THE SIGNIFICANCE OF CYTOLYSIS SYNDROME IN CHILDREN

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ABSTRACT

The measurement of aminotransferases levels has become part of the routine biochemical tests done in children regardless of their clinical symptoms. Aminotransferases (ALT, AST) are tissue necrosis markers which change in both hepatic and extra-hepatic conditions. The aim of this study was to establish the etiology and clinical significance of the cytolysis syndrome without cholestasis in children hospitalized for various pediatric conditions.

The study group consisted of 394 children (aged between 1.5 months and 16 years)with elevated values of ALT, AST. The investigation protocol applied included history, full physical examination, complete biological investigations, viral markers and liver ultrasounds.Depending on the aminotransferases values as compared to the normal value (NV), the patients were included in 3 study subgroups: 222 patients with slightlyelevated transaminases values (< 2xNV) (subgroup I), 164 patients with ALT and AST values between 2-3xNV (subgroup II) and 8 patients with TGP, TGO values > 3 x NV (subgroup III).

The ALT and AST values were determined monthly during the first 3 months, and then every 2 to 6 months. In all groups the etiology was dominated by acute bacterial (respiratory, urinary, digestive) and viral (Epstein Barr, Citomegalovirus infection) conditions.

Other causes of cytolysis syndrome were nutritional and metabolic diseases (obesity, mellitus diabetes, phenylketonuria, cystic fibrosis, congenital hypotiroidism). The etiology remained unclear in 20.31% of the cases, yet the transaminase values returned to normal after 6 months with diet and hepatoprotective therapy.

Slightly elevated ALT andASTvalues do not require thorough investigations, as they usually return to normal within the first three months. On the other hand, mildly and severe increases, which persist after three months therapy require further investigation to determine the etiology (viral infections, autoimmune, nutritional and metabolic diseases).

Key words: aminotransferases, cytolysis syndrome, child

The measurement of ALT (alanine transaminase) and AST (aspartate transaminase)levels has become part of the routine biochemical tests done in children regardless of their clinical symptoms. Aminotransferase are tissue necrosis markers which change in both hepatic and extra-hepatic conditions. ALT values increase especially in hepatic conditions, whereas AST values increase in muscular, cardiac, renal, lung and pancreatic conditions (1). The liver is a complex organ, which has many functions, and therefore no biochemical test can assess the overall liver activity by itself.Anamnesis and clinical exams play an important part in hepatic function assessment, yet hepatic function tests such as albumin, prothrombin time and bilirubinare mandatory (2). Since aminotransferase determinations are not hepatic function tests, the liver may function normally despite some isolated increases in these values.

The aim of this study was to establish the etiology and clinical significance of the cytolysis syndrome without cholestasis in children hospitalized for various other pediatric conditions.

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MATERIAL AND METHOD

Our research was conducted on a group of 394 children (aged between 1.5 months and 16 years) hospitalized in the 3rd Pediatric Clinic and the Pediatric Surgery Clinic of the "Sfânta Maria" Children's Emergency Hospital of Iaşi for various pediatric disorders(acute conditions, nutrition- and metabolism-related diseases) and medical and surgical abdomen (infected biliary malformations) between 1 January 2012 and 31 December 2012, in whom high transaminase values were detected. Aminotransferase were included in the set of usual tests done in all the hospitalized patients throughout the period under survey. The normal value (NV) of ALTranged between 10 and 45UI/l, whereas that of AST ranged between 8 and 37UI/l.

Inclusion criteria in the study were elevated ALT, AST.

The exclusion criteria from the study group were: altered values of other hepatic tests (bilirubin, albumin, prothrombin time, alkaline phosphatase, gamma GT, fibrinogen, serum iron, protein electrophoresis), family history of hepatic diseases, clinical or laboratory signs of hemolysis, blood transfusions prior to their hospitalization, known chronic diseases for which the patients were given chronic medication.

The investigation protocol applied to all the children suffering from the liver cytolysis syndrome included complete history, full physical examination, biological investigations (inflammatory syndrome, hepatic syndromes, lipid, protein and carbohydrate metabolism, urinalysis and urine culture, stool examination) and liver ultrasounds. The viral markers (HBs antigen, anti-hepatitis C virus antibodies, anti-Epstein Barr, anti-Cytomegalovirus), anti-Toxoplasma antibodies, muscular enzymes, thyroid hormones, anti-transglutaminase antibodies and iontophoresis were determined in patients with ALT and AST values two times higher than the normal value, which persisted for more than three months. The autoimmunity markers were determined only in patients with ALT and AST values that remained high after 6 months of hepatoprotective therapy.

All the patients were treated for their primary condition and they were also given hepatoprotective drugs. The ALT and AST values were determined monthlyduring the first 3 months, and then every 2 to 6 months, after hepatocytolysis identification.Whenever the high ALT and AST values persisted for more than 6 months, the condition was considered chronic.

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Depending on the ALT and AST values as compared to the NV, the patients were included in 3 study subgroups:

The first subgroupincluded 222 patients with high ALT and AST values, which were however lower than 2xNV.

The second subgroupincluded164 patients whose ALT and AST values were between 2 and 3xNV.

The third subgroup included 8 patients with ALT, ASTvalues exceeding 3xNV.

RESULTS

The cytolysis syndrome was detected in 394 patients hospitalized in the 3rd Pediatric Clinic during the term under survey.

Please note that most of the patients experienced slight average ALT and AST increases.

In the first subgroup, the etiology of the cytolysis syndrome was dominated by acute respiratory, digestive and urinary infections (42.40%), followed by viral infections - Epstein Barr (EB) (6.91%) and Cytomegalovirus (CMV) (4.61%) and finally parasitic infections with Toxoplasma gondii in 4 cases and Giardia lamblia in 20 cases. Obesity and overweight were associated with mild amino-

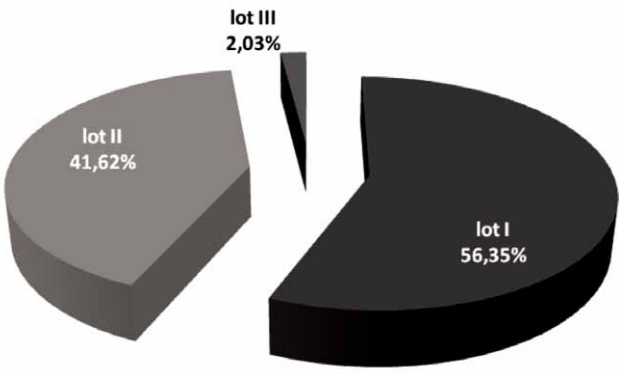

FIGURE 1. *Patients' distribution depending on their aminotransferase values*

transferase increases in 6.91% of the cases. ts etiology could not be detected in 28.11% of the cases.

The etiology of the conditions associated with mild ALT and AST increases (below 2NV) on age groups is shown in the Table 1.

TABLE 1. *Etiology of the cytolysis syndrome on age groups in the first subgroup*

Age	Etiology	No of patients	Frequent %
0-1 year	Acute infections	55	24.77
	VEB infection	3	1.35
	CMV infection	2	0.90
1-3 years	Acute infections	22	9.90
	EBV infection	4	1.80
	CMV infection	5	2.25
	Lambliasis	5	2.25
Over 3 years	Acute infections	15	6.75
	Obesity	15	6.75
	CMV infection	8	3.60
	EB infection	8	3.60
	Toxoplasmosis	4	1.80
	Lambliasis	15	6.75

Please note that as far as young age is concerned, disease etiology was dominated by acute viral or bacterial infections (24.77%), whereas in older children and adolescents obesity and parasitosis (6.75%) were most commonly associated.

In the second subgroup, 50.61% of the cases presented acute severe conditions with sepsis: E. Coliurinary tract infection in infants, bacterial pneumonia, acute otitis media, acute diarrheic disease caused by Campylobacter Jejuni. Nutrition- and metabolism-related diseases were also responsible for elevated aminotransferases: diabetes mellitus (3.15%), obesity (11.58%) and phenylketonuria (1.82%). A persistent cytolysis syndrome required IgA and IgG anti-transglutaminase antibodies testing, which enabled us to diagnose a celiac disease (CD) (1 case).

TABLE 2. *Etiology of the cytolysis syndromeon age groups in the second subgroup*

Age	Etiology	No of pacients	Frequence %
0-1 year of age	Acute infections	66	40.24
	EBV infection	2	1.21
	CMV infection	2	1.21
1-3 years of age	Acute infections	14	8.53
	EBV infection	3	1.82
	CMV infection	2	1.21
Over 3 years of age	Acute infections	5	3.04
	Obesity	19	11.58
	CMV infection	6	3.65
	EBV infection	10	6.09
	Diabetes mellitus tip I	7	3.15
	Toxoplasmosis	4	2.43
	Cystic Fibrosis	4	2.43
	Phenylketonuria	3	1.82
	Congenital hypotiroidism	4	2.43
	Celiac Disease	1	0.60

In the third subgroup, the 8 patients included, who's ALT andASTvalueswere 3 times higher than the NV,suffered from: infectious mononucleosis in 4 cases, E. coli urinary tractinfection in 2 cases, acute pneumococcal otitis mediain 1 case and infected biliary tract malformationsin 1 case.

The dynamic evolution of the ALT andASTvalues in the three subgroups after 3and 6 months, respectively, is shown in Fig. 2.

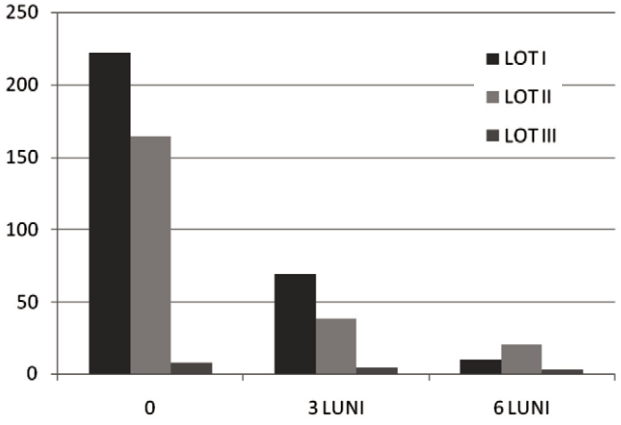

FIGURE 2. *Evolution of the ALT, AST in the three subgroups*

After 6 months of etiological treatment and hepatoprotective therapy, the transaminase values became normal in patients suffering from acute (respiratory, urinary, digestive) and viral conditions, as well as intestinal infestation. The values remained high, yet they did not exceed 2 times the NV, in case of FC, obesity, inborn hypothyroidism, phenylketonuria, infectious mononucleosis.

DISCUSSIONS

The liver biochemical testsassessed hepatic function and/or injuryand they are important markers for evaluating the intensity, complexity and morphofunctional liver lesions: hepatocellular injury, intra- or extra-hepatic cholestasis, infiltrating diseases of the liver, impairment of hepatic synthesis (3). The common serum liver chemistry tests are noted in Table 3.

TABLE 3. *The Common Serum Liver Chemistry Tests (3)*

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate	Hepatocellular damage
aminotransferase	Bilirubin Cholestasis, impaired
Bilirubin Cholestasis,	conjugation, or biliary obstruction
Alkaline phosphatase	Cholestasis, infiltrative disease, or
Prothrombin time	biliary obstruction
Synthetic function	Synthetic function
Albumin	Synthetic function
Gamma	Cholestasis or biliary obstruction
glutamyltransferase	Cholestasis or biliary obstruction
Bile acids	Cholestasis or biliary obstruction
5_-Nucleotidase	Hepatocellular damage, not
Lactate dehydrogenase	specific for hepatic disease

The aminotransferases are intracellularenzymes that are markers of hepatocellular injury. These enzymes - aspartate aminotransferase or AST and alanine aminotransferase or ALT catalyze the transfer of amino groups to form the hepatic metabolites pyruvate and oxaloacetate, respectively (4,5).

ALT is primarily localized to the liver but the AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver.ALT increased level in the circulation is more specific for liver damage than AST(4).

There are multiple causes for elevated liver enzymes: hypoxic-ischemic mechanism or bacterial toxins in sepsis, hepatitis viruses (A, B, C, D, E, Epstein Barr virus, cytomegalovirus), drugs that cause liver injury (NSAIDs, antibiotics, statins, antiepileptics, anti-tuberculosis), autoimmune diseases, nutritional and metabolic, endocrine. In infection, the mechanism of hepatocellular injury is complex, due on the one hand, hypoxia, dehydration, bacterial toxins, and on the other hand drug action: antibiotics (Erythromycin, Augmentin Biseptol, Rifampicin, Hydrazide, Nitrofurantoin), antithermal (Acetaminophen , Ibuprofen) (3).

The hepatocytolysis syndrome is current in pediatric practice. The high GPT and GOT values detected accidentally in children hospitalized for various acute or chronic conditions required a full investigation of their hepatic function in order to define the clinical significance of the cytolysis syndrome.

We noted in our research that in 56.35% of the cases the ALT andASTvalues were only slightly higher (they did not exceed 2xNV). The hepatocytolysis causes were pulmonary infections (acute rhinopharyngitis, interstitial pneumonia, acute otitis media) in 43.56% of the casesand intestinal infestation (lambliasis, oxiurosis) in 9.22% of the cases. After one month of basic condition treatment and hepatoprotective therapy, the ALT andASTvalues went down to normal. If the ALT and ASTvalues were still slightly higher after 30 days of hepatoprotective therapy, the anti-EB and anti-CMV antibodies were then measured and the tests revealedthe presence of IgG antibodies in all these cases, the latter being markers of the old infectionand the absence of any IgM antibodies. 28.11% of the cases exhibited slightly higher ALT and AST values, the cause of which remained unknown. In these patients, only the transaminase levels were higher, as the other hepatic tests (bilirubin, albumin, prothrombin time, alkaline phosphatase, gamma GT, fibrinogen, serum iron, proteinelectrophoresis) were normal. 6 months later, their transaminase levels had also returned to normal.

In the second subgroup, the etiology of the cytolysis syndrome was due in 51.82% of the cases (85 patients) to serious acute septic conditions accompanied by fever: Escherichia Coli urinary tract infection in infants and babies, bacterial pneumonia, acute otitis media, acute diarrhea caused by Campylobacter Jejuni in older children.In this case, in addition to the hypoxic-ischemic mechanism, we also suspected the toxic mechanism inherent to antipyretic drugs (Ibuprofen, Acetaminophen administeredat home before hospitalizationto alleviate high persistent fever, but without however exceeding the toxic threshold). After the basic disease had been treated, the ALT andASTvalues remained slightly higher, but returned to normal within thefollowing 3 months.

High transaminase levels (over 2xNV) also require anti-Epstein Barr, anti-Cytomegalovirus and anti-Toxoplasma antibodies tests. Acute EB infection was identified in 5 cases, whereas 10 cases had suffered from an old infection revealed by the presence of the anti- EB antibodies of the IgG type. Anti-CMV antibodies of the IgM types were detected in 4 cases (twoinfants with neonatal hepatitis and two children aged 3 or older), whereas 6 casesexhibited IgG antibodies.

11.59% of the 164 patients with hypertransaminasemia which was 2 to 3xNV were diagnosed with

various degrees of obesity. After they have been put on a low-calorie diet, with physical exercises and hepatoprotective therapy, the transaminase levels returned to normal in 15 cases. As he did not adhere to the low-calorie diet and to a healthy lifestyle, one of the patients later developed type II diabetes mellitus, whereas another one still had slightly higher transaminase values (below 2 times the NV), high LDL cholesterol levels, and the liver ultrasound revealed steatosis and hepatomegaly. The liver was not punctured for biopsy. Literature data show that the hepatic enzyme changes are significantly correlated with the parameters defining the metabolic syndrome: obesity, insulin resistance, glycemia and lipid levels. Thus, in obese patients, their transaminase levels are predictive of their later developing fasting hyperglycemia, hypertriglyceridemia, HDL-cholesterol decreaseand type 2 diabetes onset (6,7,8). 7 of the patients known as suffering from type 1 diabetes mellitusexperienced altered transaminase values during periods of metabolic imbalance and ketoacidosis, yet these values returned to normal when the glycemia levels were under control.

Cystic fibrosis (CF) may be associated with elevated ALT and AST. High transaminase values were detected in four patients known to suffer from CF. In two of the patients, they were associated with high bilirubin and alkaline phosphatase values. Their transaminase levels returned to normal 6 months after the hepatoprotective and ursodeoxycholic acid therapy had been started.In our research, we have not discovered a single child in whom hepatocytolysis was an initial manifestation of the disease.

Moderate transaminase levels were also detected in patients identified by neonatal screening: 3 infants with phenylketonuriaand 4 infants with inborn hypothyroidism. Under proper therapy, the transaminase values returned to normal in 2 casesafter 3 monthsand in all the infants after 6 months.

A single child exhibited persistent hepatocytolysis syndromeafter three months of proper food diet and hepatoprotective therapy, which urged us to test her IgA and IgG anti-transglutaminase antibodies levels, which enabled us to set the diagnosis of celiac disease (CD). Our research showed that 4% of the patients with cryptogenic hepatitis actually suffered from the silent form ofCD, which means that the serologic anti-transglutaminase antibodies screening is imperative for diagnosis setting (10).

The etiology of the disease was determined in all the children included in the third subgroup, who showed important ALT andAST value increases: infectious mononucleosis in 3 cases, E. coli infection of the urinary tract in 2 infantsand acute pneumococcal otitis mediain 2 young children.One child with high values of ALT, AST was diagnosed with biliary tract malformations and in evolution surgical treatment was necessary. Under proper therapy, the aminotransferases values returned to normal after 3 months, whereas those of the children having suffered Epstein Barr virus infections dropped dynamically and returned to normal after 6 months.

The etiology of the disease remained unclear in 20.31% of the cases, yet the transaminase values returned to normal after 6 months with diet and hepatoprotective therapy. In this case, we considered this temporary ALT andASTelevations as cryptogenic, as it was not accompanied by clinical symptoms or by alterations of the tests assessing the patients' hepatic function (albumin, prothrombin time, bilirubin).

CONCLUSIONS

Aminotransferases (ALT, AST) are important hepatic dysfunction markers, yet they are not hepatic function tests and hence they should not be used to determine the severity and prognosis of the hepatic disease. The etiology of the isolated cytolysis syndrome is extremely varied in children, the subsequent hepatic involvement management depending on the underlying disease. Slightly elevatedALT andASTvalues do not require thorough investigations, as they usually return to normal within the first three months. On the other hand, mildly and severe increases, which persist after three months therapy require further investigation to determine the etiology (viral infections, autoimmune, nutritional and metabolic diseases).

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