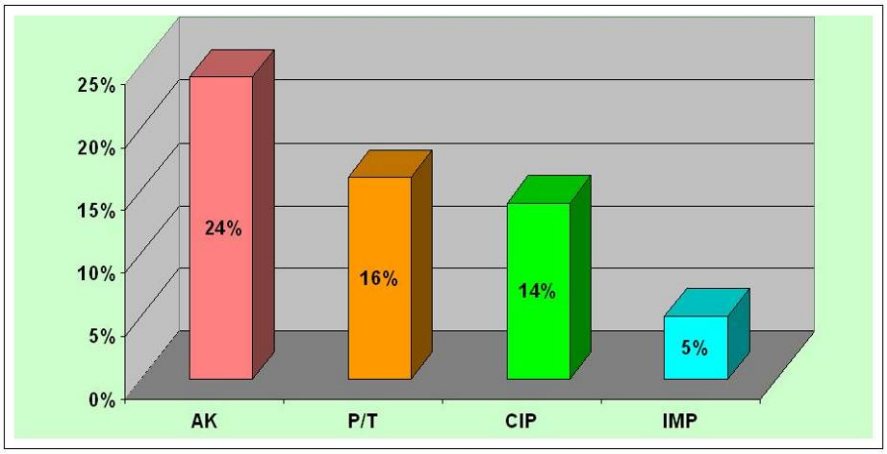

Figure 2 Low rates of antibiotics resistance encountered in our study.
(AK-Amikacin, P/T-Piperacillin/Tazobactam,
CIP- Ciprofloxacin, IMP- Imipenem).

We compared the most frequently used antibiotics in UTIs with the identified bacteria from our study. Klebsiella pneumoniae showed 100% resistance to Ampicillin. In this case, it is a well-known resistance. We did not find any strain of Klebsiella resistant to Ciprofloxacin. E. coli had the lowest resistance to Trimethoprim/Sulfamethoxazole (61%), fact that permits us, for its use in prophylactic treatment of recurrent urinary tract infections. The first line antibiotic therapy for E. coli infections should be a beta-lactam/beta-lactamase inhibitor combinations (Piperacillin/Tazobactam) with a resistance rate of 3%. Proteus was sensitive to Ciprofloxacin and Piperacillin/Tazobactam (81%, 100%, respectively). (Figure 3).

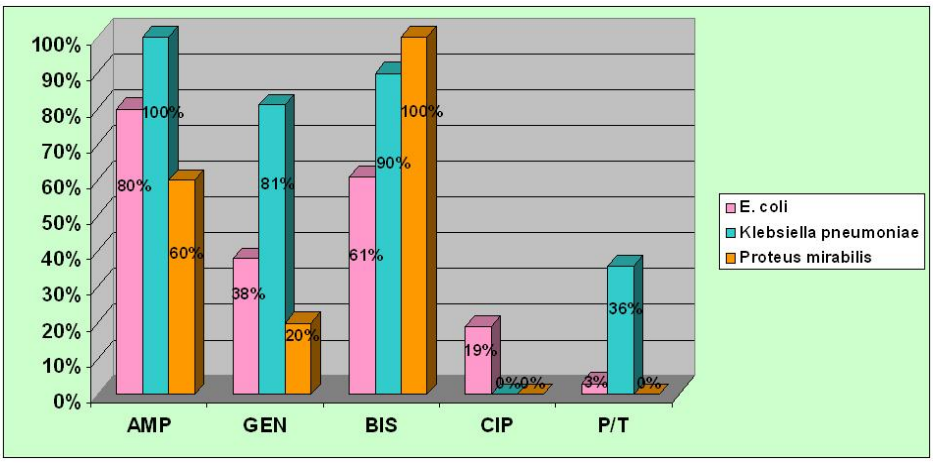

Figure 3 Distribution of antibiotics resistance between Gram-negative bacteria.
(AMP- Ampicillin, GEN-Gentamicin, BIS- Trimethoprim/Sulfamethoxazole,
CIP-Ciprofloxacin, P/T-Piperacillin/Tazobactam)

According to NCCLS standards for identification of beta lactamases (Table 1), 14 strains were identified. 9 strains were E. coli and the rest were Klebsiella pneumoniae. The MIC<16 µl/ml of Cefotetan and Cefoxitin permitted the identification of 11 strains with extended beta-lactamases spectrum (ESBL), from which 7 were E. coli types and the rest were Klebsiella pneumoniae producing high level of SHV-1 beta lactamases[1]. Hence Amp C

producing strains are revealed by CMI>32µl/ml of Cefoxitin and Cefotetan, 3 strains were discovered (two E. coli strains and one Klebsiella pneumoniae). Resistance phenotypes to Tetracycline and Trimethoprim/Sulfamethoxazole were also encountered.

Discussions

Management of children with UTIs implies a proper documentation of diagnosis, identification of the associated anatomical abnormalities, a correct antibiotic therapy according to antibiograms and a follow-up of children with renal malformations.

Enterobacteriaceae strains were the dominant bacterial species isolated from urine cultures that was in agreement with previous works[1,2]. Gram-positive cocci had a comparatively low contribution in causing UTIs. Studies reported that 90% of all acquired community UTIs and more than 30% of nosocomiale acquired UTIs are caused by E. coli. According to the demographic data, females are affected more often than males due to anatomical differences[1]. We found similar results in our study.

Trimethoprim/Sulfamethoxazole, frequently used in the prophylaxis treatment of recurrent UTIs in children for its tolerability, availability, pharmacokinetics and urinary pathogens spectrum, presented a high percentage of resistance (74%). Medical studies made in 3 different hospitals[1] showed an increasing rate of resistance to Ampicillin, Trimethoprim/Sulfamethoxazole and 1st generation Cephalosporins, similar to that documented in our study. Compared to other studies made in Europe, the resistance found to these antibiotics was higher that found in our study (Ampicillin 62%, Trimethoprim/Sulfamethoxazole 46%)[9,1].

Comparing our results with the literature data[1,2] we observed a higher resistance to Cephalosporins, which indicates an excessive use of this class of antibiotic in our hospital. The resistance to Cephalosporins is explained through the enzymatic mechanisms and efflux pumps[5,8]. The resistance rate to Aminoglycoside (Amikacin 24%, Gentamicin 47%) in our study was low, which was similar to some cohort studies made on urine samples of children with UTIs[1].

According to our study, the first line antibiotics to be used for the treatment of UTIs when the causative pathogen is unknown should be beta-lactam/beta-lactamase inhibitor combinations (Ticarcillin/Clavulanate or Piperacillin/Tazobactam). Although they presented a low rate of resistance 13% and 14%, Fluoroquinolones are used, only in some selected cases, in order to prevent the negative effects on growth cartilage. This was proved by experiments made on young animals, which showed it to have adverse effects on bone cartilage and had tendon lesion after using these antibiotics[1]. Imipenem is a broad-spectrum beta lactamase antibiotic, active against all kinds of bacteria (Gram-positive and Gram-negative bacteria, aerobic and anaerobic germs). It is the main anti-pseudomonas antibiotic, reason for which it is used in special cases, which appear to be more severe in order to avoid the emergence of resistance to Carbapenems.

Pediatric urinary tract colonizing bacteria are becoming increasingly resistant to commonly used antibiotics. In our clinic, resistance to 3rd generation Cephalosporins through the acquisition and expression of ESBL among Enterobacteriaceae was frequently seen. ESBL phenotypes have become more complex due to the production of multiple enzymes including inhibitor-resistant TEM enzymes, AmpC, enzyme hyperproduction and porin loss[1,2,3]. The high resistance levels found could be explained though the high frequency of Cephalosporins used for both prophylactic and therapeutic treatment of hospitalized children. This practice may have exerted selective pressures leading to the emergence of multidrug resistant strains, which in turn may have stimulated the acquisition of genes encoding resistance mechanisms via horizontal transfer mechanisms between bacterial strains within the hospital environment[1]. Genotypic methods based on enzyme assays, PCR and others are not suitable for routine clinical testing. The clinical manifestations of ESBLs are extremely serious hence sensitive diagnostic methods are urgently required to guide therapy, then to monitor resistance development and to implement intervention strategies are a must.

The results of this study showed that the rate of resistance to widely used antibiotics was high for Gram-negative bacteria. The most effective antibiotics against Gram-negative bacteria were Carbapenems, Fluoroquinolones and beta-lactam/beta-lactamase inhibitor combinations. Cefuroxime, Trimethoprim/Sulfamethoxazole, Ampicillin/Sulbactam, Gentamicin which is most frequently used for the treatment of community acquiring UTIs was found to be the least sensitive antibiotics for the Gram-negative microorganisms. The most important reason for resistance to antibiotics is the widespread use of antibiotics in hospitals. In order to prevent or decrease resistance to antibiotics, the use of antibiotics should be kept under supervision and always thought thoroughly before initiating, further on if found necessary it should be given in appropriate doses for an appropriate period of time and control programmes for hospital infections should be carried out periodically. A multidisciplinary approach should be used to achieve the above-mentioned goals.

Conclusions

The UTIs represent the third major cause of infections in children (after the respiratory and digestive tract infections), which when treated incorrectly can lead to some irreversible serious complications. The treatment of UTIs must be initiated with a broad-spectrum antibiotic and after obtaining the antibiotic susceptibility test results, treatment should be changed accordingly. Ampicillin and Trimethoprim/Sulfamethoxazole were frequently used for UTIs in the past but are no longer used as the first line antibiotics because of their high rate of resistance. The results of this study leads to the conclusion that empirical therapy in UTIs should consist in beta-lactam/beta-lactamase inhibitor combinations. Imipenem and Fluoroquinolones should be used only in particular cases in order not to loose its sensitivity. The high rate of multidrug

resistant bacteria seen in our study, points out the fact, that frequent and excessive use of antibiotics should be avoided in day-to-day practice, to provide a better healthy future to children of all ages.

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THE VALUE OF TOTAL AND DIFFERENT LEUCOCYTES COUNT IN THE DIAGNOSIS OF APPENDICITIS

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Abstract

Appendicitis is the most common cause of the acute surgical abdomen in the children. Sometimes the diagnosis is not very easy, especially in small children. Beside clinical examination, laboratory tests were made in every patient hospitalized with acute appendicitis. We made a retrospective study comprising consecutive patients who were hospitalized in Pediatric Surgery Unit of County Hospital of Emergencies, Târgu-Mures, from the 1-st of January to 31-th December 2009, and had the diagnosis of acute appendicitis. There were 193 patients with acute appendicitis, 119 males and 76 females. We grouped them in three categories: small children (0- 5 years), mid age children (6- 11 years) and puberty children (12- 17 years). We recorded the number of total leucocytes, neutrophiles, lymphocytes and neutrophil: lymphocyte ratio. The aim of the study was to find out if these laboratory tests were helpful for the diagnosis of appendicitis. In only 58.08% of cases we had raised leucocytes count, in 59.6% raised neutrophiles count (but with percent of 70% in small children and 66% in mid age children). In 77.27% of cases we had low values of lymphocytes (but with percent of 82, 83% in small and mid age children). The neutrophil: lymphocyte ratio was up to 3.5: 1 in 55.05% of cases (in small children the percent was 77% and in mid age children, 70%). The decreased percent of lymphocytes and a neutrophil: lymphocyte ratio up to 3.5: 1 can be important for the diagnosis of appendicitis in small and mid age children. Instead these results the diagnosis of appendicitis remains mainly clinical. Normal values of laboratory tests can not delay an appendectomy decided on clinical examination.

Key words: appendicitis, laboratory, children

Introduction

Appendicitis is the most common cause of the acute surgical abdomen in children. This illness is reported mostly in older children. The diagnosis is made, especially recording the history and by the physical examination. Abdominal pain, defense, tenderness on percussion, nausea, vomiting are the signs and symptoms of appendicitis.

Beside these, we use to make in every case some laboratory test: hemoleukograme and urine summary. Laboratory studies are not very sensitive and not very specific for appendicitis. The number of white blood cells is usually elevated [1], also the number of neutrophiles [2] or even the eosinophiles [3]. The number of lymphocytes is decreased [4]. In the same studies, the neutrophil: lymphocyte ratio upper than 3.5: 1 [5] may be an appendicitis indicator.

The aim of this study is to find out if the laboratory tests mentioned before are helped us in the diagnosis of acute appendicitis.

Material and Methods

We made a retrospective study comprising consecutive patients who were hospitalized in Pediatric Surgery Unit of County Hospital of Emergencies, Târgu-Mures, from the 1-st of January to 31-th December 2009, and had the diagnosis of acute appendicitis. There were 193 patients with acute appendicitis. We recorded age, sex, clinical symptoms and signs. We also grouped the children in three categories: small children (0- 5 years), mid age children (6- 11 years) and puberty children (12- 17 years).

Laboratory investigations were carried out also in all patients. Total leukocytes were counted, also some different white cells: neutrophiles, lymphocytes, eosinophiles. The neutrophil: lymphocyte ratio was performed. The biological reference interval for our laboratory is 4- 12 white blood cell/$10^3\mu L$. The percent are 25-40 for neutrophiles and 50-70 for lymphocytes. All patients underwent appendectomy. The histological examination was obtained in all appendix.

Results

The age of these 193 patients ranged between 1 and 17 years. The average age was 10. In categories of age, there were 31 small children, 103 mid age children and 59 puberty children. The white cell count ranged between 4 and 31/ $10^3\mu L$.

After the histological examination, we grouped all the appendicitis in cataral, phlegmonous and perforated. There were 58 cataral appendix (29.79%), 91 phlegmonous appendix (46.46%) and 46 perforated appendix (23.73%). In small children (31 patients), we had 10 cataral appendix (32.25%), 6 phlegmonous appendix (19.35%) and 15 perforated appendix (48.40%). In mid age children (103 patients), we had 30 cataral appendix (29.13%), 51 phlegmonous appendix (49.51%) and 22 perforated appendix (21.36%). In puberty children (59 patients), we had 17 cataral appendix (28.21%), 33 phlegmonous appendix (55.93%) and 9 perforated appendix (15.26%). The percents of normal and uppers values of leucocytes in different types of appendicitis are presented in table 1, the percents of normal and uppers values of neutrophiles in table 2, the normal and low values of lymphocytes in table 3

and the neutrophiles: lymphocytes ratio in appendicitis is presented in table 4.
There were 119 males (60%): 21 small boys, 57 mid age boys and 40 puberty boys. Also, there were 76 females (40%): 10 small girls, 46 mid age girls and 19 puberty girls. The male: female ratio was 1.5: 1.

Table 1: Percents of uppers values of leucocytes in different types of appendicitis.

	appendicitis	biological reference interval	upper values
all children	total appendicitis	79 (41.91%)	116 (58.08%)
all children	cataral	36 (64.4%)	22(35.6%)
all children	phlegmonous	28 (31.5%)	63 (68.5%)
all children	perforated	15 (34%)	31(66%)
small children	total appendicitis	13 (41.94%)	18 (58.06%)
small children	cataral	7 (70%)	3 (30%)
small children	phlegmonous	1 (16.7%)	5 (83.3%)
small children	perforated	5 (33.3%)	10 (66.7%)
mid age children	total appendicitis	37 (35.92%)	66 (64.08%)
mid age children	cataral	17 (56.67%)	13 (43.33%)
mid age children	phlegmonous	14 (27.45%)	37 (72.55%)
mid age children	perforated	6 (27.27%)	16 (72.73%)
puberty children	total appendicitis	27 (40.68%)	32 (59.32%)
puberty children	cataral	10 (58.83%)	7 (41.17%)
puberty children	phlegmonous	13 (39.39%)	20 (60.61%)
puberty children	perforated	4 (44.44%)	5 (55.56%)

Table 2: Percents of uppers values of neutrophiles in different types of appendicitis.

	appendicitis	biological reference interval	Upper values
all children	total appendicitis	78 (40.4%(	117 (59.6%)
all children	cataral	27 (47.45%)	31 (52.55%)
all children	phlegmonous	37 (41.3%)	54 (58.7%)
all children	perforated	14 (29.78%)	32 (70.22%)
small children	total appendicitis	9 (29.03%)	22 (70.97%)
small children	cataral	3 (30%)	7 (70%)
small children	phlegmonous	1 (16.67%)	5 (83.33%)
small children	perforated	5 (33.33%)	10 (66.67%)
mid age children	total appendicitis	35 (34%)	68 (66%)
mid age children	cataral	14 (46.67%)	16 (53.33%)
mid age children	phlegmonous	18 (35.3%)	33 (64.7%)
mid age children	perforated	3 (13.64%)	19 (86.36%)
puberty children	total appendicitis	31 (52.54%)	28 (47.46%)
puberty children	cataral	8 (47.05%)	9 (52.95%)
puberty children	phlegmonous	18 (54.54%)	15 (45.46%)
puberty children	perforated	5 (55.55%)	4 (44.45%)

Table 3: Percents of low values of lymphocytes in different types of appendicitis.

	appendicitis	biological reference interval	low values
all children	total appendicitis	44 (22.73%)	151 (77.27%)
all children	cataral	19 (32.1%)	39 (67.79%)
all children	phlegmonous	17 (19.57%)	74 (80.43%)
all children	perforated	8 (17.03%)	38 (82.97%)
small children	total appendicitis	5 (16.13%)	26 (83.87%)
small children	cataral	2 (20%)	8 (80%)
small children	phlegmonous	0	6 (100%)
small children	perforated	3 (20%)	12 (80%)
mid age children	total appendicitis	18 (17.47%)	85 (82.53%)
mid age children	cataral	9 (30%)	21 (70%)
mid age children	phlegmonous	8 (15.69%)	43 (84.31%)
mid age children	perforated	1 (4.54%)	21 (95.46%)
puberty children	total appendicitis	19 (32.2%)	40 (67.8%)
puberty children	cataral	7 (41.17%)	10 (58.83%)
puberty children	phlegmonous	8 (24.24%)	25 (75.76%)
puberty children	perforated	4 (44.44%)	5 (55.56%)

Table 4: Neutrophiles: lymphocytes ratio.

	appendicitis	≤ 3.5 : 1	≥ 3.5 :1
all children	total appendicitis	88 (44.95%)	107 (55.05%)
all children	cataral	31 (52.55%)	27 (47.45%)
all children	phlegmonous	41 (45.66%)	50 (54.34%)
all children	perforated	16 (34.05%)	30 (65.95%)
small children	total appendicitis	7 (22.58%)	24 (77.42%)
small children	cataral	2 (20%)	8 (80%)
small children	phlegmonous	1 (16.67%)	5 (83.33%)
small children	perforated	4 (26.67%)	11 (73.33%)
mid age children	total appendicitis	30 (29.12%)	73 (70.88%)
mid age children	cataral	14 (46.67%)	16 (53.33%)
mid age children	phlegmonous	13 (25.49%)	38 (74.51%)
mid age children	perforated	3 (13.64%)	19 (86.36%)
puberty children	total appendicitis	32 (54.23%)	27 (45.77%)
puberty children	cataral	8 (47.05%)	9 (52.95%)
puberty children	phlegmonous	19 (57.57%)	14 (42.43%)
puberty children	perforated	5 (55.56%)	4 (44.44%)

Discussion

The diagnosis of acute appendicitis, especially in small children remains a delicate problem for every pediatric surgeon. Clinical examination, imagistic invetigations and laboratory tests help us to take the right decision in an acute abdominal pain.

Total and differential white cells may be modified in many patients with acute appendicitis. Also, there is a wide variation in the range of white leucocytes in healty children and in children with acute appendicitis. In our serie, half of the patients were mid age children (6- 11 years). In small children, half of the appendicitis were perforated. In older children, the percent of perforated appendicitis decreases at 21%, in mid age children and 15% in puberty children. Half of the appendix in those ages were phlegmonous.

Some studies reported a raised white blood cell count in more than 90% of patients [6], other studies only in 38% [7] of patients. In our series, total leucocytes are raised in 58.08% of patients. Almost half percents had phlegmonous appendicitis and 23% had perforated appendicits. In cataral appendicitis, total leucocytes count is raised in 35% of cases but this percent is higher in flegmonous and perforated appendicitis (66- 68%). In every category of children the percents are similar. Some authors

sugested [8] that leucocyte response declines in 0- 5 years-old children with appendicitis.

The upper number of neutrophiles in total appendicitis is in 59% of cases. There are more percents of neutrophiles in small children (70%) but less percents in mid age and pubertal children (66% and 47%). The percent of neutrophiles is more representaive in small children. There are studies [2] who claim that total neutrophile count serve as a predictive parameter for appendicitis, specially in association with leucocytosis [9].

The low number of lymphocytes in total appendicitis is in 77% of cases. This percent is more representative in perforated appendicites (82%). We found low number of lymphocytes specially in small children and in mid age children (80- 90%). In children at puberty, this number of lymphocytes is not so raised (55- 75%).

The neutrophil: lymphocyte ratio in total appendicitis is more than 3.5:1 in 55% of cases. This percent is raised in small and mid age children (77% and 70%) and is decreased in puberty children (45%). The decline number of lymphocytes and a neutrophil: lymphocyte ratio more than 3.5:1 can be an important value for appendicitis [4].

There were 60% of males and 40% of females with acute appendicitis. A raised percent of male with appendicitis [10] and a decreased percent of female with appendicitis [11] was found also in literature.

We could see from these tables that the number of total white blood cell is not so representative. From all children operated with acute appendicitis only 58.08% had upper values of leucocytes and 41.91% had normal values. It is not an sensitive indicator for appendicitis. Tables 3 and 4 show us that a decreased percent of lymphocytes is more representative, especially in small and mid age children. Also, the neutrophyles: lymphocytes ratio can be important in small and mid age children.

The operative decision was taken in all these patients despite the normal values of total and differential white blood cell count. We consider these decisions were good, because we had no cases of operative or postoperative mortality.

Conclusion

The dignosis of acute appendicitis is mainly clinical. Labotratory tests and echography can increase the diagnostic accuracy. We have to cosider all the values of total and differential white blood cell. There are not important only for the diagnosis of appendicitis, but there are relevant even for the biological status of the child. However, normal values of white blood cell would not delay an appendectomy decided on clinical examination.

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SECONDARY EWING SARCOMA OF A PATIENT WITH FAVORABLE OUTCOME NEUROBLASTOMA

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Abstract

Cervical neuroblastoma is relatively uncommon. Primary neuroblastoma of the neck usually arises in the cervical sympathetic ganglia. This paper present the case of a three months old child, admitted in our clinic for cervical tumoral mass, miosis and ipsilateral upper eyelid ptosis.
Key words: neuroblastoma, intermediate risk, secondary cancer.

Background

Neuroblastoma is the most common extracranial solid tumor in infancy. It is an embryonic malignancy of the sympathetic nervous system arising from neuroblasts (pluripotent sympathetic cells). Age, stage, and biological features encountered in tumor cells are important prognostic factors and are used for risk stratification and treatment assignment. The most important of the biological markers is MYCN. There is a strong relationship between 1p loss and MYCN amplification. Deletion of the short arm of chromosome 1 is the most common chromosomal abnormality present in neuroblastoma and confers a poor prognosis. With current treatments, patients with low and intermediate risk disease have an excellent prognosis with cure rates above 90% for low risk and 70%-90% for intermediate risk. In contrast, therapy for high-risk neuroblastoma the past two decades resulted in cures only about 30% of the time. The majority of survivors have long-term effects from the treatment. Survivors of intermediate and high-risk treatment often experience hearing loss. Growth reduction, thyroid function disorders, learning difficulties, and greater risk of secondary cancers affect survivors of high-risk disease.

Case presentation

A 3 months old girl with relatively good general state was admitted in our clinic for right cervical mass, clinically similar to a cervical adenitis, miosis and ptosis of the right upper eyelid, signs that were indicated a damage of the sympathetic nervous system. Biopsy and pathology exam confirmed the suspicion and diagnosed the child with neuroblastoma.

Immunochemistry: positivity for ENS and protein associated NF improved the accuracy the diagnosis.

Other lab investigation revealed inflammatory syndrome, high level of feritine and lactat dehydrogenase.

Medulograma: Relatively normal, isolated atypical cells, possible metastasis of neuroblastoma.

CT (abdominal, pelvis, chest, skull): normal. CT (neck): tumoral mass, posterior to the carotid, with calcification and mildly shifting the trachea to the left (Fig. 1).

Cytogenetics**:** A number of 25 metaphases were analyzed and indicated no deletion of 1p 36, this finding is considered to be the most important prognostic factor (Fig. 2).

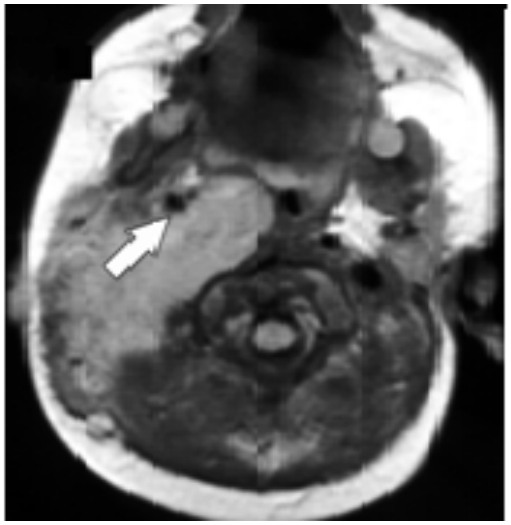

Fig.1. CT of the neck.

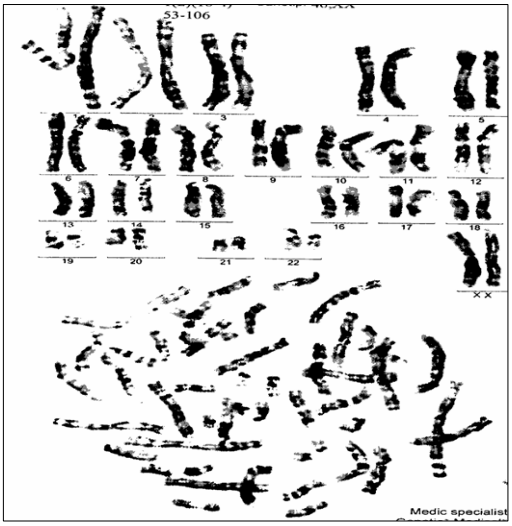

Fig. 2. Karyotype of the patient – normal.

Correlating the clinical, biological and imagistic data , the following diagnosis was established: Cervical neuroblastoma stage III – intermediate group risk.

The child received chemotherapy according NBL 94 protocol (Carboplatin + Etoposid – 3 courses Cyclophosphamide+ Adriamycin+ Vincristin – 3 courses) and had multiple admissions for cancer treatment and evaluation. Urinary tract infection,need for blood transfusion, sepsis, alopecia, toxic hepatitis, medullary aplasia have to be noted during the hospitalisation. After 19 months, the chemotherapy was stopped, the patient being declared healed.

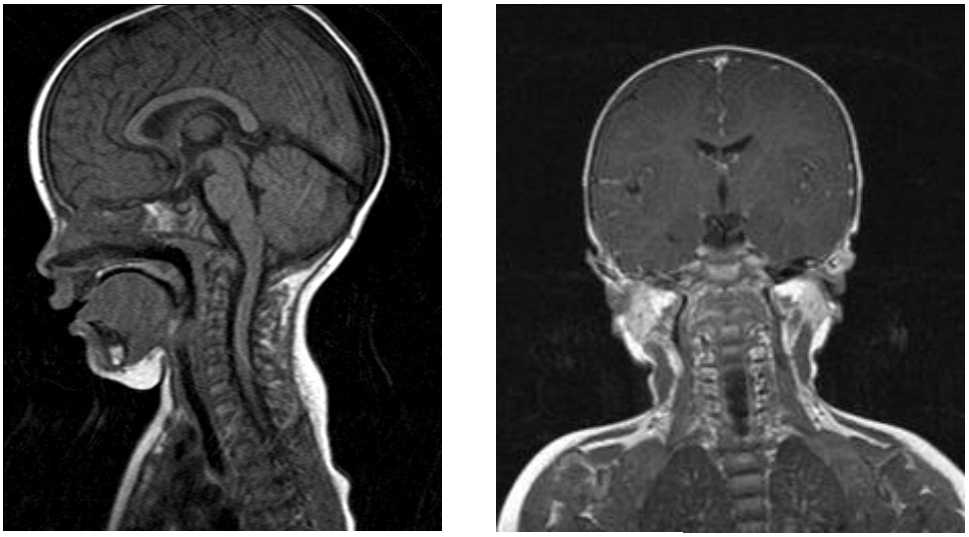

Fig. 3. Skull and neck MRI – normal.

Two years after, the patient present a tumoral mass of the left forearm. A biopsy was performed. Pathological exam revealed a PNET-stage IV, T2N1M0 (50% differentiated cells, MKI under 100, MR under 10 , stroma poor, metastasis located in the deep dermis).

Forearms X-ray: osteosclerosis alternating with osteolisis, metastasis of left radius (Fig. 4).

Forearm ultrasonography: tumoral mass of soft tissues with relatively homogeneus echo-structure, very well vascularised .

MRI result: Solid tumoral mass 9/3/3.5, deep localization, circumferential sorrounding the forearm bones, including the vascular-nervous package, the mass extends from the elbow to the radio-carpian joint, without invasion of joint space.; inflammatory diffuse changes of the radius structure (hyper-signal STIR, hiposignaling T1), osteosclerosis.

Scintigraphic bone investigation (TC 99m- MDP): slightly increased capture of left forearm, no other bones lesions (Fig. 5).

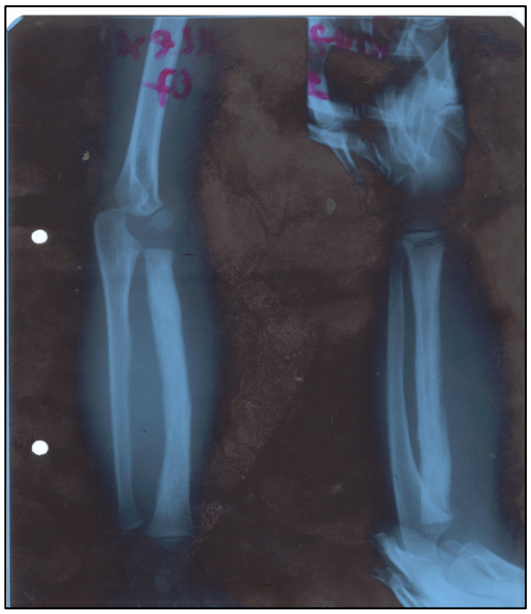

Fig. 4. Radiography reveals the bone metastasis.

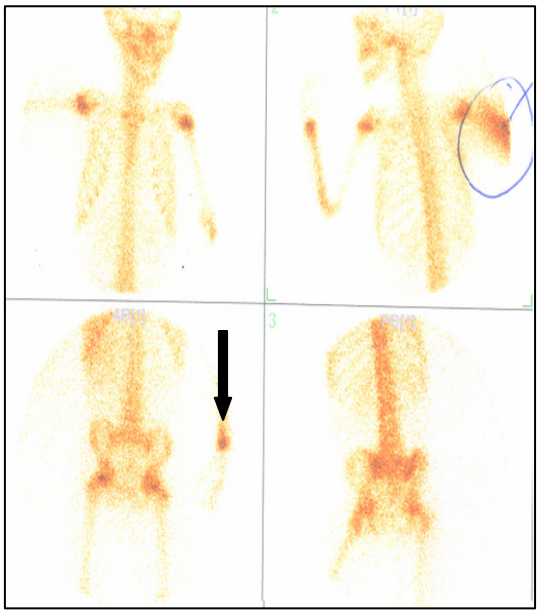

Fig. 5. Scintigraphy.

The child followed chemotherapy according to the CWS – 96 protocol. After two months, the patient was assessed by performing a MRI of the left forearm which reveals an increase of the tumor compared to the first MRI.

The interpretation of histopathology faced difficulties in differentiation of diagnosis; there was a high suspicion of second malignancy, probably soft tissue sarcoma. Therefore, a second opinion was asked from the University of Munchen who diagnosed a PNET/Ewing sarcoma (CD99, NSE, Vimentin positive; CD66, S100, CD 45 negative).

The medical staff decided for the surgical intervention of the tumor consisting in the amputation of the left forearm.

Discussion

The case is particular because primary cervical neuroblastomas are rare and account for less than 2.3% of all neuroblastomas. Considering the clinical history of this child, there is the possibility that the previous tumor also had been a Ewing sarcoma, because both types of tumor look very similar in routine staining without immunohistochemistry. Neuroblastoma continues to be one of the most frustrating childhood tumors to manage. Further consensus data are needed to provide more definitive information regarding risk stratification, treatment, and prognosis in patients with neuroblastoma.

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