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MINI REVIEW

Search for rare liver diseases: The case of glycosylation defects mimicking Wilson Disease ->

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Summary Pediatric hepatology appears to be a very specific field of paediatrics which deals mainly with rare diseases although clinical features can be commonly found—like increased activity of transaminases. Some of these rare diseases like Wilson disease are commonly looked for and recently Wilsonian like phenotypes have been described which additionally presented with abnormal glycosylation of the plasma protein transferrin. In a subgroup of those patients with specific additional clinical symptoms (cleft uvula, low blood sugar, rhabdomyolysis and dilated cardiomyopathy) phosphoglucomutase 1 deficiency was identified. We recommend screening for abnormal glycosylation of the plasma protein transferrin in children with unexplained liver injury.

Abbreviations: Tf, transferrin; IEF, iso-electrofocusing; CDG, congenital disorders of glycosylation; Sia, sialic acid; Man, mannose; GlcNAc, *N*-acetyl glucosamine; Gal, galactose.

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Introduction

Pediatric hepatology is a very specific part of paediatrics. At this age the only liver disease, which is common in Europe is non-alcoholic fatty liver disease so that all other diseases, including viral hepatitis A, B and C are becoming by now rare diseases.

On the other hand presentation pictures of these diseases like slight hepatomegaly and increased transaminase activity may be relatively common.

There is therefore a long list of liver diseases which may cause problems in differential diagnosis, especially when symptoms are not very specific [1].

Awareness of rare diseases improves diagnosis of many of them even in the early phase of liver injury. Despite the large advantage of access to relatively cheap tests and development of screening procedures, it happens that experts are not able to establish diagnosis in a significant percentage of pediatric patients.

A number of rare hepatopaties (Table 1) was described and taught to the doctors who are now becoming well aware of the need to perform diagnosis after exclusion of the more common diseases. This may be crucial for correct and often life-saving treatment as well (e.g. in the case of hereditary fructose intolerance, galactosemia, tyrosinemia, citrin deficiency, autoimmune hepatitis). Still, there is a place to search for new diseases and critical approach to primarily established diagnosis once criteria are not fulfilled.

Table 1 Possible causes to be considered in the differential diagnosis of fatty liver and increased transaminases in pediatric patients.

General or systemic causes	Genetic-metabolic causes
Obesity	Cystic fibrosis
Metabolic syndrome	Shwachman syndrome
Obstructive sleep apnea	Wilson disease
Polycystic ovary syndrome	α 1-antitrypsin deficiency
Diabetes mellitus type 1	Hereditary fructose intolerance
Thyroid disorders	Cholesterol ester storage disease
Hypothalamic-pituitary disorders	Glycogen storage disease (type I, VI, IX)
Inflammatory bowel disease	Mitochondrial and peroxisomal defects
Celiac disease	α- and β-oxidation defects
Small intestinal bacterial overgrowth	Organic acidosis
Rapid weight loss	Aβ- or hypoβ-lipoproteinemia
Anorexia nervosa	Porphyria cutanea tarda
Protein calorie malnutrition	Familial hyperlipoproteinemias
Hepatitis C	Bile acids synthesis defects
	Congenital disorders of glycosylation
	Citrin deficiency
Several drugs	Turner syndrome

Modified according to Vajro et al. [1].

For example, Wilson disease should be included into differential diagnosis in most patients with various presentations of liver disease — from increased transaminases and/or hepatic steatosis through liver cirrhosis to liver failure. There are common agreed criteria [2,3] but even though Wilson disease remains under-recognized. On the other hand still some patients do not fulfil all the criteria, so that a proportion of them are improperly treated as Wilsonian patients.

Recently some research and clinical groups identified patients with a Wilsonian phenotype who could not be confirmed by molecular analysis [4]. Below we summarize the pathways leading to the identification of a new Wilson-like presenting condition.

Non-Wilsonian Wilson-like patients

The story started in Naples where one of us investigated in collaboration with a Californian glycobiology team, the metabolic defects of four children who presented with clinical and laboratory evidences of isolated cryptogenic chronic liver disease, with histological steato-fibrosis, mild coagulopathy, elevated creatine kinase levels, resolving hypoglycaemia, hypercholesterolemia, and abnormalities of several unrelated serum glycoproteins. These include persistently low ceruloplasmin and low coagulation protein levels [4]. Serum, urinary and liver copper were borderline or within the normal limits, and negative molecular testing for Wilson disease prompted the analysis of the patients' serum glycoproteins and fibroblasts which suggested they had a novel congenital disorder of glycosylation (CDG). All had abnormal transferrin (Tf) isoelectric focusing (IEF) profiles. More detailed analysis of Tf by electrospray ionization mass spectrometry (ESI-MS) showed a plethora of glycosylation abnormalities that included loss of 1-2 sialic acids and 1-2 galactose units, typical of group II defects (Fig. 1). Tf from two patients also lacked 1-2 entire oligosaccharide chains, typical of group I disorders. Total serum N-glycans were analyzed by HPLC and matrix-assisted laser desorption/ionization mass spectrometry and also showed increased proportion of neutral glycan chains lacking sialic acids and galactose units. Analysis of patient fibroblasts eliminated CDG-Ia, through CDG-Ih, -Il and CDG-IId. Results at that point suggested that we were facing to a subset of children with clinically asymptomatic, somewhat Wilson-like, cryptogenic hypertransaminasemia and/or liver steato-fibrosis representing a novel type of CDG-X (unsolved CDG). Importantly, the clinical course was also characterized by a slowly progressive decrease of most presenting clinical and laboratory abnormalities. We therefore concluded that clinicians are encouraged to test such patients for abnormal Tf glycosylation by ESI-MS or IEF.

The group from Warsaw soon after identified some other similar patients with Wilson-like phenotypes and lab results, which finally could not be confirmed to have Wilson disease. One of them presented with elevated ALT and low ceruloplasmin concentration (12 mg/dL) and increased cholesterol concentration (295 mg/dL) at the age of five years. Liver biopsy revealed slight inflammation and fibrosis.

Based on low ceruloplasmin and increased urinary copper excretion Wilson disease was diagnosed but it was