

# World Journal of *Gastroenterology*

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Editorial board member of *World Journal of Gastroenterology*, Shinji Tanaka, MD, PhD, Professor, Department of Endoscopy, Hiroshima University Hospital, Hiroshima 734-8551, Japan

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Telephone: +1-925-2238242  
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## Liver and the defects of cholesterol and bile acids biosynthesis: Rare disorders many diagnostic pitfalls

Gaetano Corso, Antonio Dello Russo, Monica Gelzo

Gaetano Corso, Department of Clinical and Experimental Medicine, University of Foggia, 71122 Foggia, Italy

Antonio Dello Russo, Monica Gelzo, Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, 80131 Naples, Italy

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**Correspondence to:** Monica Gelzo, PhD, Researcher, Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Via Pansini 5, 80131 Naples, Italy. [monicagelzo@gmail.com](mailto:monicagelzo@gmail.com)  
Telephone: +39-81-7463653  
Fax: +39-81-7463653

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of knowledge on the causes and mechanisms of metabolic diseases that have formed the basis for their study, diagnosis and treatment. Unfortunately, it is well known that the clinical features of metabolic diseases can manifest themselves with very different characteristics and escape early detection. Also, it is well known that the prognosis of many metabolic diseases is excellent if diagnosed and treated early. In this editorial we briefly summarized two groups of inherited metabolic diseases, the defects of cholesterol biosynthesis and those of bile acids. Both groups show variable clinical manifestations but some clinical signs and symptoms are common in both the defects of cholesterol and bile acids. The differential diagnosis can be made analyzing sterol profiles in blood and/or bile acids in blood and urine by chromatographic techniques (GC-MS and LC-MS/MS). Several defects of both biosynthetic pathways are treatable so early diagnosis is crucial. Unfortunately their diagnosis is made too late, due either to the clinical heterogeneity of the syndromes (severe, mild and very mild) that to the scarcity of scientific dissemination of these rare diseases. Therefore, the delay in diagnosis leads the patient to the medical observation when the disease has produced irreversible damages to the body. Here, we highlighted simple clinical and laboratory descriptions that can potentially make you to suspect a defect in cholesterol biosynthesis and/or bile acids, as well, we suggest appropriate request of the laboratory tests that along with common clinical features can help to diagnose these defects.

**Key words:** Cholesterol; Bile acids; Liver metabolism; Gas chromatography coupled to mass spectrometry; Liquid chromatography coupled to tandem mass spectrometry

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### Abstract

In recent decades, biotechnology produced a growth

**Core tip:** The genetic defects of cholesterol and bile acid biosynthesis are characterized by a diversity

of clinical findings affecting the liver, the intestine, and the nervous system. Many of these defects are efficaciously treatable but owing to mild phenotypes many cases can escape to an earlier diagnosis and are identified after few years or adulthood with irreversible injuries or more difficult to treat. Here, we highlighted simple clinical and laboratory descriptions that can potentially make you to suspect a defect in cholesterol biosynthesis and/or bile acids, in order to reduce the diagnostic delay and to improve the prognosis of these defects.

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## INTRODUCTION

Metabolic diseases are genetic based conditions in which the defective gene results in deficiency of an enzyme that leads to metabolic disorders. Today, several hundred of genetic metabolic disorders are known, and their symptoms, treatments, and prognosis vary widely.

The genetic defects in the biosynthesis of cholesterol and bile acids have been well studied in recent decades and several of these defects are treatable with results that greatly improve the prognosis and the patient's health.

Cholesterol is essential for the maintenance of life in vertebrates<sup>[1]</sup>. It is an essential metabolite of cellular membrane structure, and is also the precursor of bile acids, steroid hormones, and oxysterols, which play multiple and important biological functions throughout the body<sup>[2,3]</sup>. Especially, the synthesis of bile acids and the bile formation plays a pivotal role to survival of organism.

Body cholesterol levels are finely regulated by the balance between mechanisms of diet cholesterol absorption, liver synthesis, biliary excretion, and peripheral tissue uptake. All this requires close molecular collaboration between the liver, the intestine and all the tissues of the whole organism<sup>[4]</sup>. Plasma levels of cholesterol are controlled by the liver through specific lipoprotein receptors, sterol transporters and intracellular nuclear receptors, which translate the signals derived from variations of cholesterol levels in selective variations of gene expression<sup>[5-8]</sup>. The liver is the main organ of cholesterol synthesis in most mammals<sup>[9,10]</sup>, through an intricate pathway involving more than 30 enzymatic steps<sup>[11,12]</sup>.

The intestine plays a pivotal role in the homeostasis of cholesterol. In fact, it is the main site for cholesterol absorption and excretion. Cholesterol that is absorbed

into the lumen of the small intestine derives from food digestion, partial reabsorption of biliary cholesterol, and from that one released by the intestinal epithelial cells. The presence of bile acids as detergents is obligatory for the solubilization and uptake of intestinal cholesterol. They are excreted from liver and reabsorbed from the intestinal lumen back to the liver through the entero-hepatic circulation<sup>[13]</sup>.

Beside cholesterol, also plant sterols (*e.g.*, campesterol and  $\beta$ -sitosterol) and stanols are absorbed by Niemann-Pick C1 Like 1 (NPC1L1), a transporter localized in the microvilli cells of small intestine in the apical plasma membrane, which facilitates their uptake and transport. NPC1L1 is also localized near to other transporters such as ATP-binding cassette G5/G8 (ABCG5/G8) that act as inverted transporters pumping cholesterol and other sterols from enterocytes back to the intestinal lumen, as well as from hepatocytes to bile ducts. Instead, the bile acids are excreted into bile *via* specific pump proteins (BSEP or ABCB11)<sup>[14,15]</sup>.

Mutations in *ABCG5/G8* genes cause Sitosterolemia (STSL, OMIM #210250), a rare autosomal recessive lipid storage disease where it is found elevated plasma levels of cholesterol and non-cholesterol sterols due to impaired intestinal absorption and biliary sterol excretion<sup>[16]</sup>.

ABCG5/G8 are controlled by cholesterol through liver X receptors (LXRs), which in turn are activated by oxysterols and other plant sterol derivatives<sup>[17]</sup>. Another target of LXR is ABCA1, which is the reverse transporter of cholesterol. By this mechanism the surplus of free cholesterol is eliminated from peripheral tissues through biliary excretion or non-biliary trans-intestinal cholesterol efflux (TICE) that, to our knowledge, has been demonstrated only in animal models<sup>[18,19]</sup>.

The fecal excretion of neutral and acidic sterols, coming from cholesterol and non-cholesterol sterols, also contributes to cholesterol balance in whole body. The production of bile acids from cholesterol is the main mechanism for removing sterols from our body. At the same time, it has been showed that bile acids play various functions in signal transduction pathways for energy metabolism regulation. Biosynthesis of bile acids occurs through two main pathways involving 17 different enzymes, many of which are predominantly expressed in the liver<sup>[20]</sup>.

Since excess and cholesterol deficiency can cause serious damage to our body's structures, cholesterol homeostasis is required to be tightly controlled. In fact, hypercholesterolemia is the main risk factor for the development of atherosclerosis and consequently of cardiovascular disease<sup>[21,22]</sup>. The different types of hypercholesterolemia, such as familial hypercholesterolemia, secondary hypercholesterolemia, polygenic hypercholesterolemia, have been well characterized<sup>[23]</sup> and will not be reported here.

Instead, inherited defects of cholesterol biosynthesis lead to severe clinical phenotypes; for example, the absence of 3-hydroxy-3-methylglutaryl CoA (HMG-

CoA) reductase, which is the main regulatory enzyme of cholesterol biosynthesis, is not compatible with life<sup>[24]</sup>. In addition, the liver cholesterol catabolism disorders, such as the synthesis of bile acids, can be the cause or can be secondary to biliary stasis, which acts significantly on the effectiveness of regulatory mechanisms in the liver and intestine<sup>[4]</sup>.

This work aims to draw the attention of physicians on clinical, diagnostic, and therapeutic knowledge published on some defects of biosynthesis of cholesterol and of bile acids. These defects have a widely variable clinical phenotype, but some signs and symptoms are common to the different genetic forms known so far. Unfortunately, since these defects also have mild phenotypes or even very mild, they can escape to an earlier diagnosis, and many cases are identified after a few years or in adulthood with irreversible injuries or more difficult to treat<sup>[25,26]</sup>.

The diagnostic laboratory path of inborn errors of biosynthesis of cholesterol<sup>[27-29]</sup> and of bile acids<sup>[26,30]</sup> is of fundamental importance for the differential diagnosis and the diagnostic accuracy of these diseases. Therefore, we need of knowledge about the laboratory tests for the metabolic study of patients that putatively suffer from these defects.

Today, the applications in the clinical field of mass spectrometry coupled with chromatography methods (gaseous or liquid) are already widely used in many laboratories, and the determination of metabolic profiles, such as sterols<sup>[31-34]</sup> or bile acids<sup>[35]</sup>, in biological fluids (blood, plasma, urine) facilitates the study of many inborn errors of metabolism including cholesterol and bile acids.

Here, we will focus on some treatable disorders for which the early diagnosis is fundamental, and this article also provides a simple diagnostic flow chart together to clinical characteristics that could be useful for the clinicians in the investigation of cholesterol and bile acid disorders.

## CHOLESTEROL BIOSYNTHESIS DEFECTS

After the discovery that Smith-Lemli-Opitz syndrome (SLOS, OMIM # 270400), a congenital multi-malformative syndrome, is due by a disorder of post-squalene cholesterol biosynthesis caused by defects in 7-dehydrocholesterol reductase<sup>[36]</sup>, other malformative syndromes have been discovered in humans caused by other cholesterol biosynthesis defects. In Table 1 are reported all defects to date discovered in the pathway of cholesterol synthesis in humans<sup>[25,28,36-52]</sup>. Generally, the onset of these diseases occurs at birth, even though some phenotypes may present during the first months of life (CDPX2)<sup>[25]</sup> or in the early infancy (SC4MOL deficiency)<sup>[49,50]</sup>. Since the phenotypes of these defects can be highly variable, in particular the patients with a mild phenotype, the diagnosis can be missed at birth and can be made very belatedly. The phenotypic spectrum of SLOS is extremely wide, and

the cases more severely affected by malformations die in utero or early after birth. Instead, the patients mildly affected suffer from less severe malformations, intellectual disability and behavioral problems<sup>[28]</sup>.

Plasma sterol analysis by gas chromatography is a useful screening test for most of these disorders, even though a negative result in plasma does not exclude disorders such as CHILD, CK, and mild CDPX2 syndromes (Table 1).

The cholesterol plasma levels in severe cases of SLOS are very low (< 20 mg/dL), while in the patients with mild phenotype may have total cholesterol levels quite variables ranging from low (< 100 mg/dL) to normal levels<sup>[27]</sup>. In fact, the mild cases of SLOS can be treated using cholesterol supplementation and simvastatin<sup>[28]</sup>. Instead, all other defects, with the exception of lathosterolosis and SC4MOL, there are no treatments that correct or attenuate the metabolic condition. Therefore, they are cured with surgical or medical treatments needed to alleviate symptoms<sup>[25,45]</sup>.

Lathosterolosis is a very rare disease with only four cases reported in literature<sup>[40-43,53]</sup>, of which two patients survived<sup>[40,43]</sup>. In particular, the first described patient<sup>[40]</sup> showed a progressive intrahepatic cholestasis that had caused liver failure at seven years when she was subjected to liver transplantation (LT), which removed liver disease, corrected the defect in cholesterol metabolism, and also improved some neurologic symptoms<sup>[54,55]</sup>.

In some conditions that influence cholesterol metabolism, LT acts as a gene therapy or as a healthy gene producer<sup>[18]</sup>. Furthermore, the normal gene expression of cholesterol biosynthesis and its physiological levels in the liver graft may influence intrahepatic availability of cholesterol, which is essential for liver-regenerative capacity<sup>[56]</sup>.

Instead, the last case of lathosterolosis has been diagnosed in a 22 mo-old male with a mild clinical and biochemical phenotype. One month after diagnosis, the patient was treated with simvastatin and it resulted in normalization of lathosterol level and neurodevelopmental improvement<sup>[43]</sup>.

SC4MOL deficiency is a recently discovered defect into the C-4 demethylase complex of cholesterol biosynthesis well described by He *et al*<sup>[49]</sup>. Until now, only five SC4MOL patients have been reported with a high variable phenotype<sup>[50]</sup>. The first patient presented the more severe phenotype characterized by a psoriasiform dermatitis, she was treated by oral statin and supplementation with cholesterol plus bile acids. After two years of treatment, the symptoms dramatically ameliorated and methylsterol levels normalized.

## BILE ACIDS SYNTHESIS DEFECTS

Hereditary biosynthesis defects of biliary acids cause fatal liver disease during childhood and/or progressive neurological diseases that occur later in infancy or in



**Table 1** Inherited defects of cholesterol biosynthesis in humans

Disorder	OMIM#	Frequency	Enzyme (blood biomarkers)	Primary site of expression	Treatable	Ref.
SLOS	270400	1:20000/1:50000	7-dehydrocholesterol reductase (7-dehydrocholesterol, 8-dehydrocholesterol)	Multisystemic	Yes Mild cases	[28,36]
Desmosterolosis	602398	9 cases	3 $\beta$ -hydroxysterol- $\Delta$ 24-reductase (desmosterol)	Multisystemic	No	[25,37]
CDPX2 <sup>1</sup>	302960	$\leq$ 1:400000	3 $\beta$ -hydroxysteroid- $\Delta$ 8, $\Delta$ 7-sterol isomerase [8-dehydrocholesterol, cholesta-8(9)-en-3 $\beta$ -ol]	Skin and skeletal systems	No	[25,38]
CHILD syndrome	308050	< 1:1000000	3 $\beta$ -hydroxysteroid dehydrogenase [4 $\alpha$ -carboxymethylcholest-8(9)- en-3 $\beta$ -ol, 4 $\alpha$ -monomethyl-and 4,4'-dimethylsterols] <sup>2</sup>	Skin and skeletal systems	No	[25,39]
Lathosterolosis	607330	4 cases	3 $\beta$ -hydroxysteroid- $\Delta$ 5-desaturase (lathosterol)	Multisystemic	Yes Two cases	[40-43]
Antley-Bixler syndrome <sup>3</sup>	201750	> 100 cases	Lanosterol 14 $\alpha$ -demethylase (lanosterol, dihydrolanosterol) <sup>2</sup>	Skin and genital systems	No	[44,45]
Greenberg dysplasia	215140	11 cases	Sterol- $\Delta$ 14-reductase (cholesta-8,14-dien- 3 $\beta$ -ol, cholesta-8,14,24-trien-3 $\beta$ -ol) <sup>2</sup>	Skeletal system	No	[25,46]
CK syndrome	300831	13 cases	3 $\beta$ -hydroxysteroid dehydrogenase (4 $\alpha$ -monomethyl- and 4,4'-dimethylsterols) <sup>2</sup>	Nervous system	No	[25,47,48]
SC4MOL deficiency	616834	5 cases	Sterol-C4-methyl oxidase (4 $\alpha$ -monomethyl- and 4,4'-dimethylsterols)	Skin and eye Systems	Yes One case	[49,50,88]

<sup>1</sup>An hypomorphic variant (#300960) has been reported in 10 male patients<sup>[25,51]</sup>; <sup>2</sup>Presence of biomarkers in tissue and/or cultured cells only; <sup>3</sup>A variant form (#613571) due to deficiency of cytochrome P450 oxidoreductase has been reported 9 subjects<sup>[45,52]</sup>. CDPX2: X-linked dominant disorder chondrodysplasia punctata-2; CHILD: Congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CK: Eponym derived from the first case; SC4MOL: Sterol-C4-methyl oxidase; SLOS: Smith-Lemli-Opitz syndrome.

the adult. Some of these diseases can be effectively treated by the administration of bile acids, so early diagnosis of these disorders is very important and life-saving. Recently, Clayton<sup>[26]</sup> and Heubi *et al.*<sup>[35]</sup> reviewed the defects to date discovered in the pathway of bile acid synthesis, which are reported in Table 2<sup>[26,35,57-77]</sup>.

The onset of these defects usually occurs in neonatal period or childhood with cholestasis, vitamin deficiency (fat-soluble), and with rickets, or hypoprothrombinemia, chronic liver disease or growth failure. Differently, the mean age of onset of symptoms for CTX is 19 years<sup>[26,30,35]</sup> and CYP7A1 deficiency usually present in adult life with hyperlipidemia<sup>[35,77]</sup>, whereas SPG5A is characterized by a high variable age of onset (from 8 to 40 years of life) with a wide phenotypic spectrum (spastic paraplegia with or without additional manifestations, including optic atrophy or cerebellar ataxia)<sup>[66-69]</sup>. The defect in bile acid synthesis causes a reduction of hepatic conversion of cholesterol to cholic acid and chenodeoxycholic acid (CDCA)<sup>[78]</sup>. Canalicular bile flow is stimulated by the increase of bile acids synthesis, even though a bile salts-independent bile flow is always present as basal state. Therefore, the lack or the reduced synthesis of bile acids causes a more or less serious reduction of bile flow (cholestasis) and regurgitation in the blood stream of normally excreted compounds (*i.e.*, conjugate bilirubin). In addition, the presence of bile acids promotes the release of gamma-glutamyl transpeptidase ( $\gamma$ -GT)

from the canalicular membrane, while the absence of bile acids in the bile, except for some cases, does not result in increased plasma  $\gamma$ -GT. In addition, since bile acids act as detergent for lipid absorption in the intestine, congenital bile acid synthesis errors can lead to steatorrhea, growth delay, and deficiencies in fat-soluble vitamins.

Among these disorders, we focused on Cerebro-tendinous Xanthomatosis (CTX, OMIM # 213700), the most common inborn error of bile acids synthesis. The clinical findings of CTX are tendon xanthomas, diarrhea, cataracts, neurological manifestations, such as polyneuropathy, pyramidal and/or cerebellar signs, intellectual disability, psychiatric disturbance, and seizures<sup>[30,79,80]</sup>. In spite of the xanthomas and premature atherosclerosis, CTX patients are usually normocholesterolemic<sup>[81]</sup>. In these patients the 25-hydroxylated C<sub>27</sub>-bile alcohols are abundantly excreted in the urine and other biological materials, the accumulation of these metabolites is due to the incomplete oxidation of the cholesterol side-chain<sup>[82]</sup>. Instead, the production of CDCA is markedly reduced and in face of almost normal production of cholic acid<sup>[83]</sup>. In addition, the reduced levels of bile acids decreased the negative feedback on two regulatory enzymes, the cholesterol 7-hydroxylase, the first rate-limiting enzyme in bile acid pathway, and the HMG-CoA reductase, which regulates cholesterol production. As a result, the increased activities of both enzymes

**Table 2** Inherited defects of bile acids biosynthesis in humans

Disorder	OMIM#	Frequency	Enzyme (urine biomarkers) <sup>1</sup>	Primary site of expression	Treatable	Ref.
CTX	213700	1:50000	Sterol 27-hydroxylase (tetrahydroxy-, pentahydroxy- and hexahydroxy-bile alcohols) <sup>2</sup>	Eye, central and peripheral nervous systems	Yes	[26,30,35]
CBAS1	607765	73 cases	3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase (3 $\beta$ -hydroxy- $\Delta$ 5 bile acids)	Liver	Yes	[26,35,57,58]
CBAS2	235555	41 cases	$\Delta$ 4-3-oxosteroid 5 $\beta$ -reductase ( $\Delta$ 4-3-oxo bile acids)	Liver	Yes	[35,59-65]
SPG5A	270800	31 cases	Oxysterol 7 $\alpha$ -hydroxylase (27-hydroxycholesterol) <sup>3</sup>	Central and peripheral nervous systems	No	[66-69]
FHCA	607748	15 cases	BAAT <sup>4</sup> (unconjugated cholic acid) <sup>3</sup>	Liver and intestine	Yes	[35,70,71]
CBAS4	214950	6 cases	$\alpha$ -methylacyl-CoA racemase (THCA) <sup>5</sup>	Liver, intestine and peripheral nervous systems	Yes	[35,72,73]
CBAS3	613812	3 cases	oxysterol 7 $\alpha$ -hydroxylase (3 $\beta$ -hydroxy-5-choleenoic and 3 $\beta$ -hydroxy-5-cholestenoic acids)	Liver	No	[35,74,75]
BACL deficiency	NR	8 cases	Bile acid-CoA ligase (unconjugated cholic acid) <sup>3</sup>	Liver and intestine	No	[76]
CYP7A1 deficiency	NR	< 1:1000000	CYP7A1 (3 $\beta$ -hydroxy-5-choleenoic and 3 $\beta$ -hydroxy-5-cholestenoic acids, 27-hydroxycholesterol) <sup>6</sup>	Cardiovascular system	No	[35,77]

<sup>1</sup>Conjugated form unless otherwise noted; <sup>2</sup>Plasma and tissue accumulation of cholestanol and cholesterol precursors; <sup>3</sup>Presence also in serum; <sup>4</sup>FHCA can be due also to mutations in *Tight junction protein-2* and *Microsomal epoxide hydrolase-1* genes; <sup>5</sup>Plasma and tissue accumulation of phytanic and pristanic acids;

<sup>6</sup>High plasma levels of total and LDL-cholesterol, and 27-hydroxycholesterol. BAAT: Bile acids-CoA aminoacid N-acyltransferase; CTX: Cerebrotendinous xanthomatosis; CYP7A1: Cholesterol 7 $\alpha$ -hydroxylase; FHCA: Familial hypercholelanemia; NR: Not reported; SPG5A: Spastic paraplegia-5A; THCA: 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-5 $\beta$ -cholestan-26-oic acid.

lead to an accumulation of bile acid precursors, such as cholestanol and various bile alcohols, and of intermediates of cholesterol biosynthesis<sup>[84]</sup>. In fact plasma sterol analyses in CTX patients reveal elevated cholestanol and cholesterol precursors levels<sup>[30,81,85]</sup>.

Treatment of CTX patients with CDCA by a negative feedback inhibits the 7 $\alpha$ -hydroxylase and the production of toxic bile acid intermediates, and reduces the production of cholesterol by the liver<sup>[82]</sup>. Clinical and laboratory parameters are improved by long-term oral administration of CDCA and without toxic effects<sup>[79]</sup>. In particular, when initiated in childhood, CDCA therapy may arrest the progression of disease and prevent neurological deterioration. Instead, once neurological impairment is manifest, a poor response to CDCA treatment may be recorded<sup>[79]</sup>. CDCA and statins therapy inhibits cholesterol synthesis reducing cholesterol precursors and cholestanol levels in plasma, and can improve lipoprotein metabolism<sup>[84]</sup>. The efficacy of treatment with HMG-CoA reductase inhibitors alone is controversial, and some adverse effects such as hepatic dysfunction and rhabdomyolysis may be observed<sup>[79,80,84]</sup>.

## DIFFERENTIAL DIAGNOSIS OF CHOLESTEROL AND BILE ACID BIOSYNTHESIS DEFECTS

Some treatable defects of cholesterol and bile acid biosynthesis that share different clinical findings are reported in Table 3. Nevertheless, these disorders are characterized by the accumulation of specific biomarkers (Tables 1 and 2) in blood and/or urine of affected patients<sup>[25,26,86,87]</sup>. Hence, accurate

identification and quantification of these metabolites are essential to address the diagnostic-therapeutic process of these defects.

The sterol profile can be easily analyzed by gas chromatography coupled to mass spectrometry (GC-MS; Table 3) in plasma, dried blood spot, red blood cell membrane and tissue homogenates<sup>[25,27,31,33]</sup>.

Furthermore, an useful screening test for many of bile acid synthesis defects is the analysis of bile acids and bile alcohols in urine, which is easily performed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS; Table 3)<sup>[26,30,35]</sup>.

## CONCLUSION

In this editorial, we have briefly focused on the main clinical signs and laboratory findings of the inherited defects of cholesterol and bile acids synthesis. In summary, the liver and the intestine are the strategic organs in the control of cholesterol and bile acids in biological fluids. Moreover, the physiologic biosynthesis of cholesterol and bile acids is essential for the most important functions of our body, including embryonic development and neuronal functions. To date, as summarized here, in humans have been discovered nine inborn defects of cholesterol synthesis and nine of the bile acids. Although these diseases are rare and some ones very rare, it is commonly believed that their frequency has been underestimated, particularly in those patients affected by mild forms. This may be due to the heterogeneity of clinical and laboratory features of these diseases, which represent the pitfalls that mask their early diagnosis but, more important, it is the lost of all cases that are never diagnosed. Moreover, many of the defects reported here are treatable and

**Table 3** Clinical and laboratory findings shared by some treatable defects of cholesterol and bile acid biosynthesis

Clinical features	SLOS <sup>1</sup>	LATHO	SC4MOL	CTX	CBAS1	CBAS2	CBAS4	Shared findings
Microcephaly	Yes	Yes	Yes	No	No	No	No	3/7
Congenital cataracts	Yes	Yes	Yes	Yes	No	No	No	4/7
Intellectual disability	Yes	Yes	Yes	Yes	No	No	No	4/7
Neurological disease	No	No	No	Yes	No	No	Yes	2/7
Developmental delay	Yes	Yes	Yes	No	No	No	No	3/7
Cholestasis	No	Yes	No	Yes	Yes	Yes	Yes	5/7
Steatosis	No	Yes	No	No	No	Yes	No	2/7
AST	Normal	High	Normal	High	High	High	Normal	4/7
ALT	Normal	High	Normal	High	High	High	Normal	4/7
γGT	Normal	High	Normal	Normal	Normal	High	Normal	2/7
Conjugated bilirubin	Normal	High	Normal	High	High	High	Normal	4/7
Total cholesterol	Very low to normal	Low to normal	Low to normal	Normal to high	Normal	Normal	Normal	n.a.
Fat-soluble vitamin	Normal	Low	Normal	Normal	Low	Low	Low	4/7
Diagnostic method								
GC-MS	Sterols (p)	Sterols (p)	Sterols (p)	Sterols (p)				
LC-MS/MS				HBA (u)	BA (u)	BA (u, p)	BA (u, p)	
Treatment	Cholesterol plus statins	Statins or LT	Cholesterol plus statins and bile acids	CDCA plus statins	Cholic acid	UDCA or cholic acid	Cholic acid <sup>2</sup>	

<sup>1</sup>Mild phenotypes; <sup>2</sup>Associated with a phytanic/pristanic acid-restricted diet. BA: Bile acids; CDCA: Chenodeoxycholic acid; HBA: Hydroxy bile alcohols; LATHO: Lathosterolosis; LT: Liver transplant; n.a.: Not applicable; (p): Plasma; (u): Urine; UDCA: Ursodeoxycholic acid. GC-MS: Gas chromatography coupled to mass spectrometry; LC-MS/MS: Liquid chromatography coupled to tandem mass spectrometry.

with good results in most of them, therefore this fact should prompt us to pay more attention to the patient history, particularly that of childhood, with symptoms compatible with these defects.

Therefore, we hope that this editorial will stimulate the reader's thinking to extend their knowledge and to take into account that today we have many clinical and laboratory tools to suspect and diagnose a rare disease including the defects of cholesterol and bile acids biosynthesis.

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