SOME BIOLOGICAL INDICATORS RELEVANT FOR THE MANAGEMENT OF CHOLESTASIS IN CHILDREN

Evelina Moraru1, Simona Ana Drochioi1,*, Paula Popovici1, Carmen Anton1, Laura Bozomitu1, Alin Ciobica2,3, Daniel Timofte1, Luminita Padurariu1 and Emil Anton1

1 “Gr. T. Popa” University of Medicine and Pharmacy, Iasi, Romania
2 “Alexandru Ioan Cuza” University, Iasi, Romania
3 Center of Biomedical Research of the Romanian Academy, Iasi Branch, Iasi, Romania

*Corresponding author: simonadrochioi@yahoo.com

Abstract: Cholestasis is a multifactorial disorder with various biological, infectious, toxic, genetic and metabolic manifestations, its principal feature presented as reduced bile flow or abnormalities in bile formation. It has lately been accepted that some specific biological markers would shorten the period needed to establish a positive diagnosis, as currently it is necessary to navigate through a complex diagnostic protocol for this disorder. The purpose of this study was to establish some biological parameters and biomarkers useful for cholestasis management in children. Two hundred thirty-two children with cholestasis were selected, during a six-year study. The biological indicators followed were serum bilirubin, gamma-glutamyl transpeptidase, aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, serum cholesterol and triglycerides. Our data showed that certain biological parameters are more often involved in the various forms of cholestasis, and the conclusions of this study could be useful in the early detection of cholestasis and appropriate disease management.

Key words: cholestasis; biomarkers; children; disease management

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INTRODUCTION

Cholestasis represents a collection of biological events determined by reduced bile flow or by abnormalities in bile formation. This is a frequent pathological condition with an incidence of 1 in 2500 births, which is also present during the neonatal period, (Girard et al., 2008). The causes and mechanisms of cholestasis are very complex and include structural abnormalities of the intra- and extrahepatic biliary tract, as well as infectious, toxic, biologic, genetic and metabolic events affecting biliary secretion (Ishak et al., 1994). It is known that liver function is influenced by multiple etiologic factors, such as infectious agents, autoimmune manifestations, metabolic or genetic diseases, drugs, etc., which may favor the appearance of cholestasis (Moraru et al., 2004).

Early identification of this disorder is important, as it allows the establishment of effective therapeutic management in a timely manner, before the occurrence of biliary cirrhosis lesions, which is very rapid in children (12 weeks) (Whittington et al., 1996). Thus, rapid disease management is essential, as cholestasis can be fatal or have irreparable consequences if not treated (Barshes et al., 2005; Benten et al., 2009). The purpose of this study was to establish some biological parameters and biomarkers useful for cholestasis management in children.

MATERIALS AND METHODS

The present report is part of a retro- and prospective study conducted over a period of 6 years. A group of
children (0-18 years), diagnosed with various pathologies leading to intra- and extrahepatic cholestasis, was analyzed.

The biological indicators selected for study were serum bilirubin, gamma-glutamyl transpeptidase (GGT), aspartate transaminase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), serum cholesterol and triglycerides.

Statistical analysis was done in MS Excel. The statistical packages used were SPSS v13 for Mac OS X (SPSS Inc. 1989-2006) and EPIINFO. The threshold for statistical significance was p<0.05.

The group of 232 children with cholestasis was subdivided into two subgroups. The first one was a subgroup of children with obstructive cholestasis and included 42 children with the following pathologies: biliary atresia, Alagille syndrome, choledochal cysts, biliary lithiasis, congenital hepatic fibrosis and cystic fibrosis, while the second consisted of 190 children with hepatocellular cholestasis with the following disorders: idiopathic neonatal hepatitis, viral hepatitis, bacterial hepatitis, metabolic hepatitis, hepatic cirrhosis, post viral infections.

RESULTS AND DISCUSSION

Cholestasis is a complex disorder with an unclear clinical background. Considering complete clinical examination often does not confirm the disease, subsequent confirmation is needed by biological and laboratory investigations. In The existence of some specific biological markers would shorten the period of establishing a positive diagnosis, which currently requires lengthy navigation through a complex diagnostic protocol. These biomarkers could have an important impact on the early management of the disease and help in understanding the mechanisms involved in cholestasis (Girard et al., 2008).

The biomarkers we focused on in this study included serum bilirubin, the excretion product of bile or gamma-glutamyl transpeptidase, which is an enzyme that transfers gamma-glutamyl functional groups and catalyzes the transfer of the gamma-glutamyl of glutathione to an acceptor that may be an amino acid, a peptide or water; this process that has increased relevance to the oxidative stress status (Siebold et al., 2010).

We were also interested in aspartate transaminase, an enzyme that catalyzes the reversible transfer of an α-amino group between aspartate and glutamate, being an important enzyme in amino acid metabolism, alkaline phosphatase, which is an enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins and alkaloids, lactate dehydrogenase – an enzyme released mainly during tissue damage, serum cholesterol and triglycerides (Czajkowski et al., 2001).

The following statistically significant data were obtained: in the group of children with obstructive cholestasis, the patients diagnosed with Alagille syndrome registered the highest GGT values, followed by patients with biliary atresia and cystic fibrosis (Table 1).

The values of total bilirubin and direct fraction were significantly decreased in the group with gallstones, while the highest value was recorded for the group with idiopathic neonatal hepatitis. Alkaline phosphatase exhibited increased values in the group diagnosed with Alagille syndrome and decreased concentrations in patients with choledochal cysts (Table 2).

The concentration of triglycerides was significantly increased in the group with Alagille syndrome (Table 3). In the group of children with hepatocellular cholestasis, triglyceride concentrations displayed significant differences only between the bacterial hepatitis group and the neonatal idiopathic hepatitis group.

In addition, the biliary lithiasis group displayed significantly decreased values of LDH, and decreased LDH values were observed in the metabolic hepatitis group, as compared to the other hepatocellular cholestasis manifestations (Fig. 1).

The total cholesterol values did not exhibit significant differences between the studied groups, while for obstructive cholestasis, total cholesterol levels were highest in the Alagille syndrome group.
Most of these biomarkers resulted in significant modifications, which could have an important impact on the management of cholestasis, since this disorder is also a consequence of the frequent manifestation of other heterogeneous pathologic entities with increased incidences in pediatric pathology (McKiernan et al., 2002). Currently there are no relevant biomarkers for this disorder, but as demonstrated in the present report, certain biological parameters are more often involved in the various forms of cholestasis. The conclusions of the study could be useful for the early detection of cholestasis and appropriate intervention. Further work in this area of research seems warranted.

**REFERENCES**


