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I. GENETICS

SYNDROME OF 9q LARGE DUPLICATION – CASE REPORT

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Abstract

Partial trisomy 9q represents a rare and heterogeneous group of chromosomal aberrations characterised by various clinical features. Associated clinical features include learning disability and pyloric stenosis.

In this paper we present a 5 months old female patient with different dysmorphic features due to excess of genetic material on the long arm of chromosome 9. This partial trisomy 9q has been analysed in detail to determine the size of the duplication and to characterise the chromosomal breakpoints.

Key words: parial trisomy 9q, cytogenetic analysis

Introduction

Partial trisomy 9q was first described by Turleau et al in 1975 in a 5-years old boy with multiple minor anomalies, short stature, mental retardation, cleft palate, ventricular septal defect and pyloric stenosis. It is a rare and heterogeneous group with respect to the chromosomal region involved in the aberration and the clinical phenotype.

Case report

The female patient was hypotrophic at birth (weight: 1825 g, length: 36 cm) and showed multiple craniofacial anomalies like dolichomicrocephaly (head circumference 30,5 cm, -4 SD below normal). She was born at term as the first child of a young couple, with no noticeable medical records. The parents were not related.

Physical examination at the age of 5 months revealed failure to thrive: weight – 3900 g, length – 55 cm, cranial circumference – 55 cm. The infant was hypotonic with caranio-facial dysmorphism consisting of: frontal between eyebrows haemangioma, small deep-set eyes, horizontal palpebral fissures, slight hypotelorism, prominent cheeks, hooked nose, protruding maxilla, small mouth, thin upper lip with a receding lower lip, mandibular hypoplasia, high-arched palate, retrognathia, low-set ears. She also

presented mild webbing of the neck and occipital haemangioma. Her nipples were wide-spaced, arms and legs long and slender. The child presented also hand anomalies (clinodactyly V, camptodactyly, overlapping fingers), long feet, long fingers and toes and abnormal fingerprints with simian crease (figure 3) and extra digital creases.

Growth retardation was apparent during postnatal development (-4 SD). Pictures of the patient at the age of 5 months are shown in figures 1 and 2. The cardiologic evaluation showed a murmur related to atrial septal defect, confirmed by ultrasonography.

The ophthalmologic assessment evidenced: nystagmus, convergent strabismus, bilateral haemangiomas of the palpebral fissures.

The computerized tomography scan of the head showed symmetrical cerebral atrophy, more severe in the frontal lobes and enlargement of the infratentorial cisterns.

Cytogenetics

Metaphase chromosomes from cultured cells and PHA stimulated peripheral blood lymphocytes of the patient were analysed by standard GTG banding. Chromosome analysis of peripheral blood showed the presence of additional chromosomal material on the terminal region of the long arm of one chromosome 9 in all metaphases analysed (20/20). The computer analyze of the metaphases was performed with the support of the cytogenetic laboratory staff at the Ulleval University Hospital in Oslo and the establishing of the exact chromosomal region involved in duplication required the acquisition of new metaphases. The karyotype of the patient was established to be 46,XX, dup(9)(q13→qter) (figures 4, 5 and 6).

In order to determine whether the chromosomal anomaly was inherited, cytogenetic analysis of the parents were performed, and the karyotypes were normal for both parents.



Fig. 1. Patient's facial dysmorphism – front.



Fig. 2. Patient's facial dysmorphism – lateral.



Fig. 3. Simian crease.

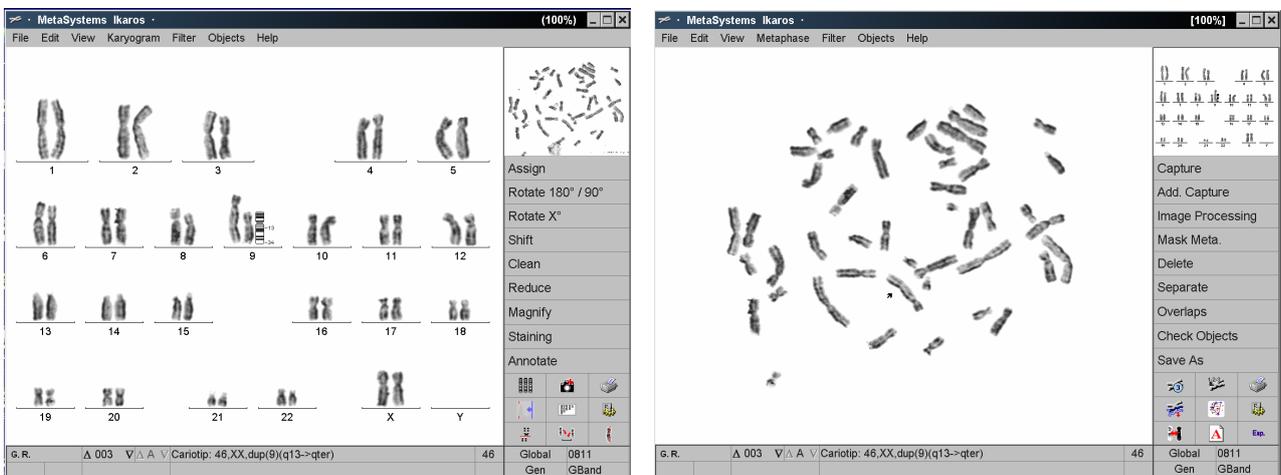


Fig. 4. Karyotype and metaphase of the patient.

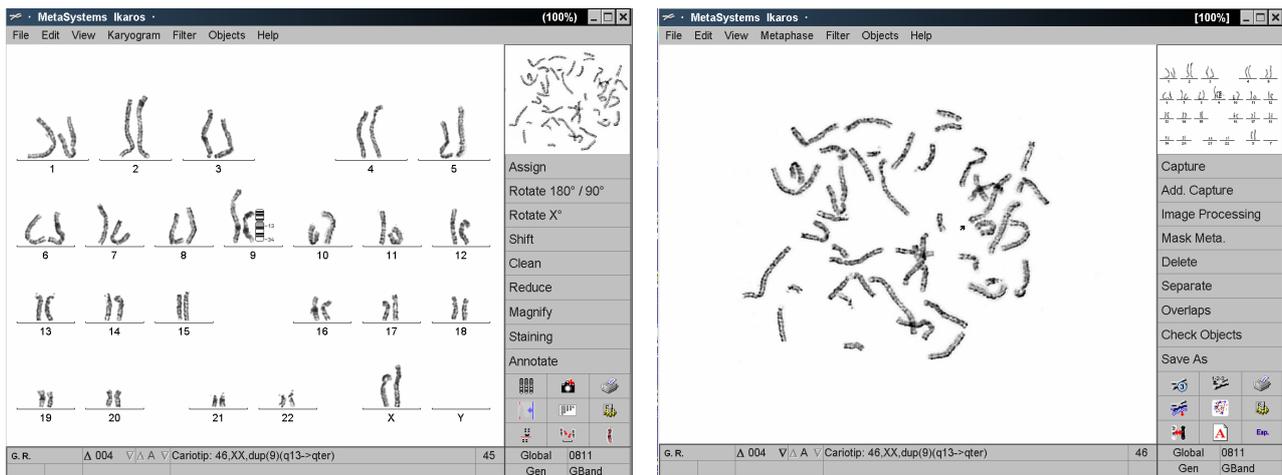


Fig. 5. Karyotype and metaphase of the patient.

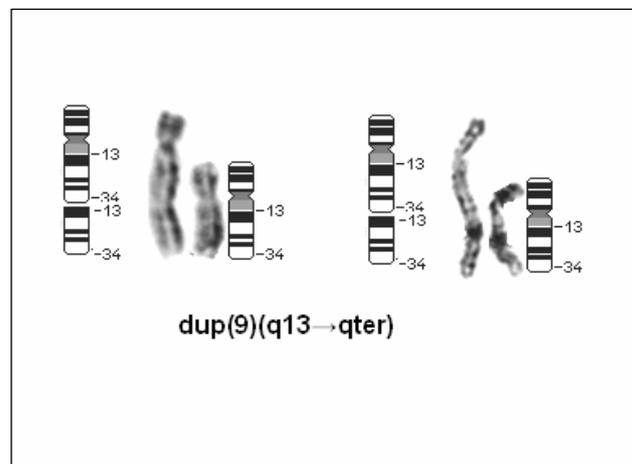


Fig. 6. Ideogram of chromosome 9, dup(9) and normal chromosome of the pair.

Discussions

We report here on a child with a de novo duplication of the long arm of the chromosome 9.

Whereas the partial trisomy 9p belongs perhaps to the more frequent chromosomal syndromes, the partial trisomy 9q seems to be rare.

The following features reveal the pathognomy of this syndrome: (1) low birth weight and simultaneously normal birth length; (2) the craniofacial dysmorphism consists of deeply set eyes, narrow palpebral fissures, beaked nose, and of receding chin; (3) the mouth typically presents an overlapping upper lip; (4) the ears are low set; (5) the hands reveal abnormally long fingers with persistent flexion and toes also appear abnormally long and, moreover, are abnormally implanted; (6) +/- pyloric stenosis.

The review of all cases of partial trisomy 9q reported in the literature demonstrates that mental

retardation, learning disability and facial dysmorphism, +/- pyloric stenosis are characteristic features of this group of chromosomal aberrations. Maraschio et al described the first patient with partial 9q duplication and obvious correlation between pyloric stenosis duplication of distinct parts of 9q in 1998. But, they only included in their study four published cases with partial trisomy 9q without pyloric stenosis even though there are some more. Assuming that 9q22-31.1 is a critical region for pyloric stenosis, there are five published cases corroborating this and at least six cases contradicting this point of view. However, some of the studies contradicting the assumption of Maraschio et al were done in the early days of chromosome banding and exact breakpoints were not verified by FISH studies. On the other hand, the case of Stalker et al from 1993 is well characterised by cytogenetic and molecular cytogenetic techniques. According to

Maraschio et al the duplication in this case spans the postulated critical region for pyloric stenosis in q12-q33, but no pyloric stenosis was reported. Moreover, in cases with complete trisomy 9 there have been no reports of pyloric stenosis. Imprinting could be another possible explanation for the fact that there are cases with duplication in 9q22.1-31. with and without pyloric stenosis. However, no cases with complete trisomy and pyloric stenosis have been described, which could be because all such cases which are viable are mosaic.

Molecular cytogenetic studies were performed in a partial trisomy 9q case with pyloric stenosis. [Anita Heller et al, 2000]. This study postulates that the critical region for pyloric stenosis (9q22.1-q31.1) may be disrupted. For the case reported in this study the region involved in duplication is inverted, therefore only molecular studies can specify whether the inversion that disrupts the gene is the cause for the pyloric stenosis.

In our case, by analysing the banding pattern of the extra chromosomal material on the long arm of chromosome 9, it was appointed as consisting of 9q13-q34.3 region. Comparing the phenotype and the

chromosomal alteration of our patient with similar cases described in the literature, it was striking the fact that such a large region involved in the duplication did not reside in a pyloric stenosis, but the cerebral anomalies present in our case were not reported previously in the literature.

For a thorough establishment of the chromosomal breakpoints the fluorescence in situ hybridization using specific probes and arrayCGH are to be performed when available for our patient.

The duplication of the arm of chromosome 9 observed in our patient was localized to q13-q34.3 region of the long arm of the same chromosome. Parental karyotypes were normal, indicating a de novo origin for the dup(9) in the proband. However, we cannot exclude the possibility of a gonadal mosaicism for the parents with an unbalanced crossover, this mechanism being the basis of duplication/deletion occurrence.

The correct diagnosis is essential not only for prognosis for the patient but also to ensure accurate estimation of the recurrence risk for the parents.

Documentation of better-characterized cases will contribute to the delineation of this syndrome.

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II. NEONATOLOGY

PERIVENTRICULAR LEUKOMALACIA ECHOGRAFICAL AND CLINICAL DIAGNOSIS

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Abstract

Periventricular leukomalacia is a relative frequent disease amongst premature newborns with severe hypoxic disorders at birth. The authors aimed to analyze, in this workout, the most involved risk factors, neurological and clinical scene and their concordance with imagistical methods used.

Key words: periventricular leukomalacia, newborn.

Introduction

Periventricular leukomalacia (PVL) is a ischemic necrosis of the white periventricular substance near the external angles of the lateral ventricles. The ending branches of the main vessels are leading to this region and, therefore, makes it more predisposed to ischemic necrosis. By microangiographic techniques it was shown that infarction is localized at the limit between afferent branches of middle cerebral artery and efferent branches of choroidal artery. The primary lesion is coagulating necrosis; after 5 – 7 days begins the necrotized tissue phagocytosis, which is finalized after approx. 2 – 3 weeks, leading to a cavity.

Material and method

The study was developed in the Premature and Neonatology Clinic of the “Louis Turcanu” Children Hospital, during 10 years: 1999 – 2008. The studied contingent included a number of 50 premature newborns selected from 212 infants with severe hypoxic disorders at birth. The including criteria for

the study were anamnestic, clinical and imagistical criteria.

Results and Discussions

Periventricular leukomalacia (PVL), profound infarction of the white substance near the external angles of the lateral ventricles, was found at 50 cases (23,58%). Its high prevalence in premature newborns is in accordance with the literature data; is known that 80 – 90% of cases appears at premature infants. Also, the localization of the lesion was typical, at the limit between afferent and efferent branches of the cerebral arteries, at 3 – 10 mm from the ventricular wall.

In the affection appearance, severe hipoxia, both in prenatal, perinatal and neonatal period, was constantly involved:

- prenatal appearance of the affection at 31 cases (matern-fetal infections, utero-placental affections, green amniotic liquid, membrane rupture after 72 hours, Apgar score <7);
- at 26 of cases prenatal factors were associated with other affections, that influenced the neuropathological and clinical table: sepsis, repeated crisis of apnea, bradycardia, bronchopneumonia, Patent Ductus Arteriosus.

The premature newborns included in this lot have clinically presented an intense neurological table, with: severe hypotonia, repeated crisis of apnea, archaic reflex diminution – especially at lower limbs, convulsions (see table).

Clinical signs	Number of cases	Percents %
Hypotonia	33	70,00
Repeated crisis of apnea	42	84,00
Archaic reflexes diminution/abolition	43	86,00
Hiperexcitability	15	30,00
Convulsions	14	28,00
Opisthotonus	12	24,00

The intensity and duration of the clinical signs were higher in cases of PVL associated with periventricular or intraventricular hemorrhage (especially in severe forms). Associated ultrasound hemorrhagic lesion was found in 21 cases (42,00%), 9 of them with germinal matrix localization and 12 with intraventricular localization.

Ultrasound diagnosis of PVL was based on the characteristics and the localization of the lesion: echogenic large band laterally positioned to the anterior horns of the lateral ventricles and to the trigones of the lateral ventricles. The hyperechogenicity in the anterior portion of the lateral ventricles has a typical localization which is localized on the antero-external side of them.

The ultrasound examination was done weekly and monitored the following aspects of the hyperechogenicity: intensity, dimension, localization, outline, homogeneity relation with the ventricular system. The echogenic intensity of the lesion has importance in order to appreciate severity and prognosis, especially in cases in which the evolution was towards cystic formations:

- 23 of cases (53,48%) were easy forms which presented periventricular echogenicity with an intensity lower than that of the choroid plexus and dimensions smaller than those of the lateral ventricular trigone;
- 8 cases (18,60%) were moderate forms which presented periventricular echogenicity with an intensity similar to that of the choroid plexus and approximately equal dimensions to those of the lateral ventricular trigone;
- 12 cases (27,90%) were severe forms which presented periventricular echogenicity higher than that of the choroid plexus and dimensions bigger than those of the lateral ventricular trigone.

The echogenity evolution was: resorption – 9 cases, cystic formations-34 cases (fig. 1).

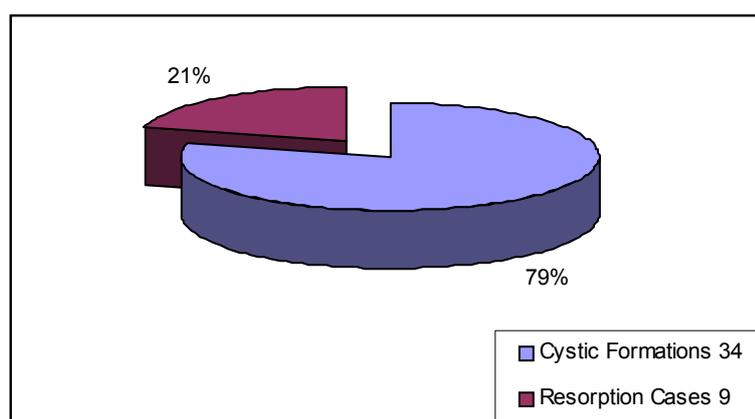


Fig. 1. Evolution of the hyperechogenical formations in periventricular leukomalacia.

The visualized cystic formations were diagnosed based on echographic characteristics: transonic formations with homogeneous contents, homogeneous echogenicity of the contents, thick walls (echogenic intense), unique in 22 cases and multiple in 19 cases. As time of appearance (excepting the cystic formations found at the first examination) the first formations were visualized at three weeks from the founding of echogenities.

Positioning of the cysts – in the anterior region (external angle of the lateral ventricles) – 37 cases;

posterior region (posterior side of the lateral ventricles) – 7 cases and only in 6 cases were found cystic formations along the entire border of the lateral ventricles (fig. 2). The anterior – extern positioning of the lesions to the anterior horns of the lateral ventricles was confirmed by the literature (Volpe J.J. 1992); these areas are known to be susceptible to perfusion pressure and cerebral blood pressure decreasing and, therefore, leading to specific leukomalacia lesions.

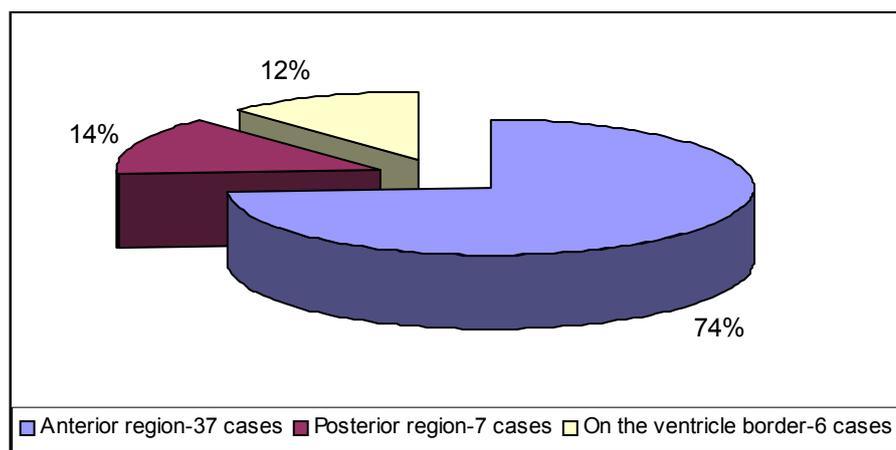


Fig. 2. Positioning of the cystic formations.

The dimensions of the cystic formations are important in order to establish the prognosis and the neurological modifications in time. The cystic formations diameters were between 3 and 12 mm. The high echogenity (moderate and severe forms of the disease) were followed by big cysts, usually multiples (20cases-48,78%). The severe clinical table was found in these cases: recurrent convulsive syndrome (22 cases), severe hypotonia (8 cases), spasticity of the inferior limbs (11 cases) and opisthotonus (14 cases).

Generally, the medium periods of persistence were: echogenity between 1 and 3 weeks and cystic formations between 3 week and 3 months. At severe forms transonic lesions and ventriculomegaly persisted until the age of 8-10 months.

At the cases where the cystic formations persisted we have visualized the following aspects:

- cystic formations – 3 cases
- cystic formations accompanied by ventriculomegaly – 6 cases
- ventriculomegaly – cerebral atrophy – 16 cases

The diagnosis of cerebral atrophy was based on ventriculomegaly accompanied by the increase of the interhemispheric space and the increase of the distance between the gyrus in the anterior region.

The rupture of the septum between the cysts and the lateral ventricles produced the evolution towards ventriculomegaly.

The cases in which the persistence of cystic formations was associated with cerebral atrophy, the following severe neurological modifications were found:

- recurrent convulsions- 16 cases;
- spastic dyplegia- 9 cases;
- sight disorders – 4 cases;
- speaking disorders –3 cases;

- hearing disorders – 3 cases;
- mental retardation –22 cases;
- minimum cerebral dysfunction –10 cases.

The specialty literature data referring to neurological disorders after PVL are varied. A study done by Pidcock and his collaborators on a lot of 127 premature newborns showed that there is a significant correlation between the appearance, dimension and localization of the cysts and the appearance of a mental disorders. From the studied cases, 42 did not show cystic formations in evolution and had a good neurological evolution unlike the 25 cases with moderate cystic lesions and 20 cases with severe cystic lesions, which developed neurological disorders in 32% and 90% of cases.

The association between PVL and periventricular and intraventricular hemorrhage is discussed a lot in the specialty literature. American authors observed associations in 28-59% of cases. In the lot that we studied there were hemorrhagic lesions (42%):

- in 9 cases subependymal hemorrhages;
- in 12 cases intraventricular hemorrhages.

The distinction between the hemorrhagic and non-hemorrhagic PVL was difficult to prove based on echography, because the echogenity has the same characteristics.

The presence of hyperechogenic lesions inside the non-dilated ventricles and in the cerebral intraventricular parenchyma (laterally from the anterior region, the posterior region and along the ventricular wall) oriented the diagnosis towards PVL associated with an intraventricular hemorrhage.

In the presence of big lesions in the cerebral parenchyma, accompanied by hyperechogenity inside the lateral, dilated ventricles, the distinction between

the hemorrhagic and non-hemorrhagic forms was very difficult to make, these forms being the severe forms of intraventricular hemorrhage (IV degree).

Conclusions

1. The moment of action upon the CNS was both in the ante and intranatal period, and in the neonatal period. The risk factors were: the Apgar score < 7 (84,43%), the presence of meconium in the amniotic liquid, uterus-placental lesions, long labor. In the majority of cases there were 2 or more risk factors.
2. The clinic and echographic table was different according to the intensity and length of the injury: 53,48%- easy forms, 18,60%- moderate forms, and 27,90% severe forms.
3. The cystic formations appeared in the evolution of most cases (79,05%) in the hyperechogenic area. Big cysts, usually multiple, followed the big echogenities. In this situation, in 48,78% of the cystic formations, the clinical table was severe.
4. The evolution towards cerebral atrophy (32%) consisted of the following aspects: the growth of the interhemispheric space, the growth of the distance between the gyri, the accentuated hyperechogenicity of these spaces, especially in the anterior region and the slow ventriculomegaly.
5. The persistence of the cystic formations (56,09%) and/or the presence of the echographical signs of the cerebral atrophy (32%) was correlated to the appearance of the neurological disorders: convulsive recurrent syndrome (32%), infantile spastic diplegia (18%), sight disorders (8%), hearing disorders (6%) and neuropsychomotor retardation (44%).
6. The periventricular and intraventricular hemorrhage was associated in 42% of cases, the distinction being difficult in the presence of a big hyperechogenic lesion localized inside the lateral ventricles and in the parenchyma.

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III. PEDIATRICS

ABDOMINAL ULTRASOUND IN THE DIAGNOSIS OF URINARY AND KIDNEY MALFORMATIONS IN CHILDREN

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Abstract

The authors tried to establish the accuracy and the positive and negative predictive value of the ultrasonography in the diagnosis of the renal malformations on a group of 116 admitted children. Positive diagnosis of the reno-urinary malformation was established based on one of the following methods: intravenous urography, voiding cystography, magnetic resonance imaging or computer tomography. Abdominal ultrasound is a noninvasive and accessible method for the diagnosis for renal system malformations with high sensibility and optimal specificity.

Key words: urinary malformations, abdominal ultrasound, accuracy

Introduction

The diagnosis of renal system malformations should be made through antenatal ultrasound screening beginning with weeks 18-20 of gestation. The early diagnosis of these malformations allows: parent's information, parent's conciliation, intrauterine surgical interventions, abortion alternative.

Objective

The authors present the sensibility, specificity, positive and negative predictive value and the accuracy

of ultrasonography in diagnosis of renal system malformations in children.

Material and methods

Group A - 116 patients with malformations of the renal system, admitted in Pediatric Clinic I, „Louis Turcanu” Pediatric Emergency Hospital Timisoara, Nephrology Department between 01 January 2006 - 31 Dec 2007. Median age was 12,91+/-5,78 yrs (neonate - 18 yrs) and sex ratio was M:F 58:58.

Group B - 100 consecutive, randomized patients without malformations of the renal system, admitted in Pediatric Clinic I, „Louis Turcanu” Pediatric Emergency Hospital Timisoara between 01 January 2006 and 31 Dec 2007. Median age was 12,3+/-3,91 yrs (neonate - 18 yrs) and sex ratio was M:F 42:58.

The authors investigated all the patients with abdominal ultrasound and sustained the kidney and urinary malformation diagnosis based on urography, voiding cystography MRI or CT.

The group B was also investigated by ultrasound and MRI or CT for other different causes, without any renal system malformations.

The accuracy and efficiency of the diagnostic criteria were analyzed (for sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, diagnostic and error odds ratios) by completing the observed contingency table.

Observed Contingency Table

*	Outcome Occurred	Outcome did not Occur	Totals
Risk Factor Present or Dx Test Positive	102 = a	9 = b	111 = r1
Risk Factor Absent or Dx Test Negative	5 = c	100 = d	105 = r2
Totals	107 = c1	109 = c2	216 = t

Confidence Level: 95 %

Compute

Chi-Square Tests

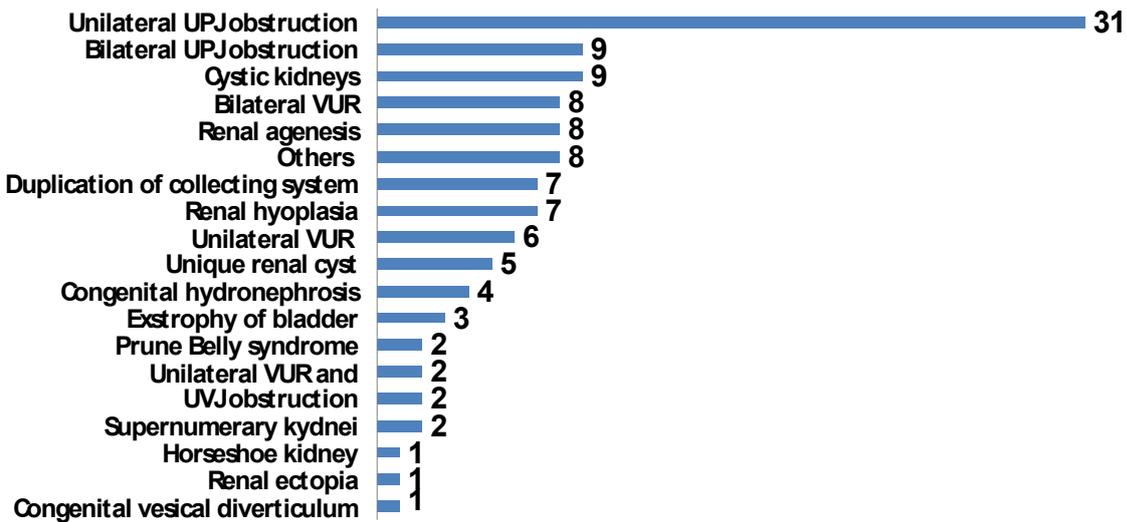
Type of Test	Chi Square	d.f.	p-value
Pearson Uncorrected	163.867	1	0.000
Yates Corrected	160.400	1	0.000
Mantel-Haenszel	163.108	1	0.000

Results

The most frequent kidney malformations were uretero-pelvic junction obstruction, cystic kidney, vesico-ureteral reflux, renal hypoplasia and renal agenesis. Other malformations were observed into a

smaller proportion. Also, we kept under observation the children with complex associated malformation and syndromes that included reno-urinary malformations.

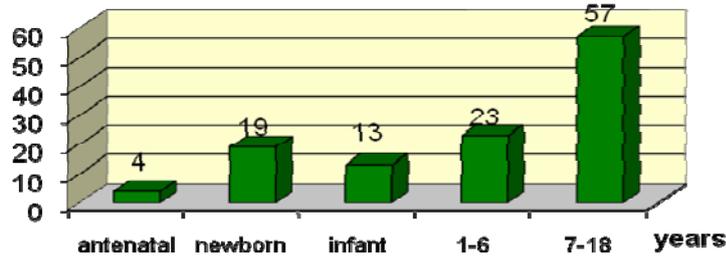
Identified renal system malformations



Median age for diagnosis was 9,64+/-5,09 years. Unfortunately, we had cases whom were diagnosed much later, even at age 7. Antenatal ultrasound

diagnostic was made in 4 cases. The newborn was diagnosed because of the association of malformations with renal failure.

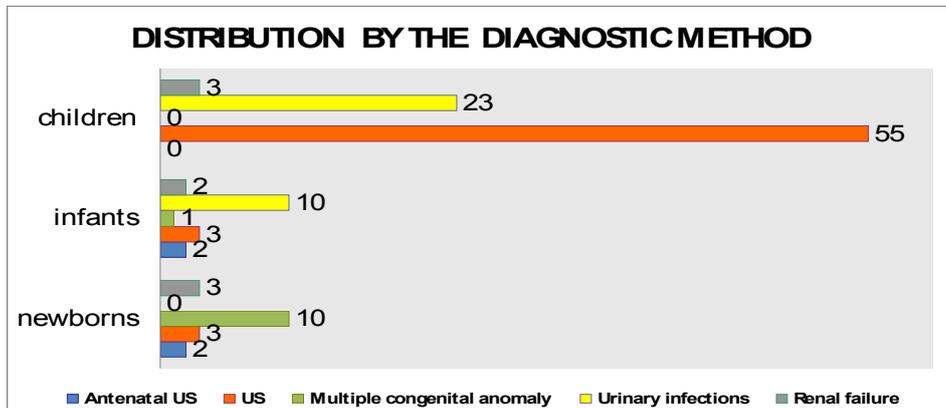
DISTRIBUTION BY AGE OF DIAGNOSIS



The renal system malformations were diagnosed late. Urinary recurrent infections determined the search for malformations, this being the most frequent way in discovering this pathology. Renal failure may be also associated; acute renal failure benefit from urological

treatment, but chronic renal failure is a drama for the patients and their families. Even if the malformations are surgically corrected, the evolution of renal failure is delayed but never stopped.

DISTRIBUTION BY THE DIAGNOSTIC METHOD



For the diagnosis of renal system malformations, in the study groups, abdominal ultrasound had the following parameters: sensitivity 95,32%, specificity

91,74%, positive predictive value 91,89%, negative predictive value 95,23%, accuracy of the method 93,51%.

Quantities Derived from the 2-by-2 Contingency Table	Value	95% Confidence Interval	
Sensitivity = $a/c1$; (use exact Binomial confidence intervals instead of these)	0,953	0,913	0,977
Specificity = $d/c2$; (use exact Binomial confidence intervals instead of these)	0,917	0,877	0,941
Positive Predictive Value (PPV) = $a/r1$; (use exact Binomial confidence intervals instead of these)	0,919	0,880	0,942
Negative Predictive Value (NPV) = $d/r2$; (use exact Binomial confidence intervals instead of these)	0,952	0,911	0,977
Diagnostic Odds Ratio = $(\text{Sensitivity}/(1-\text{Sensitivity})) / ((1-\text{Specificity})/\text{Specificity})$;	226,667	74,737	683,510
Error Odds Ratio = $(\text{Sensitivity}/(1-\text{Sensitivity})) / (\text{Specificity}/(1-\text{Specificity}))$;	1,836	1,457	2,693
Youden's J = Sensitivity + Specificity - 1;	0,871	0,790	0,918

Conclusions

Abdominal ultrasound is a noninvasive and accessible method for the diagnosis of renal system malformations with high sensibility and optimal specificity. We must complete this method with the voiding cystography, urography, MRI or CT. The isotopic scintigraphy can demonstrate the presence of renal scar and help us provide the best therapeutically way to resolve renal system malformations. The follow

up of these patients is also performed with abdominal ultrasound.

We hope that antenatal ultrasound diagnostic the renal malformations will improve in time. Although the legal basis for antenatal diagnosis exists, very few patients benefit from it. The poor medical education and the limited access for pregnant women to obstetrician's ultrasound were the premise of late diagnosis of reno-urinary malformations.

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HLA HAPLOTYPES IN THE INFANTILE POPULATION WITH DIABETOGENIC RISK

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Abstract

Aim of the study. The present study attempted to find out class II - HLA alleles in a group of children with diabetogenic risk.

Material and method. The studied lot included 38 children (aged 3 months - 18 years) grouped as follows: group A = 32 children (siblings of type 1 DM kids), group B = 5 children followed-up for impaired fasting glucose, group C = one 3 months old infant of a diabetic mother. We determined the anthropometric indexes (weight, height, waist) and, biologically, we evaluated the glucidic metabolism through fasting glycemia and HbA1c and the metabolism of lipids through serum lipids, cholesterol, triglycerides and HDLc. In the same time we determined the markers of humoral autoimmunity by measuring the: titre of anti-glutamic acid decarboxylase antibodies (GADA) and the islet cell antibodies (ICA). Of the metabolic markers we used the evaluation of C peptid concentration (normal ranges between 0,5–3 ng/ml). Class II HLA alleles were typed in 20 patients from this subgroup. HLA typing used INNO-LIPA HLA-B DRB1 tests for the allele group between DRB1*01 and DRB1*16. For the interpretation of the results we used the “DynaL Biotech pattern Matching Program S42” soft.

Results. In the studied lot, typing of class II HLA alleles revealed that of the 20 subjects evaluated, 25% were DRB1*04 while 15% were DRB1*03. In all typed cases serum C peptide and also the glycated hemoglobin ranged between normal limits.

Conclusions. Genetic predisposition represents the background for the development of the autoimmune beta-cell destructive process, but the occurrence of type 1 DM requires also the involvement of some trigger factors which are often hardly to distinguish.

Key words: *genetic, risk, diabetes mellitus, childhood.*

Introduction

Diabetes mellitus has become a real burden for the human society. Paradoxically, at present more resources are spent for complications, comparatively with those used for prevention in diabetes. Following

the new data concerning the susceptibility markers and the variable asymptomatic period in type 1 diabetes mellitus (type 1 DM), the prevention of the disease became a permanent preoccupation of the specialists, especially because this refers preponderantly to children and young subjects.

Today it is accepted that the short time prior to diagnosis in type 1 DM is just the peak of a huge iceberg, just partially explored by the immunogenetic modern studies. Genetically speaking, diabetes is a complex polygenic disease, for the developing of which, a variable number of susceptibility and protective genes, with incomplete penetrance, are contributing (1).

The presence of markers in association, in some subjects serum, both in the general population and in some belonging to subgroups with increased risk for type 1 DM, increases the probability for developing this disease (2).

Clinical manifestation of type 1 diabetes before the age of 20 years is associated with a strong HLA defined genetic susceptibility, an intensive humoral immune response to various beta cell antigens, a higher frequency of preceding infections and a shorter duration of symptoms and more severe metabolic decompensation of diagnosis (3).

Aim of the study

To determine the risk of occurrence of diabetes mellitus in children from the western part of our country; determination of genetic susceptibility through identification of HLA class II genes that predispose to the occurrence of type 1 DM.

Patients and method

The studied lot included 38 children (aged 3 months - 18 years) grouped as follows: group A = 32 children (siblings of type 1 DM kids), group B = 5 children followed-up for impaired fasting glucose, group C = one 3 months old infant of a diabetic mother. We determined the anthropometric indexes (weight, height, waist) and, biologically, we evaluated the glucidic metabolism through fasting glycemia and

HbA1c and the metabolism of lipids through serum lipids, cholesterol, triglycerides and HDLc. Of the metabolic markers we used the evaluation of C peptide concentration (normal ranges between 0,5–3 ng/ml). Class II HLA alleles were typed in 20 patients from this subgroup. HLA typing used INNO-LIPA HLA-B DRB1 tests for the allele group level DRB1*01 to DRB1*16. For the interpretation of the results we used

the “Dynal Biotech pattern Matching Program S42” soft.

Results

All cases had a normal basal C peptide level while HbA1c levels also ranged between normal limits (fig. nr.1, fig. nr.2, fig. nr.3).

All cases typed for HLA had the basal level of the C peptide between normal limits and HbA1c was also normal (Tabel I)

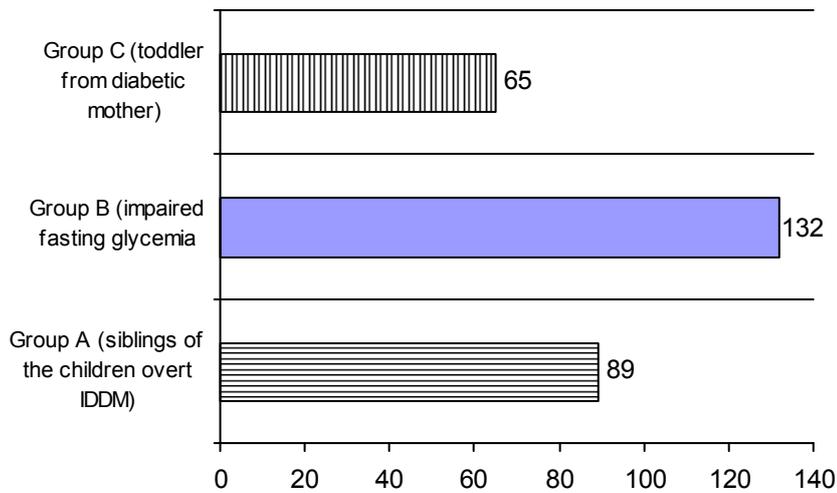


Fig. nr. 1 - Fasting glycemia (mg / dl).

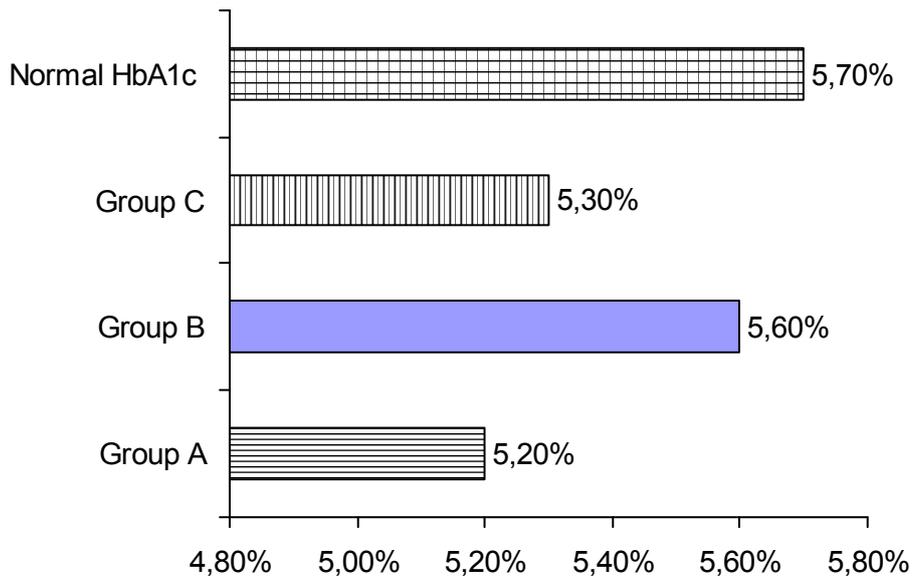


Fig. nr. 2 – HbA1c value in the studied lot

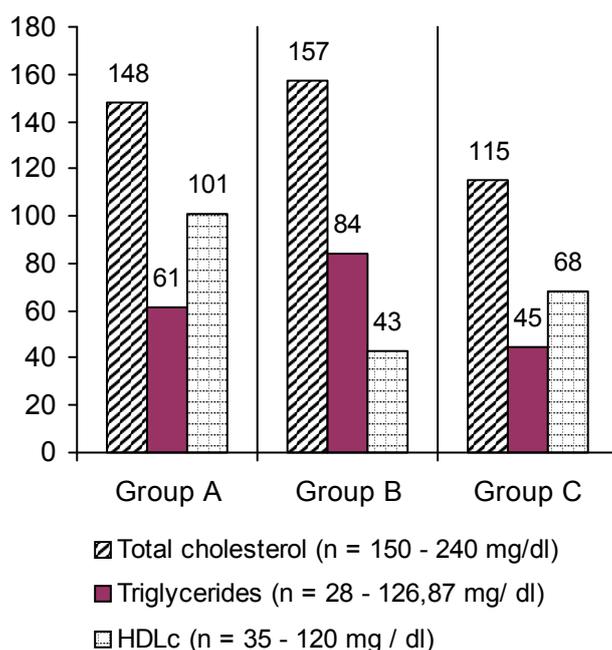


Fig. nr. 3 – Serum lipids values (cholesterol, triglycerides and HDLc) in the studied lot.

Table I. Class II HLA alleles.

Nr.Crt.	Name	Typed allele	Basal C peptide	HbA1c
1.	B.A.	DRB1*07, DRB1*11	0,8	3,55
2.	B.C	DRB1*01, DRB1*04 DRB1*04, DRB1*04	1,4	3,5
3.	B.D.	?	1,4	3,5
4.	C.A.	DRB1*04, DRB1*04	1,8	3,5
5.	C.A.	DRB1*11	2,9	3,5
6.	F.P.	DRB1*01, DRB1*11	2,0	3,6
7.	G.D.	DRB1*11, DRB1*16	0,9	3,7
8.	H.C.	DRB1*14, DRB1*15	1,0	3,5
9.	I.R.	?	0,8	3,9
10.	P.A.	?	2,7	3,9
11.	R.A.	DRB1*11, DRB1*13	1,2	3,6
12.	S.N.	DRB1*01, DRB1*04 DRB1*04, DRB1*04	2,2	3,5
13.	T.L.	DRB1*03, DRB1*16	0,7	3,52
14.	T.S.	DRB1*04, DRB1*16	0,5	3,5
15.	T.D.E.	DRB1*15, DRB1*16	1,9	3,6
16.	T.B.A.	DRB1*11, DRB1*16	1,5	3,9
17.	T.I.	DRB1*03, DRB1*04	2,9	3,8
18.	T.L.	DRB1*04, DRB1*13	2,5	3,9
19.	V.A.	DRB1*03, DRB1*13	2,9	3,9
20.	W.L	?	2,3	3,8

In the studied lot, typing of HLA class II shown 25% patients positive for DRB1*04 while 15% are DRB1*03.

Discussions

Type 1 diabetes results from the autoimmune destruction of insulin-producing beta cells and is characterized by the presence of multiple islet autoantibodies and high risk HLA haplotypes for type 1 diabetes.

The risk associated with type 1 diabetes HLA haplotypes differs between continents (4).

Presently is accepted that type 1 DM in children is associated with HLA DR3, DQB1 0201 and DR4, DQB1 0302 (3), and the decreased frequency might explain the reduced incidence of diabetes mellitus in some countries like Romania (5).

Recent studies revealed the independent role of some gene variants HLA-DRB1, especially DRB1*04 allele subtypes, that sometimes may even cancel the predisposing /protective effect of HLA-DQ allele. Various studies shown that HLA-DRB1*04 (DR4 antigen) is associated with type 1 DM in all ethnic groups except for the chinese population (Pennz et al, 1992).

HLA DRB1*04-DQB1*0302 and / or HLA DRB1*03-DQB1*0201 are observed in > 90% of

affected children and in only 40% of the general population (6).

In the studied lot, typing of HLA class II shown 25% patients positive for DRB1*04 while 15% are DRB1*03. All cases typed for HLA had a normal basal C peptide level while HbA1c levels also ranged between normal limits.

The results found in our study group seem to confirm the theory suggesting that genetic predisposition plays an important role in developing DM.

Conclusions

1. Our results are not allowing us to make considerations upon the diabetogenic risk in the studied group.
2. The following evolution of these subjects will prove if these allele are really predisposing for type1 DM also in the population we have studied.
3. Genetic predisposition represents the background for the development of the autoimmune beta-cell destructive process, but the occurrence of type 1 DM requires also the involvement of some trigger factors which are often hardly to distinguish.

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THE INTERPRETATION OF SEROLOGICAL TESTS RESULTS TO NEW BORN BABIES PREGNANCIES ORIGINATED WITH SEROCONVERSION OF TOXOPLASMA GONDII

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Abstract

Objectives: The demonstration of the serological test importance in the diagnosis of the Congenital Toxoplasmosis.

The Method: The serological test was performed through the micro enzymatic immunology technique, on a lot of 87, new born suckling babies. Along with the laboratory investigations the babies were also clinical, oftalmological and neuron-imagistic examined.

Results: The diagnosis of Congenital Toxoplasmosis was confirmed at 29 children – 33.33%, was invalid at 58 children – 66.66%. The IgM+ type serology was encountered at 23 children – 24.73%, confirming the parasitosis. IgM- type serology, IgG+ was encountered at 26 children – 29.85%, of which a lot of 6 children – 23.07% the IgG increases in dynamic confirming the congenital toxoplasmosis. The IgM- type serology, IgG- was encountered at a lot of 38 children – 40.86%, invalidating the parasitosis.

Conclusions: The serological screening is obligatory to the new born babies, originated of mothers with Gondi Toxoplasmosis seroconversion; all suckling babies with unconvulsive IgM-, IgG+ type serology, till age one.

Key words: congenital toxoplasmosis, serological test.

Introduction

The congenital infection with *Toxoplasma gondii*, a protozoan which parasites over 300 species of vertebrates is one of the most frequent infection of conceiving process result. The contamination and the producing of toxoplasmosis are possible due to the pregnant woman primo infection, which in 80% cases is asymptomatic. (2).

The large volume which occupies the thank infection, the vary paths through which the parasite arrives to the human, makes that till the age of 30, 85% of population to be contemined. The incidence of toxoplasmosis at humans is hard to be established due to the climate variability factor, the living way, the

nourishment customs, hygienically level, the high rate of insensible infections.

The maternal toxoplasmosis in not equivalent with the congenital toxoplasmosis, the infection transmission at the conceiving product is not simultaneous to maternal infection, it produces later during to the placentar stadium. In the case of maternal prime infection, the fetus infection risk average is 7%, but varies about the date of seroconversion and grows gradually depending of the pregnancy period. (4). The early track down of maternal infection admits the therapeutically involvement reducing with 50% the risk of transmission and fetal affect. (6).

The history of toxoplasmosis is a process in full procedure, even it is known for a long time like a parasitosis disease with severe evaluative potential at new born babies.

The infestation with *toxoplasma gondii* of the conceiving produce may occur an abortion, specially in the embryonic period or a complex suffering, congenital toxoplasmosis which could be asymptotically on an average of 55-80% of cases, but potentially severe ocular and neuro-psihical evaluative or on evolution, severe with postnatal death, congenital malformations (1).

The benign form, asymptomatic congenital toxoplasmosis has only a positive serology, which occurs serious problems on long way, because ineloquence and lack of specific treatment carries on to an evolution of chorioretinitis with the loss of visual acuity. (8).

The early track down of the infection at pregnant woman, of congenital infection has a huge value due to the possibility of the medical and therapeutically involvement, which can slow down or stop the disease evolution. (9).

Through the impressive average of asymptotically forms both to the woman being at the age of conceiving and also at new born baby, the

foundation of the diagnosis with toxoplasmosis comes to the laboratory methods.

The new born baby's serum may contain antibodies transplacental transmitted from mother during the pregnancy, IgG type. The exclusion of the toxoplasmosis diagnosis implies, in IgM-, IgG+ cases the track down of the serological evolution of IgG till age of one. The decreasing rate of IgG passively transmitted from mother to fetus is 50% in during 28 days, with its disappearing over 10 months. (3).

IgM is an immunoglobulin which appears in the first days of infection, first week and grows rapidly tending to a maximum serum level, for decreasing in the same time with the evolution of the chronic disease. It negativates after approximately 4-6 months, so regularly IgM cannot be detected in the sick person serum after 6 evolutionary months of infection, through standard methods of diagnosis. IgM is considered a marker of the acute infection and of congenital infection at fetus. (5).

IgG appears gradually at the end of the second week of the acute infection, tends maximum values at 6-8 weeks from infection, status still few months, decreases slowly, persists years at a low level, conferring immunity protection. IgG is determined for the establishment of a specific immunity presence. (7)

Materials and Methods

The study was performed on a lot of 87, children with provenience of confirmed seroconversion mothers. A number of 56, children did not present any symptoms. The clinical manifestation the more frequent met was the neurological ones. The ophthalmological evaluation needed both the anterior

segment examination, which proved microphthalmological problems and strabismus, and also especially the posterior one which confirmed the presence of chorioretinitis injury.

The serological examination was performed through the microenzymatical immunology technique, MEIA method, About reactive Axsym equipment, which buses a suspended solution, latex particles through the microenzymatical immunology technique, which buses a suspended solution, latex particles of a micron size to measure the analite. The particles are covered with a specific catch molecule, capture type for the analite to be measured. The efficient area of the microparticles surface increases the kinetic component and decreases the incubation time. This allows the MEIA tests to be performed in the less time of the other immunological tests.

At the samples centre, the reactive and the samples for tests are introduced in a reaction tank. This is sent to the processing center where the reactivates and samples are incubated to allow to get the reaction temperature. The reactive and the samples are combined, the resulting mixture is transferred in a matrix of inert glass. The irreversible cover with the microparticles drives to an immune complex which is stopped by the glass fibers, in the same time that the mixture rapidly flows through the big fleckles of the matrix. A conjugated mixture alcalino-phosphatic is added at the glass matrix, 4-metilunbeliferil phosphate. The mixture catalyzes the hydrolyze of metilumbriferil phosphate with metilumbeliferil.

The ingathering was performed in the monthly dynamic, till age one, on red collection tube, without anticoagulant.

The interpretation of serological results:

IgM Interpretation

0 < Index IgM < 0,500	Negative
0,500 < index < IgM 0,600	Unconcluent
0,600 < Index IgM	Positive

IgG Interpretation

0 < IgG < 2UI/ml	Unimmunized subject
2 < IgG < 5ui/ML	Unconcluent
5 < IgG	Probably immunization, due to the clinic context with the recommendation of repeating it after 2-3 weeks

Results and discussions

Serological supervising of new born babies with seroconversion mothers infirmed congenital toxoplasmosis at a lot of 38 children (IgM-, IgG+, confirms the diagnosis at 23 children (IgM+). The

average of negative serology children from seroconversion mothers represent 40.68% and with positive serology are of 24.73%.

A number of 26 new born babies – 29.58% presented at birth the following situation: IgM-, IgG+.

It must be mentioned the fact that no new born baby with unconclusive serology had any clinical manifestation, the only way to confirm the diagnosis being the serological screening. So, at a lot of 20 children the level of antibodies decreased, till the

complete disappearing near one age, infirming the congenital toxoplasmosis. At a lot of 6 children the level IgG grew in dynamic, confirming the congenital parsitosis disease. These represent 23.07% of the total of children with unconclusive serology.

Tabel 1. The serological evolution of new born babies from mothers with toxoplasmosis.

IgM -	IgG -	IgM +	IgM -	IgG
			decrease	grow up
38		23	20	6
40,86%		24,73%	21,51%	6,45%

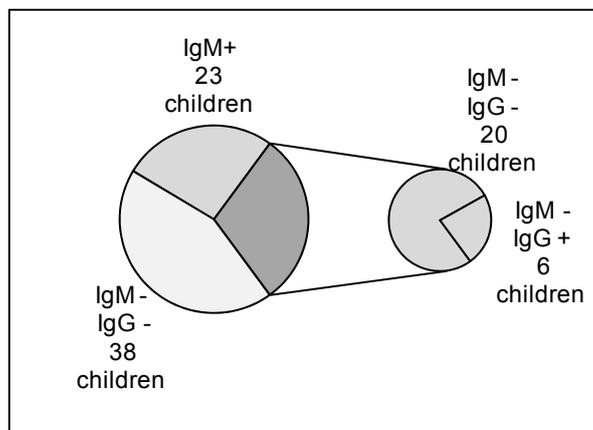


Figure 1. The serological evolution of new born babies from mothers with toxoplasmosis.

At a number of 8 children – 30.76% there was a plane stop on a period of approximately 2 months, which increased supplementary problems of diagnosis and therapy conduct. Among these in 3 cases the level

of antibodies decreased, infirming the congenital infection, the others 5 cases – 62.5% proved to be congenital toxoplasmosis.

Tabel 2. Serological evolution of children with IgM -, stationary IgG + for 2 months.

Month	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
IgG (ui/ml)	case 1	6.5	6.5	6.2	5.7	5.1	4.3	3.2	2.2	1	1	0	0
	case 2	7	6	6	5.6	5.1	5	3.3	2.1	1	0	0	0
	case 3	5.7	5.7	5.1	4.9	3.5	3	2.8	2	1.3	0.8	0	0
	case 4	5.6	5.6	6	6.3	7	7.2	7.2	7.2	7.2	7.2	7.2	7.2
	case 5	7.1	8	8	8.3	8.4	8.5	8.5	8.5	8.5	8.5	8.5	8.5
	case 6	5.8	5.8	6	6.2	6.6	6.5	6.5	6.5	6.5	6.5	6.5	6.5
	case 7	6.5	6.6	6.6	6.8	7	7.1	7.1	7.1	7.1	7.1	7.1	7.1
	case 8	5.8	5.8	6	6.1	6.5	7	7	7	7	7	7	7

A lot of 18 new born babies of the 29 confirmed ones did not have any clinical manifestation, the diagnosis being only serological. In the case of not performing the postpartum serological and monthly examination, in the dynamic during one year the diagnosis and the antiparasite treatment performance

would not be possible, the congenital toxoplasmosis, asymptotically form could pass unobserved in evolution in time guiding an ocular or neurological affect.

The final result of serological investigations to confirm the congenital toxoplasmosis shows there for

that a number of 29 children with parasites of a total of 87 suspicion (33.33%).

Conclusions

The serological examination is the main investigation in tracking down the gondi toxoplasmosis infection.

The serological screening of the new born baby is the on which infirms or confirms the congenital toxoplasmosis diagnosis. And gives the agreement to the institution of the antiparasite treatment.

It is necessary to follow the serological evolution of antitoxoplasma antibodies in the first year of living, because only like this it can be made the difference

between the cases with passing antibodies and of those with neositatized, with congenital disease. The excluding of congenital toxoplasmosis diagnosis can be performed only on the negative serology base, through the missing of antibodies mother originated, which wad performed between 8-12 months.

The unfrocking of the asymptotically congenital toxoplasmosis forms, which represented 62.06% of the total of clinical forms becomes a risk for the installing in time of the chorioretinitis.

The congenital toxoplasmosis must be taken in view within a paraclinical and clinical survey of the new born babies with neurological affects and those with troubles of eyes development, eyes motrical problems.

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SPECIFIC FORMS OF DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS – THEIR SIGNIFICANCE IN CLINICAL PRACTICE

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Abstract

Although they represent a small group of diabetes mellitus, the specific forms have a burden of difficulties in the field of diagnosis, therapy and prognostic evaluation.

In this study, the authors present their experience in the domain of specific forms of diabetes mellitus, their clinical and biological particularities, their therapeutical approach and evolution.

Diseases with associated diabetes mellitus require compulsory monitoring of glycemia for an early diagnosis and prevention of chronic complications.

Key words: child, adolescent, specific forms of diabetes mellitus

Introduction

Specific forms of Diabetes Mellitus (DM) represent a heterogeneous group of carbohydrate metabolic disturbances in which DM is associated with an isolated or complex morbid clinical picture.^[1,2]

The terminology used for this form of disease has undergone lots of changes all through the years. The term “secondary DM” was abandoned; having been considered improper as only in a minority of cases the associated pathology is the actual cause of DM. In majority of cases, DM and associated disease have a common trigger. This is the reason why the term “specific forms” or “form associated with a disease” is preferred to avoid the interpretation of inter-correlated causes.^[3,4]

Irrespective of the associated pathology, chronic hyperglycemia retains its specific particularities:

- prolonged subclinical evolution
- early vascular derogatory impact and

- potential to trigger some irreversible, severe vascular or neurological complications.^[5,6]

These considerations have justified the present study which proposes evaluation of the proportions of these specific forms of DM, describing their clinical-biological particularities and their evolution modalities.

Material and method

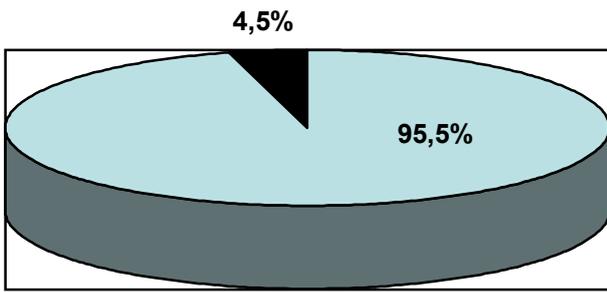
The present study is a retrospective analytic study undertaken on 2198 patients in the records of the IIIrd Pediatric Clinic, Timisoara and the “Cristian Serban” Clinical Center for Evaluation and Recuperation, during the period 1998-2007. The patients presenting chronic disorder of carbohydrate metabolism in the forms of: alterations in fasting glucose, decrease in glucose tolerance and DM type 1 and 2.

In all the patients the fasting glucose ± OGTT, HbA_{1c} were followed in correlation with other metabolic parameters – hormonal or immunological based on the associated carbohydrate metabolism disorder. The average glycemia and the insulin requirement were observed in comparison to patients without associated forms of DM.

Results

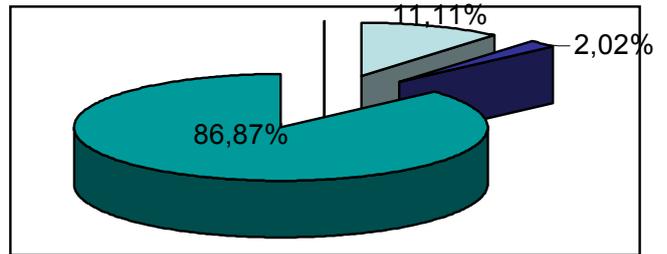
Of the 2198 children and adolescents taken in the study, 99 (4.5%) presented specific forms of diabetes (SFDM). (Figure 1).

In terms of the type of carbohydrate metabolism anomaly, 11 (11.11%) patients had altered fasting glucose (AFG), 2 (2.02%) decreased glucose tolerance (DGT) and 86 (86.87 %) had diabetes mellitus. (Figure 2).



□ Total no. of patients
 ■ Patients with specific forms of DZ

Figure 1. Distribution of patients based on the type of DM.



□ AFG ■ DGT

Figure 2. Distribution of patients with SFDM based on the type of carbohydrate metabolism anomaly.

Distribution of patients according to sex in patients without SFDM lot was as follows: 1073 (51.1%) male and 1026 female (48.9%) unlike lot of patients with SFDM in which 30 (30.3%) are boys and 69 (69.7%) are girls. (Figure 3 and Table 1).

Distribution of patients based on age is represented in table 2 and figure 4 and 5.

The specific forms of DM encountered in the studied lot were varied, the main groups being shown in Table 3.

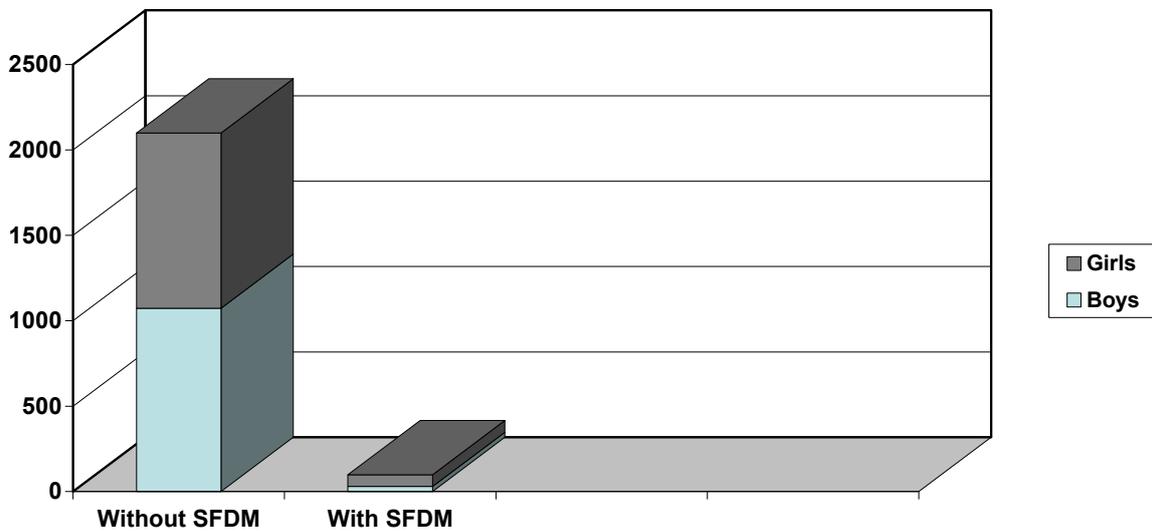


Figure 3. Distribution of patients according to sex.

Table 1. Distribution of patients according to sex.

Sex	Without SFDM	With SFDM	p
Boys	51.1 %	30.3 %	0.052
Girls	48.9%	69.7 %	0.052

Table 2. Distribution of patients based on age.

Age	Patients without SFDM	Patients with SFDM	p
< 3 yrs	1.09 %	2.02 %	0.022
3-6 yrs	5.81%	9.09 %	0.19
7-11 yrs	16.76 %	21.21 %	0.075
12-18 yrs	41.21 %	24.24 %	0.001
19-30 yrs	35.13 %	43.44 %	0.02

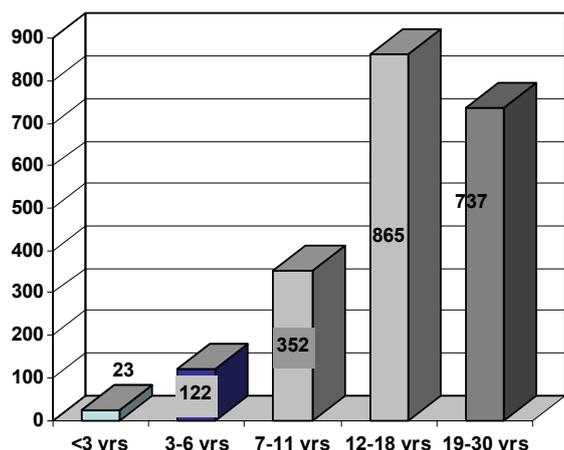


Figure 4. Distribution of patients without SFDM based on age.

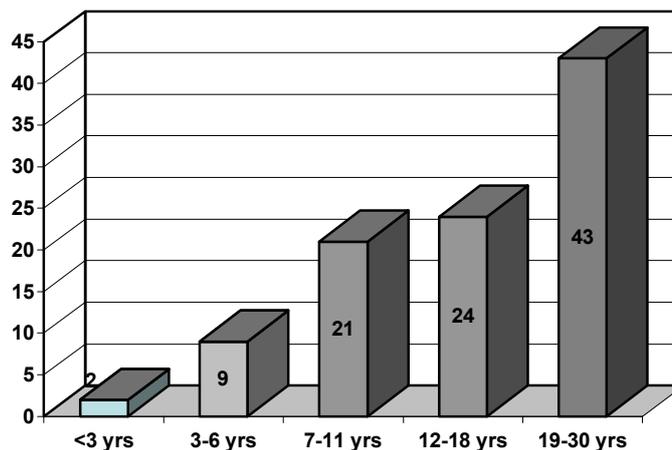


Figure 5. Distribution of patients with SFDM based on age.

Table 3. Specific forms of DM

Specific form of DM	Number of cases	Percent %
Pancreatic diseases	7	7.07
Insulin resistance syndrome (hereditary or acquired)	10	10.10
Genetic diseases	11	11.11
Associated endocrinopathies	34	34.34
Drug induced	25	25.25
Others (congenital and acquired infections, celiac disease, autoimmune disease)	12	12.13

Among the pancreatic diseases which is associated with DM, we encountered in studied lot residual inherited pancreatitis (2 cases), pancreatectomy (1 case), adenocarcinoma (1 case), hemochromatosis secondary to thalassemia (1 case) and cystic fibrosis (2 cases). (Figure 6).

Similarly in the insulin resistance syndrome group, 2 patients had type A (acanthosis nigricans, hyperandrogenism and polycystic ovary syndrome), 5 patients had type B insulin resistance syndrome (acquired by anti-receptor insulin antibodies), 1 case of HIV associated lipodystrophy and 2 patients (brothers) with spastic familial paralysis. (Figure 7).

Genetic diseases associated with DM were dominated by chromosomal disorders and those with genetic obesity:3 cases of Down syndrome and 1 case

each of Turner syndrome, Noonan syndrome, Prader-Willi syndrome, Laurence-Moon-Bardet-Biedl syndrome, Kearns Sayre syndrome, Phenylketonuria, Bourneville tuberous sclerosis and albinism. (Figure 8).

Endocrinological pathology dominate this group of patients, being represented by: hypothyroidism - 16 cases, hyperthyroidism - 11 cases, growth hormone deficiency - 1 case, the polycystic ovary syndrome - 3 cases and polyglandular autoimmune syndrome (PGA) type 2 - 3 cases. (Figure 9).

14 patients had corticotherapy induced carbohydrate metabolism anomaly, 3 patients with asparaginase induced and 8 patients by both the drugs. (Figure 10).

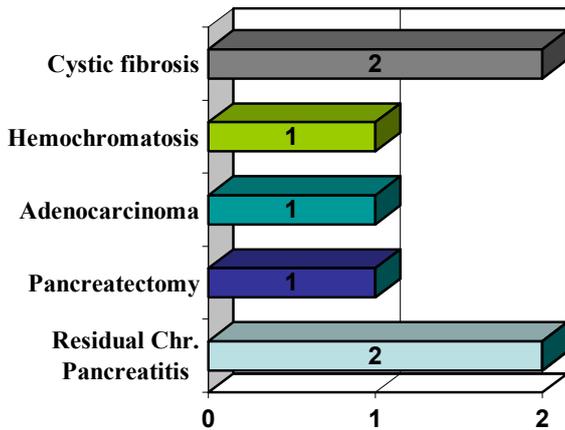


Figure 6. Pancreatic diseases associated with DM.

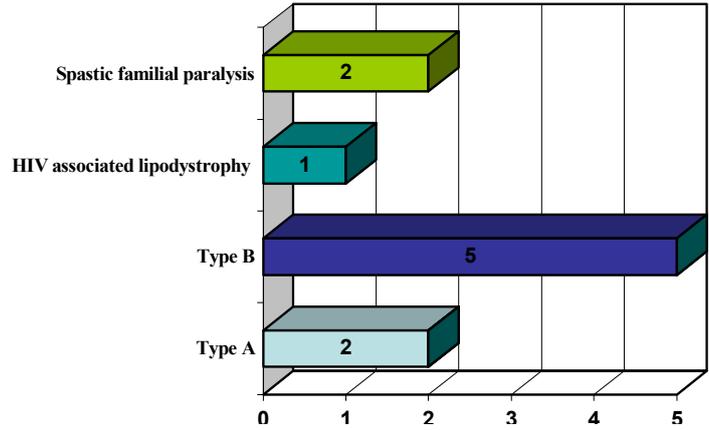


Figure 7. Insulin resistance syndrome associated with DM.

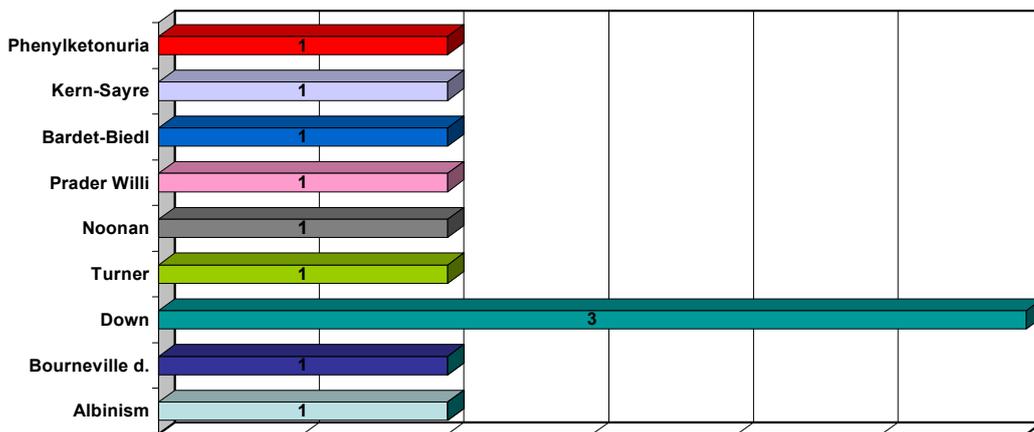


Figure 8. Genetic diseases associated with DM.

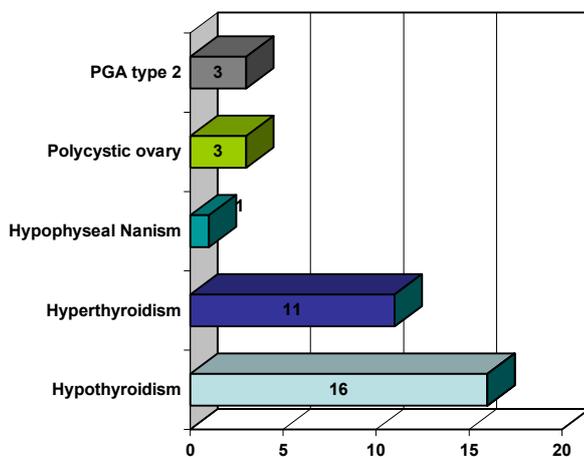


Figure 9. Endocrine diseases associated with DM.

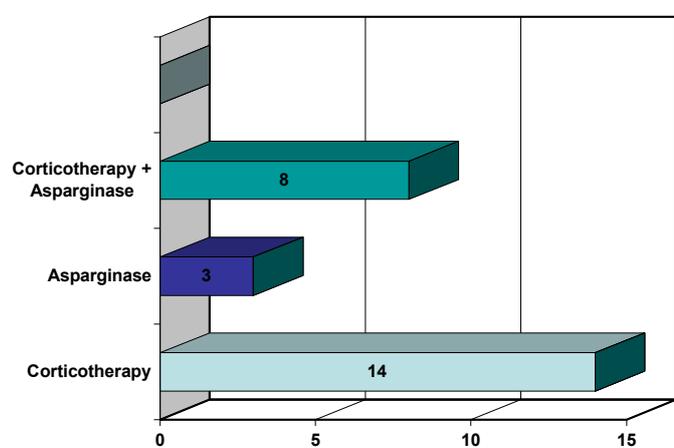


Figure 10. Drug induced DM.

Among congenital and acquired infections that are associated with DM, we observed in the study lot 3 cases of acquired infection with hepatitis C virus and 1 case each of HIV infection, congenital toxoplasmosis, congenital rubella and congenital infection with CMV. (Figure 11).

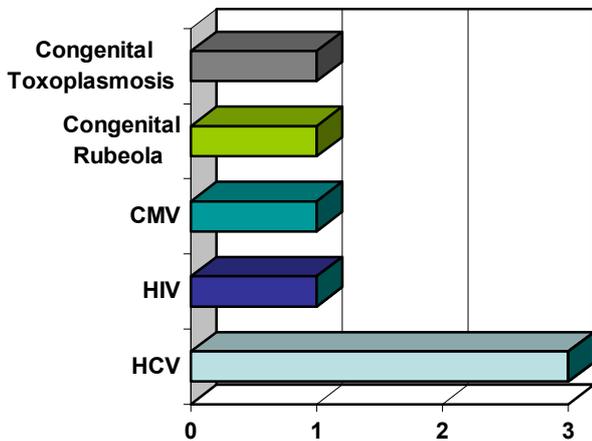


Figure 11. Infections associated with DM.

A special group was composed of: 2 cases of celiachie, 1 case of spondylitis ankylopoietica, 1 case of Takayasu arteritis and 1 case of chronic glomerulonephritis. A group of autoimmune diseases that are associated with DM is represented in Figure 12.

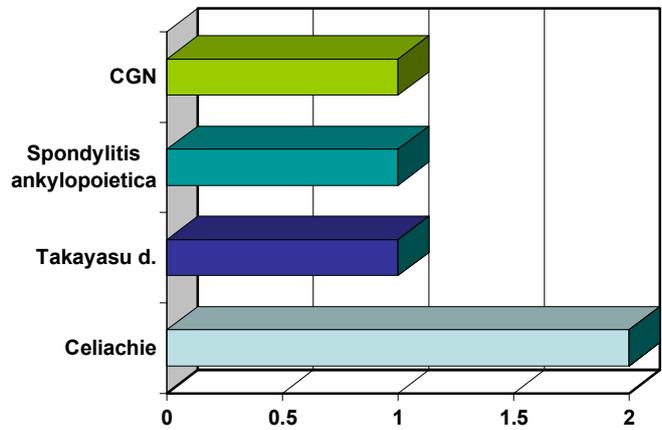


Figure 12. Autoimmune diseases associated cu DM.

Average glycosylated hemoglobin in the lot without SFDM was 9.68% while patients with specific forms of DM had an average HbA1c of 8.29%. (Figure 13 and Table 4).

Insulin requirement was lower in patients with specific forms of DM - 0.6 u/kg/day compared to those without SFDM - 0.87 u/kg/day. (Figure 14 and Table 4).

Table 4. Average Hemoglobin A1c and average insulin requirement.

	Without SFDM	With SFDM	p
HbA1c	9.68 %	8.29 %	0.066
Insulin requirement	0.87 u/kg/day	0.6 u/kg/day	0.022

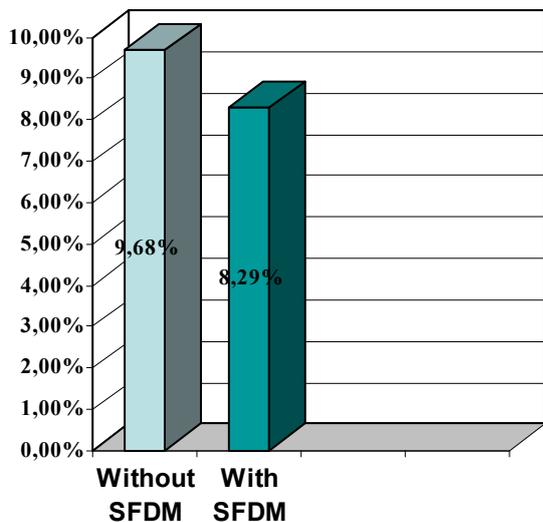


Figure 13. Average Hemoglobin A1c.

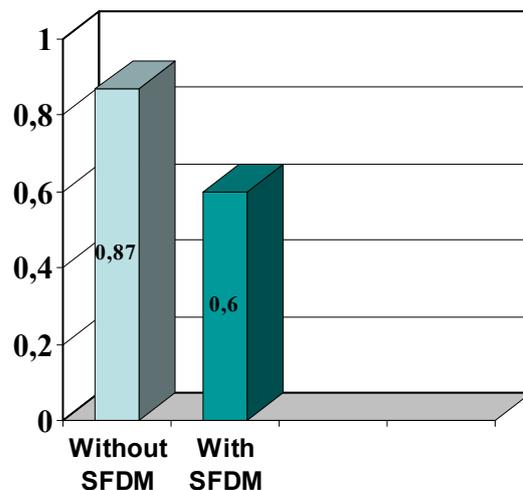


Figure 14. Average insulin requirement (u/kg/day).

Discussions

Chronic hyperglycemia indifferent of the associated pathology has the evolutive risk with regards to the long term complications of vascular or neurological origin. It is well known especially in DM type II but also sometimes in DM type I that complications precede the disease diagnosis. Unhealthy eating habits, smoking, alcoholism, use of anti-contraceptive pills are additional factors that could prompt and worsen these complications.

This is the reason why screening of glycemia disorders has become a compulsory practice, not only for people with high risk (like obesity, DM in siblings, gestational DM, dyslipidemia, polycystic ovarian disease, macrosome newborn etc) but also for the group of patients (though very limited) with diseases known to have an association with DM.

Screening using fasting glucose test, supplemented by OGTT \pm HbA_{1c} when required, will ensure an early diagnosis and thus making way to a therapeutical approach for reducing and minimizing the complications.

Specific DM, a relatively small group, making only 4.5% of the total cases of DM in children and adolescents, is a group of diseases with a high degree

of discomfort, which needs a complex therapeutical approach as it carries a much higher risk of complications. These morbid associations should be well known and recognized in our clinical practice so as to offer better hope and better quality of life to these patients.

Conclusions

1. Carbohydrate metabolism anomalies associated with other diseases represent 4.5% of the studied lot. Of these, DM represent the majority of cases - 86.7%, while AFG was noted in 11.11% of patients, and DGT in only 2.02% of cases.
2. A predominance of female patients was observed in the SFDM lot.
3. In the SFDM lot, we found almost double the number of patients < 3 years compared to the lot without SFDM, while the proportion was reverse for the 12-18 yr age group.
4. The most frequent SFDM is endocrinopathies, followed by drug induced DM.
5. Average Hemoglobina A1c and average insulin requirements were lower in patients with SFDM.

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IV. PEDIATRIC SURGERY

A 5 YEARS EXPERIENCE WITH THE DUPLICATION OF THE RECTUM

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Abstract

This paperwork presents several cases of congenital duplication according to localisation of the disease, type, complications, diagnosis and treatment.

Key words: congenital duplications.

Introduction

Congenital duplications of the alimentary tract are rare but potentially dangerous anomalies.

There is no sex predominance. Any segment of the intestinal tract may be concerned, but small bowel is more involved. Among the 764 cases of Daudet (1), 490 (64%) were small bowel duplications (57% jejunum and ileum, 7% duodenum), and 38 (about 5%) were duplications of the rectum.

Duplications are cystic or tubular structures located usually adjacent to the mesenteric border, but other locations were also reported (2, 3, 4). Rectal duplication may have diverse presentations, which include bowel or urinary obstruction, haemorrhage, infection, perforation, chronic obstipation, perianal fistula, perineal abscess, tumour of the labia major, exophytic tumour of the perineum, asymptomatic mass, pelvic floor hernia (5,6,7,8,9,10,11,12,13,14).

Therefore the diagnostic is often delayed or incorrect. The early complete excision is the choice therapy of the alimentary tract duplications. That is particularly important in rectal duplications because of the risk of late malignant change (15, 16, 17).

Material and methods

This review encompasses 6 patients with clinically different manifestations, 4 of them diagnosed and cured by first admission, while 2 have been treated elsewhere over a long period of time for perineal abscess, respectively undefined abdominal pain.

All patients were diagnosed and treated in our department from September 1992 to march 1996. This study used the patient's charts, preoperative investigations, intraoperative findings and histology. All patients underwent clinical follow-up 1 ½ - 5 y (mean 3 3/12 y) postoperative.

Case 1 (Op. 09/92)

An 11-month-old boy was recovered after a 5 months history of perineal abscess. He was twice operated but symptoms did not disappear. At admission he presented an inflamed retro anal fistula and had painful defecation. Putrid secretion flowed through fistula. Sonography findings were compatible with a retro rectal cystic tumour. After 7 days of antibiotic therapy and local betajodine bath the inflammation ceased. Through a posterior sagittal approach a retro rectal cystic tumour was removed. Histology: colonic structure.

Case 2 (Op. 03/93)

A 11-day-old male neonate was admitted with a left gluteal exophytic mass. He presented an asymmetry of the pelvis, his left thigh was hypotroph, his left foot was deformed (pes adductus). The following investigations were performed: plain x-ray and sonography of the pelvis and abdomen, echocardiography, micturating cystourethrogram, diuretic nephroscintigram, cystoscopy with retrograde ureteropyelography, nuclear magnetic resonance (NMR), urodynamik. These investigations showed the asymmetry and rotation of the sacrum and coccyx, left hip luxation, left kidney ectopy with gluteal herniation, vesicoureteral reflux II-III bilateral, spina bifida occulta with lipomeningocele and tethered cord, partial absence of the left gluteal muscles, cord anomaly, and

the left gluteal mass with continuity with the rectum. When he was 3 ½ months the mass was excised by the paramedian posterior sagittal approach.

Histology: colonic duplication.

Case 3 (Op. 09/93)

A 3-days-old female infant with a birth weight of 3210g was brought to our department with an anal cleft at “3 o’clock“(pat. in supination). Pelvic sonography showed no pathologic findings. A contrast enema was carried out: there was a diverticular structure communicating with the rectum. A transanal resection followed when the child was 3 weeks old. The postoperative course was uneventful. Histology: colonic structure.

Case 4 (Op. 07/94)

A 6-year-old girl was examined for an exophytic mass at the lower pole of the left labium minus. No other anomalies of outer genitalia, meatus urethrae or anus were observed.

Through mass (7x5cm), wich was covered by epithelium a probe was easy introduced. Paraclinical investigations detected a left ureteral duplication with ureteric ectopia and upper pole dysplasia, and vesicoureteral reflux of the lower pole. By means of a paramedian anterior sagittal approach the mass was excised. The upper pole nephroureterectomy was achieved by a subcostal incision.

Histology: rectal duplication covered by colonic and ectopic gastric mucosa.

Case 5 (Op. 02/96)

A 13 ½ -year-old boy was brought to our department after being treated over a long period for undefined abdominal pain. No pathological findings at physical examination were found. The sonography showed a precaval, subhepatic cyst with a diameter of 3 cm. Nuclear magnetic resonance scans (NMR) demonstrated the cyst located in the retroperitoneum. The excision was carried out through a right supra-umbilical transverse laparotomy. The cyst ended in the right side of the rectal wall (communication no visible) and was filled with grey fluidly-mucous content.

Histology: tailgut cyst lined by epithelium with gastric mucosa ectopy.

Case 6 (Op. 03/96)

A 3-month-old female infant was admitted for rectal bleeding. Rectal examination revealed walnut size tumour on the posterior wall of the rectum.

Sonography demonstrated a 3 x 2 cm cystic structure between sacrum and rectum. This tumour was removed by means of a posterior sagittal approach. The rectum and duplication shared the muscular layer. Six days after the operation a small dehiscence of the wound occurred. This closed spontaneously 10 days later. Histology: tailgut cyst (ectopic gastric mucosa included).

Results

The age at presentation of the 6 patients ranged from new-born to 13 ½ years (Mean: 3 4/12 yr.). The female: male ratio was 4:2.

There was a broad spectrum of clinical presentation:

-2 patients presented with extrophied perineal mass: one of them had multiple associated anomalies (AA) (case 2), the other only renal AA (case 4).

-1 neonate female was diagnosed with an anal cleft at “3 o’clock“(case 3).

-1 patient was seen because of rectal bleeding (case 6).

-2 patients came to us after previous therapy elsewhere: the first with perineal swelling was twice operated erroneously for perianal fistula (case 1), the second treated for chronic abdominal pain (case 5) with medications.

The preoperative diagnosis was extrophy of the rectum in 2 patients (cases 2 and 4), retro rectal cystic tumor in 2 (cases 1 and 6), diverticular rectal duplication in 1 (case 3), and retroperitoneal cystic tumor in 1 (case 5).

In three cases the preoperative diagnosis (AA excepted) was by clinical means only (cases: 2, 3, and 4), twice by examination and sonography (cases: 1 and 6), once sonography and NMR (case 5).

The surgical approach was perineal sagittal in 4 patient (posterior median in 2, posterior paramedian in 1, anterior paramedian in 1), transanal in 1, and laparotomy in 1.

Complete excision of the tumour was accomplished in each patient. All patients had intraoperative and postoperative antibiotic therapy, and were drained for 2-5 days postoperatively. Recovery was uneventful in all patients, except for a small wound dehiscence (case 6). Histological anatomy is shown in table I. Follow-up (mean 3 3/12 yr. postoperative): good function, good cosmesis in all cases, no complaints.

Table I. Histological anatomy of the excised structures.

>Small muscle coat	all
>Intestinal mucosa* - including crypts of Lieberkühn	all
>Gastric mucosa heterotopy	n = 3

*Taylgut cyst mucosa: cylindrical, transitional and squamous epithel, crypts of Lieberkühn.

Discussion

The embryogenesis of these abnormalities is uncertain. The most satisfactory theories of alimentary tract duplications are the partial twinning theory and that relating to the residua of the neurenteric canal. The dorsal anatomic location of most duplication is supportive of this last theory (9). However more duplications have been found in other sites on the bowel circumference (2,3,4). Perineal exophytic mass or tumour of the labia majora are other possible presentation forms of rectal duplications (12,13). Two of our patients had a very special duplication form: the rectum extrophy (cases: 2 and 4). An other one has a retroperitoneal, prerenal cystic duplication with the caudal end in the lateral wall of the rectum (case 5).

Clinic examination and sonography in the case of 5 patients provided enough information to submit the patients for surgery. A patient needed supplementary NMR investigation to improve diagnosis (case 5). Because high rate of AA, all patients with rectal duplications will be thoroughly clinicaly and, in doubt, paraclinically examined.

Differential diagnosis of rectal duplications enclose all pelvic, and some abdominal and perineal tumours. Rectal duplications can be confused with rectal polyps, haemorrhoids, anal fistula (case1), and perirectal abscess (8,10,11,18).

No patient in this series had duplication of the bladder, urethra or genitalia (19,20,21). Only one patient had an unilateral ureteral duplication (case 4). There were no duplications in our patients communicating with urinary tract or intraspinal space (22,23).

All lesions presented here fulfilled the criteria for alimentary tract duplications as defined by Ladd and Gross (24): a) contiguity with and strong adherence to same part of the alimentary tract; b) a smooth muscle coat; c) a mucosal lining consisting of one or more types of cells normally observed in the alimentary tract.

Presence of heterotopic gastric mucosa may be a source of rectal bleeding (7).

Malignant degeneration in rectal duplication in adults age is possible (15,16,17). Carcinoid tumour in a rectal duplication in children have been also reported (25). Therefore completely surgical excision is required.

These observations showed that the child with rectal duplication is a good candidate for surgical procedures planed to cure completely the child's suffering.

Early diagnosis avoids prolonged symptomatic treatment and unnecessary surgical procedures.

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BURKITT LIMPHOMA - CASE REPORT

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Abstract

We present the case of a 2 years and 8 months old girl admitted into the hospital for abdominal tumor. We come up with an exploratory laparotomy and we diagnosed tumor of the right colon with stenosis of the lumen, infiltrating the terminal part of the ileum with extension to the mezenster and retroperitoneum. The treatment in this case was surgical procedure (right hemicolectomy) associated with chemotherapy. The microscopic pathological exam showed the infiltration of the large bowel wall with lymphocytes and macrophages with an overall appearance of „starry sky”.

Key words: Burkitt lymphoma, mature B-cell lymphoma, infant.

Introduction

Burkitt lymphoma is named after Denis Parsons Burkitt, who mapped its peculiar geographic distribution across Africa. It is a high-grade B-cell neoplasm and epidemiologically has 3 major forms: the endemic (African) form, nonendemic (sporadic) form and immunodeficiency-associated variants. Burkitt lymphoma is one of the fastest growing malignancies in humans, with a very high growth fraction. It is a type of highly aggressive non-Hodgkin lymphoma (NHL), and it often presents in extranodal sites or as acute leukemia. The sporadic variant is present in North America and Europe and the endemic variant is observed in equatorial Africa. HIV-associated BL accounts for about 30% of lymphoma patients with HIV. These lymphomas have a rapid and aggressive clinical course, commonly presenting in children and young adults, with frequent bone marrow and peripheral blood involvement. It is considered to be a medical emergency and requires immediate diagnostic and therapeutic intervention.

Pathophysiology

Burkitt lymphoma (BL) is a mature B-cell lymphoma. All the symptoms are caused by rapid turnover of the mature B lymphocytes and the involvement of extranodal sites and invasion of contiguous organs. The characteristic feature of this entity is the dysregulation and mutation of the c-MYC oncogene. It often resulted from translocation of

chromosome 8 and 14 t(8:14). Other translocations are also reported causing c-MYC overexpression. The activation of C-MYC resulted in increased cell cycle progression, decreased apoptosis, increased cell growth and arrest of cell differentiation, increased cellular metabolism, and decreased cell adhesions.^[1]

Frequency Western Europe and United States: The incidence of sporadic BL is 2-3 cases per million individuals in the United States. It accounts for 1-2% of adult lymphoma cases, and up to 40% of lymphoma cases in children. Thirty to forty percent of HIV-related non-Hodgkin lymphoma (NHL) cases are Burkitt lymphoma.

International: Incidence of endemic BL in African children is much higher than in the United States. The children are usually 4-7 years. It was estimated to be 50 times higher. EBV (Ebstein-Barr Virus) infection is found in nearly all cases.

Race: No racial predilection is reported, although the endemic BL observed primarily in equatorial Africa has primary jaw involvement (70% in children aged 4-7 years versus 15-20% in the sporadic US variety).

Sex: The male-to-female ratio is 2-3:1.

Age: Endemic BL is common in children (30% of non-African pediatric lymphomas), but it is rare in adults (1-2% of all cases of NHL). Twenty to thirty percent of non-Hodgkin lymphomas (NHL) in HIV patients are Burkitt lymphoma (BL). It can present as an AIDS-defining illness and does not correlate with the CD4 counts.

Clinical forms: Three different clinical variants of Burkitt lymphoma (BL) are described: endemic, sporadic, and immunodeficiency related. Their presentations may vary^[2].

The endemic form is most commonly seen in patients in equatorial Africa, with face and jaw involvement. Other clinical presentations include abdominal masses, and ileal, cecal, ovarian, and breast involvement have also been documented. The geographic distribution of the tumor corresponds to the epidemiologic distribution of malarial infections.

The sporadic forms most often present with abdominal tumors with bone marrow involvement. Patients usually present with extranodal disease. It can also present as a leukemic type such as L3 lymphocytic

leukemia. Generalized lymphadenopathy is rare. Approximately 90% of patients with sporadic BL and 50% of patients with endemic BL have abdominal masses upon presentation.

In AIDS patients with Burkitt lymphoma, the disease usually is advanced at diagnosis and tends to involve extranodal sites. Most of these patients present with wide dissemination and bone marrow involvement. Because of their underlying immune deficiency and leukopenia, most of these patients tolerate systemic chemotherapy poorly. Death usually occurs shortly after diagnosis.

Clinical findings and symptoms

Face and jaw involvement in endemic BL (it only occurs in 15-20% of sporadic cases.) ,mandibular or maxillary mass

Abdominal masses can cause abdominal pain and distention, ascites, nausea and vomiting

Loss of appetite and/or change in bowel habits

Gastrointestinal bleeding

Signs and symptoms of acute abdomen (intestinal perforation ,right iliac fossa mass)

Renal failure as a result of retroperitoneal disease and renal involvement

Bone marrow involvement is common in BL.

CNS involvement is common, which includes the following: meningeal infiltration with or without cranial nerve (frequently third and seventh nerve) involvement .

Headaches, visual impairment, and paraplegia from spinal involvement may be initial presenting features in some cases

"B" systemic symptoms fever, weight loss, night sweats, fatigue

Ethyopathogenesis

The following are considered etiologic factors that are implicated in the pathogenesis of BL:

Viral: EBV is associated with 95% of endemic SNCC lymphomas and 20-30% of sporadic BL cases.

c-MYC oncogene activation: The classic t(8;14)(q24;q32) reciprocal translocation (85%) results in the transposition of the c-MYC proto-oncogene on chromosome 8 with one of the immunoglobulin genes on chromosome 14, which results in activation of the c-MYC gene and is considered responsible for tumor proliferation. The variant translocations involving c-MYC transposition to the other immunoglobulin genes, t(2;8) and t(8;22), are also found in BL. C-MYC mutations are also presented. ^[3]

P53 gene: Abnormalities in P53 genes have also been reported and are thought to be associated with the pathogenesis of BL

Lab Studies

Flow cytometry of biopsied tissue or bone marrow may reveal expression of immunoglobulin M (IgM) surface immunoglobulins (most common) as well as other mature B-cell markers such as CD19, CD20, CD22, CD79a, and CD10. Tdt, CD5, CD23, and CD34 negative. ^[4,5]

Cytogenetic studies may reveal one of 3 reciprocal chromosomal translocations: t(8;14)(q24;q32) in 85% of cases, t(2;8)(p12;q24), and t(8;22)(q24;q11). ^[4,5]

Serum chemistries :electrolyte imbalances occur as a result of renal infiltration with lymphoma. The rapid turnover of the Burkitt lymphoma (BL) cells may cause primary tumor lysis. Oliguric renal failure may be a presenting feature of patients with a high tumor burden, resulting in uric acid nephropathy. Serum lactate dehydrogenase (LDH) level, if elevated, corresponds with tumor burden and the extent of disease. It is also a useful indicator of the patient's response to treatment and can be used as an early nonspecific indicator of disease relapse. Liver function test results, if abnormal, may be indicative of visceral involvement with lymphoma. Beta2 microglobulin is a predictor of the extent of disease and is used as a surrogate marker for early relapse. Serum uric acid levels, if high, reflect the high-grade nature of the disease and correlate with the probability of tumor lysis syndrome with initiation of cytotoxic therapy. Complete blood counts may reveal pancytopenia (anemia, thrombocytopenia, and/or leukopenia) due to the involvement of the bone marrow.

Imaging Studies

CT scan of the abdomen and pelvis can be used to evaluate for abdominal and pelvic lymphadenopathy, masses, and visceral involvement. This helps in determining the extent of the disease and may aid in determining the most suitable site for biopsy. CT scanning of the chest should be performed to complete the staging workup. CT scan or MRI of the brain or spinal cord is indicated if neurologic signs are present. Findings on gallium scan provide an estimate of the extent of disease, and gallium scan is used as a follow-up tool in assessing sites of relapse.

Diferential diagnosis

Burkitt lymphoma must be distinguished from other primary abdominal tumors in childhood, including Wilms tumor, neuroblastoma, and peripheral neuroectodermal tumor. In the bone marrow, it must be differentiated from B and T precursor and myeloid leukemias. In peripheral B-cell lymphomas, the major

differential diagnosis is with diffuse large B-cell lymphoma.^[6]

Procedures for diagnosis

Laparotomy was indicated for initial diagnosis and for resection of the disease years ago; it is not recommended by current guidelines. The diagnosis of BL or BLL(Butkitt-like lymphoma) is made by obtaining a biopsy of the tumor mass for histopathology, immunochemistry, and flow cytometry. Cytogenetic studies to identify C-Myc mutation will aid in the diagnosis. *Bone marrow aspirate and biopsy*: the aspirate should be sent for cytogenetic studies. If lymphoma cells are present in the aspirate, flow cytometry/immunophenotyping should be ordered to further characterize the disease.^[6] Bone marrow is involved in 20% of sporadic cases and 8% of endemic cases. Obtaining bilateral biopsy and aspirate specimens is highly recommended. *Lumbar puncture* (LP) is considered part of the staging workup. LP should be performed to ascertain meningeal involvement. The CSF should be sent for cytology and, possibly, flow cytometry in addition to the usual studies. Intrathecal chemotherapy is usually given at the time of initial LP.

Histologic Findings

Extranodal involvement shows monotonous morphology with cells of uniform size and shape. The cytoplasm is scanty, and the nucleus is round or slightly irregular with slightly coarse chromatin and several nucleoli. Mitotic figures are frequently seen. The description of "starry sky appearance" is because of the scattered macrophages with phagocyte cell debris under the microscope. However, the starry sky pattern is not pathognomonic for BL and may be observed in other highly proliferative lymphomas. Immunophenotype and cytogenetic studies are aiding the diagnosis of BL.

Staging

Ann Arbor system and Jude/Murphy staging are commonly used.

Stage I Single tumor (extranodal)
Single anatomic area (nodal)

Stage II Single tumor (extranodal) with regional node involvement

Primary gastrointestinal tumor
Lymphoma involving sites on the same side of the diaphragm

Stage III Lymphoma involving sites both above and below the diaphragm

Stage IV Any of the above with CNS or bone marrow involvement at presentation

Medical Care

Patients in whom BL is suspected should be admitted to the hospital. These patients experience rapidly progressive of extranodal sites; therefore, a diagnostic workup should be completed as soon as possible. Consultation with a hematologist and hematopathologist should be obtained as soon as possible. Measures should be taken to prevent tumor lysis syndrome

Surgical Care

The role of surgical debulking in patients with BL has become controversial because of improved response rates (ie, up to 90%) with combination chemotherapy alone. Historically, most patients who presented with large masses, particularly abdominal disease, underwent an exploratory laparotomy, at which time an effort was made to debulk as well. With newer sophisticated interventional radiology approaches, an adequate diagnosis can be reached in almost all patients without major surgical intervention. In current clinical practice, effective and durable responses are observed with combination chemotherapy, obviating the role of surgical debulking.

Tracheotomy is indicated if the patient's airway is compromised from the physical pressure of a large tumor mass and exploratory laparotomy due to bowel obstruction (often before the diagnosis was made)

Patients with uncontrolled gastrointestinal bleeding also may need exploratory laparotomy or endoscopic procedures for hemostasis.

Pericardiocentesis is indicated for patients presenting with cardiac tamponade.

Paracentesis is indicated if large ascites is one of the presenting complaints.

An excisional lymph node biopsy is usually necessary to reach an accurate diagnosis.

A semipermanent intravenous catheter such as a peripherally inserted central catheter (PICC) line or medicine port should be arranged with interventional radiology or surgery to aid chemotherapy, medications, blood products, and fluid management.

Treatment

Systemic combination chemotherapy is the treatment of choice for all stages of Burkitt lymphoma (BL). It should be started as soon as possible as the diagnosis is made. With current short, intensive chemotherapy approaches, cure rates have been reported in the range of 90% for children and up to 89% in adults. Most protocols incorporate cyclophosphamide, methotrexate, vincristine, and

doxorubicin, with or without corticosteroids. Two to 3 months of treatment is now considered sufficient depending on the stage of disease, with reported cure rates of 90-100%. Radiation has no role in the management of any stage of disease. BL is considered to be a systemic disease^[7,8].

Based on the extent of disease and LDH level and cytogenetic studies, patients can be stratified into low-risk and high-risk categories.^[9]

Low-risk category: Patients have low tumor burden, as determined by low LDH level, completely resected abdominal disease, or a single extra-abdominal site of disease. In such cases, combination chemotherapy (preferably via a clinical trial) should be considered.

High-risk category: Patients have high tumor burden, as determined by a high LDH level, and extensive abdominal or extra-abdominal disease. These patients are at high risk for relapse. Combination chemotherapy in the setting of a clinical trial is the recommended way to treat these patients. High-dose methotrexate, anthracyclines, alkylating agents, and intrathecal chemotherapy are usually used. Patients who have CNS or bone marrow disease should be considered for enrollment in clinical trials involving consolidation with high-dose chemotherapy with autologous stem cell rescue^[10,11].

Mortality/Morbidity

Approximately 90% of pediatric patients with BL treated with current intensive chemotherapy regimens have long-term disease-free survival. For those experience relapse, as many as 25% of patients may be able to achieve a long-term disease-free survival through high-dose therapy with autologous hematopoietic stem-cell transplantation.

Case report

We present the case of a 2 years and 8 months old girl, who was admitted in Pediatric Surgery Clinic after transferring her from a pediatric department with the following symptoms: colic-like abdominal pain in the right hemiabdomen and abdominal distension, bilious vomiting ,fever, nocturne sweats., change in bowel habits with present intestinal transit. Two months ago she was admitted into Pediatric Clinic with an acute viral pneumonia, Mallory-Weis syndrome and intestinal parasitizes (Giardia lamblia).After that she had recurrent abdominal pain, fatigue, loss of the appetite with weight loss.

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

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

Imagistic data: X-ray thoracic and abdominal did not offer useful diagnostic information. Barium enema showed the barium column stopped below the hepatic angle of colon which is more dilated. MRI abdominal: revealed posterior pancreas displacement ,dilatated ascendant part of the large intestine with enlarged and dualised wall, much thicker than normal, with ileum displacement to the right,small quantities of liquid in the interhepato-diaphragmatic and parietocolic right space; normal findings for liver, kidneys, spleen; (Fig.1).

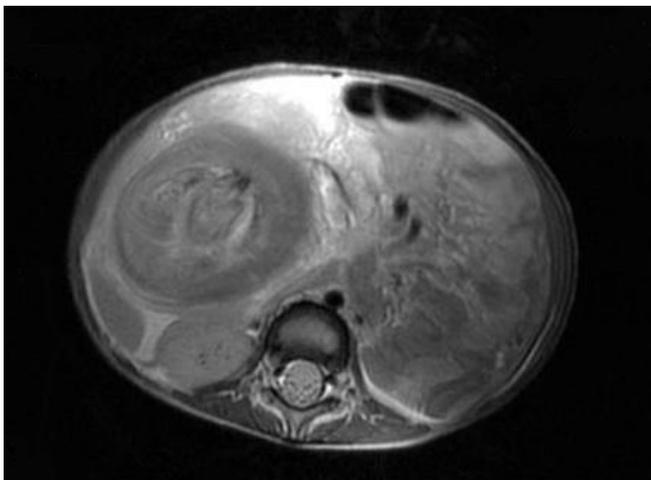


Fig. 1: Burkitt lymphoma, abdominal MRI.

Treatment: After all these investigations we decided to do exploratory laparotomy in order to establish the diagnostic and the treatment. After a short period of preoperative preparation we performed a median laparotomy. We found moderate ascite liquid,

endoluminal tumor of the caecum and ascendant colon extended on about 10-15 cm in length, with stenosis of the lumen, infiltrating the terminal part of the ileum with extension to the mezenfer and retroperitoneum.(Fig.2).



Fig. 2: Burkitt lymphoma, intraoperative details.

We practiced right hemicolectomy with ileotransversoanastomosis termino-terminalis, with biopsy of the mesenteric and epiploonal ganglia and peritoneal drainage. The postoperative care was done in the Intensive Care Unit in the first 5 days, then in the Surgery Compartment and it consisted of solution of parenteral nutrition (glucose, amino acids), antibiotics (piperacillin tazobactam), electrolytes, vitamins .The evolution was favorable and she was transferred in Oncology Department for chemotherapy.

medium shapes and scanty cytoplasm , round noncleaved nucleus and several nucleoli with high mitotic activity and macrophages with the appearances of the “starry sky”.The "starry sky appearance" frequently was seen both in ileum and in paracolic and epiploonal ganglia (Fig.3).We have not had possibility to do cytogenetic studies and flow cytometry of biopsied tissue or bone marrow.The diagnostic was Burkitt lymphoma,(abdominal beginning) with high grade of malignancy.

Histopathology findings revealed enlarged bowel wall infiltrated with atypic lymphoid cells with

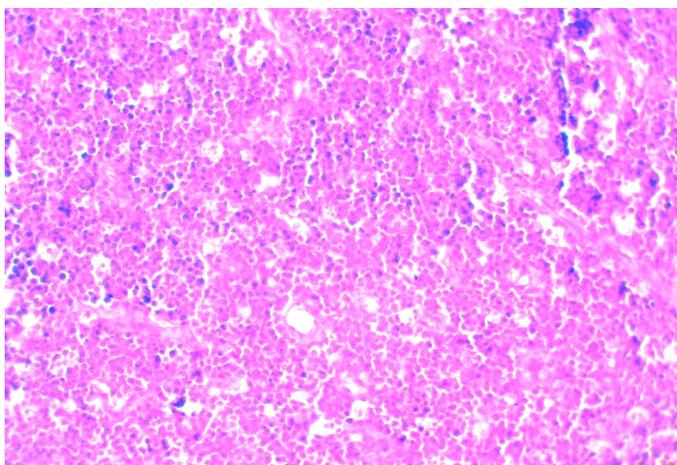


Fig. 3: Burkitt lymphoma showing the “starry sky appearance” (Hx-E, x 20).

Discussions

With newer sophisticated interventional radiology approaches, an adequate diagnosis can be reached in almost all patients without major surgical intervention. CT scan of the abdomen and pelvis helps in determining the extent of the disease and may aid in determining the most suitable site for biopsy. Histopathology, immunochemistry and flow cytometry of the biopsied tissue establish the diagnosis. Effective and durable responses (up to 90%) are observed with combination chemotherapy alone, obviating the role of surgical debulking.

In this case we suspected abdominal tumor according with anamnesis, clinical findings and

laboratory data. In malignancy disease there is pancytopenia, but high number of leucocytes and thrombocytes was showed in blood exam. The abdominal MRI suggests terminal ileum caecum intussusception in the ascendent part of the large intestine and did not offer any information about tumor or lymphadenopathy. We performed exploratory laparotomy with right hemicolectomy with ileotransversoanastomosis termino-terminalis and biopsy of the mesenteric and epiploonal ganglia in order to establish the extend of disease. Lymphoma cells were not presented in the bone marrow aspirate or in central spinal liquid. According to Ann Arbor system and Jude/Murphy staging this case was stage II.

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ESOPHAGOPLASTY IN CHILDREN - A 28 YEARS SINGLE CENTRE EXPERIENCE

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Abstract

The need for esophageal replacement in children has been dramatically reduced over the past 2 decades. Despite this fact, esophageal substitution is still required for resistant caustic or peptic esophageal stricture or long gap esophageal atresia. The purpose of this study is to present the authors experience in colon and gastric tube esophagoplasty in children. We retrospectively reviewed the records of 70 patients who underwent esophagoplasty for data regarding demographics, initial esophageal diseases, complications, and mortality. The follow-up period was 25-30 years Twenty-two cases (31,4%) had proximal stricture. 14 patients required surgical revision of the anastomosis after failure to respond to dilatation The global mortality rate was 7,14%. Despite the complications, the long-term outcome of the patients was considered good to excellent in terms of normal weight gain, absence of dysphagia, and other gastrointestinal symptoms

Key words. Esophageal stenosis, gastric tube esophagoplasty, colic tube esophagoplasty.

Introduction

Various alternatives for esophageal substitution have been proposed and their respective drawbacks widely discussed. Every effort is made for the preservation of the patient’s native esophagus after caustic ingestion.

Satisfactory results have been reported for all forms of esophageal replacement, although the numbers reported are small.

Purpose

The aim of the study is to retrospectively evaluate authors experience regarding the indication, clinical presentation, technique, complication and results in esophagoplasty during the last 28 years

Material and method

We retrospectively reviewed the records of 70 patients who underwent esophagoplasty for data regarding demographics, initial esophageal diseases, complications, and mortality. The operative technique was scrutinized for the presence or absence of esophagectomy, the choice of the intestinal segment, the type of pull-through. The intraoperative as well as the postoperative complications were recorded, and the mortalities reviewed. The period of follow-up and the presence of specific symptoms such as dysphagia, regurgitation, abdominal pain, and repeated chest infection were recorded

Results

From 1975 to 2003 37 children underwent colonic interposition and 33 children underwent gastric tube esophagoplasty for esophageal replacement. The indications for surgery are presented in Table 1.

Table 1. Indication for surgery.

Diagnostic	Gastric tube
Esophageal atresia	2
Caustic strictures	67
Peptic strictures	1

Most patients (95,5%) had post caustic esophageal stenosis, who did not respond to conservative treatment (endoscopic dilatation).

All the children were fed exclusively through a Stamm gastrostomy before the definitive operation.

The patients’ age range was 2 months to 17 years (Table 2). There were 37 boys and 33 girls.

Table 2. Age at surgery.

Age	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-17
Number of cases	7	29	15	7	3	2	2	5
%	10	43	21	10	4	3	3	7

As clinical symptoms all the patients had various grades of dysphagia for solids, liquids, vomiting and weight loss.

All patients had barium enema, and 20% had endoscopic evaluation.

30% of the patients with strictures had their first dilatation at 6 to 8 weeks from the injury. Dilatation

was mainly antegrade dilatation using the Savary Gillard dilators over a guidewire (fig2). All patients undergo dilatation once every 2 weeks in the first 3 months, then once every month for the next 3 months, and once every 2 months for 6 months. Dilatations were conducted under general endotracheal anesthesia in all patients.



Fig. 1 Endoscopic dilatation.

Table 3. Endoscopic stenosis location.

Esophageal stenosis	1/3 inf.	1/3 middle	1/3 sup
Cases	15	25	30
%	21,5	35,5	43

The surgical techniques used were:

- Anisoperistaltic gastric tube replacement (Gavriliu technique).
- Isoperistaltic left colon tube esophagoplasty.
- Isoperistaltic transverse colon tube esophagoplasty (Waterstone technique).

Table. 4. Type of esophagoplasty.

Type of surgery	Placed	Nr. of cases	%
Gastric tube	Retrosternally	8	11,4
	Posterior mediastinum	25	35,7
Transverse colon tube	Retrosternally	27	38,5
	Posterior mediastinum	6	8,57
Left colon tube	Retrosternally	4	5,71
	Posterior mediastinum	0	0

The colon was placed either retrosternally or in the posterior mediastinum in the esophageal bed. When the esophageal bed was chosen, the old burned esophagus was extracted (fig. 2). Both thoracic

pathways were obtained by combined blunt finger dissection through abdominal and cervical incisions, without the need of thoracotomy.



Fig. 2. Burned esophagus with stenosis.

The colon was always interposed as an isoperistaltic segment. The esophagocolic anastomosis was performed in the neck in 2 layers, in all cases end-to-end anastomosis.

In all patients, the gastrostomy was maintained in the postoperative period to provide gastric decompression for 30 to 90 days. Also all patients had cervical, mediastinal and cervical drains left in place.

The oral intake was permitted around 10-19 days after surgery.

All patients received intravenous antibiotherapy.

There were 5 deaths in the series, with a mortality rate of 7,14%. 3 died in the early postoperative period from either respiratory or cardiac failure, and 1 died more than a year postoperatively. One child in the esophagocoloplasty group developed graft necrosis and was treated by urgent surgical revision in the second postoperative day to remove the necrotic colon. Unfortunately she developed severe mediastinitis and

died. All of these children had had complex courses after the esophagoplasty with severe complications (sepsis, esotraheal fistulae, mediastinitis, and neoesophagus necrosis).

Anastomotic leakage at the esophagogastric connection occurred in 10 patients (14,2%), all except four of which closed spontaneously. There were 2 cases of gastric tube esophagoplasty and 8 cases of colic tube esophagoplasty.

Anastomotic strictures developed in 22 patients (31,4%), 7 patients with gastric tube esophagoplasty and 15 from colic tube esophagoplasty. In all patients except 3 gastric tube and 11 colic tube the cervical stenosis was successfully treated by endoscopic dilatations

In the 14 patients requiring stricture resection, the procedure was completed successfully via a cervical approach.

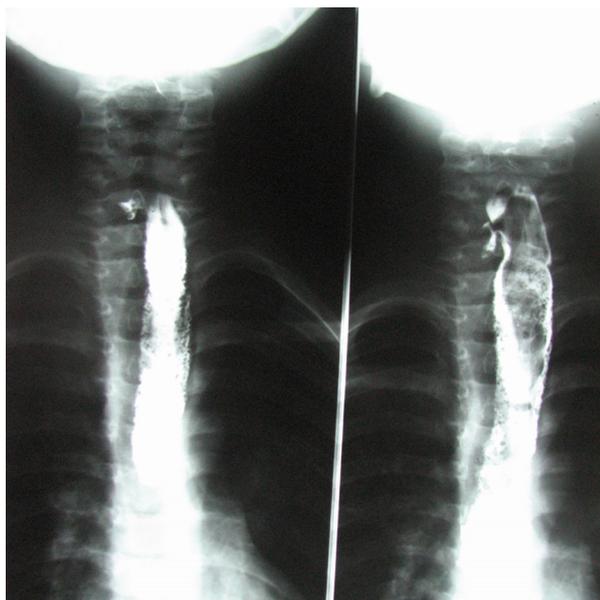


Fig. 3. Suprastenotic diverticula.



Fig. 4. Suprastenotic dilatation.

There was one late complication, an occlusive syndrome that needed reintervention.

Despite the complications, the long-term outcome of the patients was considered good to excellent in terms of normal weight gain, absence of dysphagia, and other gastrointestinal symptoms.

The follow-up period was 25-30 years.

30 patients had swallowing problems (minor), associated in 10 cases with weight lost.

Oral radiographic contrast studies have been performed at 6 month, 1 year, and 20 of follow-up; neither anastomotic stricture nor redundancy of the neoesophagus was observed (fig. 5).

All gastric tube patients were investigated regarding the presence of gastro-esophageal reflux, 28 of the with positive results, were medically treated. 20 patients from the gastric tube group also had endoscopy with mucosal biopsies. None of the had any signs of metaplasia.

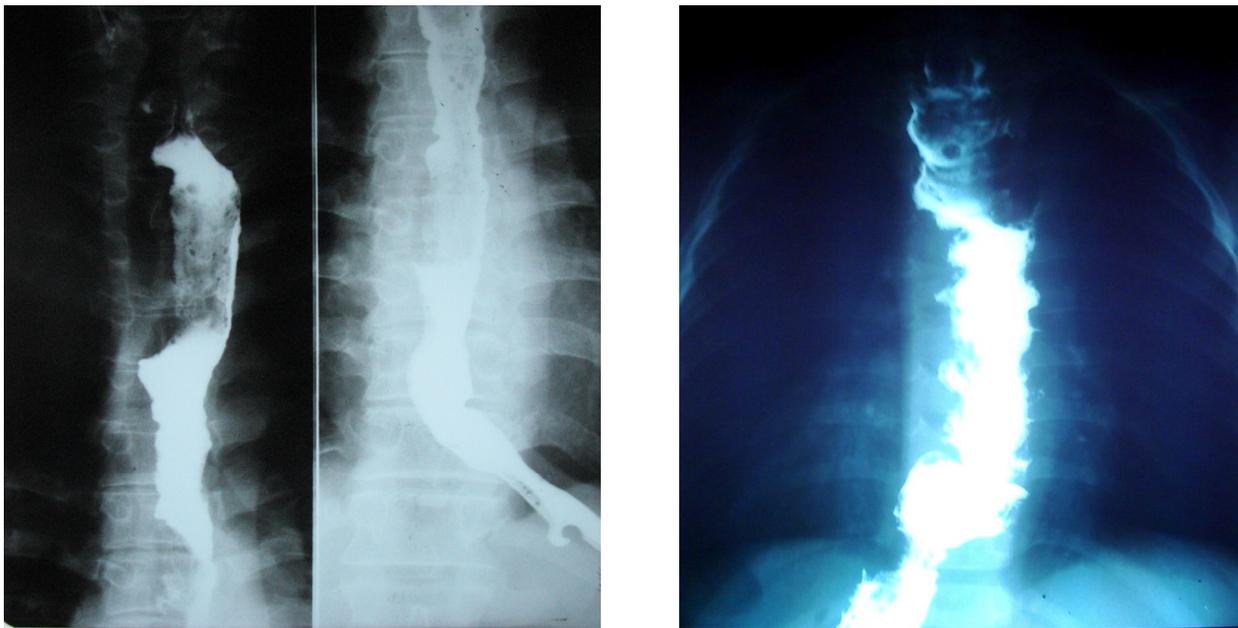


Fig. 5. Gastric tube and colic tube esophagoplasty.

Discussions

Various alternatives for esophageal substitution for intractable caustic stricture are reported in the literature, including gastric tube interposition in an isoperistaltic or antiperistaltic fashion or colonic interposition, gastric transposition, or jejunal interposition graft. Each technique has advantages and disadvantages.

The ideal esophageal substitute should conform in function as far as possible to the original structure. The patient should be able to swallow normally and experience no reflux symptoms. An additional requisition in children is that the substitute should continue functioning for many decades without deterioration.

Although no substitute functions as well as a normal esophagus, children who require this operation do not have a normal esophagus. In many cases the substitute is clearly inferior to the native esophagus.

Comparative results between colon transplant and gastric tube esophagoplasty may conclude that they are both acceptable procedures of esophageal substitution. Colon interposition is the most commonly used operation in children.

The major early complication of the esophagocoloplasty remains graft necrosis with an incidence between 0% and 20%. Gradual infarction of the colonic interposition secondary to venous obstruction may occur weeks or months after surgery. This complication will require another esophageal

substitute. In our series only one children had this major complication.

Removal of the strictured native esophagus is required because of an increased risk of malignant changes and chronic inflammation in the burned esophagus left in place on long-term follow-up. In the same way, removal of a failed graft is better than its withdrawal, but it is not always possible.

Late complications of esophageal substitution occur with varying frequency and can affect the ultimate function of the transplant. Stricture of the cervical anastomosis after leakage can lead to varying degrees of dysphagia. Twenty-two cases (31,4%) had proximal stricture. 14 patients required surgical revision of the anastomosis after failure to respond to dilatation. Redundancy of the interposed colonic graft in the chest may lead to stasis and dysphagia because of kinking of the transplant. Careful removal of the excess colonic segment from its proximal end before esophagocolic anastomosis and suture of the transplant to the margins of esophageal hiatus may decrease the incidence of this complication.

Postoperative bowel obstruction is always a potential problem after abdominal surgery. This complication occurred in one patient.

In reports of children who underwent esophagocoloplasty or gastric tube esophagoplasty, there is always a great concern for postoperative life-threatening complications and mortality rates. An important result of the present series of patients is the

global mortality rate (7,14%), the same as the mortality rate of 6% to 9% observed in other reported series of esophageal substitution.

The overall quality of life was considered good for most of the patients.

In conclusion, our experience demonstrates that esophagocoloplasty and gastric tube esophagoplasty are satisfactory surgical methods for esophageal replacement in children.

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THE ONIZUKA TECHNIQUE IN TREATING THE CLEFT LIP AND PALATE

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Abstract

By studying the Eurocleft Project 1996 – 2000 report, after analyzing the reports received from 201 European centers which treat cleft lip and palate (CLP), we notice the existence of many approaches for treating this particular malformation, utilizing very different surgical techniques, hardly finding similar methods (1).

The author analyzed the results obtained by utilizing the Onizuka as the main treatment scheme of the CLP, through a prospective study including 63 children with CLP, treated in the Pediatric Surgery and Orthopedics Department of the “Sf. Maria” Children Hospital, in Iasi, between January 1995 – December 2004. From this lot, 9 (14,29%) patients had only a cleft lip, and 54 (85,71%) had a cleft lip and palate. 41 (65,08%) patients had the cleft on the left side, 13 (20,63%) on the right side, and 9 (14,28%) had bilateral clefts. 34 (53,97%) patients were boys and 29 (46,03%) patients were girls. Most of the patients were operated at the age of 5-6 months. All the patients were operated by the author.

CLP represents a common malformation, by some authors is considered to be the 2nd most frequent congenital malformation found in live newborns: 1 in every 700-800. Generally it is considered that 25% of the cases have only a cleft lip, and 50% of the cases have a complete cleft lip and palate (2,3,4,5,6,7). The malformation is an infirmity due to the multiple consequences such as: esthetical appearance, psychological effect, defective speech, malnutrition and the associated pathologies.

The surgical treatment of CLP represents the most important part of the treatment process, due to the fact that this intervention corrects the esthetical appearance of the child, a very important step for the family, for the social insertion of the patient and last but not least it prevents otitis and respiratory infections, it assures normal speech, it corrects the dentition, which will lead to a healthy nutrition, therefore a life that is closer to normal.

Due to the complexity of this malformation and the multiple long-term implications, multiple treatment schemes have been created as well as numerous

surgical methods for each step of the treatment. None of the treatment schemes has proven to be ideal.

Key words: cleft lip and palate, surgical treatment.

Method and Material

There has been a prospective study on a lot of 63 patients who suffered from CLP, treated in the Pediatric Surgery and Orthopedics Department of the “Sf. Maria” Children Hospital, in Iasi, between January 1995 – December 2004. From this lot, 9 (14,29%) patients had a cleft lip and 54 (85,71%) had a cleft lip and palate. 41 (65,08%) patients had the cleft on the left side, 13 (20,63%) on the right side, and 9 (14,28%) patients had bilateral clefts. 34 (53,97%) patients were boys and 29 (46,03%) were girls. Most of the patients were operated at the age of 5-6 months. All the patients were operated by the author.

Results and Discussions

The study was a prospective study, which took place between January 1995 – December 2004. I have utilized the Onizuka technique for the cheilo-plasty in all the patients. In 3 cases I have utilized the first version of the surgical technique, published by the author in 1980 (8), in order to use, later on, only the version modified by Onizuka, published in 1991 (9) (fig. 1, A and B).

I have used the first version of the Onizuka technique, a method that resembles the Millard technique modified for extending the outer margin of the cleft, only in 3 cases, with a satisfying result, but later on using the revised method by Onizuka. The results have improved, especially the esthetical aspect of the nostril. As a result I have used, since then, this technique in most situations.

As well as in other techniques, a pre operator drawing is needed, based on the contour lines of the upper lip. Although it is an extremely precise method, conceived for complete cleft lip and palate, knowing the meaning and exact position of every dot, the method can be used for any kind of cleft. Even though the author makes no reference in utilizing his technique in bilateral CLP, I have used this method in bilateral clefts either in two steps, or one.

Regardless of the anatomo-clinic shape and the timing of the used surgical treatment used for CLP, in most of the patients (41 – 65,08%) the cheiloplasty was practiced between 4-6 months of age. The extremities were between 3 months and 3 years due to certain different situations: associated pathologies (most frequently were respiratory affections – infections of the upper airways, bronchitis, pneumonia

and bronchopneumonia; dystrophy, anemia, acute ORL affections), associated congenital malformations (cardiac malformations, Pierre Robin syndrome). There were, however, many uncontrollable social difficulties, which prevented the families to consult a doctor in time, or due to the lack of education have unallowably delayed the starting or continuing of the treatment.

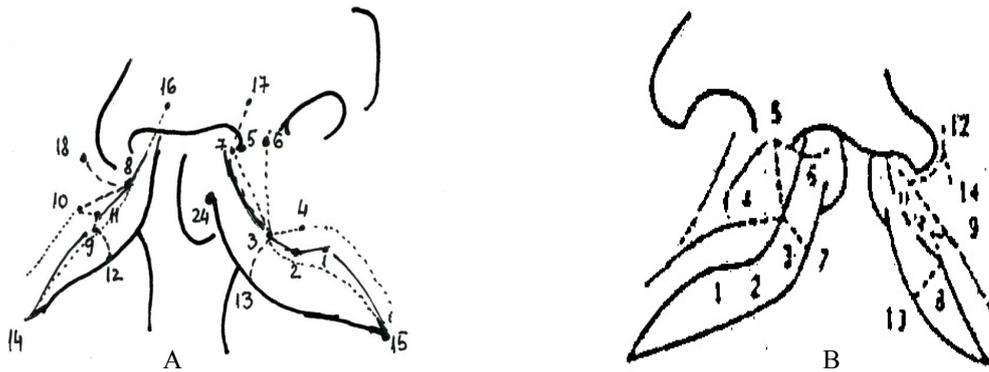


Fig. 1. The Onizuka Method (A. First version; B. Second version – the basic guide points for marking the incisions).



Fig. 2. A 5 year old patient with a CLP, operated using the Onizuta technique (first version).



Fig. 3. 5 months old patient, pre operator aspect.



Fig. 4. Same patient – imediatly post operation aspect.

The presented results are guidelines. When the mother leaves the maternity, instead of respecting the given advice to meet with the pediatric surgeon for a preliminary consult, and returns for the operation (cheiloplasty) with the child at 1 year old, or from different social/financial reasons returns for the uranostaphilography at the age of 5 years or comes at the age of 15 years for an orthodontic treatment it is difficult to talk about therapeutic protocols.

As a conclusion, I consider, as well as other authors, that the Onizuka technique has many advantages compared to other cheiloplasty methods: clear and precise identification of all the anatomical guides that define the pre operator scheme; post operator scars do not cross the nostril gap; the use of a triangular flap used in the reconstruction of Cupidon's bow creates a natural philtrum; this flap does not perpendicularly cross the philtrum, like in the other techniques and as a result lower the frequency of hypertrophic scars; the tip of the triangular flap,

positioned correctly, leads to the accentuation of the philtrum's fossa; by aligning the incisions, the philtrum's margins are not destroyed, instead it overlays enhancing the contour; it corresponds with the groove of the upper lip (8,9,12). One of the disadvantage of using this technique, however major, is the fact that the method is precise, rigorous and as a result it must be perfectly known, and the pre operator drawing must be prepared in detail, because a wrong cut in a flap leaves little room for errors, unlike the Millard technique which allows correcting, on the way, the different errors (8,9,12).

Regarding the esthetical and functional results, I believe that the Onizuka technique offers plenty of satisfactions to the patients, as well as the surgeons, being a good choice in the treatment of this pathology, fact exemplified by the evolution of patients over time.

However, in spite of the already achieved results regarding the surgical methods, the results of CLP treatments, unilateral and bilateral, are not universally

fit. Particularly, deficiencies of the growth and evolution of the palate appear even if the patients are treated by experimented teams. All the factors that significantly contribute, over time, to these unfavorable results remain, for the time being, obscure. Regardless of the type of the chosen treatment, surgeons cannot explain why that particular method, used in similar clefts, at the same age, has different results. Why some cases have a normal evolution, with a good facial aspect, palate shape, and dental

occlusion, whilst other results are of a lesser quality, is still an enigma. This is why a series of questions is raised: Do the different result have any connection to the dexterity of different surgeons? Are there significant differences in the palate deformation in the moment of the uranostaphilography that force every cleft to be differently classified? Does the pre surgical orthopedic treatment really influence the palate growth, or does it just help with repositioning the palate segments? (8,9).

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FACTORS OF MORTALITY AND MORBIDITY IN NECROTIZING ENTEROCOLITIS

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Abstract

Necrotizing enterocolitis (NEC) is a devastating disease that is rapidly becoming the leading cause of neonatal mortality and morbidity. It is the most common gastro intestinal emergency among neonates and is characterized by severe inflammation and necrosis of the intestines mainly affecting the terminal ileum. The overall incidence of NEC can range from 0,72 to 1.8 per 1000 live births mainly preterm and low birth weight infants being affected(6). Mortality rates are high and ranged from 12% to 50% (5, 8, 10). A single institutional study was performed analyzing the patients admitted between 2003 and 2007 at the Children's Hospital "Louis Turcanu" with the confirmed diagnosis of NEC. A total of 17 patients were included in the study. Data regarding age, sex, gestational age, birth weight, maternal age, Bell stage, predisposing conditions, diet, method of treatment being collected. We compared the mortality rates between distinct subgroups of the patients with data from previous reports in the literature. NEC had occurred in 17 patients, 9 boys and 8 girls. 15 patients were preterm infants or were small for gestational age. Previous to NEC 13 patients were fed with formula and 4received human milk. There were 15 patients under 2500g at birth and 2 over 2500g. In 10 cases the debut of the disease was in the first 2 weeks of life. Overall mortality was 53%. Preterm infants had a higher mortality rate (57%) than term infants (33%). Morality rates increase with Bell stages from none in Stage I A to 100% for stage III A and 85% for stage III B. NEC develops mainly in preterm infants. Preterm infants also tend to develop more severe cases and necessitate surgical interventions more often. In term neonates NEC have usually an underlying condition. NEC occurs more often in formula fed infants. Factors like the age of the patient and maternal age have poor influence on mortality.

Key words: necrotizing enterocolitis, preterm infants, risk factors.

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in premature newborn infants (1, 2). With aggressive management leading to the salvage of premature infants from the pulmonary standpoint, the incidence of NEC is increasing, and it is thought that NEC will soon replace pulmonary insufficiency as the leading cause of death in premature infants (3).

Although the exact etiology remains unknown, research suggests that it is multifactorial; ischemia and/or reperfusion injury, exacerbated by activation of proinflammatory intracellular cascades, may play a significant role.

Early signs of NEC are indistinguishable from sepsis neonatorum. The signs and symptoms are quite variable, ranging from feeding intolerance to evidence of sepsis, shock, peritonitis, and death. The usual presentation includes abdominal distension, gastric residuals, bilious vomiting, and bloody stools. Lethargy, apnea, and hypoperfusion also may be a prominent feature. Physical findings found on serial examination comprise progressive abdominal tenderness, muscular guarding, and abdominal wall erythema. The presence of an abdominal mass may indicate localized perforation or progressive peritoneal irritation. However, these physical findings may be minimal and misleading, even in infants with progressive disease leading to perforation (4).

The distal ileum and proximal colon are most commonly involved in necrotizing enterocolitis, although any region of the bowel may be involved. The aspect of the intestine is characterized by severe inflammation and patchy necrosis with/without perforation.

Until recent year's improvements in obstetrical and neonatal care that allowed survival of more and more low birth weight newborns, NEC was a poor defined entity. NEC becomes more frequent after the development of neonatal intensive care units in the 70's. For this reason NEC is considered to be an

„iatrogenic” disease caused by the medical progress (5).

Several epidemiologic studies have determined the overall incidence of NEC range from 0.72 to 1.8 per 1000 live births (6). It occurs in 1-5% of all neonatal intensive care admissions and 5-10% of all very low birth weight (<1500 g) infants (7). Between 30 and 50% of the patients require surgical treatment (5, 8, 9). Mortality rates are high and ranged from 12% to 50% (5, 8, 10). The main risk factor for NEC is prematurity and/ or low birth weight. It is estimated that NEC occurs in 3% to 7% of preterm and low birth weight infants (8).

An important correlating factor of NEC development in these premature neonates is related to formula feeding versus human maternal milk. Studies had been carried out that compared incidence, morbidity and mortality for NEC in infants fed with formula and human milk. The results suggested that human milk reduce the incidence of NEC in preterm or low birth weight infants (11, 12, 13). Preterm infants fed exclusively with formula develop NEC 6-10 times more often than those fed breast milk alone and 3 times more common than those who received formula plus breast milk (14).

Mortality rates are tightly correlated with birth weight. Several reports showed a high incidence of NEC in the 401-750 gram infants – as high as 11.5% whereas the infants with a higher birth weight in the 1251-1500 grams have a decreased incidence of 4% (8).

An important observation that confirms the relationship between prematurity and NEC is that full term infants rarely develop NEC. It is estimated that only one in 20 000 term babies develop NEC (15). NEC in full term neonates generally has an underlying congenital condition (15). Several reports mentioned that in full-term neonates NEC develop almost exclusively in patients fed with formula or mixture of human milk and formula (16, 17, 18). Other risk factors for NEC in term neonates are: peripartum asphyxia, polycythemia, umbilical catheterization, endotracheal intubation, sepsis. If it occurs in full term infants, NEC mortality and morbidity rates are similar as in preterm infants (5, 15).

Since prematurity is the single most important risk factor for NEC, it is possible that absent or reduced levels of specific factors that are normally expressed during later periods of gestation may contribute to the development of this condition. With this in mind, exogenous replacement of key factors may be clinically valuable as a means to reduce the incidence of NEC. Several potential preventive strategies have aimed at induction of gastrointestinal maturation with

steroids, improvement in host defense with breast milk fêting or oral immunoglobulins, change in bacterial colonization with antibiotics, probiotics or fêting modifications, and reduction or antagonism of inflammatory mediators, none of which have led to consistently positive therapeutic results (19).

The main purpose of this study was to determine the presence of risk factors for the development of NEC that could improve the management strategy of this devastating disease in our institution. An extensive literature review was performed and the obtained data was compared similar studies.

Materials and methods

We reviewed the medical charts for all the patients that had the diagnostic of NEC and were admitted at “Louis Turcanu” Children Hospital in Timisoara during a 5 year period (2003-2007).

We recorded for each patient the presumed factors influencing morbidity and mortality: age of patient, sex, gestational age, birth weight, age of the mother, Bell stage, associated or underlying medical conditions. Patients were considered preterm if gestational age was under 36 weeks. Patients were divided by birth weight in 2 groups: <2500g and >2500g. The patient was considered small for gestational age if gestational age was over 36 weeks and birth weight was under 2500g. Maternal age was divided in 3 groups < 20, 20-30 and > 30 years. For staging the disease we used the criteria proposed described by Bell et al (20, 21).

For statistical analysis of the data we used EPSS (v 1.7) for Windows. Pearson bivariate correlation coefficient was calculated for each factor. P values < 0.05 are considered significant. Means between groups were tested using independent sample t-test.

Results

In the 5 years period 17 patients, 9 boys and 8 girls had the diagnostic of NEC. There were significant differences regarding mortality between boys and girls ($t= 3.337$, $p < 0.05$). Age at admission ranged between newborn and 7 months, mean 28 days. In 10 of the cases the disease debut was before 14 days of life. The highest mortality was in the group where the debut of the disease was after the first 4 weeks of life, but with low correlation coefficient ($p > 0.05$).

Most of the patients (82%) were preterm infants. One infant was small for gestational age and only 2 were full term infants. Mortality rates were higher in preterm infants 57% vs. 33% ($t= 0.716$, $p > 0.05$).

The majority of the patients (13) were fed using formula and only 4 received a human milk regime. We

didn't found significant differences in mortality rates between the two regime group ($t= 0.127, p> 0.05$).

There were 15 patients under 2500g and 2 over 2500g. Mortality rates for the 2 groups are 60% and 50%. Pearson correlation coefficient for birth weight is 0.935.

Maternal age ranged between 20 and 41 years. 7 mothers were under 30 years old. No mothers under 20 years old were encountered. Mortality was higher for the group 20-30 years.

In table 1 are summarized the main factors analyzed by us.

Table 1 Correlation between risk factors and outcome.

Groups	Criteria	Patients	Mortality	P value
Gestational age	< 36 weeks	14	57%	0.485
	>36 weeks	3	33%	
Birth weight (g)	<2500	15	53%	0.935
	>2500	2	50%	
Regime	Human milk	4	50%	0.901
	Formula	13	53%	
Debut (days)	< 14	10	50%	0.525
	14-28	3	33%	
	>28	4	75%	
Sex	M	9	22%	0.005
	F	8	87%	
Maternal age (y)	<20	0	-	0.226
	20-30	7	71%	
	>30	10	40%	

Surgical treatment was necessary for 9 patients, 1 full term and 8 preterm infants. Surgical intervention for NEC included laparotomy, resection of the affected bowel and creation of a stoma. All patients that underwent surgery were included in bell stage III.

Mortality rates vary with Bell stages from 0% in Stage I A, 16% in stage II A to 100% for stage III A and 85% for Bell stage III B. Pearson correlation coefficient for Bell stages was 0,01.

Table 2 Correlation between Bell stage and mortality rates.

Stage	Preterm	Full term	Total	Mortality
IA	1	0	1	0%
IB	0	0	0	0
IIA	4	2	6	16%
IIB	1	0	1	0%
IIIA	1	1	2	100%
IIIB	7	0	7	85%

There was a relatively large spectrum of predisposing conditions. Cardiac malformation and anemia were present in 6 patients. Perinatal asphyxia and cerebral hemorrhage were present in 7 patients. Other predisposing conditions were oligoamnios and intraamniotic infection. Associated disease included

Down syndrome, lissencephaly, inguinal hernia, umbilical hernia, congenital muscular dystrophy, hypospadias, undescended testis. Only 2 preterm infants had no predisposing conditions. All term infants had at least one of the predisposing conditions, mean 2 conditions/ patient.

Table 3 Predisposing conditions.

	N	Cardiac malformations	Perinatal asphyxia	Cerebral hemorrhage	Anemia	Intraamniotic infection	Oligoamnios
Preterm	14	4	6	6	4	2	1
Term	3	2	1	1	2	1	0

Overall mortality was 53%. NEC was the direct cause of death in 8 patients, 7 preterm and one term infant. One preterm patient had mild signs of NEC and recovered after treatment. He had lissencephaly, patent ductus arteriosus and atrial septal defect and died from severe pulmonary disease after he had recovered from NEC.

Discussion

NEC is one of the most severe gastrointestinal emergencies in the neonatal period. Besides many animal and human studies, the morbidity and mortality rates have not improved significantly in the last decades. Several epidemiological studies have indicated that 90% of NEC develops in preterm infants (1, 2, 6, 10, 22). Prematurity is associated with higher morbidity and mortality rates for NEC (24, 25). In our study preterm and low birth weight infants represented approximately 88% of the cases and had a significant higher mortality rate than full term infants. In full term infants NEC have usually an underlying congenital condition (15). This was also the case of our 3 term infants, which had a higher rate of predisposing conditions, 2.1/ patient vs. 1.6/ patient. The most frequent predisposing condition was perinatal asphyxia and cerebral hemorrhage but neither one of the disease has statistical influence for mortality ($p > 0.05$). Other predisposing conditions were congenital cardiac malformations, anemia, oligoamnios and intraamniotic infection.

In our study no case of NEC did develop in a full term healthy infant. These findings are similar with that of Martinez-Tallo et al which found only 3 healthy full term newborns from 24 infants with NEC and Maayan-Metzger et al where 50% of infants had major known risk factors predisposing them for NEC (16, 23).

In Bell stage I group is only one preterm patient whom suffered fully recover after medical treatment. Bell stage II patients had a total of 16% mortality rate which is higher than that found by Bell et al (15%) for the same stage (20). 71% of Bell stage II and 88% of Bell stage III patients are preterm suggesting that premature patients developed more

severe forms of NEC. This is probably due to poor intestinal defense mechanism. These patients had the highest number of surgical intervention and the highest mortality also.

In most of the cases the disease developed before 14 days of life (6). NEC developed in almost 60% of our cases before 14 days of life but the highest mortality was in the infants that developed NEC after 4 weeks of life. Because of the small dimension of the group we could not affirm that the age of the patient has statistical significant influence on mortality.

Previous reports suggested that human milk diet reduce the incidence of NEC (11, 12, 13). These was the case of our study were 76% of the patients were previously fed with formula. We didn't found significant differences between mortality rates in human milk and formula fed groups ($t = 0.205$, $p > 0.05$). This suggest that human milk despite it reduces the incidence of NEC, have poor or no influence in the mortality rates of NEC after it occurs.

Despite maternal age is a known risk factor for prematurity (26) it has no influence on mortality from NEC (27). Rates of mortality are similar between maternal age groups.

Overall 53% mortality is similar to those in the previous reports (5, 8, 10). Statistic correlation between mortality and risk factors is low due to the small contingent analyzed. Larger cohorts are necessary in order to receive statistically significant results.

Conclusions

NEC develops mainly in preterm infants. Preterm infants also tend to develop more severe cases and necessitate surgical interventions more often. In term neonates NEC had usually an underlying condition.

NEC occurs more often in formula fed infants.

Factors like the age of the patient and maternal age have poor influence on mortality

Strategies to prevent perinatal predisposing factors for NEC in both preterm and full-term infants are the key to reduce NEC incidence.

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

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