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REVIEW

Persistent hypertransaminasemia in asymptomatic children: A stepwise approach

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Abstract

We aimed to examine the major causes of isolated chronic hypertransaminasemia in asymptomatic children and develop a comprehensive diagnostic flow diagram. A MEDLINE search inclusive of publications throughout August 2012 was performed. We found only a small number of publications that had comprehensively investigated this topic. Consequently, it was difficult to construct a diagnostic flowchart similar to those already available for adults. In children, a "re-testing panel" prescription, including gamma-glutamyl transpeptidase and creatine kinase in addition to aminotransferases, is considered a reasonable approach for proficiently confirming the persistence of the abnormality, ruling out cholestatic hepatopathies and myopathies, and guiding the subsequent diagnostic steps. If re-evaluation of physical and historical findings suggests specific etiologies, then these should be evaluated in the initial enzyme retesting panel. A simple multistep diagnostic algorithm incorporating a large number of possible pediatric scenarios, in addition to the few common to adults, is available. Accurately classifying a child with asymptomatic persistent hypertransaminasemia may be a difficult task, but the results are critical for preventing the progression of an underlying, possibly occult, condition later in childhood or during transition. Given the high benefit/cost ratio of preventing hepatic deterioration, no effort should be spared in diagnosing and properly treating each case of persistent hypertransaminasemia in pediatric patients.

Key words: Transaminase; Aminotransferase; Hypertransaminasemia; Liver disease; Children

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INTRODUCTION

The measurement of serum transaminase levels has become part of the routine biochemical evaluation that takes place before surgery or for the investigation of pathologies not necessarily related to liver injury in many countries. An investigation of unexpected hypertransaminasemia is important for differentiating muscular and hepatic disease; to institute timely and specific treatment for progressive, but still asymptomatic, treatable liver conditions [*e.g.*, Wilson's disease, autoimmune hepatitis (AIH), and non-alcoholic fatty liver disease (NAFLD)]; to furnish genetic counseling for hereditary disorders; and/or to setup appropriate preventive measures (*e.g.*, avoidance of viral hepatitis transmission). Moreover, prevention of possible hepatic deterioration has a high benefit/cost ratio by avoiding the need for eventual liver transplantation[1].

Currently, the most frequent cause of hypertransaminasemia in both adults and children is obesity, although obesity-related liver disease is still sometimes erroneously

considered cryptogenic because of a poor perception of obesity among medical practitioners[2-4]. In adults, the causes of isolated hypertransaminasemia other than obesity-related liver disease are limited to viral hepatitis, toxic damage, autoimmune hepatobiliary diseases, celiac disease, Wilson's disease, and hereditary hemochromatosis[5,6], whose diagnostic work-up is well established[4,6-11]. The problem is more complex in children, in whom individually rare genetic/metabolic conditions collectively constitute 20%-30% of liver diseases[12,13]. Therefore, persistent hypertransaminasemia in a child should alert the physician to the possibility of an underlying hepatic or multisystem metabolic disorder and prompt a referral to a specialized center for diagnostic evaluation. However, despite extensive investigation, the etiology of some cases may have to be defined as truly unknown (cryptogenic)[12,14].

There are only a few reports examining the possible causes of isolated chronic hypertransaminasemia in asymptomatic pediatric populations[12,14-16], and often these studies are biased by flawed inclusion and exclusion criteria, and/or an inadequate diagnostic work-up. Consequently, there is no diagnostic algorithm for the differential diagnosis of unexpected chronic hypertransaminasemia in pediatric patients.

The aim of this report is to develop a comprehensive diagnostic algorithm that includes many of the frequent causes of isolated asymptomatic hypertransaminasemia in children and adolescents. We examined current adult guidelines and expert opinions, and then performed a MEDLINE search inclusive of publications throughout August 2012 using the key words: transaminase, aminotransferase, hypertransaminasemia, liver disease, and children. We also evaluated reports from specialized tertiary pediatric hepatology centers. A secondary aim was to provide a basis for future studies on the cost/benefit ratio of diagnostic assessment procedures.

TRANSAMINASES: BACKGROUND ON ORIGINS, LEVELS, AND THRESHOLD LEVELS

Aminotransferases are normally present in circulation at low levels. They are intracellular enzymes produced principally by hepatocytes, and their increase in serum is therefore indicative of liver cell injury. However, aspartate aminotransferase (AST) is also found in cardiac and skeletal muscles, the kidneys, brain, pancreas, and lungs, and in erythrocytes, in decreasing order of concentration. Additionally, alanine aminotransferase (ALT) is present in skeletal muscle and kidneys, but at low concentrations, and its increase in the circulation is more specific for liver damage than AST. Aminotransferase serum levels depend not only on the tissue of origin, but also on the enzyme half-life, which is longer for ALT than AST. Thus, in diseases such as muscular dystrophy, patients can have AST and ALT serum values that are elevated to the same degree, instead of the expected prevalent elevation of AST[17].

In clinical practice, normal parameter values are within 2 standard deviations of the mean value obtained in healthy individuals. This implies that 5% of the results of healthy subjects fall outside this range. While transaminase reference intervals for adults have recently been revised[18,19], this has not occurred for children. England *et al*[20] recently proposed ALT centiles stratified by sex and age in a healthy European population. They propose an ALT upper limit of normal of 60 IU/L in boys and 55 IU/L in girls during the first 18 mo of life. The range changes to 40 IU/L in boys and 35 IU/L in girls after the age of 18 mo. The Screening ALT for Elevation in Today's Youth (SAFETY) study conducted on a population of North American patients aged between 12 and 17 years shows that the upper limit of normal used by most laboratories for ALT is too high to detect chronic liver disease and that less than half of North American hospitals utilize gender-specific values. In that study, the ALT thresholds in use had a low sensitivity for the detection of chronic liver damage (30%-40%). Using the National Health and Nutrition Examination Survey (NHANES) ALT threshold of 25.8 IU/L for boys and 22.1 IU/L for girls, the sensitivity improved to 70%-80%, while the specificity was only reduced from approximately 90% to approximately 80%[21].

Clinical recommendation

In the pediatric population, there is no established reference range of ALT and AST. ALT thresholds currently in use have a low sensitivity for the detection of chronic liver damage. In teenagers, the biologically-determined and gender-specific ALT threshold of 25.8 U/L for boys and 22.1 U/L for girls established by NHANES increases this sensitivity, with only a modest specificity reduction.

APPROACH TO ASYMPTOMATIC HYPERTRANSAMINASEMIA

Table 1 summarizes the most frequent causes of persistently-elevated transaminase levels in asymptomatic children, schematically classified under the categories of viral, autoimmune, metabolic, and other types of hepatobiliary diseases or extrahepatic causes of hypertransaminasemia.

A detailed evaluation of medical and family history and an accurate clinical examination are crucial in determining the likely etiology of hypertransaminasemia, as they may indicate towards possible muscle or liver conditions.

Initial step: The retesting panel

A stepwise approach contemplates repeating the tests to confirm the results[5,9,10]. In adults, timing of retesting is not firmly established because it has usually been empirically guided by the degree of transaminase alterations found {mild [< 5 times upper limit of normal (× ULN)]; moderate (5-10 × ULN); marked (> 10 × ULN)}.

In pediatric patients, information about gamma-glutamyl transferase (GGT) rather than alkaline phosphatase values might help to determine whether the liver injury

Table 1 Main causes of asymptomatic hypertransaminasemia in children

Hepatic origin	Extrahepatic origin
Obesity (non-alcoholic fatty liver disease)	Duchenne/Becker muscular dystrophy (prevalence: 1:4700)
Viral infections (major and minor hepatotropic viruses)	Other myopathies (*e.g.*, caveolinopathies; prevalence: 1:14000 to 1:120000)
Autoimmune liver disease (prevalence: 1:200000)	Myocardiopathies
Celiac disease and inflammatory bowel disease	Nephropathies
Wilson's disease (prevalence: 1:30000)	Hemolytic disorders
Cystic fibrosis (prevalence: 1:2500) and Shwachman-Diamond syndrome (prevalence: 1:50000)	Macro - AST (prevalence: 30% of children with isolated aspartate aminotransferasemia)
Alpha1 antitrypsin deficiency (prevalence: 1:7000)	
Other genetic and metabolic diseases[1]	
Toxic: Drugs and alcohol	
Cryptogenic hypertransaminasemia	

[1]Refer to Table 3. AST: Aspartate aminotransferase.

is predominantly hepatocellular or cholestatic[5]. Creatine phosphokinase (CPK) should also be evaluated to rule out occult muscle disease[22].

As in adults[5,10,23], in many asymptomatic children, abnormal values can show normal values when re-tested[12,14-16,23]. The reported percentage of patients who normalize aminotransferase serum values within 6 mo from the first detection of abnormality ranges from 26% to 73.6%[12,14-16]. A fluctuating pattern (transient/self-limiting or intermittent) is frequently observed at all ages, and more than one retesting may be warranted even for a mild increase of transaminases. In areas with a high prevalence of hepatitis B (HBV) and C (HCV) virus infection and in high-risk populations, it is advisable to request viral markers at the time of repeat testing to accelerate the screening protocol[9,10]. Recently, Senadhi[24] recommended that HBV and HCV screening is warranted in all asymptomatic patients with mild transaminase elevations.

In selected patients who participate in strenuous sports, liver tests should be repeated after at least one week without exercise, especially if hypertransaminasemia was associated with high CPK or with elevation of other enzymes of muscle origin[25]. If high CPK and hypertransaminasemia are confirmed, it is mandatory to exclude muscular diseases, which are often clinically asymptomatic during the first 5-6 years of life and can be recognized only after a detailed and oriented neurologic examination[22]. In addition to the well-known muscular dystrophies, myocyte injury, necrosis induced by drugs or toxins, and increased exercise are possible causes of high CPK and hypertransaminasemia. Additionally, some mitochondrial, endocrine and metabolic myopathies, and gluten enteropathy are also causes of high CPK and hypertransaminasemia. A serum elevation of CPK ranging from 450 to 5000 U/L (normal upper limit: 150 U/L) accompanying isolated asymptomatic hypertransaminasemia can also be a marker of a caveolinopathy, a group of newly described and still poorly understood muscle diseases that affect the limb-girdle, distal muscles, and heart. A diagnosis may be particularly challenging in pediatric patients that are only mildly symptomatic[26].

First, second, and third line investigations

The evaluation of patients with confirmed hypertransaminasemia should include first (and eventually second and third) line investigations (Table 2). If the patient's history or physical examination suggests a particular disease, selected first-line investigations should already be part of the retesting panel. However, some authors suggest that first-line exams for hepatocellular causes of liver disease should be performed without the need to confirm hypertransaminasemia in patients with increased serum levels of ALT > 3-5 × ULN[27]. Historically, a hypertransaminasemia duration of approximately 6 mo has been arbitrarily used to determine chronic liver disease. However, it is unwise to wait for 6 mo before investigating a possible cause of liver damage, as some hepatopathies, such as autoimmune liver disease or Wilson's disease, can become rapidly life-threatening without appropriate treatment[28].

In the case of protracted isolated AST elevation, the possibility of macro-AST should be investigated by polyethylene glycol and/or electrophoresis testing. Macro-AST is a condition characterized by the presence in serum of a macromolecular complex formed by association with other plasma components [*e.g.*, immunoglobulin G (IgG)] or by self-polymerization. Due to their large size, macro-AST components cannot be filtered by renal glomeruli and are retained in the plasma. The condition is benign, but may cause diagnostic uncertainty and lead to useless, invasive, expensive, and time-consuming testing[29].

Clinical recommendation

Aminotransferase levels should be retested upon finding hypertransaminasemia in asymptomatic patients. At this time, the levels of CPK (for muscular disease) and GGT (for biliary involvement) should also be evaluated. An accurate clinical history and physical examination are of paramount importance for guiding an appropriate investigation and avoiding expensive and unnecessary tests.

MOST COMMON LIVER DISEASES

Non-alcoholic fatty liver disease

NAFLD is the most common cause of hypertransaminasemia in children and adolescents[12,14,16,21]. In clinical practice, NAFLD is usually suspected by the finding of hypertransaminasemia and ultrasonographic fatty liver in an obese child[30,31]. Although the ALT serum level is a useful diagnostic tool, it is not a sensitive marker of NAFLD. It is common to observe the entire histological spectrum of NAFLD in patients with normal ALT levels[22,32]. The evaluation of both AST and ALT values is important because an increased AST/ALT ratio has been reported to reflect a progressive and more serious condition [fibrotic

Table 2 Retesting panel; first, second, and third line investigations in children with asymptomatic mild hypertransaminasemia

Retesting panel[1]	First line panel		Second and third line panels
	Liver function tests	Etiology tests	
ALT	Conjugated and unconjugated bilirubin	Viral markers (HAV, HBV, HCV)	Urinary copper, molecular ATP B7 analysis
AST	Protein electrophoresis	Minor hepatotropic viruses serology	HCV RNA, HBV DNA
CPK	Serum albumin	(*e.g.*, EBV, CMV)	Genetic and metabolic enlarged screening[2] ("non-
GGT	Prothrombin time and partial	Ceruloplasmin, serum copper	alcoholic fatty liver disease bin")
	thromboplastin time	ANA, SMA, LKM, LC1, anti-SLA,	Sweat test
	Blood cell count	total IgG	Fecal elastase, steatocrit
	Hepatic ultrasonography	Serum α1 antitrypsin	Other hepatic imaging techniques (MRI, ERCP, CT, *etc.*)
	If only AST elevation is confirmed: PEG	EMA, tTgasi IgA, deamidated AGA	Liver biopsy[3]
	test and electrophoresis for macro-AST	IgA (< 2 yr), total IgA	Jejunal biopsy (after celiac disease serology)

[1]After at least one week off from exercise; [2]Genetic and metabolic enlarged screening: blood gases, lactic acid, serum ammonium concentrations, blood and urinary amino acids, urinary reducing substances, urinary organic acids, transferrin isoforms, screening test for congenital disorders of glycosylation, α1 antitrypsin phenotype; [3]Modified from the reference of 28. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PEG: Polyethylene glycol; CPK: Creatine kinase; GGT: Gamma-glutamyl transferase; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; ANA: Antinuclear antibodies; SMA: Smooth muscle antibodies; LKM: Anti-microsomal antibodies; LC1: Anti-liver cytosol antibodies type 1; SLA: Soluble liver antigen; IgG: Immunoglobulin G; EMA: Anti-endomysial antibodies; tTgasi: Anti-tissue transglutaminase antibodies; AGA: Anti-gliadin antibodies; IgA: Immunoglobulin A; ATP B7: ATP binding protein 7; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography.

Table 3 Fatty liver disease; possible causes in likely asymptomatic children and adolescents

General or systemic	Genetic-metabolic causes	Drugs/chemicals
Obesity	Cystic fibrosis	Ethanol
Metabolic syndrome	Shwachman syndrome	Ecstasy, cocaine, solvents
Obstructive sleep apnea	Wilson's disease	Nifedipine
Polycystic ovary syndrome	Alpha 1-antitrypsin deficiency	Diltiazem
Diabetes mellitus type 1	Fructosemia	Estrogens
Thyroid disorders	Cholesterol ester storage disease	Corticosteroids
Hypothalamic-pituitary disorders	Glycogen storage disease (type Ⅰ, Ⅵ and Ⅸ)	Methotrexate
Inflammatory bowel disease	Mitochondrial and peroxisomal defects	Prednisolone
Celiac disease	α- and β-oxidation defects	Valproate
Protein calorie malnutrition	Organic acidosis	Vitamin
Rapid weight loss	Abeta or hypobetalipoproteinemia	Zidovudine and HIV treatments
Anorexia nervosa	Porphyria cutanea tarda	Solvents
Small intestinal bacterial overgrowth	Homocystinuria	Pesticides
Hepatitis C	Familial hyperlipoproteinemias	
	Bile acids synthesis defects	
	Congenital disorders of glycosylation	
	Citrin deficiency	
	Turner syndrome	

Modified from the references of 30 and 38. HIV: Human immunodeficiency virus.

non-alcoholic steatohepatitis (NASH)][33].

Due to the worldwide obesity epidemic, obesity may be erroneously accepted as a normal condition even in the presence of abnormal liver function tests[2]. Conversely, in the presence of obesity, all other conditions associated with abnormal transaminase levels, such as celiac disease[34,35], Wilson's disease[36], autoimmune hepatitis[37], or muscular diseases[22], must be investigated and excluded. In many of these diseases, prompt treatment will avoid irreversible disease progression[38] (Table 3).

Abdominal ultrasound and liver function tests should be performed as a first step in the diagnosis of possible NAFLD in children[39]. Ultrasonography, however, detects fat levels above 30% only. Waist circumference is a valid surrogate marker of central obesity, which is closely correlated with liver involvement[40]. When pediatric NAFLD is suspected, other liver diseases should be excluded based on an age-driven algorithm[39]. In obese children and adolescents with disordered breathing during sleep, sleep apnea syndrome should be viewed as a risk factor for NAFLD. Interestingly, weight loss, avoidance of a sedentary life, and effective treatment of sleep apnea syndromes resulted in a significant improvement of liver enzyme levels[41,42].

Clinical recommendation: NAFLD and NASH are diagnoses of exclusion even in obese children with hypertransaminasemia. Other fatty liver causing diseases should be investigated based on the patient's age and clinical features.

Viral infections

Serological markers of hepatitis viruses are part of the first-line etiology investigation panel (Table 2). A positive

history of blood or blood-derivative transfusion, tattooing, ingestion of potentially-contaminated food, and the ethno-geographic origin of the patients give a clue as to a possible infectious etiology. Although immigration and international adoption from endemic areas are well-recognized risk factors, hepatitis B shows an emerging presentation of subclinical chronic hepatitis B in children[43].

In countries where universal vaccination against HBV has been introduced, a significantly-reduced rate of HBV infection in children and mother-to-infant transmission has been observed. However, international adoption and immigration maintain an ample reservoir of HBV infection. Although significantly less infectious than HBV, HCV infection remains a widespread problem in the absence of an effective vaccine. In Western countries, perinatal transmission is currently the primary mode of HCV spread in children, which accounts for approximately 65% of cases[44]. Although hypertransaminasemia may suggest HCV infection, adult[45] and pediatric HCV carriers[46] may have normal or fluctuating aminotransferase levels even in the presence of serious liver damage.

Among the conditions falling within the category of adult cryptogenic hypertransaminasemia is a new entity called "occult" HCV infection. Said entity is characterized by fluctuating serum levels of HCV RNA, while the virus genome and its replicative intermediate RNA-negative strand are detectable in the liver and in peripheral blood mononuclear cells with or without antibodies to HCV[47]. Similarly, "occult" HBV infection has been recognized in patients with cryptogenic hepatitis B surface antigen (HBsAg)-negative chronic liver disease[48]. Intrahepatic replicative activity (HBV covalently closed circular DNA and pregenomic RNA) has recently been described in adults with occult hepatitis B infection. HBV occult infection seems to be relatively frequent in immunized children born to HBsAg-positive mothers. HBsAg negativity is not sufficient for excluding the presence of HBV DNA. These findings emphasize the importance of considering occult HBV infection in hypo-endemic areas[49].

In pediatric patients, hepatitis A virus infection may be followed by up to 1 year intermittent hypertransaminasemia due to relapsing viremia, which does not evolve to chronic liver damage[50]. Other hepatotropic viruses are a frequent cause of liver disease. Epstein-Barr virus and/or cytomegalovirus should be excluded in patients with a history of fever, lymphadenopathy (mainly latero-cervical), pharyngitis, asthenia, and/or hepatosplenomegaly. In patients with paucisymptomatic immunodeficiency, coxsackievirus and adenovirus may be the cause of liver enzyme alteration. Gastrointestinal infection by rotavirus can be accompanied by self-limiting hepatic and non-hepatic transaminase elevation in 20% of infected patients[51].

Currently minor, rather than major, hepatotropic viruses are a common cause of hypertransaminasemia in children in developed countries[12,15,16].

Clinical recommendation: Viral serological markers are part of the first-line investigation panel.

Toxic causes

An accurate medical history is crucial in determining the possible role of toxin-induced hepatotoxicity in children with hypertransaminasemia[52]. In adults, diagnostic scores have been proposed and evaluated to define the association between drugs and liver disease[53,54]. Alcohol abuse can induce liver disease and hypertransaminasemia even in childhood, especially in adolescents[6]. It has been suggested that elevated serum GGT levels, and/or an AST/ALT ratio > 1, and/or an increase in mean corpuscular volume may help in identifying excessive drinking[55]. Carbohydrate deficient transferrin is another tool for identifying unhealthy occult drinking[56]. If medication or alcohol are suspected causes of hypertransaminasemia in an adolescent, aminotransferases should be retested after 6-8 wk of controlled or monitored abstinence[57]. In addition to prescribed or over-the-counter medications and herbal remedies, illegal drugs or substances of abuse should be considered in differential diagnoses and be carefully investigated[58,59].

Autoimmune liver disease

AIH is a progressive inflammatory liver disease without a known etiology, and is characterized histologically by interface hepatitis and serologically by high levels of transaminases, IgG, and positive autoantibodies[60]. The exact prevalence of autoimmune hepatitis is unknown, but it is approximately one in 200000 in the general population of the United States[61]. Sometimes, the histology of autoimmune hepatitis is associated with bile duct injury-determining overlap syndrome or autoimmune sclerosing cholangitis (ASC); this condition is different from primary sclerosing cholangitis, which is characterized by inflammation and fibrosis in the intrahepatic and/or extrahepatic bile load in the absence of interface hepatitis[62,63]. It is important to perform a cholangiography in all children with the histological features of autoimmune hepatitis, as ASC is as prevalent as AIH in childhood, and thus only cholangiography can differentiate between these conditions[64]. There are two types of AIH classified according to antibody profile: type 1 [anti-nuclear antibodies and anti-smooth muscle antibodies (SMA)] and type 2 [anti-liver kidney microsomal antibody (LKM1); and/or antibodies to liver cytosol type 1 (anti-LC1)][65]. Anti-soluble liver antigen (anti-SLA) antibodies can be positive in otherwise autoAb-negative patients. These antibodies cannot be detected by immunofluorescence, and require enzyme-linked immunosorbent assay and immunoassays for identification. Type 2 may tend to be more severe and prevalent in children, adolescents, and young adults than in the older population[60]. The absence of autoantibodies in a child with hypertransaminasemia does not exclude the diagnosis of autoimmune hepatitis. In fact, seronegative but empirically steroid-responsive autoimmune hepatitis has been reported[66-68]. Conversely, the increase in serum gamma-globulins is not universal in AIH. As for Wilson's disease, the diagnosis of autoimmune hepatitis may be difficult because it is not based on specific markers. Consequently, a scoring system

has been devised[69,70] that gives positive predictive values for females, the presence of other autoimmune diseases, hypergammaglobulinemia, and positivity for ANA, SMA, LKM1, LC1 and ASLA. It also gives negative scores for viral markers and a positive history for drugs and alcohol use. A simpler score based on only four items[71] has not yet been fully validated in children. Primary biliary cirrhosis is not observed during childhood, although very rare cases of anti-mitochondrial autoantibody positivity have been reported[72].

AIH (and ASC) may present with only hypertransaminasemia, which can occur in children with apparent good health. It should therefore be investigated with appropriate examinations; if left untreated, cirrhosis may develop.

Clinical recommendation: Autoimmune hepatitis should be rapidly identified in order to administer prompt therapy and avoid cirrhotic evolution. Hypertransaminasemia and hypergammaglobulinemia may be the only findings of seronegative autoimmune hepatitis. It is important to perform a cholangiography in all children with the histological features of autoimmune hepatitis because, in childhood, autoimmune sclerosing cholangitis is as prevalent as autoimmune hepatitis.

Celiac disease and hypertransaminasemia

Celiac disease may be associated with liver involvement in both adults and children. Isolated hypertransaminasemia may be the first manifestation of clinically silent celiac disease[73,74]. It is currently controversial[75] as to whether, in children less than 2 years old, AGA-IgA and IgG should be tested, because of a diagnostic sensitivity higher than that of anti-endomysium antibodies and anti-transglutaminase antibodies at that age. Selective non-responsiveness to HBV immunization in a hypertransaminasemic child may be a clue to undiagnosed celiac disease[76].

So-called "celiac hepatitis" is the most common hepatopathy in celiac patients and is characterized by a moderate increase of transaminase levels usually associated with minimal and non-specific liver lesions of the lobule and portal tracts. A gluten-free diet generally results in normalization of the liver enzymes and repair of histological damage. Due to high disease prevalence, patients with a known diagnosis of celiac disease and persistent hypertransaminasemia should be tested for other possible causes of liver damage before ascribing liver function test abnormalities to celiac disease. Co-existing causes of hepatopathy have been reported[77]. Celiac disease may present as hepatic steatosis in obese children with hypertransaminasemia resistant to weight loss. In such cases, the addition of a gluten-free diet is necessary to resolve their liver abnormalities[34].

Celiac disease can be associated with a variety of autoimmune liver diseases, including AIH, autoimmune cholangitis, and overlap syndromes, with a frequency of AIH peaking at 2.9% in celiac disease children less than 10 years old[74]. Autoimmune hepatic involvement can either precede or follow the diagnosis of celiac disease. It is necessary to diagnose AIH associated with celiac disease promptly, because it is not responsive to a gluten-free diet alone and requires long-term associated immunosuppressive therapy[78].

Wilson's disease and hypertransaminasemia

The prevalence of Wilson's disease is estimated at one in 30000 in most populations (Table 4). The prevalence is as high as one in 10000 in China, Japan, and Sardinia[79]. It may present at any age. Usually, the onset of symptomatic liver disease is at approximately 12 years of age[80]. It is only during adolescence or early adult life that patients usually present with complicating neurological and psychiatric manifestations. The most important laboratory diagnostic clues are hypoceruloplasminemia (< 20 mg/dL in 85%-95% cases), increased free serum copper, increased intrahepatic copper (> 250 μg/g dry weight), and increased basal and post-penicillamine challenge urinary copper excretion[81,82]. These findings are not specific if considered individually, and several conditions may be responsible for false negative and false positive results. Therefore, a score (the "Ferenci score"), which takes into account the Kayser-Fleischer ring, neuropsychiatric symptoms, the occurrence of Coombs negative hemolytic anemia, increased urinary copper, decreased serum ceruloplasmin, increased copper content of hepatocytes, and the presence of causative mutations, has been devised to distinguish between an unlikely/probable/highly-likely diagnosis of Wilson's disease[81]. More recently, a new cut-off value for urinary copper excretion in asymptomatic children with Wilson's disease has been suggested. The new value of 40 μg/24 h replaces the previously-used 100 μg/24 h[83,84]. The post-penicillamine challenge urinary copper estimation has been reported to be poorly sensitive in asymptomatic children[84]. A molecular diagnosis and/or haplotype analysis of the region surrounding ATP7B on chromosome 13 should be considered in children with enigmatic liver disease, especially those with features of NAFLD[84,85]. Wilson's disease-like hypoceruloplasminemic liver disease has been recently described in congenital disorders of glycosylation (CDG) type X[84,86,87]. Non-Wilsonian high urinary copper excretion has been reported in pediatric nodular regenerative hyperplasia[84].

Clinical recommendation: The criteria adopted for the diagnosis of Wilson's disease are non-specific if considered individually. The Ferenci score will distinguish between unlikely, probable, and highly-likely diagnoses of Wilson's disease. New pediatric cut-off values and the real value of post-penicillamine urinary test in asymptomatic cases need careful consideration.

OTHER DISEASES

Disorders, such as inborn errors of metabolism and/or congenital conditions affecting the liver, are much more

Table 4 Clinical and laboratory findings for orienting diagnosis of some genetic metabolic liver diseases

Clinical/laboratory findings	Possible genetic-metabolic cause	Prevalence	Liver involvement
Pancreatic failure, hematological disorders	Shwachman syndrome	1:50000	+++[1]
Asymptomatic, hemolysis	Wilson's disease	1:30000	+++
Previous neonatal cholestasis, hepatomegaly	Alpha 1 antitrypsin deficiency	1:7000	+++
Hypoglycemia, hepatomegaly	Glycogen storage disease (type Ⅰ, Ⅵ and Ⅸ)	From 1:100000 to 1:1000000	+++
Fructose refusal, hepatomegaly	Hereditary fructose intolerance	1:20000	+++
Lethargy, increased serum ammonia levels	Urea cycle defects	1:30000 (all disorders)	++
Lethargy, increased serum ammonia levels	Urea cycle defects	1:30000 (all disorders)	++
Chubby face, fatty liver, specific serum amino acids pattern	Citrin deficiency	1:20000 in East Asia	++
Failure to thrive, lactic acidosis	Mitochondrial diseases	1:8500 (all disorders)	+
Failure to thrive, ketoacidosis, hypoglycemia	Organic acidosis	1:1000 (all disorders)	+
Mild coagulopathy, clinical phenotype	Congenital disorders of glycosylation	From 1:10000 to 1:100000	+
Short stature, female gender, karyotype	Turner syndrome	1:2000	+
Failure to thrive, positive sweat test	Cystic fibrosis	1:2500	+

[1]First 1-2 yr of life; +: Possible; ++: Frequent; +++: Almost always.

common in pediatric patients than in adults (Table 3). These diseases are rare when considered individually, but represent a large group if considered collectively. It is difficult to establish their incidences; in most cases, they are relatively asymptomatic and may therefore remain undiagnosed[88]. Although many etiologies present in the neonatal period with cholestasis or acute illness, several may become manifest only later in infancy or childhood. Extreme care is required to avoid misdiagnosing these cases. This is particularly true if the patients have NAFLD-like symptoms that risk being considered part of the NASH syndrome[38]. Laboratory investigations for genetic metabolic diseases that may often be responsible for a NAFLD-like fatty liver picture should be guided by age and clinical/family history (Table 4). We will comment only on the most relevant metabolic liver diseases and refer the reader to a series of comprehensive reviews for specific information regarding the less common ones[89,90].

Hepatic derangement with severe, but self-limiting, hypertransaminasemia and variable histological patterns may be the sole initial evident manifestation of Shwachman-Diamond syndrome (incidence: 1:50000 worldwide). The mechanisms that can contribute to liver damage in these patients are not known[91]. Citrin deficiency (incidence: 1:20000 in East Asia), a condition now also recognized in Western countries, may present with a pattern of neonatal cholestasis and increased levels of blood citrulline, or NAFLD in children and adolescents[92]. Hereditary fructose intolerance (incidence: 1:20000 worldwide) typically occurs with a pattern of early-onset cholestasis during weaning. However, it may present later in patients who spontaneously follow a low fructose diet because of instinctive fructose refusal/dislike or avoidance. In these cases, medical observation may be dictated by the incidental finding of hypertransaminasemia, hepatomegaly, and/or bright liver by ultrasound observation. Feeding history is crucial for the diagnosis, which is confirmed by molecular analysis of gene mutations[93]. Mitochondrial diseases are often multisystem, but some cases may present with exclusive or prevalent mild liver involvement [*e.g.*, mitochondrial DNA depletion syndrome due to deoxyguanosine kinase (DGUOK, OMIM 251880)]. Some congenital disorders of glycosylation (incidence: 1:50000-1:100000) may present as chronic isolated hypertransaminasemia. Children with clinically asymptomatic, cryptogenic hypertransaminasemia with liver steatosis-fibrosis and mild coagulopathy should be screened for CDG[86,87]. Congenital hepatic fibrosis (CHF, incidence: unknown) is a developmental disorder of the porto-biliary system. It is one of the fibropolycystic diseases, which include Caroli disease, autosomal dominant polycystic kidney disease, and autosomal recessive polycystic kidney disease. Clinically, it is characterized by non- cirrhotic portal hypertension, and rarely complicated by (porto-) pulmonary hypertension and hepatopulmonary syndrome. Hepatocellular function is relatively well-preserved, unless cholangitic episodes are present. Hereditary familial hemochromatosis (incidence: 1:20000 worldwide) most often presents after the transition to maturity, and is well-discussed in studies on adult patients and outside the scope of this article. Alpha 1-antitrypsin deficiency (incidence: 1:7000) presents clinical symptoms only in a minority of affected people. In infancy, the most common presentation is cholestasis. During childhood, it may present with minimally symptomatic disease that becomes significant liver disease only in 10%-15% of patients, often after several years of a near-normal quality of life, and may progress to decompensated liver disease[94]. Glycogenosis types Ⅵ and Ⅸ may be associated with elevated ALT and a soft hepatomegaly that is often not discernible at clinical examination, but without the gross metabolic abnormalities that are typically observed in the other types of glycogenosis. Cystic fibrosis rarely has a prevalent or exclusive hepatic presentation[95]. Nodular regenerative hyperplasia is an infrequently-identified liver disease characterized by non-fibrotic nodular hepatocyte regeneration, secondary portal hypertension, and mild stable abnormalities of liver function tests. In adults, it is usually associated with malignant prothrombotic or rheumatological conditions. These associations are rarely encountered in pediatric practice. The diagnosis is sometimes suggested by minimal histological changes

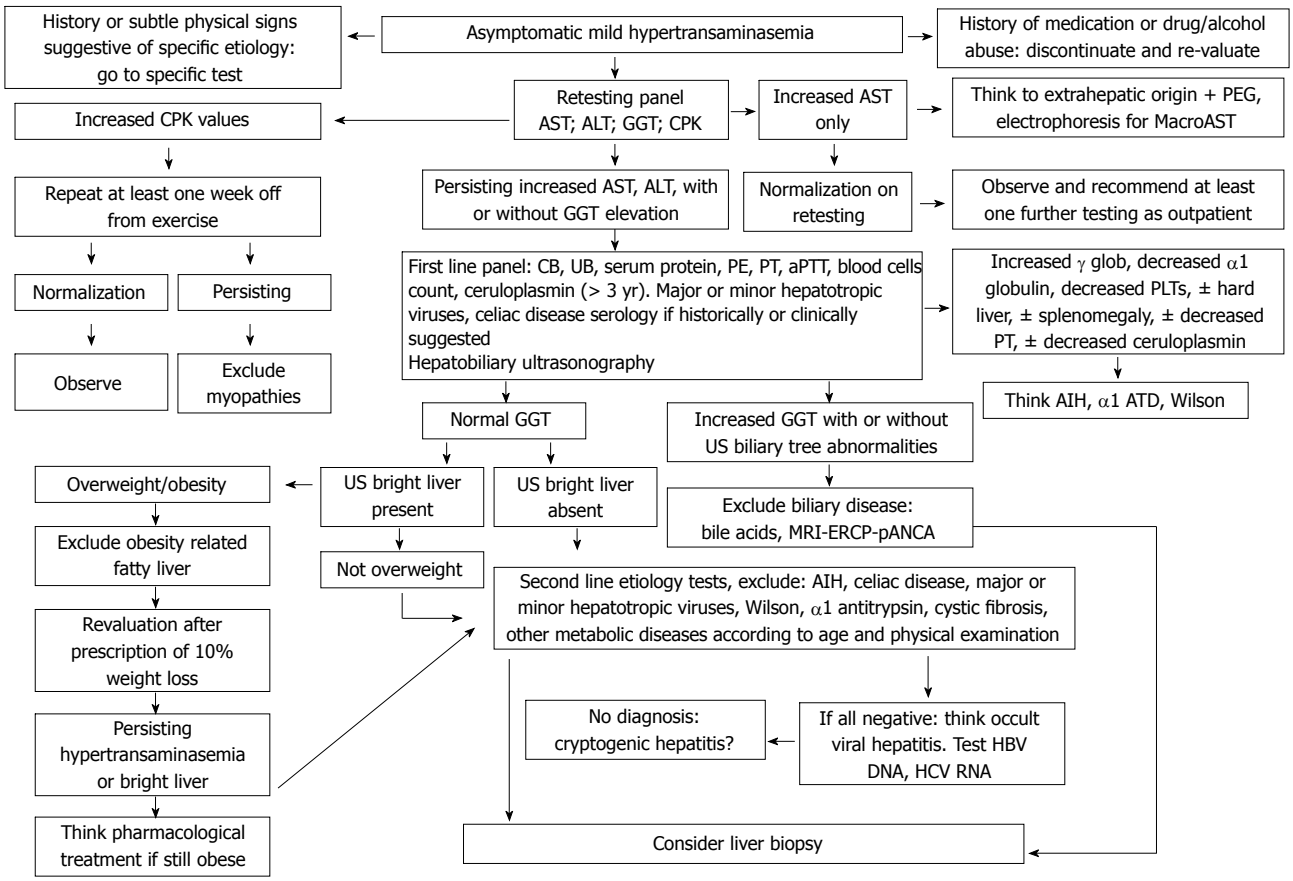

Figure 1 Diagnostic algorithm for the diagnosis of pediatric mild chronic asymptomatic hypertransaminasemia. Modified from the reference of 28. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CB: Conjugated bilirubin; UB: Unconjugated bilirubin; CPK: Creatine kinase; GGT: Gamma-glutamyl transferase; PE: Pulmonary embolism; PEG: Polyethylene glycol; PT: Prothrombin time; PTT: Partial thromboplastin time; US: Ultrasound; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography; pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AIH: Autoimmune hepatitis; α1 ATD: α1-antitrypsin deficiency.

(*e.g.*, sinusoidal dilation)[96].

TRANSAMINITIS AND CRYPTOGENIC HEPATITIS

The term "transaminitis" was coined to describe overall liver enzyme leakage without hepatotoxic consequences in adult patients receiving drug therapy of any type. Hypertransaminasemia is due to an unknown effect of the drug (*e.g.*, changes in hepatocellular membranes due to lipid lowering) or underlying conditions (*i.e.*, fatty liver)[97]. Childhood "cryptogenic" hepatitis appears to be a symptomless disease characterized by isolated hypertransaminasemia that onsets during the first 4 years of life, and mild to moderate histologic liver lesions. Although the frequency of spontaneous remissions is low, childhood chronic cryptogenic hepatitis appears, in the short-term, to be a non-progressive disease. This diagnosis can only be attempted once all other known causes of liver disease are excluded[14,15].

DISCUSSION AND CONCLUSION

Given the large number of pediatric conditions that may be responsible for isolated persistent hypertransaminasemia, one can conclude that even asymptomatic children should undergo an intensive liver work-up. Based on the possibility of a fluctuating pattern, it seems reasonable to repeat ALT and AST testing to confirm hypertransaminasemia, rather than embarking on expensive investigations that may prove to be useless. An enzyme panel costs approximately $30, whereas tests to identify only some of the most common causes of elevated liver enzymes (such as serology for hepatitis B and C infection and ultrasonography for NAFLD) cost approximately $400[10]. However, the cost-benefit considerations of a stepwise diagnostic approach *vs* a simultaneous (and timesaving) testing approach in children should not deter from the need to avoid repeated vein punctures, which is often a traumatic experience. As seen in patients with a fever of unknown origin, in asymptomatic children with cryptogenic hypertransaminasemia, ordering investigations as screening procedures in the hope that something abnormal will be identified might have a number of disadvantages. These disadvantages include: possible adverse reactions or complications, loss of the patient's faith in the medical staff, high testing costs, and a soporific effect on the doctor's diagnostic mental activities[98].

The prescription of a "retesting panel", which in-

cludes the determination of GGT and CPK in addition to aminotransferase levels, has the advantage of confirming the persistence of the abnormality, helping to rule out, at least in part, cholestatic hepatopathies and myopathies, and guiding the subsequent diagnostic steps that are shown in Figure 1. Testing serum bile acids and cholangiography are other means to better assess cholestasis. If reassessment of physical and anamnestic findings suggests specific etiologies, these should be checked in the initial enzyme retesting panel (*e.g.*, viral serologies or hepatorenal ultrasonography for viral hepatitis and NAFLD, respectively). In the presence of even subtle symptoms or signs (*e.g.*, jaundice, ascites, pruritus, hepatomegaly, and/or splenomegaly), complete testing to identify the possible cause of liver disease should be included in the initial retesting.

The first line panel in asymptomatic hypertransaminasemic patients should consist of liver ultrasonography, liver function tests, and a number of investigations for the most frequent etiologies. Second and third line investigations are justified either by the inconclusive first line panel or to explore specific plausible conditions. Liver biopsy is part of these panels, but its exact timing and role remains a controversial issue[28,39,99-101]. It has been shown that in those patients with negative etiological investigations, a liver biopsy will most likely not add further useful information[10,15], and considering that a percutaneous liver biopsy samples only 1:50000 of the liver, sampling error is an obvious limitation which can lead to misdiagnosis and staging inaccuracies[102]. The competence of the pediatric liver disease pathologist is paramount. Steatosis of the liver in a non-obese individual may suggest a metabolic/genetic hepatopathy[14,38].

In conclusion, here we provide an overview of pediatric persistent hypertransaminasemia and list a series of metabolic, genetic, gastrointestinal, and extrahepatic causes that should be taken into account in clinical practice. The number of these etiologies constitutes a wider field of what one usually considers in adulthood. Importantly, information derived from the combination of the patient's history, physical examination, and basic laboratory data are necessary to reach a timely and correct diagnosis. We also provide a stepwise approach that should always be guided by clinical scenarios.

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REFERENCES

1 **Rook M**, Rosenthal P. Caring for adults with pediatric liver disease. *Curr Gastroenterol Rep* 2009; **11**: 83-89 [PMID: 19166664 DOI: 10.1007/s11894-009-0013-7]
2 **Riley MR**, Bass NM, Rosenthal P, Merriman RB. Underdiagnosis of pediatric obesity and underscreening for fatty liver disease and metabolic syndrome by pediatricians and pediatric subspecialists. *J Pediatr* 2005; **147**: 839-842 [PMID: 16356443 DOI: 10.1016/j.jpeds.2005.07.020]
3 **Franzese A**, Vajro P, Argenziano A, Puzziello A, Iannucci MP, Saviano MC, Brunetti F, Rubino A. Liver involvement in obese children. Ultrasonography and liver enzyme levels at diagnosis and during follow-up in an Italian population. *Dig Dis Sci* 1997; **42**: 1428-1432 [PMID: 9246041]
4 **Morisco F**, Pagliaro L, Caporaso N, Bianco E, Sagliocca L, Fargion S, Smedile A, Salvagnini M, Mele A. Consensus recommendations for managing asymptomatic persistent non-virus non-alcohol related elevation of aminotransferase levels: suggestions for diagnostic procedures and monitoring. *Dig Liver Dis* 2008; **40**: 585-598 [PMID: 18395501 DOI: 10.1016/j.dld.2008.02.003]
5 **Pratt DS**, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000; **342**: 1266-1271 [PMID: 10781624 DOI: 10.1056/NEJM200004273421707]
6 **Clark DB**, Lynch KG, Donovan JE, Block GD. Health problems in adolescents with alcohol use disorders: self-report, liver injury, and physical examination findings and correlates. *Alcohol Clin Exp Res* 2001; **25**: 1350-1359 [PMID: 11584156 DOI: 10.1111/j.1530-0277.2001.tb02358.x]
7 **Cobbold JF**, Anstee QM, Thomas HC. Investigating mildly abnormal serum aminotransferase values. *BMJ* 2010; **341**: c4039 [PMID: 20675393 DOI: 10.1136/bmj.c4039]
8 **Giboney PT**. Mildly elevated liver transaminase levels in the asymptomatic patient. *Am Fam Physician* 2005; **71**: 1105-1110 [PMID: 15791889]
9 **Giannini EG**, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ* 2005; **172**: 367-379 [PMID: 15684121 DOI: 10.1503/cmaj.1040752]
10 **Green RM**, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002; **123**: 1367-1384 [PMID: 12360498 DOI: 10.1053/gast.2002.36061]
11 **Krier M**, Ahmed A. The asymptomatic outpatient with abnormal liver function tests. *Clin Liver Dis* 2009; **13**: 167-177 [PMID: 19442912 DOI: 10.1016/j.cld.2009.02.001]
12 **Iorio R**, Sepe A, Giannattasio A, Cirillo F, Vegnente A. Hypertransaminasemia in childhood as a marker of genetic liver disorders. *J Gastroenterol* 2005; **40**: 820-826 [PMID: 16143887 DOI: 10.1007/s00535-005-1635-7]
13 **Matsui A**. Hypertransaminasemia: the end of a thread. *J Gastroenterol* 2005; **40**: 859-860 [PMID: 16143897 DOI: 10.1007/s00535-005-1675-z]
14 **Zancan L**, Bettiol T, Rini A, Giacchino R, Gandullia P, Vajro P, Marcellini M, Musumeci S, Di Leo G, Balli F, Bragetti P, Calacoci M, Barbera C. Chronic idiopathic hypertransaminasemia. *Minerva Pediatr* 1996; **48**: 209-216 [PMID: 8926957]
15 **Bugeac N**, Pacht A, Mandel H, Iancu T, Tamir A, Srugo I, Shaoul R. The significance of isolated elevation of serum aminotransferases in infants and young children. *Arch Dis Child* 2007; **92**: 1109-1112 [PMID: 17652319 DOI: 10.1136/adc.2007.121194]
16 **Nobili V**, Reale A, Alisi A, Morino G, Trenta I, Pisani M, Marcellini M, Raucci U. Elevated serum ALT in children presenting to the emergency unit: Relationship with NAFLD. *Dig Liver Dis* 2009; **41**: 749-752 [PMID: 19362523 DOI: 10.1016/j.dld.2009.02.048]
17 **Kohli R**, Harris DC, Whitington PF. Relative elevations of serum alanine and aspartate aminotransferase in muscular dystrophy. *J Pediatr Gastroenterol Nutr* 2005; **41**: 121-124 [PMID: 15990642 DOI: 10.1097/01.WNO.0000161657.98895.97]
18 **Piton A**, Poynard T, Imbert-Bismut F, Khalil L, Delattre J, Pelissier E, Sansonetti N, Opolon P. Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group. *Hepatology* 1998; **27**: 1213-1219 [PMID: 9581673 DOI: 10.1002/hep.510270505]
19 **Prati D**, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. Updated definitions of healthy

ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**: 1-10 [PMID: 12093239]
20 **England K**, Thorne C, Pembrey L, Tovo PA, Newell ML. Age- and sex-related reference ranges of alanine aminotransferase levels in children: European paediatric HCV network. *J Pediatr Gastroenterol Nutr* 2009; **49**: 71-77 [PMID: 19465871 DOI: 10.1097/MPG.0b013e31818fc63b]
21 **Schwimmer JB**, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, Sirlin CB. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. *Gastroenterology* 2010; **138**: 1357-1364, 1364.e1-2 [PMID: 20064512 DOI: 10.1053/j.gastro.2009.12.052]
22 **Veropalumbo C**, Del Giudice E, Esposito G, Maddaluno S, Ruggiero L, Vajro P. Aminotransferases and muscular diseases: a disregarded lesson. Case reports and review of the literature. *J Paediatr Child Health* 2012; **48**: 886-890 [PMID: 20500440 DOI: 10.1111/j.1440-1754.2010.01730.x]
23 **Lazo M**, Selvin E, Clark JM. Brief communication: clinical implications of short-term variability in liver function test results. *Ann Intern Med* 2008; **148**: 348-352 [PMID: 18316753]
24 **Senadhi V**. A paradigm shift in the outpatient approach to liver function tests. *South Med J* 2011; **104**: 521-525 [PMID: 21886053 DOI: 10.1097/SMJ.0b013e31821e8ff5]
25 **Pettersson J**, Hindorf U, Persson P, Bengtsson T, Malmqvist U, Werkström V, Ekelund M. Muscular exercise can cause highly pathological liver function tests in healthy men. *Br J Clin Pharmacol* 2008; **65**: 253-259 [PMID: 17764474 DOI: 10.1111/j.1365-2125.2007.03001.x]
26 **Bruno C**, Sotgia F, Gazzerro E, Minetti C, Lisanti MP. Caveolinopathies. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, 1993-2007 [PMID: 20301559]
27 **Musana KA**, Yale SH, Abdulkarim AS. Tests of liver injury. *Clin Med Res* 2004; **2**: 129-131 [PMID: 15931347 DOI: 10.3121/cmr.2.2.129]
28 **Vajro P**, Di Cosmo N, Capuano G. Approach to the asymptomatic child with protracted hypertransaminasemia. In: Guandalini S. Essential Pediatric Gastroenterology, Hepatology and Nutrition. New York: McGraw-Hill, 2005: 335-344
29 **Caropreso M**, Fortunato G, Lenta S, Palmieri D, Esposito M, Vitale DF, Iorio R, Vajro P. Prevalence and long-term course of macro-aspartate aminotransferase in children. *J Pediatr* 2009; **154**: 744-748 [PMID: 19111320]
30 **Roberts EA**. Pediatric nonalcoholic fatty liver disease (NAFLD): a "growing" problem? *J Hepatol* 2007; **46**: 1133-1142 [PMID: 17445934 DOI: 10.1016/j.jhep.2007.03.003]
31 **Alisi A**, Manco M, Vania A, Nobili V. Pediatric nonalcoholic fatty liver disease in 2009. *J Pediatr* 2009; **155**: 469-474 [PMID: 19772998 DOI: 10.1016/j.jpeds.2009.06.014]
32 **Fishbein MH**, Miner M, Mogren C, Chalekson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity of steatosis. *J Pediatr Gastroenterol Nutr* 2003; **36**: 54-61 [PMID: 12499997 DOI: 10.1097/00005176-200301000-00012]
33 **Patton HM**, Lavine JE, Van Natta ML, Schwimmer JB, Kleiner D, Molleston J. Clinical correlates of histopathology in pediatric nonalcoholic steatohepatitis. *Gastroenterology* 2008; **135**: 1961-1971.e2 [PMID: 19013463 DOI: 10.1053/j.gastro.2008.08.050]
34 **Franzese A**, Iannucci MP, Valerio G, Ciccimarra E, Spaziano M, Mandato C, Vajro P. Atypical celiac disease presenting as obesity-related liver dysfunction. *J Pediatr Gastroenterol Nutr* 2001; **33**: 329-332 [PMID: 11593131 DOI: 10.1097/00005176-200109000-00019]
35 **Tucker E**, Rostami K, Prabhakaran S, Al Dulaimi D. Patients with coeliac disease are increasingly overweight or obese on presentation. *J Gastrointestin Liver Dis* 2012; **21**: 11-15 [PMID: 22457854]
36 **Spindelboeck W**, Deutschmann A, Lackner K, Weitzer C, Erwa W, Hauer A Ch, Ferenci P, Deutsch J. Obesity and Wilson disease in Childhood and adolescence. *J Pediatr Gastroenterol Nutr* 2009; **48** Suppl 3: E63
37 **Adams LA**, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic Fatty liver disease. *Am J Gastroenterol* 2004; **99**: 1316-1320 [PMID: 15233671 DOI: 10.1111/j.1572-0241.2004.30444.x]
38 **Cassiman D**, Jaeken J. NASH may be trash. *Gut* 2008; **57**: 141-144 [PMID: 18192446 DOI: 10.1136/gut.2007.123240]
39 **Vajro P**, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, Durmaz O, Lacaille F, McLin V, Nobili V. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr* 2012; **54**: 700-713 [PMID: 22395188 DOI: 10.1097/MPG.0b013e318252a13f]
40 **Manco M**, Bedogni G, Marcellini M, Devito R, Ciampalini P, Sartorelli MR, Comparcola D, Piemonte F, Nobili V. Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis. *Gut* 2008; **57**: 1283-1287 [PMID: 18218674 DOI: 10.1136/gut.2007.142919]
41 **Verhulst SL**, Jacobs S, Aerts L, Schrauwen N, Haentjens D, Rooman RP, Gaal LV, De Backer WA, Desager KN. Sleep-disordered breathing: a new risk factor of suspected fatty liver disease in overweight children and adolescents? *Sleep Breath* 2009; **13**: 207-210 [PMID: 19002513 DOI: 10.1007/s11325-008-0231-5]
42 **Kheirandish-Gozal L**, Sans Capdevila O, Kheirandish E, Gozal D. Elevated serum aminotransferase levels in children at risk for obstructive sleep apnea. *Chest* 2008; **133**: 92-99 [PMID: 18187742 DOI: 10.1378/chest.07-0773]
43 **Sciveres M**, Maggiore G. Hepatitis B "by proxy": an emerging presentation of chronic hepatitis B in children. *J Pediatr Gastroenterol Nutr* 2007; **44**: 268-269 [PMID: 17255843 DOI: 10.1097/MPG.0b013e31802c69bb]
44 **Stephenne X**, Sokal EM. Hepatitis C in children and adolescents: mode of acquisition, natural history and treatment. *Acta Gastroenterol Belg* 2002; **65**: 95-98 [PMID: 12148447]
45 **Puoti C**, Bellis L, Guarisco R, Dell' Unto O, Spilabotti L, Costanza OM. HCV carriers with normal alanine aminotransferase levels: healthy persons or severely ill patients? Dealing with an everyday clinical problem. *Eur J Intern Med* 2010; **21**: 57-61 [PMID: 20206870 DOI: 10.1016/j.ejim.2009.12.006]
46 **Iorio R**, Giannattasio A, Sepe A, Terracciano LM, Vecchione R, Vegnente A. Chronic hepatitis C in childhood: an 18-year experience. *Clin Infect Dis* 2005; **41**: 1431-1437 [PMID: 16231253 DOI: 10.1086/497141]
47 **Pham TN**, Coffin CS, Michalak TI. Occult hepatitis C virus infection: what does it mean? *Liver Int* 2010; **30**: 502-511 [PMID: 20070513 DOI: 10.1111/j.1478-3231.2009.02193.x]
48 **Fang Y**, Shang QL, Liu JY, Li D, Xu WZ, Teng X, Zhao HW, Fu LJ, Zhang FM, Gu HX. Prevalence of occult hepatitis B virus infection among hepatopathy patients and healthy people in China. *J Infect* 2009; **58**: 383-388 [PMID: 19329189 DOI: 10.1016/j.jinf.2009.02.013]
49 **Shahmoradi S**, Yahyapour Y, Mahmoodi M, Alavian SM, Fazeli Z, Jazayeri SM. High prevalence of occult hepatitis B virus infection in children born to HBsAg-positive mothers despite prophylaxis with hepatitis B vaccination and HBIG. *J Hepatol* 2012; **57**: 515-521 [PMID: 22617152 DOI: 10.1016/j.jhep.2012.04.021]
50 **Arslan S**, Caksen H, Oner AF, Odabaş D, Rastgeldi L. Relapsing hepatitis A in children: report of two cases. *Acta Paediatr Taiwan* 2002; **43**: 358-360 [PMID: 12632793]
51 **Teitelbaum JE**, Daghistani R. Rotavirus causes hepatic transaminase elevation. *Dig Dis Sci* 2007; **52**: 3396-3398 [PMID: 17431773 DOI: 10.1007/s10620-007-9743-2]
52 **Navarro VJ**, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006; **354**: 731-739 [PMID: 16481640 DOI: 10.1056/NEJMra052270]

53 **Maria VA**, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997; **26**: 664-669 [PMID: 9303497 DOI: 10.1002/hep.510260319]

54 **Aithal GP**, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol* 2000; **33**: 949-952 [PMID: 11131457 DOI: 10.1016/S0168-8278(00)80127-0]

55 **Liangpunsakul S**, Qi R, Crabb DW, Witzmann F. Relationship between alcohol drinking and aspartate aminotransferase: alanine aminotransferase (AST: ALT) ratio, mean corpuscular volume (MCV), gamma-glutamyl transpeptidase (GGT), and apolipoprotein A1 and B in the U.S. population. *J Stud Alcohol Drugs* 2010; **71**: 249-252 [PMID: 20230722]

56 **Conigrave KM**, Davies P, Haber P, Whitfield JB. Traditional markers of excessive alcohol use. *Addiction* 2003; **98** Suppl 2: 31-43 [PMID: 14984240 DOI: 10.1046/j.1359-6357.2003.00581.x]

57 **Aragon G**, Younossi ZM. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleve Clin J Med* 2010; **77**: 195-204 [PMID: 20200170 DOI: 10.3949/ccjm.77a.09064]

58 **Fidler H**, Dhillon A, Gertner D, Burroughs A. Chronic ecstasy (3,4-methylenedioxymetamphetamine) abuse: a recurrent and unpredictable cause of severe acute hepatitis. *J Hepatol* 1996; **25**: 563-566 [PMID: 8912157 DOI: 10.1016/S0168-8278(96)80217-0]

59 **Devlin RJ**, Henry JA. Clinical review: Major consequences of illicit drug consumption. *Crit Care* 2008; **12**: 202 [PMID: 18279535 DOI: 10.1186/cc6166]

60 **Mieli-Vergani G**, Vergani D. Autoimmune hepatitis. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 320-329 [PMID: 21537351 DOI: 10.1038/nrgastro.2011.69]

61 **Boberg KM**. Prevalence and epidemiology of autoimmune hepatitis. *Clin Liver Dis* 2002; **6**: 635-647 [PMID: 12362572 DOI: 10.1016/S1089-3261(02)00021-1]

62 **Maggiore G**, Riva S, Sciveres M. Autoimmune diseases of the liver and biliary tract and overlap syndromes in childhood. *Minerva Gastroenterol Dietol* 2009; **55**: 53-70 [PMID: 19212308]

63 **Kerkar N**, Miloh T. Sclerosing cholangitis: pediatric perspective. *Curr Gastroenterol Rep* 2010; **12**: 195-202 [PMID: 20425475 DOI: 10.1007/s11894-010-0104-5]

64 **Mieli-Vergani G**, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? *Semin Liver Dis* 2009; **29**: 297-306 [PMID: 19676002 DOI: 10.1055/s-0029-1233529]

65 **Bridoux-Henno L**, Maggiore G, Johanet C, Fabre M, Vajro P, Dommergues JP, Reinert P, Bernard O. Features and outcome of autoimmune hepatitis type 2 presenting with isolated positivity for anti-liver cytosol antibody. *Clin Gastroenterol Hepatol* 2004; **2**: 825-830 [PMID: 15354284 DOI: 10.1016/S1542-3565(04)00354-4]

66 **Maggiore G**, Roux K, Johanet C, Fabre M, Sciveres M, Riva S, Fournier-Favre S, Bernard O. Seronegative autoimmune hepatitis in childhood. *J Pediatr Gastroenterol Nutr* 2006; **42**: E5-E6

67 **Gassert DJ**, Garcia H, Tanaka K, Reinus JF. Corticosteroid-responsive cryptogenic chronic hepatitis: evidence for seronegative autoimmune hepatitis. *Dig Dis Sci* 2007; **52**: 2433-2437 [PMID: 17429719 DOI: 10.1007/s10620-006-9665-4]

68 **Heringlake S**, Schütte A, Flemming P, Schmiegel W, Manns MP, Tillmann HL. Presumed cryptogenic liver disease in Germany: High prevalence of autoantibody-negative autoimmune hepatitis, low prevalence of NASH, no evidence for occult viral etiology. *Z Gastroenterol* 2009; **47**: 417-423 [PMID: 19418409 DOI: 10.1055/s-0028-1109146]

69 **Vergani D**, Alvarez F, Bianchi FB, Cançado EL, Mackay IR, Manns MP, Nishioka M, Penner E. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. *J Hepatol* 2004; **41**: 677-683 [PMID: 15464251 DOI: 10.1016/j.jhep.2004.08.002]

70 **Ebbeson RL**, Schreiber RA. Diagnosing autoimmune hepatitis in children: is the International Autoimmune Hepatitis Group scoring system useful? *Clin Gastroenterol Hepatol* 2004; **2**: 935-940 [PMID: 15476158 DOI: 10.1016/S1542-3565(04)00396-9]

71 **Hennes EM**, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008; **48**: 169-176 [PMID: 18537184 DOI: 10.1002/hep.22322]

72 **Gregorio GV**, Portmann B, Mowat AP, Vergani D, Mieli-Vergani G. A 12-year-old girl with antimitochondrial antibody-positive autoimmune hepatitis. *J Hepatol* 1997; **27**: 751-754 [PMID: 9365052 DOI: 10.1016/S0168-8278(97)80093-1]

73 **Vajro P**, Fontanella A, Mayer M, De Vincenzo A, Terracciano LM, D'Armiento M, Vecchione R. Elevated serum aminotransferase activity as an early manifestation of gluten-sensitive enteropathy. *J Pediatr* 1993; **122**: 416-419 [PMID: 8441098 DOI: 10.1016/S0022-3476(05)83430-4]

74 **Vajro P**, Paolella G, Pisano P, Maggiore G. Hypertransaminasemia and coeliac disease. *Aliment Pharmacol Ther* 2012; **35**: 202-203; author reply 203-204 [PMID: 22150542 DOI: 10.1111/j.1365-2036.2011.04895.x]

75 **Foucher B**, Johanet C, Jégo-Desplat S, Sanmarco M, Dubucquoi S, Fily-Nalewajk S, Olsson NO, Lakomy D, Escande A, Chrétien P, Fortenfant F, Chevailler A, André C, Goetz J, Humbel RL, Monier JC, Sibilia J, Taillefer MF, Abreu I, Fabien N. Are immunoglobulin A anti-gliadin antibodies helpful in diagnosing coeliac disease in children younger than 2 years? *J Pediatr Gastroenterol Nutr* 2012; **54**: 110-112 [PMID: 21857243 DOI: 10.1097/MPG.0b013e31823255c9]

76 **Vajro P**, Paolella G, Nobili V. Children unresponsive to hepatitis B virus vaccination also need celiac disease testing. *J Pediatr Gastroenterol Nutr* 2012; **55**: e131 [PMID: 22576672 DOI: 10.1097/MPG.0b013e31825d4ac9]

77 **Di Biase AR**, Colecchia A, Scaioli E, Berri R, Viola L, Vestito A, Balli F, Festi D. Autoimmune liver diseases in a paediatric population with coeliac disease - a 10-year single-centre experience. *Aliment Pharmacol Ther* 2010; **31**: 253-260 [PMID: 19878151 DOI: 10.1111/j.1365-2036.2009.04186.x]

78 **Caprai S**, Vajro P, Ventura A, Sciveres M, Maggiore G. Autoimmune liver disease associated with celiac disease in childhood: a multicenter study. *Clin Gastroenterol Hepatol* 2008; **6**: 803-806 [PMID: 18258488 DOI: 10.1016/j.cgh.2007.12.002]

79 **Cox DW**, Roberts E. Wilson Disease. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, 1993-1999 [PMID: 20301685]

80 **Dhawan A**, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl* 2005; **11**: 441-448 [PMID: 15776453 DOI: 10.1002/lt.20352]

81 **Ferenci P**, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. *Liver Int* 2003; **23**: 139-142 [PMID: 12955875 DOI: 10.1034/j.1600-0676.2003.00824.x]

82 **Vajro P**, Nicastro E. Wilson's disease. In: Jara P. International Hepatology Updates: Liver diseases in children. Barcelona: Edition Permanyer, 2009: 73-90

83 **Nicastro E**, Ranucci G, Vajro P, Vegnente A, Iorio R. Re-evaluation of the diagnostic criteria for Wilson disease in children with mild liver disease. *Hepatology* 2010; **52**: 1948-1956 [PMID: 20967755 DOI: 10.1002/hep.23910]

84 **European Association for Study of Liver.** EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012; **56**: 671-685 [PMID: 22340672 DOI:10.1016/j.jhep.2011.11.007]

85 **Caprai S**, Loudianos G, Massei F, Gori L, Lovicu M, Maggiore G. Direct diagnosis of Wilson disease by molecular

genetics. *J Pediatr* 2006; **148**: 138-140 [PMID: 16423615 DOI: 10.1016/j.jpeds.2005.07.036]
86 **Mandato C**, Brive L, Miura Y, Davis JA, Di Cosmo N, Lucariello S, Pagliardini S, Seo NS, Parenti G, Vecchione R, Freeze HH, Vajro P. Cryptogenic liver disease in four children: a novel congenital disorder of glycosylation. *Pediatr Res* 2006; **59**: 293-298 [PMID: 16439595 DOI: 10.1203/01.pdr.0000196378.30165.26]
87 **Calvo PL**, Pagliardini S, Baldi M, Pucci A, Sturiale L, Garozzo D, Vinciguerra T, Barbera C, Jaeken J. Long-standing mild hypertransaminasaemia caused by congenital disorder of glycosylation (CDG) type IIx. *J Inherit Metab Dis* 2008; **31** Suppl 2: S437-S440 [PMID: 19067230 DOI: 10.1007/s10545-008-1004-9]
88 **Scriver CR**, Beaudet AL, Sly WS, Valle D, Childs B. The metabolic and molecular Bases of inherited disease. 9th ed. New York, 2005
89 **Kelly D**. Diseases of the liver and biliary system in children. 3rd ed. Oxford, 2008
90 **Suchy FJ**, Sokol RJ, Balistreri W. Liver disease in children. 3rd ed. Oxford, 2007
91 **Toiviainen-Salo S**, Durie PR, Numminen K, Heikkilä P, Marttinen E, Savilahti E, Mäkitie O. The natural history of Shwachman-Diamond syndrome-associated liver disease from childhood to adulthood. *J Pediatr* 2009; **155**: 807-811.e2 [PMID: 19683257 DOI: 10.1016/j.jpeds.2009.06.047]
92 **Vajro P**, Veropalumbo C. Citrin deficiency: learn more, and don't forget to add it to the list of neonatal cholestasis and the NASH trash bin. *J Pediatr Gastroenterol Nutr* 2010; **50**: 578-579 [PMID: 20479677 DOI: 10.1097/MPG.0b013e3181dee0e3]
93 **Wong D**. Hereditary fructose intolerance. *Mol Genet Metab* 2005; **85**: 165-167 [PMID: 16086449]
94 **Mailliard ME**, Gollan JL. Metabolic liver disease in the young adult. *Best Pract Res Clin Gastroenterol* 2003; **17**: 307-322 [PMID: 12676121 DOI: 10.1016/S1521-6918(02)00148-8]
95 **Resti M**, Adami Lami C, Tucci F, Mannelli F, Rossi ME, Azzari C, Vierucci A. False diagnosis of non-A/non-B hepatitis hiding two cases of cystic fibrosis. *Eur J Pediatr* 1990; **150**: 97-99 [PMID: 2126237 DOI: 10.1007/BF02072047]
96 **Fabre A**, Audet P, Vilgrain V, Nguyen BN, Valla D, Belghiti J, Degott C. Histologic scoring of liver biopsy in focal nodular hyperplasia with atypical presentation. *Hepatology* 2002; **35**: 414-420 [PMID: 11826417 DOI: 10.1053/jhep.2002.31103]
97 **Dujovne CA**. Side effects of statins: hepatitis versus "transaminitis"-myositis versus "CPKitis". *Am J Cardiol* 2002; **89**: 1411-1413 [PMID: 12062737 DOI: 10.1016/S0002-9149(02)02356-1]
98 **de Kleijn EM**, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. *Medicine* (Baltimore) 1997; **76**: 401-414 [PMID: 9413426 DOI: 10.1097/00005792-199711000-00003]
99 **Iorio R**, Verrico A, Giannattasio A. Is liver biopsy mandatory in children with chronic hepatitis C? *World J Gastroenterol* 2007; **13**: 4025-4026 [PMID: 17663524]
100 **Kumari N,** Kathuria R, Srivastav A, Krishnani N, Poddar U, Yachha SK. Significance of histopathological features in differentiating autoimmune liver disease from nonautoimmune chronic liver disease in children. *Eur J Gastroenterol Hepatol* 2013; **25**: 333-337 [PMID: 23085577 DOI: 10.1097/MEG.0b013e32835a68a1]
101 **Ovchinsky N**, Moreira RK, Lefkowitch JH, Lavine JE. Liver biopsy in modern clinical practice: a pediatric point-of-view. *Adv Anat Pathol* 2012; **19**: 250-262 [PMID: 22692288 DOI: 10.1097/PAP.0b013e31825c6a20]
102 **Ratziu V**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906 [PMID: 15940625 DOI: 10.1053/j.gastro.2005.03.084]

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