This issue includes the proceedings of the

6th SYMPOSIUM
Progress in Molecular Diagnosis and Treatment of Genetic Based Pediatric Malignancies

and

3rd SYMPOSIUM
of Historical Section PAPS

9–10 june 2006
Zegrze, Poland

The symposium is held under scientific supervision of Polish Union of Oncology

With medial support of Polish Regional Television TVP3

and press support of „Konsyliarz” magazine
This symposium is sponsored by
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Introduction

Celiac disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten, i.e. a protein present in cereals, occurring in genetically susceptible individuals, in whom ingestion of gluten induces typical changes in small intestine mucosa [16]. The development of reliable serological screening tests has dramatically increased our awareness of CD as a common condition. The prevalence of CD in a healthy population of Europe, United States, Australia and Asia varies between 1:100 – 1:300 [17, 24, 36, 37]. In Poland CD screening tests in healthy population have not been done, yet. Due to the fact that the prevalence of CD in Europe is so high, it is expected that even about 380 thousand of CD patients live in Polish country.

CD has extremely changed since the moment Dutch physician Willem Dicke had described the clinical aspects of the disease [13]. Nowadays, so called classical type of CD with chronic diarrhea, abdominal distension, poor weight gain, starting under 2 years of age, occurs rather rare. CD appears in each age after the introduction of gluten to the diet, and in many older patients presents atypical non-gastrointestinal symptoms or has a silent form with minimal or no clinical symptoms [10]. Gastrointestinal symptoms of CD represent the tip of the celiac iceberg presented by Logan [32]. Because of atypical manifestations, many patients with CD remain undiagnosed or are treated symptomatically. In adults, CD is diagnosed on average over 10 years after the first symptoms [21]. The lack of proper treatment, i.e. a strict gluten free diet (GFD), increases the risk of life-threatening complications that are difficult to manage, such as cancers and malignant lymphomas [7]. There is also strong evidence that in unrecognized CD patients the frequency of other autoimmune diseases is higher than in general population [58].

Pathogenesis

CD is a highly genetically determined disease with the major genetic factor being the expression of specific HLA class II antigens. About 90–95% of CD patients express HLA-DQ2 molecule, the rest of them are HLA-DQ8-positive [33]. These HLA-DQ receptors have the capacity to bind the...
specific gliadin peptides that have been implicated in CD. HLA-DQ molecules present on the surface of antigen presenting cells (macrophages, dendritic cells), i.e. cells, which catch the gliadin peptides and present them in association with specific HLA-DQ receptors to T lymphocytes [43].

Gluten contains peptides presenting extremely high affinity to DQ2 and DQ8 receptors [51]. These toxic peptides are characterized by high glutamine content, i.e. the amino acid which is a substrate for the enzyme – tissue transglutaminase (tTG). tTG catalyzes deamination of glutamine into glutamic acid. This reaction increases about 100-times the affinity of toxic peptides, and is essential for significant stimulation of gliadin-specific – T lymphocytes (Fig. 1). Activated gliadin-specific T lymphocytes produce pro-inflammatory cytokines responsible for histological changes in intestinal mucosa [10, 11].

Toxic peptides are present in wheat, barley and rye [9]. Corn, rise and, as recently has been shown, pure oats do not contain toxic peptides active in CD [23].

The recent reports by Shan et al. shows that digestion of recombinant gliadin with gastric and pancreatic enzymes in vitro produces the highly stable 33-mer peptide that is rich in proline and glutamine, and which contains all known toxic peptides [51]. This 33-mer peptide is resistant to brush border enzymes, but it can be easily degestive by endopeptidases coming from intestinal bacteria [51].

Findings showing that gut bacteria could deprive gliadin peptides of toxicity open a new therapeutic possibility with using probiotics, i.e. non-pathogenic bacteria regulating gut microflora ecosystem. It is not excluded that bacterial endopeptidases could be also used in preparation of non toxic cereals [12].

HLA-DQ2 and -DQ8 are common in human population. This haplotype is present in 20–30% of health controls, suggesting that activation of pathological processes could be influenced by other genes. It seems that HLA class I related gene – the major histocompatibility complex class I chain-related gene A (MICA) is an attractive candidate for better understanding of physiopathological mechanisms of CD [31]. MICA molecule is mainly expressed on the intestinal epithelium and is recognized by T lymphocytes, CD8+ lymphocytes and natural killer cells. The binding of MICA to cells induces cytotoxic and inflammatory responses in the intestine. Lopez-Vazquez et al. found an association of the MICA A5.1 allele with atypical form of CD. Up to 29% of patients with atypical CD expressed A5.1 allele in comparison to 13% of patients with typical CD and 7% of healthy population. The mechanism by which atypical manifestations are triggered is connected with the fact that MICA-A5.1 is responsible for secretion of soluble form of MICA molecule. This protein reacts with cytotoxic and pro-inflammatory lymphocytes and inhibits their activation in intestine by MICA present in gut epithelium.

Clinical symptoms

The classical clinical picture of childhood celiac disease consists of prolonged diarrhea with failure to thrive, abdominal distension, vomiting. Severe malnutrition and even cachexia can occur when diagnosis is delayed. This type of presentation has decreased in many European countries over the past few decades. The factors responsible for this change might be explained by the exclusion of gluten from the diet of babies and promotion of natural feeding [14]. Studies performed in United States on children with recognized CD showed that older age of CD onset and atypical manifestations were results of prolonged breast feeding [14]. On the other hand Swedish observed that breast feeding decreased occurrence of CD in children before 2 years of age, and high doses of gluten introduced to the baby’s diet independent on the age without protection of breast milk increased the risk of CD [26]. Presented results open the discussion on the period of introduction of gluten to the infant diet. Experimental data show that oral tolerance is developed only in early ontogeny, thus too late administration of gluten to the diet could be responsible for gluten intolerance. It seems that low amounts of gluten in the diet before 6 months of life, but introduced during breast feeding could prevent the development of CD [25]. However, intake the gluten either before 3 month of life or under 7 month of life increased the risk of CD [46].

In Poland Szafurska-Szczepeń observed the decreased frequency of classical form of CD in children starting from 1990 [55]. Children presented atypical symptoms, such as low weight, short stature, anemia, abdominal pain. Ludvigsson at al. reported similar tendency in children before 2 years old, in whom in addition, irritability and muscle wasting were found [34].

Recently, increased frequency of CD reaching 3.4% was found in patients with irritable bowel syndrome (IBS) [15, 53]. These patients tend to experience diarrhea, vomiting, recurrent abdominal pain, constipation, nausea. Our studies also showed high frequency of CD in children with IBS (1:60) [4].

Many symptomatic patients with newly diagnosed CD initially present with non-gastrointestinal manifestations of CD. Atypical symptoms of CD are presented in Table 1.
logical lesions was found only in patients with autoimmune hepatitis [59].

Unexplained infertility could be also a syndrome of atypical CD [29]. Incidences of menstrual irregularities and spontaneous abortions appear more often in women with CD than in general populations [29]. In children with CD pubertal delay can occur.

Other atypical syndromes of CD are recurrent oral ulcers and arthritis. Up to 3% of children with juvenile arthritis present CD [54].

Nowadays, dermatitis herpetiformis is considered to be a cutaneous manifestation of gluten sensitivity [27]. Dermatitis herpetiformis is a severe itchy, blistering skin disease with abnormalities occurring on the elbows, knees and buttocks. In intestinal biopsy typical for CD histological lesions are found. The treatment with a GFD approves skin and intestinal abnormalities.

**Associated conditions**

CD is associated with a number of autoimmune and non-autoaggressive genetical diseases (Table 2). Autoimmune disorders occur ten times more frequently in adult patients with CD than in general populations. Up to 8% of patients with type 1 diabetes have the characteristic features of CD in small intestinal biopsy [8, 48]. This figure may be an underestimate, as serial screening of individuals with type 1 diabetes over a period of years has identified additional cases who initially had negative serological tests [8]. CD is also more often recognized in patients with autoimmune thyroiditis [54, 61], Sjögren’s syndrome [35], cardiomyopathy [47], autoimmune myocarditis [18] and in autoimmune endocrinological disorders [45].

The incidence of CD in individuals with Down syndrome is between 5% and 12% [20]. About one third of patients present atypical non-gastrointestinal syndromes. An increased prevalence of CD, which ranges from 4.1 to 8.1%

**Table 1**

Nongastrointestinal symptoms of celiac disease

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron and folic acid anaemia</td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Pubertal delay</td>
</tr>
<tr>
<td>Unexplained infertility, spontaneous abortions</td>
</tr>
<tr>
<td>Epilepsy with intracranial calcifications</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
</tr>
<tr>
<td>Depression, irritability</td>
</tr>
<tr>
<td>Osteopenia /osteoporosis</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Dental enamel hypoplasia</td>
</tr>
<tr>
<td>Recurrent oral ulcers</td>
</tr>
<tr>
<td>Unexplained hypertransaminasemia</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
</tbody>
</table>

The most common non-gastrointestinal manifestation of CD, especially in adults is iron and folic acid anemia. About 11% of adults with anemia resistant to oral iron or folate supplementation have CD [3, 41]. When patients represent unexplained iron deficiency anemia the frequency is lower ranging up to 8%. In children, short stature is the most common non-gastrointestinal symptom of CD. The incidence of CD in this group is 8–10% [56].

Numerous studies confirm that disturbances in bone mineral density are often symptoms in celiac patients. Osteoporosis is one of the well-known complications of untreated CD [28, 44]. A GFD in children reverses bone density abnormalities and the beneficial effects of gluten withdrawal are persistent [42]. Contrary to pediatric cases, in adults affected by osteoporosis, a GFD does not reduce the risk of fractures [57]. In children dental enamel hypoplasia of permanent teeth could be a single manifestation of CD [1].

A number of neurological and psychological manifestations, including epilepsy with intracranial calcifications, primary ataxia, autism, depression, headaches, have been reported in patients with CD, but the evidence for their association with CD in children is weak [65]. Our studies on frequency of CD at risk group of children did not confirm occurrence of CD in children with epilepsy and autism [4].

There is some evidence for unexplained hypertransaminasemia in untreated patients with CD. Up to 9% of adults with elevated serum transaminases present CD [61]. In biopsies of liver obtained from these patients only nonspecific inflammatory changes were found, and the level of enzymes appeared to normalize on a GFD [61]. Sjögren et al. found a nonspecific increase of anti-gliadin antibodies (AGA) in a numbers of liver diseases, such as alcoholic cirrhosis (20%), primary biliary cirrhosis (16%), primary sclerosing cholangitis (24%), hepatitis HCV (11%) [52]. However, the evidence of an increase of CD confirmed by histo-

**Table 2**

Diseases associated with celiac disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus type 1 1</td>
<td>5–8%</td>
</tr>
<tr>
<td>Autoimmune thyroitidis</td>
<td>4–5%</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>5%</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>6,4%</td>
</tr>
<tr>
<td>Juvenile arthritidis</td>
<td>6,6%</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>7,9%</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>2,1–5,76%</td>
</tr>
<tr>
<td>Autoimmune myocarditis</td>
<td>4,4%</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>5–12%</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>4–8%</td>
</tr>
<tr>
<td>Wiliams syndrome</td>
<td>8,2%</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td>2–8%</td>
</tr>
</tbody>
</table>
has also been reported in Turner syndrome [2, 50] and in Wiliams syndrome (8, 2%) [19].

Based on retrospective studies the frequency of selective immunoglobulin (Ig) A deficiency in CD was between 1.7% and 7.7% [6].

There is strong evidence that first-degree relatives of diagnosed CD cases are at increased risk for CD with a prevalence of 4% to 5% [22]. The frequency of CD is lower in second-degree relatives.

Diagnosis

Although serological tests have been improved during last years, still biopsy of small intestine is necessary for CD recognition. According criteria established by European Society of Gastrology, Hepatology and Nutrition in 1990, CD diagnosis is based upon histological evidence of typical small intestinal mucosal abnormalities and clinical improvement after introduction of gluten free diet [62]. CD affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine. Because the histological changes in CD may be patchy, it is recommended that multiple biopsy specimens should be obtained from the jejunum and examined according modified Marsh scale (Fig. 2) [38, 40].

There is strong evidence that villous atrophy (Marsh grade III) is a characteristic histopathological feature of CD [22]. The presence of infiltrative changes with crypt hyperplasia (Marsh grade II) is compatible with CD but with less clear evidence. Diagnosis in these cases is dependent on positive serological tests. When serological tests are negative, other conditions for the intestinal changes should be considered. The presence of infiltrative intraepithelial lymphocytes alone (Marsh grade I) is not specific for CD. Concomitant positive serology increases the likelihood of CD. In such cases it is recommended additional strategies, such as determination of the HLA antigens, repeat biopsy or a trial of treatment with a GFD and repeated measurement of antibodies [22].

Thus, intestinal biopsy together with determination of specific antibodies in sera provides definitive CD diagnosis. As a GFD improved the intestinal lesions [64], it should be stressed that GF diet should not be introduced before planned biopsy.

Serological tests are frequently used to identify individuals for whom the biopsy procedure. They are also useful for screening the population to determine the prevalence of CD and for monitoring of a GFD therapy [64].

A comparison between several commercial available serological tests demonstrated that determination of anti-endomysial antibodies (EMA) by an indirect immunofluorescence technique (IIF) and anti-human recombinant tissue transglutaminase antibodies (hrtTG-Ab) by immunoenzymatic (ELISA) method are superior to anti-gliadin antibodies (AGA) and anti-guinea pig tissue transglutaminase antibodies (gTG-Ab) [63, 64]. The sensitivity and specificity of those tests range about 90%. Our studies showed that also anti-reticulin antibodies (ARA) determined by IIF are characterized by very high sensitivity (98%) and specificity (100%) [64].

Thus, the autoantibodies produced against the same autoantigen, i.e. tissue transglutaminase [30], should be employed for diagnosis and screening of CD. Our observations confirm that in some patients EMA/ARA tests are negative, but hrtTG-Ab are present, so it seems that determination of autoantibodies by two tests performed by different methods are needed.

---

**Fig. 2** Histopathological lesions in celiac patients
Screening tests

Screening tests should be done at risk groups:
- in first degree relatives of known CD cases,
- in patients with diseases associated with CD (Table 1)
- in patients with atypical syndromes (Table 2).

Epidemiological studies have shown that screening tests at risk groups should be done in 2–3 years old children [5]. As the occurrence of CD at risk groups is increasing with age, it is recommended to repeat serological tests in the case of negative results.

Some authors suggest that due to the high prevalence of CD and occurrence of atypical forms of CD, screening tests should be done not only at risk groups, but in the whole population (mass-screening) [39].

Conclusions

1. Celiac disease is a very common disorder with prevalence 1:100 – 1:300.
2. Most people with CD manifest atypical non-gastrointestinal syndromes or silent form of the disease.
3. Screening tests should be done at least at-risk groups of patients.

Acknowledgment

The study was support by the projekt PBZ/KBN-097/P06/2003.

References

Polyoma BK virus nephropathy in children after kidney transplantation

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Abstract

Polyoma BK virus nephropathy in transplanted kidney may lead to premature graft failure in up to 10% of adult patients. In children there are only very few data from the literature on this problem. We examined retrospectively the material (kidney biopsies and nephrectomy specimens) collected at the Department of Pathology, the Children's Memorial Health Institute from 1997–2004. Two out of 69 patients developed Polyoma BK virus associated nephropathy (2.9%). In one of them virus caused injury resulted in graft lost.

Key words: children, kidney transplantation, nephropathy, polyoma BK virus

Introduction

Polyomaviruses hominis type 1, known also as BK virus represents a family of DNA viruses. BK virus genome shares a homology with other viruses of the family: JC virus and SV40 virus [3]. This homology has important implications for some diagnostic procedures. Primary BK virus infection occurs during childhood and about 75% of adults are seropositive. The humoral response results in production of antibodies in various classes of immunoglobulins. In a host with normal immunity the infection has a clinically indolent course, which is subclinical or with slight flu-like symptoms [3]. After primary infection virus particles persist mainly in epithelial cells of urinary tract including kidneys.

The clinical course is different in immunocompromised patients [1, 3]. In both inherited and secondary immune dysfunctions previously “silent” virus undergoes reactivation. In some patients this results in an injury of infected organs, viremia and sometimes generalized disease. In practice BK virus caused organ injury is mainly observed in transplanted kidneys. In up to 10% of adult patients after kidney replacement Polyoma BK virus associated nephropathy (PAN) occurs, sometimes leading to graft failure [1, 3]. The prevalence of PAN seems to become more and more frequent, probably because of using modern, potent immunosuppressive drugs.

According to data from the literature PAN was diagnosed 6–270 weeks after kidney transplantation (KT) – average 44 weeks. In retrospective studies PAN was associated with graft failure in 10–100% patients after 12–240 weeks of follow up [3]. In morphological picture kidney injury consist of necroinflammatory damage of tubules with occurrence of characteristic nuclear inclusions containing virus particles [1–4]. This damage, in some patients, subsequently results in irreversible scarring of renal parenchyma and organ lost.

To classify a morphological pattern of PAN a 3-step system is proposed [1, 3]. In stage (or pattern) A there is only focal involvement of tubular medullar epithelium. Nuclear inclusion and inflammatory cells are not numerous. In this stage a false-negative diagnosis is probable because of sam-
pling error, particularly in kidney core biopsies. In stage B a pattern of necroinflammatory injury is evident occurring multifocally or diffusely. Nuclear inclusions are numerous, they may be observed in tubular as well as Bowman capsule epithelial cells. The inflammatory infiltrates include lymphocytes, plasma cells and polymorphonuclears. The differential diagnosis in such cases may sometimes be difficult. It includes acute cellular rejection, other viral infections (particularly CMV virus and Adenovirus) as well as tubular cells nuclear pleomorphism occurring during regeneration after acute tubular necrosis or recovery from acute cellular rejection. In difficult cases immunomorphology should be used with SV40 antibody. This antibody, originally developed for SV40 virus, is useful because of above mentioned homology of BK and SV40 viruses. „In situ” hybridization also may be used for more precise diagnosis. In stage C diffuse, chronic injury is seen with fibrosis and scarring of kidney parenchyma. In this stage virus specific changes may be very focal and again difficult to observe.

When PAN is diagnosed antiviral therapy should be considered, but there are no specific drugs against BK virus. In some cases therapy with cidofovir is helpful [3].

Little is known about PAN in children after kidney transplantation but probably it occurs comparable to adults [5, 6]. The aim of our study is to examine the prevalence of PAN after KT in our, pediatric group of patients.

Material and methods

Patients

Retrospectively, 102 microscopic slides collected at the Department of Pathology, the Children’s Memorial Health Institute. Material including core biopsies and nephrectomy specimens were obtained from 69 KT pediatric patients. All biopsies were performed in 1997–2004 because of transplanted organ injury. There were no protocol biopsies. In all patients calcineurin inhibitors have been used as basic immunosuppression.

PAN diagnosis

PAN was primarily diagnosed with light microscopy from HE slides. The diagnosis was confirmed by the immunohistochemical method using SV40 T Ag antibody (Calbiochem). Anti-mouse IgG labeled with biotin was used as the secondary antibody (Vector). The reaction was visualized by Vectastatin ABC kit (Vector) and AEC substrate chromogen (Dakocytomation).

Results

PAN was microscopically diagnosed in 2 out of 69 patients (2.9%).

Case 1

In the first patient (6 year old girl) the diagnosis was established from the nephrectomy specimen. The operation was performed 12 months after KT in the patient with allograft function injury (creatinine level was 5 mg%) and severe pneumonia. As the patient did not improved after therapy with antibiotics, the immunosuppression was stopped and nephrectomy was decided. Macroscopically the kidney was enlarged (12 × 7 × 6 cm) and firmed. Microscopically there were changes in kidney cortex and medulla (Fig. 1). Numerous nuclear inclusions of characteristic morphology were found in tubular cells as well as in epithelium of Bowman capsule of numerous glomeruli. The infected cells were also seen in tubular lumina. Extensive inflammatory infiltrates were observed. They consisted of lymphocytes, plasma cells and polymorphonuclears. Interstitial oedema was also found. No necrotic foci were observed. There were no morphological signs of cellular vascular rejection (no arteritis). The number of inflammatory cells (lymphocytes) not exceeded 4 per 10 tubular epithelium cells (pattern t1 according to Banff classification). Reaction with SV40 antibody was strongly positive in infected cells (Fig. 2). The pattern found was consistent with stage B changes. It was found that in this patient core kidney biopsy was performed 3 months earlier. Origi-
nally, only borderline changes (according to Banff classification) were diagnosed. In second review of slides PAN in stage A was diagnosed. In those slides there were only a few foci of infected tubular cells in the medullar part of biopsy specimen (Fig 3). Finally, after nephrectomy the patient improved, no specific antiviral drugs were used, dialysis program has been started.

Case 2

In the second patient (8 years old girl) core kidney biopsy was performed because of transplanted organ dysfunction 18 months post KT (creatinine level was 4.6 mg%). Microscopically extensive changes consistent with PAN stage B were found. Nuclear inclusions were found in tubular epithelium, there were also prominent exfoliations of infected cells. Inflammatory infiltrates consist of lymphocytes and plasma cells focally forming t1-type pattern according to Banff classification. No features of cellular vascular rejection were observed. After diagnosis of PAN antiviral therapy with cidofovir was administered. It resulted in slowly improving renal function (finally, creatinine level was 2.4 mg%).

Discussion

In the analyzed group of pediatric patients PAN was observed in 2/69 (2.9%). This result is in line with studies concerning adult patients. The prevalence of PAN is 1–7% according to retrospective studies [3]. PAN was diagnosed on average 44 weeks post-transplantation including a peak around the fist 24 weeks, i.e. similar as in our patients. Persistence of PAN was associated with irreversible allograft failure in 10–100%. In our both patients clinical course was rather severe with evident injury of transplanted kidney function. In one patient kidney injury was so severe that, particularly in the context of severe pneumonia, the only reasonable treatment was nephrectomy after stopping of immunosuppression. Morphological findings confirmed very extensive damage of the kidney parenchyma. It is possible, that in this patient earlier proper diagnosis would be helpful. In the first biopsy of the patient the PAN pattern was observed, but morphological changes are discrete and difficult to observe.

In the second patient the main problem in microscopic diagnosis was to determine the etiology of injury as well as excluding of the acute cellular rejection. PAN diagnosis was preferable because of identification of infected cells. It should be mentioned however that coexistence of PAN and „true” acute cellular rejection could exist. The final result of treatment (antiviral therapy, no anti-rejection therapy) confirmed BK virus etiology as main factor of kidney injury.

In summary we can conclude that transplanted kidney biopsy should to be considered as the useful method of PAN diagnosis, but it should be stressed that visible organ injury during PAN occurs rather late in a course of BK virus caused disease. Other methods, for example, serial viral load measurements may be very helpful.

Acknowledgment

The study was supported by internal grant from the Children’s Memorial Health Institute.

References

Primary malignant liver cell tumours in children – different treatment strategies

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Abstract

Malignant liver cell tumours in children still present a real diagnostic and therapeutic challenge. The histology of these tumours is often not clearly defined, and the differentiation between hepatoblastoma (HBL) and hepatocellular carcinoma (HCC) is sometimes difficult. Intermediate forms between HBL and HCC called „Transitional Liver Cell Tumours” (TLCT) can also be observed. The introduction of complex treatments (chemotherapy and operation) has led to an increase in the 3-year survival rate of patients with HBL of over 70% but not improved the survival rate of children with HCC and TLCT, which is still not higher than 40%. The most important factors affecting the final results of treatment in children with malignant liver cell tumours still are microscopic radical operations, the presence of extrahepatic spread of disease, and distant metastases. The aim of this study is the analysis of the results of treatment in children with malignant liver cell tumours using 3 different treatment strategies: typical anatomical liver resection, atypical borderline non anatomical liver resection for giant tumours and liver transplantation. The results of treatment of 59 children with primary malignant liver cell tumours treated during last 20 years have been analysed; the patients consisted of 29 patients with HBL (children up to 4 years of age), 10 patients with TLCT (children over 5 years of age) and 20 patients with HCC. Liver resection (typical or atypical) was performed in 39 children and liver transplantation (primary or secondary) was performed in 8 children. Type and size of tumour, response of tumour to chemotherapy, the possibility of radical resection, type of operation and its microscopic radicality and final results of complex treatment against the morphology of the tumour were analysed in all patients. Clear differences in the treatment response are indicated, depending on the histology of the tumour. Very good results with a complex treatment have been confirmed in the group of small children with HBL, except for patients with an unfavourable histology (anaplasia or SCUD-small cell undifferentiated HBL), patients with TLCT and HCC demonstrated unsatisfactory results after complex treatment. Detailed histological analysis also demonstrated difficulties in achieving microscopic radicality in the operative treatment of patients with TLCT and HCC as well as in children with HBL in cases the tumour size exceeded 10 cm in diameter. In conclusions, it is suggested that it worth verifying the indications for traditional surgical treatment and adapting the treatment to the histology of tumour as well as broadening the indications for liver transplantation as a primary operation, which may guarantee microscopic surgical radicality.

Key words: liver tumours in children, liver resections, liver transplantation

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Introduction

Primary malignant liver cell tumours are the most common hepatic tumours in children. They account to 70% of all hepatic lesions encountered in paediatric age group [20, 25]. These tumours represent a heterogeneous group, whereby hepatoblastoma (HBL) tend to occur predominantly in younger children and hepatocellular carcinoma (HCC) in older children and adolescents. The rare intermediate tumours, „Transitional Liver Cell Tumours” (TLCT) are on the borderline between HBL and HCC: they have intermediate clinical and histological features, their biological behaviour is not completely known and the treatment strategy has not yet been defined [16, 18]. The histological picture of liver cell tumours is often unclear, which makes the differentiation between HBL, HCC and TLCT sometimes difficult [18]. This results in difficulties in selection and standardisation of the best treatment strategies, aggravated by the high percentage of giant tumours or multifocal lesions [14, 15], the unpredictable response to chemotherapy [15, 18] and big differences in biological behaviour between HBL, HCC and TLCT [15–18]. Advances in liver surgery [3, 4], the determination of risk factors, and standardisation of the protocols of chemotherapy have significantly improved the results of treatment of HBL in children [5, 19]. However this has not affected the treatment results for HCC and TLCT, where – despite the application of different treatment strategies – results still remain poor [7, 15–18].

The aim of the study is to analyse the treatment results of children with malignant liver cell tumours using three different treatment strategies: typical anatomical liver resection, atypical borderline non anatomical liver resection for giant tumours and liver transplantation. The most reliable surgical procedures for different types of tumours are discussed.

Materials and methods

Retrospective analysis of the methods and results of surgical treatment in 59 patients with malignant liver cell tumours treated during last 20 years in the Children’s memorial Health Institute in Warsaw was carried out. The patients consisted of 29 children with HBL, 10 children with TLCT, and 20 children with HCC. The age of the children with HBL ranged from 1 month to 4 years (mean 1.3 years), of children with TLCT from 5 to 17 years (mean 10 years), and of children with HCC from 2 to 20 years (mean 12.2 years). The final diagnosis was based on surgical biopsies before treatment, the resected specimen after surgery or post mortem protocols, together with previously described clinical and histological criteria [16, 18, 20, 25]. Before initiating therapy (chemotherapy, surgery) all patients underwent radiological examination with imaging techniques (angio-CT scan, USG). Further monitoring of tumour response to chemotherapy was carried out with the same scanning procedure. Initial chemotherapy was introduced prior to surgery in the majority of patients. Before 1989, chemotherapy for HBL and TLCT was given on an individual basis (mainly VCA) and after 1990 was switched to PLADO, while for HCC chemotherapy consisted mainly of VCAF or PLADO. Radical surgical treatment, either resection of the tumour with part of the liver or orthotopic liver transplantation (OLT), was undertaken in 47 of 59 children according to previously described standards [12, 14]. Partial liver resection (typical or atypical) together with resection of the tumour was performed in 39 children and OLT (primary or secondary) in 8 patients. Typical liver resections were undertaken when the localisation of tumour allowed resection within the planes of the segmental division of the liver as proposed by Couinaud [4, 6]. In cases of atypical resection due to the location or size of the tumours, the planes of resection differed from the anatomical division of the liver. Primary OLT was undertaken when traditional liver resection was impossible, whereas secondary OLT was done in cases of local tumour recurrence after previous liver surgery. Follow-up ranged from 1 to 20 years. Retrospective analysis investigated the type and size of the tumour, the response of chemotherapy, the possibility of radical tumour resection, biliary complications, microscopic radicality of surgery, and the final results after complex treatment.

Results

Nature and size of malignant liver cell tumours

„Resectability” of a tumor was determined by analyzing the nature and size of the lesion. All hepatic lesions were divided into three categories depending on the localization and type of the tumor: lesions up to 5 cm, up to 10 cm, and over 10 cm or multifocal (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Initial diameter of tumour before treatment</th>
<th>Up to 5 cm</th>
<th>Up to 10 cm</th>
<th>Over 10 cm or multifocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBL n=29</td>
<td>–</td>
<td>8 (27.5%)</td>
<td>21 (72.5%)</td>
</tr>
<tr>
<td>TLCT n=10</td>
<td>–</td>
<td>2 (20%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>HCC n=20</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td>11 (55%)</td>
</tr>
</tbody>
</table>

In cases of HBL and TLCT most lesions (about 70-80%) were very advanced (with diameter greater than 10 cm or multifocal) (Fig. 1). In children with HCC advanced lesions were noted in about 50% cases, and lesions of up to 5 cm in 30% of patients. Despite the high percentage of very advanced lesions in patients with HBL and TLCT, after initial chemotherapy about 80% of tumours were found to be resectable (table 2). In cases of HCC, despite the higher percentage of relatively small lesions, only 35% of tumors were assessed as traditionally suitable for resection and 65% of tumors were assessed as not resectable according to traditional criteria.
Treatment of malignant liver cell tumours

Obvious differences depending on the histology of the tumour were demonstrated in the response of the tumours to treatment (Table 3). A good response after initial chemotherapy was noted in 56% of children with HBL, as opposed to only 11% of patients in whom no response was noted. In cases of TLCT and HCC the majority of patients (80% and 91% of cases, respectively) showed no response to initial chemotherapy.

Clear differences between the types of malignant liver cell tumours have been demonstrated with respect to the microscopic radicality of surgery (Table 4). Complete microscopic radicality was documented in 70% of children with HBL. Detailed histologic examination in cases of TLCT and HCC indicated that complete microscopic radicality in these tumours is very difficult to achieve. Traditional liver resections performed in children with TLCT and HCC showed incomplete microscopic radicality in 75% and 71% of patients, respectively. Microscopic radicality and incidence of postoperative biliary complications depended on the type of performed resection (Table 5).

Table 4

Microscopic radicality after resection of malignant liver cell tumours

<table>
<thead>
<tr>
<th>Microscopic radicality</th>
<th>radical</th>
<th>not radical</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBL* n=23</td>
<td>16 (70%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>TLCT n=10</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>HCC* n=7</td>
<td>2 (29%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>* patients after OLT were excluded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In cases of typical liver resections microscopic radicality was documented in 71% of patients and postoperative biliary complications occurred only in 4% of children. In contrast, in atypical liver resections a lack of microscopic radicality was noted in 73% of patients with postoperative biliary complications observed in 33% of children.

Table 5

Microscopic radicality and biliary complications and the type of resection

<table>
<thead>
<tr>
<th>Microscopic radicality</th>
<th>Biliary complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>radical</td>
<td>not radical</td>
</tr>
<tr>
<td>typical resections n=24</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>atypical resections n=15</td>
<td>4 (27%)</td>
</tr>
</tbody>
</table>

In cases of typical liver resections microscopic radicality was documented in 71% of patients and postoperative biliary complications occurred only in 4% of children. In contrast, in atypical liver resections a lack of microscopic radicality was noted in 73% of patients with postoperative biliary complications observed in 33% of children.

Final results of treatment of malignant liver cell tumours

Analysis of the treatment results indicated very satisfactory final results in children with HBL and unsatisfactory results in patients with TLCT and HCC (Table 6). Out of the whole group of children with HBL 63% are alive without recurrence of disease at follow-up of 1 year and longer, and in the group of patients after surgery the survival rate is 74%.

Table 3

Response to initial treatment of malignant liver cell tumours

<table>
<thead>
<tr>
<th>Reduction of tumour after chemotherapy</th>
<th>Up to 50%</th>
<th>Up to 25%</th>
<th>No reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBL*</td>
<td>15 (56%)</td>
<td>9 (33%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>TLCT</td>
<td>2 (20%)</td>
<td>2 (10%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>HCC*</td>
<td>1 (9%)</td>
<td>10 (91%)</td>
<td></td>
</tr>
<tr>
<td>* patients after OLT were excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In contrast, in the groups of patients with TLCT and HCC 30% and 19% of patients, respectively are alive without recurrence of disease at follow-up of 1 year and longer and in the groups of patients having undergone surgery the survival rates are only 33% and 43% respectively.

Liver transplantation

Primary OLT was done in 2 children with HBL and in 4 children with HCC, while secondary OLT was performed in 1 patient with TLCT and in 1 patient with HCC (Table 7).

<table>
<thead>
<tr>
<th>Type of liver transplantation</th>
<th>Primary OLT</th>
<th>Secondary OLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBL n=2</td>
<td>N=2</td>
<td>–</td>
</tr>
<tr>
<td>1pat. – died after 6 mo. (PTLD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1pat. – alive (NAD 1y. after OLT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLCT n=1</td>
<td>–</td>
<td>N=1 died 1,5 y. (metastases)</td>
</tr>
<tr>
<td>HCC n=5</td>
<td>N=4</td>
<td>N=1 alive (NAD 1y. after OLT)</td>
</tr>
<tr>
<td>2pat. – alive (NAD 2y. after OLT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2pat. – died (PNF, infection)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PTLD – post transplant lymphoproliferative disease, PNF-primary graft non function.

Three of 6 children after primary OLT are alive without recurrence of disease with a follow-up longer than 1 year and the remaining 3 children died due to reasons not connected with malignancy. The only death after OLT due to dissemination of malignancy was noted in a patient with TLCT and a history of unsuccessful attempts at traditional radical surgery.

Discussion

Primary malignant liver cell tumours, despite their relatively low incidence in children, represent a real diagnostic and therapeutic challenge due to their not completely known biology and wide spectrum of morphology. Hepatoblastoma and hepatocellular carcinoma, located on the opposite sides of the spectrum, account together for over 90% of primary malignant hepatic tumours in children [11]. Malignant hepatic tumours contribute to about 70% of all primary hepatic tumours, and about 0.5–2% of all malignant diseases in children [9, 23]. The incidence of malignant liver tumours is higher in the first 2–3 years of age and in children over 10 years of age. The first age peak is dominated by HBL and the second by HCC. Incidence and age peaks on the other hand are unknown for TLCT. It seems, however, that the age distribution for TLCT is similar to that of HCC in children [16, 18]. Data from the presented series seem also to confirm this statement.

Causes of malignant liver cell tumours are not well known. Genetic, environmental, and viral factors have all been considered as contributing factors. The best explanation for the development of HBL is the theory of interrupted organogenesis, an inappropriate continuation of proliferation of persistent embryonic tissue which transforms further into embryonal tumour [11]. In contrast to HBL, it has been proven that transmission and incorporation of the DNA of HBV or HCV onto human genetic material as well as the effect of metabolic factors generating liver cirrhosis serve as oncogenic factors for HCC [9]. The etiology of TLCT is less known. According to the hypothesis proposed by Zimmermann [18], these tumours arise from the cellular lines developing on the transitional ways between blastemic tumours and adult-type tumours, which would explain the atypical biological behaviour of these lesions [16]. The different etiology of HBL, TLCT, and HCC, as well as their different clinical picture and biological behaviour seems to require different treatment strategies. The introduction of new radiological imaging techniques has increased the accuracy with which the localisation and extension of the tumour within the liver can be assessed, allowing monitoring of chemotherapy and detailed planning of the extent of surgery. Modern diagnostic instruments do not allow, however, the prediction of biological behaviour. This seems to be the most serious difficulty standing in the way of prompt therapeutic decision, in addition to the fact that apart from HCC these are not well standardised [7, 15–19].

Despite the introduction of chemotherapy, the most important factor in deciding on the final treatment of malignant liver cell tumours is still the “resectability” of the tumour. The microscopic radicality of surgery is the critically important factor [24]. This is closely related to the nature of the tumour and its response to initial chemotherapy, which substantially influences the possibility of radical surgery [10, 14, 16, 19]. Striking differences in initial tumour size, response to initial chemotherapy and resectability between...
HBL, TLCT, and HCC were noted in the presented series. Whereas the vast majority of patient with HBL and TLCT presented with over 10 cm or multifocal giant tumours in children with HCC these features were noted in only about 50% of children. At the same time only children with HBL demonstrated a satisfactory rate (about 50%) of patients with good response to initial chemotherapy. These data explain the high number of children, up to 80% of patients with HBL, in whom tumours liable for resections with the use of traditional hepatic surgery could be found. Similar data have been also reported by others [10, 11]. It appears that this effect is related to the high sensitivity to chemotherapy of HBL, resulting not only in a reduction of tumour mass but also in an increase of tumour density, reduction of vascularity and increase of the tumour’s „resistance” to surgical manipulation [10]. This together with the limited propensity of HBL to form micro metastases in healthy liver tissue, permits microscopically radical surgery to be carried out in the majority of patients during traditional liver surgery [11, 16]. In contrast to this HCC, compared to HBL, presented a clearly higher percentage of multifocal lesions, a bad response to chemotherapy, and more aggressive biological behaviour what results in a clearly lower percentage of resectable lesions. In the presented series the percentage of resectable lesions in patients with HCC did not exceed 39% of children. In the presented series a very low (lower than 30% of patients) percentage of tumours which demonstrated microscopic radicality after traditional hepatic surgery was noted. Similar data have been published also by others [7, 10, 15, 17, 19, 23]. The potential for resectability seems to be also limited by liver cirrhosis associated with HCC in a majority of patients and additionally affecting the possibility of traditional liver surgery [7, 10, 15, 17, 19, 23, 25]. Fibrolamellar HCC remains the only subtype of HCC in which the potential radicality of traditional hepatic surgery has been claimed to be higher [9, 15, 17]. However, this has been contradicted by others [7, 22, 23]. In the presented series the only microscopically radical surgery in HCC was achieved in FL-HCC.

In cases of TLCT, in contrast to HBL and HCC, despite tumours of considerable size with a bad response to initial chemotherapy, a high percentage of resectable lesions was noted. In the presented series however, due to the giant size of the tumours, surgery was connected with many technical difficulties (atypical resections) and resulted in a high percentage of patients in whom microscopic radicality was impossible, determining the final outcome of treatment. Unclear etiology and biological behaviour of TLCT as well as the small group of analysed patients does not, however, permit a definitive assessment of the resectability of these tumours.

Analysis of the microscopic radicality of surgery and the incidence of biliary complications indicated their clear dependence on the type of surgical resection. In the presented series typical resections, despite the type of tumour, which were possible with smaller tumours and performed in agreement with the planes of liver division [3, 4, 6], had a high percentage of microscopic radicality and a low percentage of postoperative biliary complications. Atypical resections on the other hand, performed in cases of giant marginally resectable tumours or in cases with liver cirrhosis, were connected with a low percentage of microscopically radical operations and a significant incidence (30% of patients) of postoperative biliary complications. These data, confirmed by others [7, 14, 16-18], cast some doubt on the arguments in favour of performing atypical liver resections, especially in HCC and TLCT cases with aggressive biological behaviour. For these cases alternative therapeutic strategies are needed other than traditional hepatic surgery.

The assessment of the final results of treatment in the presented series of children with malignant liver cell tumours showed clear differences between HBL and HCC or TLCT cases. Very good results in small children with HBL, except in cases with an unfavourable histology (anaplasia or small cell undifferentiated SCUD) have been confirmed, while really unsatisfactory results after the treatment of patients with TLCT and HCC were noted. The results of treatment in patients with HBL, similar to other published series [5, 9, 11, 19, 23, 24], seems to confirm already accepted therapeutic strategies for HBL.

It also appears that the reason for the large discrepancy between the results of treatment achieved in HBL and HCC or TLCT is a result of the different biological nature of these tumours, the lack of sensitivity to chemotherapy of these tumours, and the limited possibilities of achieving microscopic radicality during traditional hepatic surgery. These differences are also the basis to look into new treatment strategies which might be used to treat children with malignant liver cell tumours, particularly HCC or TLCT and patients with HBL presenting with very large tumours.

In the last decade the interest of paediatric oncologists in a more extensive incorporation of orthotopic liver transplantation in the treatment of malignant liver cell tumours has increased. However, the role of OLT as a routine treatment strategy for these tumours in children is still a matter of debate, due to limited experience and relatively small series of patients [1, 7, 8, 12, 15, 22, 23]. Because of that the main indications for OLT in paediatric oncology remain non resectable tumours [1, 2, 8, 9, 13, 15, 17, 19, 21–23].

In the presented series of patients with malignant liver cell tumours OLT was carried out in 8 patients. Particularly encouraging results were achieve in the group of patients with primary OLT, of whom 3 patients are alive without evidence of disease and the deaths of the remaining 3 children were due to reasons not connected with malignancy. These results indicate potential possibilities to expand the indications for OLT as a routine alternative treatment to traditional hepatic surgery, for patients with TLCT and HCC as well as for a limited group of patients with HBL with marginally resectable tumours. The use of OLT in these cases allows the problem of doubtful surgical microscopic radicality to be excluded which is a weak point of traditional liver surgery.

The encouraging results of the use of OLT in paediatric liver malignancies (mainly not resectable HBL), which have already been published [1, 2, 8, 13, 21, 22] and which documents at least two years’ survival by 50–70% of patients,
are in agreement with the results achieved in the presented series. However the role of secondary OLT in patients with recurrence of tumour after primary treatment by traditional hepatic resection remains unclear. It seems that the indications for OLT after primary unsuccessful traditional liver surgery may be limited due to the high incidence of recurrence of malignancy after OLT [21, 22]. In the presented series, out of two patients who underwent secondary OLT, one patient with TLCT died because of disseminated malignancy, and the follow-up of another patient with FL-HCC, because of typical tumour recurrences even after several years [9, 11, 23], is not long enough to allow any prognostic conclusions.

Results of the presented series together with the results of other already published series seem to document the need to differentiate between treatment strategies for malignant liver cell tumours. This differentiation must consider not only the size and location of the lesion but also the tumour’s nature and type, which may lead to different biological behaviour determining the long-term results. The use of traditional liver surgery (hepatectomy procedures) seems to be appropriate for the treatment of smaller lesions of all types and in the majority of radiologically documented, evidently resectable HBL cases, with the predictable possibility of microscopically radical surgery. In cases of giant tumours and majority of HCC and TLCT cases, the indications for liver transplantation as a primary surgical treatment should be considered. Such a strategy based on the biological behaviour of different malignant liver cell tumour will increase the possibility of full surgical microsurgical radicality significantly determining the final treatment outcome.

References

Utilization of internal sphincter in the reconstruction of anorectal malformations in girls

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Abstract

Recto-cutaneous or recto-vestibular fistulas are the most common types of anorectal malformations in girls. Among the different methods of reconstruction of these defects the most frequently recommended are posterior sagittal anorectoplasty (PSARP) as described by Peòa and anterior sagittal anorectoplasty (ASARP) as described by Mollard; both of these procedures exist in several modifications. The aim of the study is to compare the results after surgical treatment of girls with anorectal malformations and external fistula using both approaches. The results in 55 girls with anorectal malformations and external fistula using both approaches. The results in 55 girls with anorectal malformations and external fistula (recto-cutaneous, recto-vestibular, recto-vaginal, and recto-cloacal) were analysed. In 28 girls posterior sagittal anorectoplasty (PSARP) as described by Peòa with resection of the end of fistula was performed. In 27 girls anterior sagittal anorectoplasty (ASRP), a modification of Okada operation with preservation of the external fistula, was performed. In both groups of the defects congenital associated anomalies were noted. Reconstructive surgery in all girls operated on with ASARP procedure was preceded by a daily dilatation of the fistula to obtain an appropriate diameter size as well as manometric studies of the fistula to assess the quality of internal sphincter muscle. After reconstruction of ARMs in both groups the postoperative results of continence were clinically assessed with the use of 4 clinical methods and anorectal manometry.

In the group having undergone ASARP operation the presence of the internal sphincter was confirmed before and after reconstruction of defects. In the group having undergone PSARP operation the presence of an internal sphincter was confirmed after operation only in 3 children. The best functional results as demonstrated by both clinical and manometric studies occurred in the group of girls operated on with ASARP technique in whom the whole external fistula was preserved.

In conclusion, the results achieved demonstrated the need of internal sphincter saving procedures by utilizing the whole fistula during reconstruction of anorectal malformations to improve the results of postoperative continence.

Key words: Anorectal malformations; internal sphincter; manometry
**Introduction**

Recto-cutaneous or recto-vestibular fistulas are the most common types of anorectal malformations in girls. Among the different methods of reconstruction of these defects the most frequently recommended are posterior sagittal anorectoplasty (PSARP) as described by Peña [20] and anterior sagittal anorectoplasty (ASARP) as described by Mollard [16], and known in several modifications [12, 27, 28]. The introduction of the modern concept of function of the external sphincter based on anatomical and physiological studies [2] and operative procedures, known as PSARP, for the reconstruction of anorectal malformations (ARM) [19] has been a breakthrough in the treatment of these anomalies and resulted in a significant improvement in postoperative continence [20]. This concept however does not include the possibility of utilization of the internal anal sphincter (IAS), documented in all fistulas in an experimental model of ARM [13]. ASARP, understood as an operative procedure analogous to PSARP, makes use of the whole fistula as an embryologic form of ectopic anus [11] together with the IAS [9]. This operative procedure also described as an „internal sphincter saving procedure” has been shown to improve postoperative continence [1]. However, better functional results after utilization of IAS in reconstructive procedures for ARM have been denied by some authors due to recto-urogenital / recto-cutaneous innervation defects [15]. The aim of the study is to assess the possibilities of utilizing the IAS during reconstructive procedures for ARM in girls with external fistula operated on with PSARP and ASARP procedures.

**Materials and methods**

The records of 55 girls treated in the CMHI in Warsaw for anorectal malformations with external fistula (recto-cutaneous, recto-vestibular, recto-vaginal, and recto-cloacal) between 1987 and 1999 were retrospectively analysed. Reconstructive procedures for ARM were performed in all patients. 28 consecutively treated girls (group 1) were treated using posterior sagittal anorectoplasty (PSARP) as described by Peña [19] with resection of the end of fistula. In the next 27 consecutively treated girls (group 2), modified anterior sagittal anorectoplasty (ASARP), a further modification of Oka-da’s operation [23] with utilization of the whole external fistula, was performed. None of the operated girls were excluded from the study. In both groups the type of defect (type of fistula) and associated congenital anomalies were assessed. The group of girls operated on using the ASARP procedure underwent several dilatations of the fistula prior to reconstructive surgery until a diameter of 10 H was achieved. In this group manometric studies of the fistula were performed before the operation to assess the quality of the internal sphincter muscle. In both groups of patients, after the standard course of dilatation and at least 6 months after reconstruction of defects or colostomy closure, postoperative continence was clinically assessed with the use of 4 clinical scales: Kelly [8], Holschneider and Rintala [26], Kiesewetter and Chang [10], and Peña [21]. The assessment of continence was finally completed with anorectal manometric studies.

Dantec 5500 was used for the manometric studies, with continuous 30 ml/h flow, together with Polyvinyl Zetetics Medical PMCA4-A multichannel catheters with a latex balloon and 3-cm distance between the orifices [23, 24]. Manometric studies were performed in the lithotomy position without sedation. During the studies the following parameters were evaluated:

- Length of high pressure zone (HPZ) in mm obtained during profilometry
- Maximal anal resting pressure (MARP) in cm H$_2$O obtained during profilometry
- Recto-anal relaxation reflex (RARR), assessed by % of decrease of MARP after insufflations of air into a latex balloon located in rectum. RARR was described as full (F) when at least a 50% decrease of MARP was recorded and partial (P) when only 25–50% decrease of MARP was achieved
- Voluntary anal squeeze pressure (VASP), assessed by % of increase of MARP during voluntary anal squeezing of the external anal sphincter (EAS). VASP was recorded as positive when the achieved pressure reached the level of at least 2 $\times$ MARP
- Rectal sensation to balloon distension (RSBD) in ml was the lowest volume of insufflated air which lead to filling of the rectal distension.

Results of manometric studies in both groups were compared to the results of studies obtained in the same way in age-matched controls, each consisting of 10 patients without ARM which served as a standard for manometric values.

**Results**

**Assessment of the type of fistula and associated congenital anomalies**

In both groups, ARM with recto-cutaneous or recto-vestibular fistula was found in 86% of patients (Table 1). Vaginal and cloacal defects had the lowest incidence in both groups. Embryological and anatomical similarities, which mandated a nearly identical surgical approach, were the reason that both groups of girls with vestibular and vaginal fistulas were analysed together in further studies. The most common type of ARM in group 1 was recto-vestibular/vaginal fistula and in group 2 recto-cutaneous fistula. There was no significant statistical difference between both groups with respect to the type of ARM. In each group chi$^2$ test indicated a significantly lower incidence (p<0.01) of vaginal and cloacal fistula.

In both groups of girls with ARM and external fistula the most common associated congenital anomalies were genito-urinary defects (Table 2), recorded in about 45% of all treated patients and in over 85% of girls with associated congenital anomaly. CUN defects were found in about 10% of patients of each group. There was no significant statistical difference between both groups with respect to the incidence of associated congenital anomalies. In each group chi$^2$
test indicated a significantly higher incidence (p<0.05) of genito-urinary defects and skeletal defects.

In both groups the presence of associated congenital anomalies was recorded in over 50% of girls with ARM and external fistula (Table 3). Associated congenital anomalies occurred most commonly in patients with cloacal fistula and less commonly in patients with recto-cutaneous fistula. There was no significant statistical difference between groups with respect to the incidence of associated congenital anomalies in different types of ARM. However, in each group chi² test showed statistically significant differences (p<0.01) between different types of ARM with respect to the incidence of associated congenital anomalies.

Assessment of internal sphincter muscle in the fistula

Manometric studies were undertaken in all patients before reconstructive operation in group 2 and compared to results obtained in healthy controls (Table 4).

In all patients from group 2 manometric studies before the reconstruction of ARM revealed the presence of functioning IAS in the fistula as determined by HPZ, MARP, and RARR (Fig. 1). There were no significant statistical differences between the results of manometric studies obtained from the fistula of girls with ARM and manometry of the anorectal region in healthy subjects. However, there were differences in the quality of RARR in some patients. Although a positive RARR was noted in the fistula of all girls with ARM, the full reflex was recorded in only 70% of patients. In the remaining 30% of girls the reflex was weaker (partial) remaining between 25–50% of MARP.

Assessment of continence after reconstruction of ARM

The results of continence after reconstruction of ARM in group 1 (PSARP with resection of the end of fistula) and group 2 (ASARP with utilization of the whole fistula) are summarised in Table 5. Clinical assessment of continence revealed higher medium score values in group 2 after ASARP. Statistically significant differences between the results after PSARP and ASARP only appeared with the Kelly and Peña scores. The Holschneider/Rintala score was borderline

---

**Table 1**

Incidence of different types of defects

<table>
<thead>
<tr>
<th>Type of ARM – type of fistula</th>
<th>(n)</th>
<th>% of patients</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recto-cutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>33%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(12)</td>
<td>45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recto-vestibular or vaginal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(15)</td>
<td>53%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(11)</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloacal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>14%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

Incidence of associated congenital anomalies

<table>
<thead>
<tr>
<th>Associated congenital anomalies</th>
<th>(n)</th>
<th>% ACA</th>
<th>% tot</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genito-urinary defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(13)</td>
<td></td>
<td>87%</td>
<td>(46%)</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(12)</td>
<td></td>
<td>86%</td>
<td>(45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12)</td>
<td></td>
<td>80%</td>
<td>(43%)</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(8)</td>
<td></td>
<td>57%</td>
<td>(30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alimentary tract defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td>27%</td>
<td>(14%)</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td>29%</td>
<td>(15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td></td>
<td>20%</td>
<td>(11%)</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
<td>36%</td>
<td>(19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUN defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td></td>
<td>13%</td>
<td>(7%)</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(3)</td>
<td></td>
<td>22%</td>
<td>(11%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% ACA – % of children in the group with associated congenital anomalies;
% tot – % of children with congenital anomaly in the whole group.

---

Type of ARM – type of fistula (n) % of patients (Statistical test) p-value
Recto-cutaneous (9) 33% Fisher NS
(12) 45%
Recto-vestibular or vaginal (15) 53% Fisher NS
(11) 41%
Cloacal (4) 14% Fisher NS
(4) 14%
and the Kiesewetter/Chang score showed no statistically significant difference. The manometric studies indicated statistically significant better medium results in group 2 after ASARP for all studied manometric parameters. The most significant statistical difference between both groups (p<0.001) was in connection with MARP. Manometric results achieved in group 2 were similar to the results obtained in the group of healthy controls (Table 6). 96% of girls from group 2 demonstrated evident RARR and all patients in this group had adequate HPZ after reconstruction of ARM. There were also no differences in the

(p=0.08) and the Kiesewetter/Chang score showed no statistically significant difference.

The manometric studies indicated statistically significant better medium results in group 2 after ASARP for all studied manometric parameters. The most significant statistical difference between both groups (p<0.001) was in connection with MARP. Manometric results achieved in group 2 were similar to the results obtained in the group of healthy controls (Table 6). 96% of girls from group 2 demonstrated evident RARR and all patients in this group had adequate HPZ after reconstruction of ARM. There were also no differences in the

Table 3

Incidence of different types of defects

<table>
<thead>
<tr>
<th>Type of ARM – type of fistula</th>
<th>(n)</th>
<th>% of pat. with ACA</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>(15)</td>
<td>54%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>(14)</td>
<td>52%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recto-cutaneous</td>
<td>(2)</td>
<td>17%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>Recto-vestibular or vaginal</td>
<td>(11)</td>
<td>73%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>Cloacal</td>
<td>(4)</td>
<td>100%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4

Manometric studies of the fistula before reconstruction of ARM in group 2 and anorectal manometry in control group

<table>
<thead>
<tr>
<th></th>
<th>Group 2 before reconstruction</th>
<th>Control group</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(fistula) n=27</td>
<td>(anus) n =10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age SD (years)</td>
<td>32,29 ± 22,30</td>
<td>25,50 ± 15,50</td>
<td>t-Student</td>
<td>NS</td>
</tr>
<tr>
<td>HPZ (mm) mean value SD</td>
<td>19,55 ± 3,93</td>
<td>20,40 ± 3,09</td>
<td>t-Student</td>
<td>NS</td>
</tr>
<tr>
<td>MARP (cm H₂O) mean value</td>
<td>63,33 ± 16,87</td>
<td>75,0 ± 12,69</td>
<td>t-Student</td>
<td>NS</td>
</tr>
<tr>
<td>Positive RARR (n) %pac</td>
<td>(27) 100%</td>
<td>(10) 100%</td>
<td>t-Student</td>
<td>NS</td>
</tr>
<tr>
<td>Type of RARR* (n) %</td>
<td>(19) 70% / (8) 30%</td>
<td>(10) 100% / (0) – Fisher</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

HPZ, high pressure zone; MARP, maximal anal resting pressure; RARR, recto-anal relaxation reflex; *F, number (n) and % of patients with full RARR; P, number (n) and % of patients with partial RARR.

Fig. 1 Manometric studies of fistula in girls before reconstruction of ARM: recto-vestibular fistula (above) and recto-cutaneous fistula (below). Recto-anal relaxation reflex (RARR) is seen after insufflation of air into rectal balloon (arrows and numbers)
### Table 5
Clinical score and results of manometric studies in girls after PSARP and ASARP

<table>
<thead>
<tr>
<th></th>
<th>Group 1 after PSARP n=28</th>
<th>Group 2 after ASARP n=27</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age SD (years)</td>
<td>13.96 ± 3.70</td>
<td>7.22 ± 2.43</td>
<td>t-Student</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Kelly score mean value SD</td>
<td>4.10 ± 2.06</td>
<td>5.07 ± 1.10</td>
<td>t-Student</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Holschneider/Rintala score mean value SD</td>
<td>10.03 ± 3.27</td>
<td>11.48 ± 2.63</td>
<td>t-Student</td>
<td>NS (p=0.08)</td>
</tr>
<tr>
<td>Medium value SD (after transformation of scale)</td>
<td>(1.32 ± 0.72)</td>
<td>(1.59 ± 0.57)</td>
<td>t-Student</td>
<td>NS (p=0.1)</td>
</tr>
<tr>
<td>Kiesewetter/Chang* score %G / %P / %B</td>
<td>46% / 39% / 14%</td>
<td>63% / 33% / 4%</td>
<td>t-Student</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Medium value SD (after transformation of scale)</td>
<td>(1.25 ± 0.80)</td>
<td>(1.63 ± 0.56)</td>
<td>t-Student</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>met. Pena** %F / %P / %IN</td>
<td>46% / 33% / 21%</td>
<td>66% / 30% / 4%</td>
<td>t-Student</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Constipation (2 and 3 deg.) (n) % pat.</td>
<td>(9) 32%</td>
<td>(10) 37%</td>
<td>Fisher</td>
<td>NS</td>
</tr>
<tr>
<td>HPZ (mm) mean value SD</td>
<td>23.78 ± 8.07</td>
<td>27.77 ± 4.12</td>
<td>t-Student</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>MARP (cm H2O) mean value SD</td>
<td>48.92 ± 25.72</td>
<td>74.44 ± 26.21</td>
<td>t-Student</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RSBD (ml) mean value SD</td>
<td>40.71 ± 27.07</td>
<td>53.70 ± 38.24</td>
<td>t-Student</td>
<td>NS</td>
</tr>
<tr>
<td>Positive RARR (n) % pac</td>
<td>(3) 11%</td>
<td>(26) 96%</td>
<td>Fisher</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Positive VASP* (n) % pac</td>
<td>(14) 50%</td>
<td>(26) 96%</td>
<td>Fisher</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*G, good continence; P, medium continence; B, bad continence (after author of scale); **F, full continence; P, partial continence; IN, incontinence (after author of scale); HPZ, high pressure zone; MARP, maximal anal resting pressure; RSBD, rectal sensation to balloon distension; RARR, recto-anal relaxation reflex; VASP, voluntary anal squeeze pressure; positive VASP* – pressure reaching the level of at least 2×MARP; (n), number of patients.

### Table 6
Manometric studies in the age-matched controls

<table>
<thead>
<tr>
<th></th>
<th>Control group for PSARP n=10</th>
<th>Control group for ASARP n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age SD (years)</td>
<td>13.00 ± 1.33</td>
<td>7.50 ± 2.01</td>
</tr>
<tr>
<td>HPZ (mm) mean value SD</td>
<td>31.20 ± 3.79</td>
<td>27.60 ± 4.19</td>
</tr>
<tr>
<td>MARP (cm H2O) mean value SD</td>
<td>93.00 ± 10.59</td>
<td>78.0 ± 14.75</td>
</tr>
<tr>
<td>RSBD (ml) mean value SD</td>
<td>20.00 ± 6.66</td>
<td>32.0 ± 7.88</td>
</tr>
<tr>
<td>Positive RARR (n) % pac</td>
<td>(10) 100%</td>
<td>(10) 100%</td>
</tr>
<tr>
<td>Positive VASP* (n) % pac</td>
<td>(10) 100%</td>
<td>(10) 100%</td>
</tr>
</tbody>
</table>

HPZ, high pressure zone; MARP, maximal anal resting pressure; RSBD, rectal sensation to balloon distension; RARR, recto-anal relaxation reflex; VASP, voluntary anal squeeze pressure; Positive VASP* – pressure reaching the level of at least 2×MARP; (n), number of patients.
value of MARP between manometric studies of the fistula, the same studies undertaken in group 2 after reconstruction of ARM and healthy controls.

The results of manometric studies of patients from group 2 indicated that the manometric parameters describing the proper function of IAS, both before and after reconstruction of ARM, did not differ significantly in this group from the normal values of healthy controls (table 4–6). The study revealed also that in both groups (group 1 and 2) there were no significant statistical differences in RSBD or the incidence of postoperative constipation (Table 5).

Discussion

Significant improvement have been achieved during the last two decades in the treatment of anorectal malformations. Both the knowledge of the anatomy, physiology, and pathogenesis of ARM and the methods of surgical correction and assessment of results have radically changed [9, 12, 19–21]. The introduction and popularization of a treatment concept described by Alberto Peña [2, 19] and the acceptance of the role of the internal anal sphincter (IAS) in the mechanism of continence [13] have had an important influence on improving the results of surgical corrections of ARM. Scientific documentation of improvements in the results of treatment still remains a problem due to differences in classifications applied in the past and the present and the subjectivity of clinical methods for assessing continence. Not only the preservation of the external sphincter (EAS) but also the utilization of the internal sphincter (IAS), which are both still a matter of debate, seem to be important.

ARMs with an external fistula in female patients, occurring in about 90% of all girls with ARM [20, 21], offer a classic opportunity to study the development of IAS and the influence of its preservation during surgery on postoperative continence. In the presented series ARMs with recto-cutaneous or recto-vestibular fistula were recorded in 86% of patients. These results are similar to data published by Peña [21], who found these fistulas to be the most common ARM occurring in girls. In the presented series, in contrast to older studies [4], the most common ARM was recto-vestibular fistula, occurring in 40% of patients of both groups. This probably resulted from differences in classification and difficulties in the detailed clinical assessment of the perineum. Such differences in classification and difficulties in assessment may be responsible for the differences between data from published series on the incidence of associated congenital anomalies. In this series associated congenital anomalies were noted in more than 50% of girls with ARM and external fistula. A high incidence of associated anomalies points to the need of active screening, also in the group of patients with „few defects”, in whom the incidence of associated anomalies was underestimated in the past [3, 18]. In these studies associated congenital anomalies were recorded in 17% of girls with recto-cutaneous fistula and in 73% of girls with recto-vestibular/vaginal fistula. Heinen [5] also stressed the possibility of understanding the occurrence of congenital CUN anomalies, which both in his series and in the presented series were equal, occurring in 10% of girls with ARM. Underestimation of these defects could be connected with the problem of a broad application of modern imaging techniques (CT, NMR) in diagnostic schedules in patients with ARM [7, 14].

The use of clinical scales for the assessment of continence indicated clear differences in postoperative continence between both study groups. In group 1, compared to age-matched controls, the results of postoperative continence, as assessed by all four clinical scales, were distinctly worse with results achieving statistical difference. The most significant statistical difference in the assessment of continence was noted when using the Holschneider/Rintala scale, which appears to be the most sensitive scale for all methods. In group 2, clinical assessment of postoperative continence with three of the four methods did not reveal significant statistical differences compared to healthy controls. The only statistical differences were noted when using the Holschneider/Rintala scale, which indicated even delicate disturbances of continence between both study groups, and could be explained by utilization in group 2 of the whole length of the fistula containing the IAS, and the use of ASARP (in comparison with PSARP) allowing a limitation in the length of separation of the fistula during reconstruction of ARM [1]. Manometric studies for the assessment of continence also indicated better results in postoperative continence in group 2 after the ASARP procedure. A direct comparison of all manometric parameters indicated statistically significant better results in group 2. This together with the fact, that no statistical differences were noted between the manometric studies in group 2 and the manometric results obtained in healthy controls, is a strong argument for the use of the ASARP procedure as a surgical technique for the reconstruction of ARM in girls.

The presence and function of the internal anal sphincter in the fistula in patients with ARM, as well as its utilization during reconstruction and its influence on the quality of postoperative continence are still a matter of debate. In the presented series manometric studies were used for the assessment of the quality and function of IAS in girls with ARM and external fistula. The lack of differences in the results of manometric studies of the fistula in girls with ARM and the result in age-matched healthy controls, clearly point to the functional presence of IAS in the fistula. These results together with the evidence of recto-anal relaxation reflex in the fistula in all girls before surgery for ARM and the evidence of RARR in 96% of patients from group 2 after reconstruction of defects not only proves the presence of IAS but also its full reflexive ability. The evidence of RARR in 3 patients after PSARP procedure was probably connected with remnants of the IAS remaining after resection of the end of the fistula, while evidence of partial RARR in the fistula of girls with ARM prior to reconstruction could be explained by partial maldevelopment of the IAS and the presence of a common vagina and fistula wall resulting in disturbances in relaxation of IAS, as has been noted in other studies [23].
The interpretation of the results achieved allows the conclusion to be drawn that an embryologically well developed and functionally efficient IAS is always present in the external fistula in girls with ARM despite the type of defect. These results also confirm the results of embryological experimental studies by Kluth and Lambrecht [11, 13] and of studies by Nievelstein in human embryos [17], which considered the fistula in ARM to be part of the ectopy of the primitive anal canal, providing the basis for the utilization of the whole fistula during reconstructive ARM procedures.

The results of histologic studies by Meier-Ruge [15] and Holschneider [6] remain in opposition to this suggestion. Disturbances in the innervation of the distal part of the fistula, similar to typical aganglionosis or Hirschsprung disease, hypoganglionosis, dysganglionosis, or intestinal neuronal dysplasia [15] are claimed to be responsible for the high incidence of constipation connected with preservation of the fistula during reconstruction of ARM [6]. These observations, however, are not confirmed by others [22, 25] and in the presented series the incidence of postoperative constipation after reconstruction of ARM was not different in patients, irrespective of whether the procedures had utilized or not utilized the whole external fistula. Although the controversy respecting ARM procedures with potentially hypoplastic, yet functionally completely efficient internal sphincters is still there and will generate further detailed studies, the better results of continence achieved here in the group in whom an "internal sphincter saving procedure" was carried out suggests that this procedure should be the procedure of choice for all girls with anorectal malformations.

References

The impact of probiotic Lactobacillus casei and paracasei strains on cytokine profile in children with atopic dermatitis

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Abstract

Probiotic bacteria have been shown to improve the severity of allergic disease such as atopic dermatitis. We presented novel Lactobacillus casei and paracasei strains which improved the clinical status of children with cow milk protein allergy. The aim of this study was to evaluate the impact of those novel Lactobacillus strains on the level of interleukin (IL)-5, IL-10, IL-12, tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma and transforming growth factor (TGF)-beta in blood cell cultures of infants with atopic dermatitis. The study included 30 children with cow milk protein allergy at the mean age 10 months. Blood cells were incubated with the mixture of three selected Lactobacillus strains and polyclonal activator phytohemagglutinin (PHA). The level of cytokines was measured in culture supernatants by immunoenzymatic assays. The levels of TGF-beta, TNF-alpha, IL-12 and IFN-gamma were markedly higher after incubation with probiotic bacteria as compared with PHA. Only differences in IFN-gamma level did not achieve statistical significance. In contrast, IL-10 and IL-5 were produced in significantly lower amounts when cells were activated by the mixture of Lactobacillus strains than by PHA. Our results show that novel probiotic Lactobacillus casei and paracasei strains can affect the immune system by induction of both regulatory and proinflammatory cytokine production and by inhibition of pro-allergic cytokine profile.

Key words: allergy, atopic dermatitis, Lactobacillus, probiotics

Introduction

Probiotics are defined as viable microorganisms that exhibit beneficial health effects when consumed in adequate amount [5]. Most current probiotics are lactic acid bacteria, especially Lactobacillus and Bifidobacterium species. It is known clinical fact that Lactobacillus rhamnosus GG can be successfully used for the treatment of atopic dermatitis [6]. Probiotics (Lactobacillus rhamnosus strain GG and Escherichia coli strain O83) protect also from the development of allergic diseases when they are administrated to atopic mothers or newborns [7, 8, 10].

Recently, we observed that novel probiotic Lactobacillus strains genetically identified as L. casei and L. paracasei significantly decreased the severity of atopic dermatitis in infants with cow milk allergy [4]. Clinical examinations showed the significant improvement of atopic dermatitis symptoms measured by SCORAD index in children rece-
iving probiotics as compared with the placebo group. Immunological examinations showed a decrease in level of IgE in children receiving probiotics as compared with placebo group. In contrast to clinical and immunological findings Lactobacillus application did not significantly change the composition of gut microflora. These results suggest that beneficial impact on allergy development is dependent on direct activation of the immune system by probiotics.

It is supposed that lactobacilli contribute to the activation of regulatory T-helper cell immune response and to the maintenance of Th1/Th2 cytokine homeostasis [3, 18]. They were shown to enhance production of pro-inflammatory Th1 cytokines and/or to reduce Th2 dominance in allergic patients [12, 13].

The aim of this study was to evaluate the impact of novel probiotic Lactobacillus casei and paracasei strains on the level of pro-inflammatory (IL-12, IFN-gamma, TNF-a-lpha), proallergic (IL-5) and regulatory (TGF-B), IL-10) cytokines in blood cell cultures obtained from allergic infants.

Material and methods

Patients’ characteristics

The study included 30 children aged 3 months – 15 months (mean age 10 months) with atopic dermatitis caused by cow milk allergy. The severity of changes measured by SCORAD index was 32.5. The infants participated in the study with the informed consent of their parents and the study was approved by the Ethics Committee of the Children’s Memorial Health Institute.

Genetic identification of Lactobacillus strains

Lactobacillus bacteria were isolated from human (infant) and animal (rat) alimentary tract and from fermented milk beverages, and than collected at Collection of Industrial Microorganisms of the Institute Fermentation Technology and Microbiology LOCK 105 of Technical University, Lodz. Finally, twenty four Lactobacillus strains were identified by analysis of 16S ribosomal RNA (rRNA) sequences according Salama et al. [16]. Total DNA was extracted from bacteria as previously described by Tailiez et al. [17]. After PCR amplification of 16S rRNA gene, sequencing with universal 343 F and 1406 GR primers was done using BigDye Terminator Cycle Sequencing (Applied Biosystem, USA). Sequences were read in ABI 377 apparatus (Applied Biosystem, USA) and analysed by computer comparison with BLAST software.

Three Lactobacillus strains (LOCK 0900, 0908, 0919) presenting the highest antagonism against pathogens, the highest adherence to Caco-2 epithelial cell line, and the highest viability in low pH and high bile salt concentration [1] were chosen for analyses of cytokine activation in blood cultures.

Blood cultures

The cell cultures were prepared from the whole blood. Heparinized blood was diluted (1:5) with RPMI-1640 medium (Sigma) without fetal calf serum with antibiotics (Sigma). Blood sample (150 µl) and equal quantity of the mixture of heat inactivated probiotic Lactobacillus casei and paracasei in final concentration 2,5 × 10^9/mL was added to a microtitter well. As a positive and negative control polyclonal activator phytohemagglutinin (PHA) (Difco Laboratories, Detroit, USA) in final concentration 10 µg/mL and alone cultivated medium were used respectively. The cultures were incubated at 37°C in humid air containing 5% CO₂ for 72 hours. After this time supernatants were collected and frozen at –70°C until analysis.

Cytokine determination

The cytokine level was determined in supernatants using R&D System Kits according to the instructions of the manufacturer. Briefly, 50 µl of supernatants was added to a microtitter well coated with the specific monoclonal antibody and left for 24 hour in 4°C. After incubation the wells were washed and 100 µl of detection antibody was added to each well and the plates were incubated for 2 hours in room temperature. Then the wells were washed again and 100 µl of streptavidin was added for 20 minutes. Finally, the plates were washed and 50 µl of solution containing o-phenylenediamine dihydrochloride (Sigma) was added. The reaction was stopped with acid sulphuric and the plates were read on micro-ELISA reader at 450. The amounts of cytokines were calculated from the standard curve. The results were expressed in pg/mL as arithmetical means.

Statistical analysis

The results were statistically analyzed using nonparametric Mann-Whitney test. P<0.05 was considered as statistically significant.

Results

Both, PHA and mixture of Lactobacillus strains induced production of pro-inflammatory cytokines in blood cell cultures of allergic children (Fig. 1). Lactobacillus antigens activated statistically higher amounts of TNF-alpha (p=0,0455) and IL-12 (p=0,0081) than PHA. Although the levels of IFN-gamma in cultures incubated with the Lactobacillus was higher in comparison with PHA, but the differences did not achieve statistical significance.

In contrast to activation of pro-inflammatory cytokines, pro-allergic IL-5 was only activated by PHA (Fig. 2). IL-5 level in supernatants of cell blood cultures incubated with the mixture of Lactobacillus strains was below the sensitivity of the assay.

Analyses of regulatory cytokines showed that Lactobacillus bacteria significantly (p=0,0323) increased the level of TGF-beta, in comparison with PHA. Interestingly, IL-10 was induced in significantly (p<0,0001) lower amounts when blood cells were incubated with Lactobacillus than after incubation with PHA.
Discussion

Allergy was recently described as being the result of a deficit of bacterial stimulation during childhood [21]. The administration of probiotic bacteria, mainly *Lactobacillus rhamnosus* GG into breast-feeding mothers and to newborn babies led to a high inhibition (50%) of the risk of atopic dermatitis in children [7, 8]. Different *Lactobacillus* and *Bifidobacterium* strains have been shown to be useful in the treatment of atopic dermatitis in children [6, 15, 19, 20].

Our group presented novel probiotic *L. casei* and *L. paracasei* strains, which in infants significantly reduced the severity of atopic dermatitis [4]. The results of the present study show that novel selected probiotic strains are potent in-

![Fig. 1](image1.png)  
**Fig. 1** The level of pro-inflammatory Th1 cytokines in blood cultures of allergic infants

![Fig. 2](image2.png)  
**Fig. 2** The level of pro-allergic IL-5 in blood cultures of allergic infants

![Fig. 3](image3.png)  
**Fig. 3** The level of regulatory cytokines in blood cultures of allergic infants
ducers of pro-inflammatory cytokines and TGF-beta1 in allergic children. In contrast, they do not trigger pro-allergic cytokines produced by type 2 helper cells.

It is believed that probiotics exert the beneficial effects in allergic patients by regulation of Th1/Th2 cytokine profile. Allergic diseases are characterized by expression of a type 2 cytokine profile. Indeed, IL-4, IL-5, IL-13 and IL-9 are involved in the initiation and maintenance of the allergic reactions [11]. Thus, probiotic bacteria resulting in reduction of Th2 cytokines release and enhance of Th1 cytokine production can exert beneficial effects in allergic patients.

The presented probiotic strains activated IL-12, TNF-alpha and IFN-gamma production in higher amounts than known polyclonal activator PHA. Simultaneously IL-5 secretion was not detected. Our results correlate with studies performed with known probiotic strains. Pochard et al. [12] showed that Lactobacillus bacteria including L. rhamnosus GG inhibited production of IL-4 and IL-5 in blood mononuclear cells isolated from allergic patients, and this effect was dependent on enhanced production of IL-12 and IFN-gamma. Among the soluble factors that influence the Th1/Th2 balance, IL-12 is a key cytokine responsible for initiating and maintaining IFN-gamma-producing Th1 cells. A wide diversity of microbial components trigger this cytokine by reactions with pattern recognition receptors, such as Toll-like receptors (TLR), which in human are widely expressed in gut epithelium, intestinal dendritic cells, lymphocytes [14].

On the other hand, it is necessary to stress that continuous activation of immune response with the production of inflammatory cytokine could be devastating to the host. Therefore, probiotic strains should control and prevent an inappropriate and dangerous activation of inflammatory cascades and should augment development of tolerance towards allergens. We demonstrated that our selected probiotic strains induced production of TGF-beta1 and in lower amounts IL-10, i.e. the regulatory cytokine playing role in maintaining the balance between Th1/Th2 responses and in induction of oral tolerance [9]. TGF-beta blocks the differentiation of Th1 and Th2 cells via inhibition of the transcriptional factors required for expression of INF-gamma and IL-4. IL-10 can also inhibit both IL-12 synthesis and Th1 differentiation, but in some mouse model IL-10 produced by lung dendritic cells appeared to be critical for Th2 responses to inhaled antigens [2].

Concluding our study showed that novel probiotic Lactobacillus casei and paracasei strains can affect the immune system by induction of both regulatory and proinflammatory cytokine production and by inhibition of pro-allergic cytokine profile.

Acknowledgment

This study is supported by the State Committee for Research (project 2P05E 067 26) and Institute Danone.

References


Comparison of histological changes in liver biopsy specimens in patients with biliary atresia of poor and good prognosis

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Abstract

In order to compare intrahepatic histological changes in patients with biliary atresia of poor and good prognosis, we have examined retrospectively 29 liver biopsy specimens taken during hepatoportoenterostomy modo Kasai. We divided the material into two groups: 12 biopsy specimens were qualified to the first – unfavorable group with poor prognosis, because patients died or needed liver transplantation within 2 years after Kasai procedure and 17 biopsy specimens were qualified to the second – favorable group with good prognosis, because children have survived over 5 years with native liver. Presence of prominent giant cell transformation, lobular inflammation and features of ductal plate malformation differed in these two groups. Lobular cholestasis in zone 2 and 3 was of statistical significance in patients with poor prognosis.

Key words: biliary atresia, hepatoportoenterostomy, ductal plate malformation, giant cells transformation, lobular inflammation, cholestasis

Introduction

Biliary atresia (BA) is the commonest cause of infantile cholestasis and leading indication for liver transplantation in children. [1]. Progressive fibro-inflammatory changes lead to irreversible cholangiopathy with complete obliteration of extra and intrahepatic bile ducts, though basic pathomechanisms of disease remain unclear. BA could also result from a developmental aberration occurring between 11 and 13 weeks gestation [13]. Destructive character of BA leads to death in the first 2 years of life if untreated [4]. The only chance to limit disease progression is to establish bile flow by Kasai hepatoportoenterostomy with best results if procedure is performed before 8 weeks of age. [11]. Introducing liver transplantation (LTx) in children opened new era in outcome of BA treatment, reaching overall 5 year survival in almost 80% of patients. LTx timing is an important factor influencing outcome so it is crucial to distinguish early prognostic factors. Characteristic histopathological changes in liver include cholestasis, inflammation, fibrosis and ductular proliferation. Prognostic value of liver histopathology is believed to be crucial but so far no firm criteria were established [4].

The present study is based on a histological analysis of the intrahepatic histopathological changes in patients with poor and good prognosis of the disease. The aim of the study was to compare the stage of liver fibrosis, inflammation, ductular proliferation, giant cell transformation and cholestasis in surgical specimens taken during hepatoportoenterostomy modo Kasai from patients who had good and poor prognosis.
Patients, material and methods

The Children’s Memorial Health Institute is the referral hospital for children with biliary atresia. From children hospitalized between May 1991 and April 2001 who underwent Kasai hepatopancreatoduodenostomy at age between 30 and 70 days (average 55 days) we distinguished two groups according to clinical outcome after operation: 12 liver biopsy specimens were qualified to the first – unfavorable group with poor prognosis, because patients, 16% male and 74% female, died or needed liver transplantation within 2 years after Kasai procedure (Table 1A) and 17 other liver biopsy specimens were qualified to the second – favorable group with good prognosis, because patients, 23% male and 77% female, survived over 5 years with no complications (Table 1B). The liver wedge biopsies were collected during Kasai procedure. The research was carried out in accordance with the recommendations of the Bioethical Commission in the hospital.

Histological examination

All liver biopsy specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections displaying at least 10 portal tracts were routinely stained by Hematoxylin-Eosin, Periodic Acid-Schiff method, with and without diastase, Gomori silver stain, Azan method. In the course of evaluation histological activity of the disease, each sample was described using Ludwig classification for fibrosis and inflammation [2]. Liver fibrosis was assessed as follows: grade 1 mild fibrosis: expansion of fibrous tissue in the portal tract; grade 2 moderate fibrosis with portal to portal bridging; grade 3 severe fibrosis with portal to portal bridging; grade 4 cirrhosis with a reconstruction of hepatic lobules. Inflammatory changes were classified as grade 1 minimal inflammation; grade 2 mild inflammation; grade 3 moderate inflammation; grade 4 severe inflammation. The following categories of lesions were investigated: piecemeal necrosis, lobular inflammation, microabscesses, focal necrosis, portal and lobular inflammation, giant cell transformation, cholestasis, cholangitis, bile duct dilatation, cholangiolitis. These histological criteria were assessed as follows [7] – grade 0 absent; 1 minimally present; 2 moderately present; 3 severe present.

Immunohistochemical study

The ductal and ductular phenotype was examined on paraffin embedded tissue using monoclonal antibodies directed against Cytokeratin 7 (OV-TL1:50 Dako) and 19 (RCK 108 1:100 Dako) and SMA by means of EnVision system DAKO. This method allowed to determine changes specific for ductal plate malformation by the positive staining on bile ductules epithelia and abnormal ductal structures. Immunologic staining for SMA was performed by an immunoperoxidase method allowed to demonstrate the lobular and portal architecture of the liver. One negative control was used from the liver tissue obtained from a child with autoimmune hepatitis.

Table 1

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Group I: The first unfavorable group, patients died or needed liver transplantation within 2 years after Kasai procedure</td>
</tr>
<tr>
<td>No patients</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>1 F</td>
</tr>
<tr>
<td>2 M</td>
</tr>
<tr>
<td>3 M</td>
</tr>
<tr>
<td>4 F</td>
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<tr>
<td>5 F</td>
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<td>6 F</td>
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<td>9 F</td>
</tr>
<tr>
<td>10 F</td>
</tr>
<tr>
<td>11 F</td>
</tr>
<tr>
<td>12 F</td>
</tr>
</tbody>
</table>

<p>| B. Group II: The second favorable group, patients survived over 5 years with native liver after Kasai procedure |</p>
<table>
<thead>
<tr>
<th>No patients</th>
<th>Age at Kasai procedure (days)</th>
<th>Survival/L.Tx (ages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>52</td>
<td>5.7</td>
</tr>
<tr>
<td>2 M</td>
<td>60</td>
<td>6.1</td>
</tr>
<tr>
<td>3 F</td>
<td>61</td>
<td>6.1</td>
</tr>
<tr>
<td>4 F</td>
<td>48</td>
<td>6.2</td>
</tr>
<tr>
<td>5 F</td>
<td>68</td>
<td>6.3</td>
</tr>
<tr>
<td>6 F</td>
<td>38</td>
<td>8.1</td>
</tr>
<tr>
<td>7 F</td>
<td>42</td>
<td>8.4</td>
</tr>
<tr>
<td>8 F</td>
<td>63</td>
<td>8.8</td>
</tr>
<tr>
<td>9 F</td>
<td>63</td>
<td>10.0</td>
</tr>
<tr>
<td>10 F</td>
<td>55</td>
<td>10.0</td>
</tr>
<tr>
<td>11 F</td>
<td>65</td>
<td>10.3</td>
</tr>
<tr>
<td>12 M</td>
<td>63</td>
<td>11.0</td>
</tr>
<tr>
<td>13 F</td>
<td>39</td>
<td>11.6</td>
</tr>
<tr>
<td>14 F</td>
<td>48</td>
<td>12.0</td>
</tr>
<tr>
<td>15 F</td>
<td>55</td>
<td>12.7</td>
</tr>
<tr>
<td>16 F</td>
<td>69</td>
<td>16.9</td>
</tr>
<tr>
<td>17 M</td>
<td>58</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Statistical analysis

Chi-square Independence test and Kolmogorov-Smirnov test (significance level 0.05) was applied for the purpose of comparison the various histopathological intrahepatic changes with the age at Kasai procedure and length of survival period or time to the liver transplantation after operation.
Results

Morphological changes and cytokeratin expression in the liver

The frequency of histological changes is demonstrated in Table 2. We have found fibrosis, inflammatory changes in the portal tracts and lobules, cholestasis in zone 3, bile ductular proliferation with abnormal structures (concentric, tubular, reduplicated), cholangiolitis in all cases, but the intensity of these changes was different (Table 3).

Table 2

Histological changes in the first group of patients with poor prognosis and in the second group of patients with good prognosis

<table>
<thead>
<tr>
<th>No of cases (%)</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Zone 2</td>
<td>83%</td>
<td>41%</td>
</tr>
<tr>
<td>Zone 3</td>
<td>83%</td>
<td>35%</td>
</tr>
<tr>
<td>Ductules</td>
<td>66%</td>
<td>29%</td>
</tr>
<tr>
<td>Ducts</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>Dilatation of bile ducts</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>33%</td>
<td>41%</td>
</tr>
<tr>
<td>Cholangiolitis</td>
<td>66%</td>
<td>41%</td>
</tr>
<tr>
<td>Bile ductular proliferation</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Piecemeal necrosis</td>
<td>66%</td>
<td>64%</td>
</tr>
<tr>
<td>Giant cell transformation</td>
<td>66%</td>
<td>29%</td>
</tr>
<tr>
<td>Foci of hematopoiesis</td>
<td>66%</td>
<td>41%</td>
</tr>
<tr>
<td>Abnormal structures (concentric, tubular, reduplicated)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ductal plate malformation</td>
<td>66%</td>
<td>35%</td>
</tr>
<tr>
<td>Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>33%</td>
<td>35%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>66%</td>
<td>64%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 3

Comparison of significant histological parameters in the first group with poor prognosis and the second group with good prognosis

The degree of fibrosis was similar in both groups at the time of Kasai procedure: we found moderate fibrosis of portal tracts and fibrous portal to portal septa in 4 infants from the first unfavorable group, in 6 infants from the second favorable group and severe fibrosis with septal bridging in 8 infants from the first unfavorable group, in 11 infants from the second favorable group (Fig. 1C). Cirrhosis was absent at the time of Kasai procedure.

Mild inflammatory changes with the presence of diffuse polymorphous infiltration consisted of granulocytes and lymphocytes in the portal tracts and fibrous septa were observed in all cases, but piecemeal necrosis was not a constant feature. In contrast, lobular inflammation was more prominent in the first unfavorable group. Prominent inflammation with massive infiltration of granulocytes and lymphocytes was seen only in two cases from the first unfavorable group, aged 49 days and 60 days at the time of Kasai procedure. They had also features of destructive cholangitis. We observed active necro-inflammatory lesions of the bile ducts and concentric fibrosis around their lumina. One of these patients died 7 months after Kasai procedure and the second one needed liver transplantation 8 months after Kasai procedure.

In summary, cholangitis was seen in 4 and cholangiolitis in 8 patients from the first group as slight inflammation and infiltration of epithelial bile duct cells with few lymphocytes (periductal and intraepithelial infiltration). We found similar changes in 7 patients from the second favorable group. We didn’t observe any paucity of intrahepatic ducts.

Bile ductular proliferation, seen in all cases in both groups was present at the limiting plate, in periportal zones and in the center of portal tracts, often as curved, tubular, concentric structures, and was not always associated with the inflammation. The degree varied between cases of the same group but was not dependent on other factors.

Ductal plate malformation, persistence of fetal biliary structures, seen in 8 cases (66%) from the first unfavorable group and 6 cases (41%) from the second favorable group was characterized by an increased number of bile ducts at the limiting plate, without connective tissue between the lobule, irregular contours of the ductal lumina, lack of the centrally located bile duct and lack of a portal venule. These structures were curved, concentric, sometimes around a fibrous core in the portal tract (Fig. 1D). Their distribution was irregular, they were not present in all portal tracts. The expression of CK7 and CK19 was useful to identify features of ductal plate malformation, especially when inflammatory infiltrates were abundant (Fig. 1D).

Hepatocytic giant cells were observed in 8 infants from the first unfavorable group (66%) and in 5 infants from the second favorable group (29%) of examined material. The number of nuclei ranged from 8 till 15 nuclei, usually they had bile pigment accumulation in the center forming often intralobular rosettes. Many well-defined rosettes were partially lined by giant cells (Fig. 1B).
The distribution of cholestasis was significantly different in both groups (Fig. 1A). Cholestasis in zone 1 was seen in all cases, but regular in zone 2 and 3 in the first group and was statistically different from the second group. Chi-square Independence test and Kolmogorov-Smirnov test performed on liver specimens from patients with the first unfavorable group and the second favorable group (significance level 0.05) showed dependency between cholestasis in zone 2 and 3.

Fig. 1 Demonstration of histological changes in biliary atresia
A. Cholestasis in zone 3, focus of hematopoesis (H&E)
B. Giant cell transformation (H&E)
C. Severe fibrosis (H&E)
D. Features of ductal plate malformation CK7 and CK 19 (EnVision)

Discussion

There are two clinical forms of biliary atresia: embryonic and perinatal. The embryonic type occurs in 35% of patients, is characterised by early onset of neonatal cholestasis without jaundice free period and ductal plate remnants are often present in the liver. The perinatal type occurs in 65% of patients, has a later onset of cholestasis and jaundice free period may be present after physiological jaundice. The proposed prognostic factors after Kasai procedure include age at operation, ductal size at porta hepatic, grade of liver fibrosis, ductal plate malformation and ductular proliferation [7, 9, 16]. Our work based on the retrospective selection of patients at the same age during Kasai procedure, but different survival with native liver. The grade of fibrosis was similar in both groups and we didn’t observe any cirrhotic changes, and age of the patients ranged from 31 to 69 days. Some authors believe that hepatic fibrosis, rather than age, is an important prognostic factor [14]. In our material, two infants who underwent Kasai hepatopportoenterostomy at the age of 31 and 39 days, pro-
gressed quickly to liver failure and liver transplantation after 4 and 1.8 years respectively. In the initial biopsy they presented similar changes like other patients from the first, unfavorable group, but lobular inflammation, giant cell transformation, ductal plate malformation and cholestasis in zone 3 were exceptionally severe. It doesn’t mean, as pointed in the literature, that outcome of early hepatic portoenterostomy for biliary atresia is worse, but it may reflect a difference in the pathogenesis of the disease – fetal and perinatal type, phenotype for different disease processes [15].

Ductal plate malformation may indicate an early onset of disease and can be seen in cases, when injury of bile ducts occurs early in fetal life with destruction and without selection of immature bile ducts. Ductal plate is formed around 9 weeks of gestation and from 12 weeks of gestation begins the remodeling with incorporation into the connective tissue surrounding portal vein branches. The process of remodeling leads until term and by 4 weeks of life bile structures are similar to those of adult bile ducts. That is why the presence of ductal plate malformation in neonates is of pathological significance. The differential diagnosis of the persistence of fetal structures includes marginal ductular proliferation in neonatal cholestasis. In the literature it is pointed, that, when diagnosis is made on the basis of surgical and radiological findings, retrospective examination of the liver showed presence of ductal plate malformation in 21% – 85%. Other conditions of BA represent injury in a later stage with destruction of fully formed extrahepatic and intrahepatic bile ducts [3, 5, 12]. It is connected with abnormality of mesenchymal tissue around primitive bile ducts and disturbance in the epithelial-mesenchymal interactions [13]. In our material, ductal plate malformation was seen in 8 infants (66%) in the first unfavorable group and in 6 infants (35%) in the second favorable group. It was not consistent with degree of fibrosis. Presence of ductal plate malformation may play role as an indicator of prognosis.

Ductular proliferation, reported by some authors as predictor of poor prognosis [16] was observed in our material in all patients in both two groups and was rather associated with cholestasis. Ductal proliferation was more intensive when ductal plate malformation was present. Epithelial cells forming bile ducts expressed CK7 and CK19 in addition to CK8 and CK 18 which was also positive in hepatocytes. Former immunohistochemical assessments showed that the number of CK7 positive cells in initial biopsy is significantly higher in a poor bile drainage group [8]. We didn’t demonstrate differences of the expression of CK7 and CK19 because of lack of morphometric study.

Predominance of giant cells in the biopsy specimens of patients with poor prognosis was well documented in our material. These giant cells are not regenerative/proliferative cells, they can be considered as a fusion of rosette forming hepatocytes and they are not associated with viral infection [10]. In the present study we have demonstrated that bile duct proliferation, cholestasis, cholangioliis are almost invariably present at the time of surgical biopsy during Kasai procedure, indicating that neonatal reaction to cholestasis is similar to adult liver.

In summary, presence of prominent giant cell transformation, lobular inflammation and features of ductal plate malformation differed in these two groups. Lobular cholestasis in zone 2 and 3 was of statistical significance in patients with poor prognosis.

Acknowledgment

Research was supported by Grant Nr PB 695/PO5/2001/21 and PB 0722/PO5/2004/27.

References

Paraganglioma associated with neuroblastoma: rare composite tumor in a 16-year-old girl

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Abstract

Composite pheochromocytomas are very rare and account for only 3% of both adrenal and extraadrenal pheochromocytomas. We report herein a case of 16-year-old girl with tumor of the retroperitoneal space. In her history she had episode of circulatory-respiratory collapse with pulmonary oedema during induction to general anaesthesia. Diagnosis from microscopic examination was unclear: paraganglioma in specimens obtained by core needle biopsy; neuroblastoma in material from open tumor biopsy. Preoperative imaging and scintigraphic studies as well as laboratory tests did not allow to distinguish between paraganglioma and neuroblastoma. Preoperative studies have not shown any metastasis; the tumor size did not decrease after 4 courses of chemotherapy for neuroblastoma. After preoperative preparation with phenoxybenzamine patient underwent surgical removal of the tumor. Histopathologic study revealed paraganglioma with extensive areas of fibrosis. Patient remains disease free in 2 years follow up. In case of composite pheochromocytomas/paragangliomas an adequate preoperative diagnosis is not always possible using clinical, laboratory and imaging studies. In particular cases, even histopathologic examination of the biopsy specimen did not allow to establish firm diagnosis.

Key words: composite paraganglioma, pheochromocytoma-neuroblastoma

Introduction

Composite pheochromocytomas are very rare and account for only 3% of both adrenal and extraadrenal pheochromocytomas [1]. These tumors contain a ganglioneuroma or less frequently a ganglioneuroblastoma component. Children with composite pheochromocytomas according to the literature tended to be older than patients with classical pheochromocytoma, and the tumors were mainly functional (catecholamine secreting) [5]. Some of these cases were associated with neurofibromatosis and multiple endocrine neoplasia [1, 8]. Extraadrenal paraganglioma is rare in the pediatric po-
pulation and occur mostly in older children and adolescents [12]. We report herein a rare case of 16-year-old girl with a composite tumor (paraganglioma with neuroblastoma component) located in the retroperitoneal space.

Case report

A 16-year-old girl was referred to the Department of Oncology in Szczecin, Poland for the treatment of the retroperitoneal tumor. She had 2-year history of periodic, recurrent abdominal pain managed with spasmolytic agents. She did not have any additional complaints. On physical examination she was in good general condition, antropometrically presenting short height, and slightly disturbed body proportions (long body corpse and short extremities) similar to her mother. Her blood pressure and glycemia was normal, she did not have any episodes of vomiting, hypertension, or tachycardia. On physical examination there was an ill-defined, slightly tender, non-movable mass over the left side of her abdomen. Abdominal ultrasonography revealed left paraspinal mass, with intensive vascularity and mixed echogenicity. Fine needle aspiration biopsy detected atypical cells. Contrast enhanced computed tomography of the abdomen revealed a left retroperitoneal tumor (65 mm × 46 mm × 90 mm) below the pancreatic tail, attached to aorta and reaching aortic bifurcation. The mass was well defined, good vascularized, a pressure effect on the left iliopsoas muscle and lower pole of the left kidney was seen. The tumor displaced left renal, splenic and lower mesenteric vessels. There was no extension in the vertebral foramina (Fig. 1A, Fig. 1B).

During induction to general anaesthesia, she had an episode of circulatory-respiratory collapse with pulmonary oedema. Using epidural analgesia, core needle biopsy of the tumor was performed, and the specimen was delivered for hematoxylin/eosin staining as well as for immunohistochemical studies. These studies were performed with commercially available antibodies (S-100 protein, chromogranin, synaptophysin, MIB-1, NSE and vimentin) and according to standard protocols. Pathological studies of the tumor revealed paraganglioma.

In further diagnostic evaluation Metaiodobenzyl guanidine I 131 scintigraphy (MIBG) revealed uptake only within the tumor in left mid-abdomen with no metastasis. Laboratory data included urine catecholamine metabolites revealed increased level of vanilmandelic acid (VMA) (15,2 – 16,1 mg/24 h, N: 0,41 – 3,74). Based on these findings, pheochromocytoma or neuroblastoma was suspected. Open tumor biopsy was performed and histological evaluation revealed neuroblastoma (Fig. 2A, Fig. 2B). N-myc was not amplified in the molecular study of the tumor sample. Treatment with combination chemotherapy was executed (PACE protocol for III stage neuroblastoma: 4 preoperative cycles of vincristine, doxorubicin, cyclophosphamide and cisplatin). Tumor response for oncological treatment was judged as negative. Tumor size remained unchanged; whereas significant decrease of previously elevated level of VMA in 24-hour urine collection was noted (8,6 mg/24 h vs 15,2 mg/24 h).

Patient was referred to the Department of Pediatric Surgery, Collegium Medicum in Bydgoszcz, for the surgical treatment. After 3-week preoperative preparation with phenoxybenzamine patient underwent surgery. Transperitoneal approach was used for the complete removal of the tumor. Macroscopically tumor displayed hemorrhagic areas. Histopathologic study revealed paraganglioma with extensive areas of fibrosis (Fig. 3A, Fig. 3B). There was no perioperative and postoperative complications. In 2 years follow up patient remains free of disease.

Discussion

Composite pheochromocytomas – ganglioneuro (blasto) mas are rare composite tumors of both adrenal and extra-adrenal pheochromocytomas [6]. Other non-pheochromocytomas...
Cytoma components have been also reported [2,3,7,10]. Such type of pheochromocytoma is designated “composite” or “mixed”, depending whether the pheochromocytoma and non-pheochromocytoma components show the same embryonic origin [4]. Pediatric composite pheochromocytomas associated with neuroblastomatous elements are very rare [8]. According to the fact that these tumors exhibit areas of divergent differentiation, the diagnosis can be complicated. Yoshimi et al described pathological features of composite pheochromocytoma-ganglioneuroma. Histologically, the two components of this tumor were minimally admixed with abrupt transition [13]. In other reported case, Pytel et al have described intimately admixed areas of ganglioneuroma and paraganglioma and this histomorphological finding allowed to proper diagnose composite paraganglioma [9]. One can conclude that histology of composite tumors may vary in each case. According to literature pheochromocytoma component in composite tumors is usually predominant [5]. To avoid the misdiagnosis of concomitant histological pattern in composite tumor, it is essential to adequately sample the tumor specimen. In case of composite tumors, the most challenging situation for pathologist, is when multiple histological patterns are present in the same tumor, and when there is limited amount of tissue available for evaluation (such as core needle biopsy). For these reasons authors reevaluated microscopic specimens obtained from the tumor by open biopsy (Fig. 2A, Fig. 2B). Surprisingly, one of three independent pathologists (all from reference centers) recognized in examined specimens only paraganglioma, but not with neuroblastoma components as was done by the others. This could illustrate problems in equivocal judgement of histomorphological studies in case of rare tumors when multiple histological patterns are present in the same tumor.

Further problems which are arising is that because of the rarity, adjuvant therapy standards and final outcomes for
composite pheochromocytomas / paragangliomas with neuroblastoma component yet has not been well established. Nakagawara et al suggested that the metastatic pattern is defined by the major component of tumor; one can ask the question if the tumor would not metastasize to the other organs, even if the foci of neuroblastoma are small [8]. In our case, although preoperative evaluation did not reveal any signs of metastatic disease, the suspicion of neuroblastoma really existed and chemotherapy protocol for neuroblastoma component was administered. After complete surgical resection of the tumor our patient did not demonstrate any signs of disease recurrence in 2 year follow up.

Conclusions

We can conclude, that in case of composite pheochromocytomas / paragangliomas an adequate preoperative diagnosis is not always possible using clinical, laboratory and imaging studies. In particular cases, even histopathologic examination of the biopsy specimen did not allow to establish firm diagnosis. Composite or mixed tumors in children are rare and difficult to diagnose and treat. In these cases good communication between specialists involved in diagnostics and the treatment of the patient (surgeon, oncologist, radiologist and pathologist) is required.

References

Katedra i Klinika Chirurgii Dziecięcej Collegium Medicum UMK w Bydgoszczy
we współpracy z:

Kliniką Chirurgii i Urologii Dzieci i Młodzieży AM w Gdańsku

oraz

SEKCJĄ HISTORYCZNĄ PTCHD
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Mają przyjemność zaprosić do udziału w VI Sympozjum
Postępy w diagnostyce molekularnej i leczeniu nowotworów o podłożu genetycznym u dzieci
oraz III Sympozjum Sekcji Historycznej PTChD

9–10 czerwiec 2006 r.
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Program Sympozjum obejmuje tematykę podłoża genetycznego wybranych nowotworów: raków tarczycy i guzów chromochłonnych. Staramy się pokazać, w jaki sposób postęp biologii molekularnej może przyczynić się do poprawy wyników leczenia tych chorób. Zdając sobie sprawę z wagi profilaktyki w rodzinie występujących rozrostów nowotworowych zaplanowano także wystąpienia poświęcone nowotworom dziedzicznym u dzieci i poradnictwu genetycznemu. Podejmujemy także tematykę historii chirurgii dziecięcej idąc tropami zapomnianych sprzętów, ewolucji technik operacyjnych i anegdoty w chirurgii dziecięcej.

W ramach każdej z sesji zaproszeni znawcy zagadnienia przedstawią problemy nowoczesnej diagnozetyki molekularnej, ale także bardziej tradycyjnego rozpoznawania nowotworów (obrazowanie, badania mikroskopowe). Pokazane zostaną także sposoby leczenia zachowawczego i zabiegowego, włącznie z profilaktycznym stosowaniem leczenia chirurgicznego. Mamy nadzieję, jak co roku, gościć liczne grono uczestników, przedstawicieli różnych dyscyplin medycznych. Chcielibyśmy, aby nasze Sympozjum było także okazją do pogłębienia wzajemnej współpracy zarówno w dziedzinie badań naukowych jak i praktyki klinicznej. Liczymy także na uwagi i propozycje Państwa mogące pomóc w zaplanowaniu formy i tematyki naszych spotkań w przyszłych latach.

Przewodniczący
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Przewodniczący Komitetu
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PROGRAM – ZEGRZE 2006

9 CZERWCA (piątek)

VI SYMPOZJUM „POSTĘPY W DIAGNOSTYCE MOLEKULARNEJ I LECZENIU NOWOTWORÓW O PODŁOŻU GENETYCZNYM U DZIECI”

10.00 – 10.15 OTWARCIE SYMPOZJUM

• Przewodniczący Komitetu Organizacyjnego – dr P. Kluge
• Prezes Polskiej Fundacji Europejskiej Szkoły Onkologii – dr W. Różycki-Gerlach
• Prezes Polskiej Unii Onkologii – dr J. Meder
• Prezes Polskiego Towarzystwa Chirurgów Dziecięcych – prof. A. Chilarski
• Prezes Sekcji Historycznej PTChD – prof. Cz. Stoba
• Prezes Sekcji Chirurgii Onkologicznej PTChD i Prezes Polskiej Akcji Onkologii Dziecięcej – prof. A. I. Prokurat

10.15 – 11.00 WYKŁAD SPECJALNY

“Endocrine surgery in children” – Prof. Henning Dralle – Martin Luther University, Halle-Wittenberg, Department of Surgery

11.00 – 11.15 PRZERWA NA KAWĘ

11.15 – 13.30 SESJA 1 – Guzy chromochłonne u dzieci

Przew.: M. Litwin, J. Lubiński, A. I. Prokurat
1. Guzy chromochłonne u dzieci – punkt widzenia hipertensjologa. – M. Litwin (30 min.)
2. Genetyka kliniczna w pheochromocytoma. – J. Lubiński (30 min.)
3. Leczenie operacyjne guzów chromochłonnych u dzieci. – A. I. Prokurat (30 min.)
4. Leczenie złośliwych postaci pheochromocytoma. – J. Krajewska (30 min.)
5. Ogólnopolski Rejestr Guzów Chromochłonnych. – M. Pęczkowska (15 min.)

13.30 – 14.15 WYKŁAD SPECJALNY

“Radioiodine therapy in radiation induced thyroid childhood cancer” – Prof. Christoph Reiners, University Hospital Wuerzburg, Clinic and Policlinic of Nuclear Medicine

14.00 – 15.00 OBIAD

15.00 – 17.15 SESJA 2 – Zróżnicowane raki tarczycy u dzieci

Przew.: I. Kozłowiec-Gudzińska, S. Sporny, P. Kluge
1. Rak tarczycy u dzieci – różnice w zachowaniu biologicznym i leczeniu – D. Handkiewicz-Junak (30 min.)
2. Rola BAC w diagnoście zmian patologicznych tarczycy – S. Sporny (30 min.)
3. Leczenie chirurgiczne raka tarczycy u dzieci – J. Harasymczuk (30 min.)
4. Rola medycyny nuklearnej w leczeniu zróżnicowanych raków tarczycy u dzieci – I. Kozłowiec-Gudzińska (30 min.)
5. Rejestr raków tarczycy u dzieci w PPGGL – M. Pacholska (15 min.)

17.15 – 17.30 PRZERWA NA KAWĘ

17.30 – 19.00 ZEBRANIE ZARZĄDU GŁÓWNEGO PTCHD

19.00 – 19.30 WALNE ZGROMADZENIE CZŁONKÓW SEKCJI CHIRURGII ONKOLOGICZNEJ PTCHD

20.00 KOLACJA PRZY GRILLU
10 CZERWCA (sobota)

III SYMPOZJUM SEKCJI HISTORYCZNEJ PTCHD
EWOLUCJA TECHNIK OPERACYJNYCH.
TROPEM ZAPOMNIANYCH SPRZĘTÓW.
CHIRURGIA DZIECIĘCA W ANEGDOCIE.

7.30 – 8.30 ŚNIADANIE

09.00 – 09.10 POWITANIE PROF. CZESŁAW STOBA

09.10 – 10.15 WALNE ZGROMADZENIE CZŁONKÓW SEKCJI HISTORYCZNEJ PTCHD

10.15 – 10.30 PRZERWA NA KAWĘ

10.30 – 11.30 SESJA I
1. Tropem moich podręczników chirurgii dziecięcej. – Cz. Stoba
2. Wkład kobiet – chirurgów dziecięcych w rozwój tej specjalności w Polsce, w świetle danych statystycznych – I. Mazurkiewicz-Latawiec
3. Stuletni szpital dziecięcy w Łodzi. – A. Chilarski
4. Obrazy z życia Oddziału Chirurgii Dziecięcej w Kielcach. – P. Wolak, A. Porębska

11.30 – 11.45 PRZERWA NA KAWĘ

11.45 – 13.00 SESJA II
1. Przepuklina przeponowa w dziejach medycyny światowej i polskiej. – J. Skalski, D. Pypłacz
2. Szczecińska historia pewnej fotografii. – I. Mazurkiewicz-Latawiec
3. Choroba Hirschsprunga czyli historia pewnego nieporozumienia. – M. Bukowski, A. Żakowiecka
4. Zaburzenia lateralizacji przełożenia pni tętniczych i wady ułożenia narządów w dawnym polskim piśmiennictwie medycznym. – J. Skalski, D. Pypłacz, M. Gładki
5. Jan Kossakowski odbrązowiony. – A. Cedro

13.00 ZAKOŃCZENIE SYMPOZJUM

13.00 – 14.00 OBIAD
Guzy chromochłonne u dzieci – punkt widzenia hipertensjologa

Mieczysław Litwin
Klinika Nefrologii, Nadciśnienia Tętniczego Transplantacji Nerek,
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Guz chromochłonný/przyzwojak stanowi rzadką przyczyną nadciśnienia tętniczego w wieku rozwojowym. Jednak nietypowy przebieg kliniczny, trudności w leczeniu farmakologicznym, możliwość rozwoju poważnych powikłań narządowych i nierozpoznanie guza złośliwego powodują, że w każdym przypadku nadciśnienia w stopniu 2 u dzieci starszych i u każdego dziecka młodsze-
x z nadciśnieniem, należy przeprowadzić wstępną diagnostykę w kierunku guza chromochłonnego/przyzwojaka. W odróżnieniu od dorosłych, w wieku dziecięcym guz chromochłonný/przyzwojak częściej występuje pozanadnerczowo, rodzinnie i ma charakter złośliwy, a nadciśnienie tętnicze ma charakter utrwalony. Diagnostyka wstępna opiera się na ocenie wydalania katecholamin i ich metabolitów z moczem oraz ultrasonograficznym badaniu jamy brzusznej. Podejrzenie guza chromochłonnego/przyzwojaka na podstawie diagnostyki wstępnej jest wskazaniem do wykonania scyntygraficznych badań obrazujących tkankę chromochłonną. Leczenie farmakologiczne nadciśnienia w okresie przedoperacyjnym opiera się na antagonistach receptora alfa-adrenergicznego, a u chorych z objawami pobudzenia beta-adrenergicznego dodatkowo podaje się beta adrenolityki. W każdym przypadku potwierdzonego rozpoznania guza chromochłonnego/przyzwojaka należy zabezpieczyć materiał do badań molekularnych.

Phaeochromocytoma/paraganglioma in children – hypertesniologist view. Phaeochromocytoma/paraganglioma is a rare cause of arterial hypertension in childhood. However, variable clinical course, problems with pharmacologic therapy, risk of severe target organ damage and malignancy cause that in every case of older child with arterial hypertension in stage 2 and every young child with hypertension screening towards pheochromocytoma/paraganglioma is obligatory. Opposite to adults, pheochromocytoma/paraganglioma in children is often extraadrenal, familial and malignant. Screening tests are based on evaluation of catecholamine excretion in urine and sonographic examination of abdominal cavity. Positive results of screening tests are an indication to scintigraphic evaluation for presence of chromophilic tissue. Hypotensive therapy is based on alpha-adrenergic blockers and in cases with beta-adrenergic stimulation beta-blockers are added. In any case of phaeochromocytoma/paraganglioma molecular diagnosis is obligatory.

Genetyka kliniczna pheochromocytoma

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Międzynarodowe Centrum Nowotworów Dziedzicznych, PAM Szczecin

„Phaeochromocytoma” jest rzadkim guzem neuroendokrynnym z bardzo zróżnicowaną prezentacją kliniczną. Najczęstsze objawy kliniczne to bóle głowy, nadmierna potliwość, dodatkowe skurcze serca i nadciśnienie.

Biochemiczne badania w kierunku „pheochromocytoma” wskazane są nie tylko u osób z wyżej wymienionymi objawami, ale i u pacjentów z przypadkowo wykrytymi guzami nadnerczu lub ze zidentyfikowaną predyspozycją genetyczną (MEN2, VHL, NF1, mutacje SDHB i SDHD). TK lub MRI oraz 123I-MIBG są wykorzystywane do lokalizowania guzów aktywnych biochemicznie.

Preferowaną procedurą chirurgiczną jest laparoskopowe usuwanie guzów. Usunięcie „pheochromocytoma”, odpowiednio wcześnie, gwarantuje bardzo wysoki odsetek wyleczeń.
Leczenie operacyjne guzów chromochłonnych u dzieci

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Katedra i Klinika Chirurgii Dziecięcej CM UMK, Szpital Uniwersytecki im. dr A. Jurasza w Bydgoszczy

Pheochromocytoma jest guzem wywodzącym się z komórek chromafinowych rdzenia nadnerczy lub zwojów współczulnych. Wy- stępuje w lokalizacji nadnerczowej lub pozanadnerczowej. W lokalizacji nadnerczowej lokalizuje się wzdłuż osi kręgosłupa począwszy od jamy czaszki poprzez szyję, klatkę piersiową po dolne obszary jamy brzusznej. Ok. 10–20% przypadków pheochromocytoma wykazuje jest u dzieci. Nie wykazano korelacji między wielkością guza a intensywnością objawów klinicznych. Histologicznie łagodne jak i złośliwe postaci pheochromocytoma u dzieci mogą prezentować zarówno cechy guza łagodnego /brak atypii komórkowej, brak mitoz/ jak i histologiczne cechy niepokoju onkologicznego /mitozy, martwica, polimorfizm jąder, naciekanie naczyń lub torebki guza/. Do rozpoznania formy złośliwej guza upoważnia wykazanie odległych niewydzielających przerzutów tkankowych. U dzieci możliwe są także postaci mieszanego guza /composit pheo/ zawierające komponent neuroblastoma lub ganglineuroblastoma i wymagające modyfikacji sposobu postępowania.


Leczenie złośliwych postaci pheochromocytoma

Jolanta Krajewska
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Jednym pewnym kryterium złośliwości guza jest obecność przerzutów odległych w tkankach nie zawierających skupisk komórek chromochłonnych – zwykle w płucach, wątrobie, kośćach lub węzłach chłonnych, gdyż na podstawie badania histopatologicznego nie jest możliwe jednoznaczne odróżnienie postaci łagodnych od złośliwych. Kryteria miejscowej złośliwości histopatologicznej (martwica w guzie, inwazja naczyń lub torebki, naciekanie otoczenia, atypia jąder, wysoki indeks mitotyczny, diploïa DNA) oraz kryteria kliniczne (młody wiek w chwili ujawnienia choroby, duże wymiary guza, jego pozanadnerczowa lokalizacja, brak wychwytu MIBG przez guz, przetrawle pooperacyjne nadciśnienie tętnicze) zwiększają ryzyko złośliwości, ale nie stanowią wy- starczającej przesłanki.

Postępowaniem z wyboru jest radykalny zabieg operacyjny poprzedzony przygotowaniem farmakologicznym (blokada receptorów? – adrenergicznych). U pacjentów z chorobą uogólnioną konieczne jest dalsze leczenie. Leczeniem 1-szego rzutu jest stosowanie 131 I MIBG. Odpowiedź, pod postacią >50% redukcji masy guza i poziomu hormonów uzyskuje się u 30–60 % chorych a u 50–75% znaczącej poprawy samopoczucia i jakości życia. Pewne nadzieje wiąże się z wprowadzeniem do terapii analogów somatostatyny znakowanych Y-90, które mogłyby stanowić alternatywę zwłaszcza dla chorych, u których zastosowanie 131 I MIBG jest niemożliwe (brak gromadzenia radioznacznika w guzie) lub nieskuteczne. Niemniej, gęstość receptorów somatostatynowych na guzach chromochłonnych jest często mniejsza niż na guzach neuroendokrynnych przewodu pokarmowego. Obecnie czynione są próby stosowa- wania także zimnych analogów somatostatyny, ale wstępne wyniki nie są zachęcające.

Chemioterapię, opartą o cyklofosfamid, winkrystynę i dakarbazynę stosuje się u chorych z nawrotową chorobą lub szybką progresją oraz w tych przypadkach, w których inne metody nie przyniosły korzyści. W większości pacjentów odpowiedź jest jednak krótkotrwała. Klasyczna teleradioterapia stosowana jest rzadko ze względu na małą promienioczuność guzów chromochłonnych.
Ogólnopolski Rejestr Pheochromocytoma

Mariola Pęczkowska
Instytut Kardiologii Klinika Nadciśnienia Tętniczego, Warszawa, ul Alpejska 42

Częstość występowania genetycznych postaci guza chromochłonnego wśród chorych z tzw. sporadycznym pheochromocytoma oscyliuje się na ok. 25%. Do trzech znanych już wcześniej zespołów nowotworowych – zespołu gruczolakowatości wewnątrzwydzielniczej typu 2 (MEN 2), zespołu von Hippela – Lindaua i nerwiakowłókniakowatości typu I (NF1) trzeba obecnie dodać nowo wyodrębniony zespół paraganglioma/pheochromocytoma (PPS/PGL). Zważywszy, że wszystkie te zespoły są zespołami wielonowotworowymi, wczesna diagnostyka i leczenie a następnie wnikliwe, okresowe badania kontrolne mają olbrzymie znaczenie.

Ogólnopolski Rejestr Pheochromocytoma powstał w 2003 roku. Za cel Rejestru uznał konieczność poprawy diagnostyki chorych z pheochromocytoma oraz ustalenie odpowiednich i nowoczesnych standardów leczenia. W ramach działalności Rejestru wszyscy zgłoszeni chory_z mają wykonywane badania genetyczne w kierunku dziedzicznych postaci pheochromocytoma (badania genów SDHB, SDHC, SDHD, VHL, protoonkogenu RET). Rozpoznanie nerwiakowłókniakowatości typu I ustalane jest na podstawie klinicznych kryteriów NHI. W przypadku wykazania dziedzicznych postaci pheochromocytoma, osoby te są hospitalizowane w Klinice Nadciśnienia Tętniczego Instytutu Kardiologii w Warszawie, gdzie przeprowadzane są badania w kierunku odpowiednich zespołów chorobowych. Badaniami genetycznymi objęci są również członkowie rodzin, co stwarza możliwości wykrycia nosicielstwa mutacji i objęcia wczesną opieką profilaktyczną osób z grupy ryzyka.

Aktualnie w Rejestrze znajduje się 271 osób – w tym 192 – index cases: 172 z guzem chromochłonnym, 18 z paraganglioma głowy i szyi oraz 2 osoby z guzem chromochłonnym i paraganglioma oraz 79 członków rodzin nosicieli. Nosicielstwo mutacji (SDHD, SDHC, SDHB, RET, VHL) stwierdzono u 24,8% chorych. Chorych do 18 roku życia było 15 (8,7%) – wyniki badań genetycznych dostępnne są dla 10 osób: u 9 (90%) stwierdzono dziedziczne postaci pheochromocytoma – VHL u 6, MEN 2B u 1, mutację genu SDHB – u 1, SDHD – u 1. Tylko u 3 osób wywiad rodzinny w kierunku pheochromocytoma bywał pozytywny.

Radioiodine therapy in radiation induced thyroid childhood cancer

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After the Chernobyl reactor accident on April 26th 1986, the incidence of thyroid cancer in children and adolescents living in contaminated areas of the Ukraine and Belarus increased significantly. Totally, between 1986 and 2002 4600 cases of thyroid cancer have been observed among those aged 0–18 years at the time of the reactor accident. It is estimated, that approximately 40% of those cases are associated with radiation exposure and 60% are spontaneous cases.

Starting with 01/04/1993, a joint project on the combined treatment with surgery and radioiodine has been launched. Thyroid surgery was performed in the Center for Thyroid Tumors in Minsk, Belarus, and radioiodine therapy followed in Germany at the Universities of Essen (until the end of 1994) and afterwards the University of Würzburg.

Until the end of 2005, 242 children and adolescents had received totally in 987 1-week courses of radioiodine therapy. The number of girls was 144 and the number of boys 98. The age at the time of radioiodine therapy ranged from 7 to 19 years with a mean age of 12.7 2.5 years. Histologically, 236 of the cancers had been classified as papillary and only 2 as follicular cancers. 152 out of those 242 patients suffered from locally advanced tumor stage pT4 (33%). In nearly all of the children (235 out of 242 = 97%) lymph node metastases in the neck were detected during surgery or follow-up. 104 out of 242 children (= 43%) revealed distant metastases (nearly all of them to the lungs). Up to now, 234 patients received more than one course of radioiodine therapy, so that the effectivity of the preceeding treatment course could be checked by a consecutive radioiodine wholebody scan. Totally, 131 children (56%) are in complete remission, 70 children (30%) in stable partial remission and 33 children (40%) in partial remission. With respect to the subgroup of children with distant metastases, the rate of complete remissions is 35%, stable partial remissions 34% and partial remissions 31%. All of the children and adolescents treated with radioiodine are alive.
Paediatric differentiated thyroid cancer – differences in biology and treatment

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Zróżnicowany rak tarczycy (ZRT) jest naj częstszym nowotworem endokrynym zarówno u dzieci jak i dorosłych. Ponieważ w wie- lu pracach wykazano, że ZRT rozpoznawany poniżej 40 roku życia charakteryzuje się dobrym rokowaniem, może się również wy- dawać, że dotyczy to także dzieci. Niemniej w porównaniu do osób dorosłych ZRT u dzieci charakteryzuje się co najmniej kilko- ma istotnymi różnicami: 1) większym zaawansowaniem miejscowym; 2) typem przerzutowania: a) częstsze przerzuty do regional- nych węzłów chłonnym oraz narządów mięśniowych; b) płuca stanowią prawie jedyną lokalizację przerzutów odległych; c) przerzuty do płuca są z reguły funkcjonalne; 3) wysokim odsetkiem nawrotów, przy bardzo niskiej umieralności z powodu choroby nowotworowej.

Biorąc pod uwagę częste nawroty lokalne i regionalne, celem leczenia ZRT u dzieci powinno być nie tylko zapewnienie długiego okre- su przeżycia całkowitego, ale przede wszystkim przeżycia wolnego od nawrotu choroby nowotworowej. Ten ostatni czynnik od- grywa u dzieci tak istotną rolę, gdyż wpływ na poprawę jakości życia, zmniejsza niepokój oraz zaburzenia psychologiczne w okre- sie dorastania, redukuje konieczność skomplikowanych i kosztownych usług medycznych oraz może przekładać się na wydłuże- nie całkowitego czasu przeżycia.

Duże zaawansowanie choroby podczas rozpoznania, częste wznowy oraz dobre wyniki leczenia skojarzone są ku agre- sywnemu postępowaniu terapeutycznemu. Optymalny schemat leczenia dzieci z ZRT powinien rozpoczynać się całkowita/prawie całkowità tyroidektomią z centralną limfadenektomią, poszerzoną o zmodifikowaną limfadenektomię boczną w przypadku prze- rzutów do węzłów chłonnym tej okolicy. Terapia radiowodna, stanowiąca uzupełnienie leczenia chirurgicznego stosowana jest w celu zniszczenia pozostawionych kikutów tarczycy i/lub ognisk nowotworowych.

Chociaż dane literaturowe wskazują na bardzo dobre wyniki leczenia ZRT u dzieci należy poszukiwać nowych schematów lecze- nia, których skuteczność najlepiej mierzyć wydłużeniem czasu wolnego od nawrotu choroby nowotworowej. Powinno się również poszukiwać czynników molekularnych wpływających na ryzyko nawrotu, przerzutów odległych czy zgonu z powodu choroby nowo- wotworowej.

Rola BAC w diagnostyce zmian patologicznych tarczycy

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Biopsja aspiracyjna cienkoigłowa (BAC) stała się najszyszą i najbardziej czulą metodą rozpoznawania zmian guzowatych gru- czołu tarczowego. Głównymi jej zaletami są: możliwość wyodrębnienia chorych, u których wskazane jest leczenie chirurgiczne, mała inwazyjność zabiegu i stosunkowo niewielki koszt procedury. BAC służy nie tylko do rozpoznawania pojedynczych, twar- dych i szybko rosnących guzów tarczycy, ale również mnogich zmian patologicznych, zapaleń oraz wszelkich nieprawidłowości struktury mięśnia wykrytych ultrasonograficznie ewentualnie podczas badania szczerbograficznego. BAC tarczycy jest szczególnie przydatną metodą diagnostyczną na obszarze endemii wola, gdzie powiększony gruczoł tarczowy odnotowuje się u wielu osób. Rutynowe stosowanie BAC oznacza zmniejszenie liczby niepotrzebnych operacji tarczycy i prowadzi do zwiększenia odsetka ra- ków wykrytych w pooperacyjnym badaniu patomorfologicznym.

BAC tarczycy nie jest trudnym do wykonania zabiegiem i nie grozi poważniejszymi powikłaniami. Stwarza możliwość ujawnienia złośliwych nowotworów we wczesnym stadium rozrostu, co zwiększa szansę pełnego wyleczenia. Jednak, jak wiele innych metod diagnostycznych, jest obarczona pewnym ryzykiem błędu. Nieprecyzyjne lub fałszywe rozpoznania mogą być skutkiem zła jakości aspiratów, nieumiejętnego pobierania materiału, błędnej interpretacji ujawnionych zaburzeń struktury komórek oraz zbliżonych obrazów cytologicznych w łagodnych i złośliwych zmianach rozrostowych nabłonka pęcherzyków tarczycy.
Rola medycyny nuklearnej w leczeniu zróżnicowanych raków tarczycy u dzieci

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Raki tarczycy zajmują szczególne miejsce wśród nowotworów złośliwych występujących u dzieci. Ich biologiczna agresywność w odróżnieniu od innych nowotworów wieku dziecięcego jest mniejsza a przerzuty odległe obserwuje się dopiero w zaawansowanej fazie choroby. Raki tarczycy obejmują ok. 10% wszystkich guzów złośliwych i ok. 35% wszystkich raków występujących u dzieci. Zróżnicowane raki tarczycy (ZRT) stanowią 90–95% dziecięcych raków tarczycy. Występują niezwykle rzadko poniżej 5 r. ż. a ok. 70% przypadków wykrywanych jest w wieku 11–17 lat. W odróżnieniu od dorosłych ZRT u dzieci prezentują odmienne zachowanie związane z większą agresją biologiczną, tendencją do szybszego rozprzestrzeniania się w układzie chłonnym, oraz tendencją do wznow węzłów. Jednocześnie w przeciwieństwie do dorosłych charakteryzują się bardzo dobrym rokowaniem odległym. Mała liczba przypadków ZRT w poszczególnych ośrodkach oraz względnie łagodny ich przebieg utrudnia ocenę występowania i leczenia ZRT u dzieci.

Rejestr raków tarczycy u dzieci w PPGGL

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