The clinical spectrum of inherited diseases involved in the synthesis and remodeling of complex lipids. A tentative overview

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Abstract

Over one hundred diseases related to inherited defects of complex lipids synthesis and remodeling are now reported. Most of them were described within the last 5 years. New descriptions and phenotypes are expanding rapidly. While the associated clinical phenotype is currently difficult to outline, with only few patients identified, it appears that all organs and systems may be affected. The main clinical presentations can be divided into (1) Diseases affecting the central and peripheral nervous system. Complex lipid synthesis disorders produce prominent motor manifestations due to upper and/or lower motoneuron degeneration. Motor signs are often complex, associated with other neurological and extra-neurological signs. Three neurological phenotypes, spastic paraparesis, neurodegeneration with brain iron accumulation and peripheral neuropathies, deserve special attention. Many apparently well clinically defined syndromes are not distinct entities, but rather clusters on a continuous spectrum, like for the *PNPLA6*-associated diseases, extending from Boucher-Neuhauser syndrome via Gordon Holmes syndrome to spastic ataxia and pure hereditary spastic paraplegia; (2) Muscular/cardiac presentations; (3) Skin symptoms mostly represented by syndromic (neurocutaneous) and non syndromic ichthyosis; (4) Retinal dystrophies with syndromic and non syndromic retinitis pigmentosa, Leber congenital amaurosis, cone rod dystrophy, Stargardt disease; (5) Congenital bone dysplasia and segmental overgrowth disorders with congenital lipomatosis; (6) Liver presentations characterized mainly by transient neonatal cholestatic jaundice and non alcoholic liver steatosis with hypertriglyceridemia; and (7) Renal and Immune presentations. Lipidomics and molecular functional studies could help elucidating the mechanism(s) of dominant versus recessive inheritance observed for the same gene in a growing number of these disorders.

Key words : Complex lipids, phospholipids, inborn errors of metabolism, spastic paraplegia, neurodegeneration with brain iron accumulation, peripheral neuropathy, ichthyosis, retinal dystrophy, chondrodysplasia, hepatic steatosis.

Introduction

The quantitative importance of lipids in the nervous system makes the brain and peripheral nerves a privileged target for defects of complex lipids synthesis and remodeling. However, besides the role of complex lipids in neurological functions and signaling, this review highlighs the importance of these molecules in photoreceptor function, the epidermal water barrier, bone and liver metabolism. This chapter is an attempt to give a clinical overview of this new group of IEM focusing on neurological, muscular, cardiac, ophthalmological, dermatological, orthopedic and hepatic presentations.

1. Neurological presentations

Both central (CNS) and peripheral nervous systems are frequently involved in complex lipid synthesis and remodeling disorders. Careful grouping of patients in well-defined neurological syndromes is a practical and useful approach for clinicians (*Tables 1 and 2*). However, due to the rapidly growing number of diseases and the expanding phenotype of many of these diseases, this approach needs a constant update. As general messages, we wish to highlight the following points:

- Complex lipid synthesis and remodeling disorders produce prominent motor manifestations due upper and/or lower motoneuron degeneration. In fact, these movement disorders are the most remarkable neurological presentations in this category of diseases. Motor signs are often complex, associated with other neurological and extra-neurological signs.
- These disorders should be considered in patients with cerebral-palsy like phenotype, spastic paraparesis, ataxia, NBIA (neurodegeneration associated with brain iron accumulation) and peripheral neuropathy of unknown origin.
- In general, psychiatric disturbances are rare. They have been described in different NBIA, especially as late-onset manifestations, but they rarely appear in other types of complex lipid biosynthesis disorders.
- Epilepsy is also rare as a prominent sign; however, there are some defects that produce early severe refractory epilepsy.
- Developmental delay (DD) and intellectual disability (ID) are commonly present, as in many other neurometabolic diseases, but in general associated with other neurological and extra-neurological signs as “syndromic mental retardation”. These additional signs are often useful to the diagnostic approach. Additionally, one

interesting message learnt from these IEM is the inclusion of serum alkaline phosphatase in the metabolic work-up of mental retardation for the detection of GPI-anchor-synthesis defects (Krawitz et al, 2013). Three neurological phenotypes, spastic paraparesis, NBIA and peripheral neuropathies, deserve especial attention (*Tables 1 and 2*).

Hereditary spastic paraparesis (HSP) – Table 1

HSP is a heterogeneous group of genetic disorders in which the main feature is progressive spasticity in the lower limbs due to pyramidal tract dysfunction as a result of a 'dying back' degeneration of the cortico-spinal tracts. The critical role of complex lipids in signal transduction and membrane rigidity/fluidity may partly explain how defects in synthesis and remodeling of these lipids often lead to the degeneration of some of the longest, and therefore most vulnerable, axons in the CNS. HSP refers to a syndrome that includes lower extremity weakness and spasticity, each of varying degree, age of onset and progression. There are more than 50 genetic types of HSP, many of them described in the last years (Lo Giudice T et al. 2014). They are classified clinically as "pure" or "uncomplicated" and "complex" or "complicated" (Harding 1983). While some genetic types of HSP usually manifest as "uncomplicated" – e.g. SPG4 HSP due to spastin gene mutation, the single most common form of autosomal dominant HSP –, other genetic types usually present as complex HSP syndromes (Fink, 2013). In general, HSP due to complex lipid biosynthesis defects are autosomal recessive and complicated forms of HSP. Cerebellar involvement, axonal neuropathy, ichthyosis and ocular abnormalities are amongst the most commonly associated symptoms, together with abnormal brain MRI, especially thin corpus callosum. Rather "pure" HSP, although not invariably, can be observed in SPG28 due to phospholipase A1 deficiency and mutations in *DDHD1* (Bouslam et al, 2005) (Liguori et al, 2014) as well as SPG56 due to cytochrome P450 hydroxylase deficiency and mutations in *CYP2U1* (Tesson et al, 2012). About 13 different genes associated with HSP and defects in lipid biosynthesis and remodeling have been described until now. They participate in different biological functions, especially phospholipid remodelling (PNPLA6, CYP2U1, DDHD1 and DDHD2), fatty acid hydroxylation (CYP2U1) as well as sphingolipids biosynthesis (FA2H, B4GALNT1).

Neurodegeneration with Brain Iron Accumulation (NBIA) – Table 1

NBIA syndromes represent a group of degenerative extrapyramidal monogenic disorders with accumulation of iron in the brain, usually in the basal banglia (Gregory and Hayflick 2011). In general, NBIA cause progressive dystonia, bulbar symptoms and pyramidal signs in young children whereas parkinsonism usually appears later. Cognitive decline occurs in some subtypes of NBIA, but more often cognition is relatively spared. Cerebellar atrophy is a frequent finding. So far, 10 different genetic forms have been described (Levi et al, 2014). Two forms are linked to mutations in genes directly involved in iron metabolism: neuroferritinopathy (*FTL* gene) and aceruloplasminemia – where the *ceruloplasmin* gene product is defective. In the other forms, the link with iron metabolism is not evident. The biochemical pathways involving lipid metabolism and membrane/organelles (mitochondria) remodeling seem to play an important mechanistic role in NBIA disorders. At least 4 genes, *PANK2*, *PLA2G6*, *COASY* and *FA2H*, encode proteins involved in lipid metabolism. The protein encoded by *c19orf12* is linked to the mitochondrial outer membrane and is presumably connected with lipid metabolism although it has not been completely characterized yet (Hartig et al., 2011).(Tiranti this issue)

Peripheral neuropathies – Table 2

The diagnosis of peripheral neuropathies, rely on clinical and electrophysiological criteria. The general classification depends on whether there is an involvement of large fibers – i.e. motor weakness, loss of deep reflexes, muscle atrophy, sensory ataxia – versus small fibers – autonomic dysfunction, abnormal temperature sensibility pinprick loss – and whether the neuropathy is predominantly demyelinating or axonal. The lipid composition of myelin and transport of lipid-associated myelin proteins contribute to the observed vulnerability of myelin in lipid metabolism disorders (Chrast et al, 2011). Currently, more than 20 genes have been linked to IEM of lipid biosynthesis and remodeling defects. Different subtypes of peripheral neuropathies have been described in these disorders. Most of them are associated with other neurological and extra-neurological sings such as spastic paraparesis, white matter abnormalities, ocular and hearing impairment. However, peripheral neuropathy may be the presenting and/or predominant symptom in some of these diseases. Likewise, diseases of complex lipids biosynthesis and remodeling may

present with:

- sensory and autonomic neuropathies, especially defects in serine metabolism either with an early onset – then associated with a global encephalopathy – or with an onset during adolescence to adulthood – with a less severe phenotype (Dick 1993; Rotthier et al. 2012; Murphy et al, 2013; Suh et al, 2013, 2014).

- demyelinating neuropathies, mainly found in peroxisomal defects such as biogenesis defects related to PEX genes, adrenomyeloneuropathy, X-linked adrenoleukodystrophy and Refsum disease – although peroxisomal diseases can also manifest with axonal neuropathies

- axonal neuropathies, often associated with HSP and usually sharing common pathological pathways with HSP.

2. Muscular and cardiac symptoms – *Table 3*

Complex lipid synthesis and remodeling disorders may present with the following skeletal and cardiac muscle predominant manifestations:

- Recurrent rhabdomyolysis with myoglobinuria and myalgia. This is a well-recognized presentation of beta-oxidation defects such as LCHAD and TFP deficiencies (Olpin et al, 2005), as well as Lipin-1 deficiency (Michot et al, 2010). These episodes are frequently triggered by catabolic or other stressful situations. A rare peroxisomal defect, racemase deficiency, has been reported as a cause of recurrent rhabdomyolysis in adults (Kapina et al, 2010).

- Childhood myopathy mimicking congenital dystrophy, with or without heart involvement. Isolated muscle forms include a severe myopathic phenotype at birth due to 3-hydroxyacyl-CoA dehydratase 1 (PTPLA) deficiency (Muhammad et al, 2013) and the Chanarin-Dorfman syndrome (alpha/beta hydrolase 5 (ABHD5) deficiency). Myopathies with variable cardiac involvement encompass (i) an early onset form with mental retardation and abnormal mitochondrial morphology – i.e. choline kinase beta (CHKB) deficiency (Mitsuhashi et al, 2011), (ii) severe early encephalopathies with seizures and associated signs – i.e. defects in dolichol metabolism (Lefeber et al, 2011, Barone et al, 2012); (iii) Sengers syndrome; and (iv)

an adult onset myopathy and cardiomyovasculopathy – i.e. neutral lipid storage disease or triglyceride deposit (PNPLA2) (Kaneko et al, 2014).

- Primary or prominent cardiac presentations revealed by dilated or hypertrophic cardiomyopathy, such as *DK1* mutations (Kapusta et al, 2012), Barth syndrome (Clarke et al, 2013) and Sengers syndrome (Mayr et al, 2012).

3. Ophthalmological presentations – *Table 4*

Cataract

Lens membrane contains the highest cholesterol content of any known membrane, indicating the importance of normal cholesterol metabolism in lens maintenance. At least 3 inborn errors of cholesterol biosynthesis – mevalonate kinase deficiency, Conradi Hunermann syndrome, Smith Lemli Opitz syndrome – and one disease of bile acids synthesis – cerebrotendinous xanthomatosis – may be associated with opacities of the crystalline lens. Syndromic cataracts may also be observed in several other IEM related to complex lipids synthesis, either as a diagnostic sign or as an isolated presenting sign like in Lowe syndrome.

Retinal dystrophies – retinitis pigmentosa, Leber congenital amaurosis, early onset retinal dystrophy and Stargardt disease

There are over four hundred known inherited diseases in which the retina, macula or choroids are substantially involved (Rattner et al 1999 ; Retnet).

Retinitis pigmentosa (RP) is the name commonly given to a group of diseases with degeneration of the retina leading to a progressive visual field loss, night blindness and abnormal or non recordable electroretinogram. In typical RP, rod photoreceptors are affected more severely than cones early in the disease. A deficiency in dim light is often the first visual symptom and is due to the degeneration or malfunctioning of rods throughout the retina. Diffuse loss of both rod and cone sensitivity leads to blindness. Biochemical studies have revealed that the pathophysiology related to the degeneration of the photoreceptor cells of the retina can be divided into 3 large groups: (i) a primary biochemical defect inherent to the photoreceptor cells; (ii) a primary biochemical defect in neighboring retinal cells such as the retinal pigment epithelium (RPE) – a CNS derivative that separates the retina from the choroidal circulation; and (iii) a peculiar sensitivity of the photoreceptors or the retinal pigment epithelium to a generalized metabolic defect (Drijja 2001). In secondary RP, the

retinal degeneration is associated with other systemic abnormalities, including neurological dysfunction, hearing loss, dysmorphism, skin abnormalities, nephropathy and myopathy. Although the basic pathophysiology of RP is not known, the occurrence of RP in metabolic disorders suggests that it might be induced by abnormal metabolic products, errors of synthetic pathways or deficient energy metabolism (Poll-The et al 1992, Poll-The et al 2003). The lipid phase of the photoreceptor outer segment membrane is essential to the photon capturing and signaling functions of rhodopsin. The rearrangement of phospholipids in the bilayer accompanies the formation of the active intermediates of rhodopsin following photon absorption. ABCA4 is implicated in the transport of a retinal phospholipid compound across membranes of the photoreceptor outer segment disc. All-trans retinal released from rhodopsin is reduced to all-trans retinol and subsequently shuttled to the RPE cells where it is sequentially converted back to 11-cis retinal for the regeneration of rhodopsin (Molday et al 2010). These last steps involve consecutively lecithin:retinol acyl transferase (LRAT) and RPE 65 isomerase. All these steps have been found implicated in various forms of RP and Leber congenital amaurosis (LCA) (Mackay et al 2013).

LCA is a severe retinal dystrophy with infantile onset that presents with profound visual impairment, inability to fixate and nystagmus from birth or within the first few weeks of life. It is the most severe form among the spectrum of these disorders arising within the first few years of life and affecting both rod and cone photoreceptors, also called childhood or early onset retinal dystrophy (EORD) (Gu et al, 1997). The term juvenile RP has also been used to describe EORD. Autosomal recessive RP falls into this spectrum of disorders with onset typically later in childhood or beyond. Depending on the age at diagnosis, the retinal appearance may be normal or there may be a variety of abnormalities including vascular narrowing, macular atrophy, peripheral white dots at the level of the RPE and retinal pigmentation. The full-field electroretinogram (ERG) is usually non-detectable with conventional ERG testing or severely decreased before the age of 1 year. LCA, EORD and RP may be considered as a continuum spectrum of retinal dystrophies, in which LCA represents the most severe form due to its age of onset and functional outcome.

Stargardt disease is the most common autosomal recessive, early onset macular dystrophy. Affected individuals display significant loss in central vision with a marked

reduction in visual acuity in their first or second decade of life. Progressive decrease in visual acuity generally occurs throughout life with values reaching 20/200 or worse in the final stages of the disease. Stargardt patients also show a delay in dark adaptation and variable loss in color vision. Ophthalmoscopic examination of Stargardt patients typically reveals bilateral atrophic changes in the macula associated with the degeneration of photoreceptor cells and the underlying RPE. Two genes associated with inherited macular degenerative diseases encode proteins whose function is to process lipids in photoreceptor cells: *ABCA4* mutations cause the autosomal recessive Stargardt macular degeneration and *ELOVL4* mutations lead to the autosomal dominant Stargardt-like disease (Molday 2010). In addition to Stargardt disease, mutations in *ABCA4* are known to result in 2 more severe, but clinically distinct, retinal degenerative diseases: a cone-rod dystrophy and the autosomal recessive retinitis pigmentosa 19. Cone-rod dystrophy (CRD) is a retinal disorder in which cone photoreceptor cells degenerate before rod cells. Mutations in *ABCA4* account for 30%-60% of autosomal recessive CRD. In some cases, Stargardt disease can evolve into a CRD. Likewise, it is now generally believed that mutations in *ABCA4* result in a spectrum of related retinal dystrophies, the severity of which depends on the type of mutations, its effect on protein function, age of onset and genetic modifiers (Molday 2009).

Optic nerve degeneration – optic atrophy and glaucoma

Hereditary optic atrophy (OA) is common in neurodegenerative diseases due to IEM, especially white matter diseases and energy deficiencies, and deserves an extensive work-up (Saudubray et al, 2012). The OA and cortical blindness that occur early in the course of Krabbe disease – globoid cell leukodystrophy, galactosylceramid lipidosis – are a direct consequence of the severe loss of myelin and oligodendroglia that is characteristic of this disorder. Although the OA develops early in the disease course, it is usually overshadowed by the neurological deterioration. OA is also frequent in metachromatic leukodystrophy and may result in severely impaired vision. OA is a frequent early presenting sign of primary – Leber hereditary optic neuropathy, respiratory chain deficiencies, pyruvate dehydrogenase deficiency, biotinidase deficiency, Costeff optic atrophy syndrome – or secondary – organic acidurias – mitochondrial dysfunction. By contrast, OA appears to be a rather rare ocular finding in disorders of complex lipids synthesis compared to retinal

dystrophies. Nonetheless, visual loss and OA are early presenting sign in several disorders of dolichol synthesis and remodeling pathway (Lefeber this issue). It is also a very frequent and early significant sign in some NBIA – INAD and MPAN –,in which an impairment of mitochondrial function is strongly suspected in disease development and/or progression. In this respect, it is relevant that the mitochondria-associated membrane of the endoplasmic reticulum is major site of phospholipid biosynthesis and trafficking (Tiranti this issue).

Glaucoma is characterized by the progressive loss of visual fields due to the degeneration of the optic nerve, usually associated with increased intraocular pressure. Early onset glaucoma is a major diagnostic sign in Charcot Marie Tooth disease type 4B2, due to mutations in the gene *SBF2* that is involved in phosphoinositide metabolism.

4. Dermatological presentations – *Table 5*

About 30 inherited disorders of complex lipids synthesis, remodeling ,catabolism and transport presenting with ichthyosis have been described so far. According to the most recent ichthyosis consensus conference (Oji et al 2010), inherited ichthyoses belong to a large and heterogeneous group of mendelian disorders of cornification and involve the entire integument. This classification remains clinically based and distinguishes between syndromic and non syndromic ichthyosis forms. Bullous ichthyosis/epidermolytic hyperkeratosis was redefined as keratinopathic ichthyosis. Autosomal recessive congenital ichthyosis (ARCI) refers to harlequin ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma. At least 6 inherited lipids synthesis disorders are responsible for non syndromic ARCI, all but one - linked to epidermal lipase N deficiency – presenting at birth with a collodion baby aspect. The vast majority of ichthyosis linked to complex lipids disorders present as neuro-cutaneous syndromes, chondrodysplasia punctata or multiple congenital anomalies – CDG syndromes, neuro laxova syndrome. Among the neuro-cutaneous syndromes comprising spastic paraparesis, Sjögren-Larsson syndrome – ALDH deficiency – presents at birth with a very severe pruriginous ichthyosis that responds dramatically to Zileuton (Willemsen et al 2001). Sterol methyl-C4 oxidase, a sterol metabolism disorder, is another treatable ichthyosis with a spectacular improvement on statin and cholesterol supplement (He et al 2011).

Erythrokeratodermia variabilis (EKV), which is characterized by migratory erythematous patches and more fixed, symmetric hyperkeratotic plaques often with palmo-plantar involvement, is genetically heterogeneous; in 50% to 65% of cases, it can be caused by mutations in *GJB3* coding for a gap junction protein connexin. Previously, erythrokeratodermia was differentiated from the ichthyosis group as, in most cases, it is not generalized. However, the majority of the participants to the consensus conference thought that the inclusion of EKV into the ichthyosis classification is appropriate. Interestingly, an early EKV associated with autosomal dominant late onset spinocerebellar ataxia has been recently shown to be caused by *ELOVL4* heterozygote mutation (Cadieu-Dion et al 2014).

Another intriguing skin manifestation of complex lipids metabolism disorders is the inflammatory dermatosis – i.e. Sweet syndrome – observed in Majeed syndrome due to Lipin 2 deficiency (Ferguson et al 2005), which highlights the potential role of complex lipids in inflammation (Csaki 2013).

5. Orthopedic presentations – *Table 6*

Over 20 inborn errors affecting the synthesis or remodeling of phosphatidylcholine, phosphatidylserine, phosphatidylinositol, plasmalogens or cholesterol present with major bone and cartilage involvement. Schematically, 3 clinical entities may be recognized: congenital bone dysplasia, overgrowth disorders and inflammatory presentations.

Congenital bone dysplasia

Beside rhizomelic chondrodysplasia punctate (Brites this issue) and the already well-known defects of cholesterol and plasmalogen biosynthesis responsible for a variety of bone dysplasia and polymalformative syndromes (Waterham 2012), several original entities affecting phospholipids metabolism have been recently described. They involve mostly the synthesis, transport or activating pathways of phosphoserine (Wortmann this issue) and phosphatidyl inositides (Balla 2013): (i) Lenz-Majewski syndrome, a sclerosing bone dysplasia is caused by a gain of function mutation in the gene encoding phosphatidylserine synthase 1 (*PTDSS1*), which impairs the negative feedback regulation of the enzyme by its reaction product phosphoserine (Sousa et al, 2014, Wortmann this issue); (ii) spondylometaphyseal

dysplasia with cone-rod dystrophy is caused by mutations in the gene encoding cholinephosphatase cytidylyltransferase A (PCYT1A), a key enzyme in phosphatidylcholine biosynthesis (Yamamoto et al 2014; Wortmann this issue) – of note, a late onset form of *PCCT1A* mutations display a very different phenotype without any bone involvement (Payne et al, 2014); (iii) Yunis-Varon syndrome presenting with cleidocranial dysplasia and skeletal abnormalities has been recently linked to mutations in *FIG4* that encodes a phosphoinositide phosphatase required for the regulation of phosphatidylinositol 3,5-phosphate (PI(3,5)P2) (Campeau et al, 2013); and (iv) opsismodysplasia, a severe chondrodysplasia is due to a deficiency in inositol-1,4,5-triphosphate 5-phosphatase INPPL1 (Huber et al, 2013).

Segmental overgrowth disorders with congenital lipomatosis

The molecular etiology of somatic overgrowth syndromes has been recently clarified and allowed the clinical delineation and natural history of the PIK3CA-related overgrowth spectrum (Keppler-Noreuil et al 2014; Lindhurst et al 2012). The spectrum of diseases associated with *PIK3CA* mutations include fibroadipose overgrowth, hemihyperplasia multiple lipomatosis, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), macrodactyly, and the megalencephaly-capillary malformation syndrome (MCAP). It appears that all these phenotypes have a considerable overlap and are associated with somatic gain of functions of phosphoinositol kinase 3 resulting in an over-activation of the phosphatidylinositol/AKT/mTOR pathway. *PIK3CA* mutations are detected in affected tissues or cultured cells at varying levels, but not in the blood or saliva. There is not a clear correlation between the mutation level in either tissues or cultured cells to either the type or the severity of the manifestations. Apart from the class IA of PI3Ks, human diseases are rarely caused by activating mutations of inositide lipid kinases. Moreover, loss of function of inositol lipid kinases is rarely seen in human diseases. The only report on an inactivating mutation of the *PIP 5-kinase I* gene was associated with severe developmental abnormalities with perinatal lethality (Narkis et al 2007). Conversely, an increasing number of rare human diseases such as Joubert syndrome, Lowe syndrome, Charcot-Marie-Tooth disease type 4B1 or X-linked myotubular myopathy are linked to phosphoinositide phosphatase defects and cause very specific phenotypes (Balla 2013).

Inflammatory presentations

Recurrent aseptic necrosis and medullary infarction of long bones in an inflammatory context are a frequent diagnostic finding in Majeed syndrome and Gaucher disease. These symptoms represent a major clinical concern.

6. Hepatic presentations – *Table 7*

Complex lipids synthesis and remodeling disorders may be associated with 3 preponderant hepatic presentations.

The first presentation is a transient neonatal to early infantile cholestatic jaundice and/or liver failure followed by a neurodegenerative disorder. Beside the well-known Niemann-Pick type C disease (Vanier 2010), cholestatic jaundice may be the first manifestation of several diseases affecting the synthesis of cholesterol and bile acids. In most cases, the jaundice spontaneously resolves but psychomotor delay, peripheral neuropathy and/or motor dysfunction develop during the first decade or even later. In the so-called infantile Refsum disease – a peroxisome biogenesis defect – the neonatal jaundice is commonly followed by a 1 to 3 years phase of failure to thrive with hepatomegaly, osteoporosis and hypocholesterolemia before neurologic symptoms, RP and deafness arise (Poll-The 2007). Megdel syndrome also presents first with recurrent episodes of liver failure, similar to what is seen in mitochondrial DNA depletion syndromes, before the onset of dystonia and a Leigh-like encephalopathy (Sarig et al 2013; Wortmann this issue).

Major hepatosplenomegaly is another preponderant diagnostic sign, evocative of many lysosomal disorders involving the catabolism and recycling of complex sphingolipids. Mevalonate kinase deficiency presents early in life with acute recurrent inflammatory crisis, fever, skin rashes, arthralgia, hepatosplenomegaly and severe recurrent anemia (Houten et al 2003).

Finally, non-alcoholic liver steatosis is a presenting sign in several IEM involving triglyceride biosynthesis. Indeed, the liver is a central organ in the regulation of triglycerides metabolism; it participates in triglyceride synthesis, export, uptake and oxidation. Hepatocytes can shift from intensive fatty acid synthesis – in fed state – to rapid fatty acid breakdown – during starvation. Massive fatty liver, partly reversible, is an almost constant finding in many mitochondrial fatty acid oxidation disorders during acute crises (Saudubray et al 1999). Chronic hepatosteatosis, considered as the

fundamental cause of hepatic injuries, inflammation and fibrosis are often found in individuals with defect in triacylglycerol metabolism. Patients may present (i) either with a preponderant hepatomegaly with hypertriglyceridemia, as observed in individuals with Chanarin-Dorfman syndrome – triglyceride lipase or glycerol-3-phosphate dehydrogenase deficiency (Aguilera-Méndez et al, 2013; Wu and Mitchell this issue); or (ii) as a lipodystrophy with insulin resistance and diabetes, like in the Berardinelli-Seip syndrome (Wu and Mitchell this issue) and the most recently described late onset form of choline-phosphate cytidylyltransferase A deficiency (Payne et al 2014).

7. Other presentations

Several renal presentations have been described so far: (i) Mutations in *DGKE* result in diacylglycerol kinase epsilon deficiency and cause renal microangiopathies, leading either to a membranoproliferative glomerulonephritis or an early onset atypical haemolytic-uremic syndrome (Lemaire et al 2013; Ozaltin et al 2013; Westland et al. 2014; Wortrmann this issue); (ii) Nephrotic syndrome is a major manifestation of coenzyme Q synthesis defects (Salviati this issue) and a preponderant presenting sign in *PLCE1* mutations responsible for the nephrotic syndrome type 3; (iii) Renal Fanconi syndrome with mental retardation and cataract are cardinal signs of Lowe syndrome due to *OCRL1* mutations (Attree et al 1992; Suchy et al 2002) – *OCRL* mutations are also found in some forms of Dent disease without any cataract (Hoopes 2005); (iv) Nephronophthisis may be one of the symptoms observed in Joubert syndrome due to *INPP5E* mutations, now included in the new emerging group of ciliopathies (Bielas et al 2009); and (v) Renal cysts are a cardinal sign in the hepato-cerebro-renal Zellweger syndrome resulting from peroxisome biogenesis defects.

Disorders of complex lipids biosynthesis may also involve the immune system : (i) *PIK3CD* mutations cause a combined immune deficiency; (ii)*,PIK3R1* mutations are responsible for an autosomal recessive agammaglobulinemia; and (iii) the recently described deletions of *PLCG2, which* encodes phospholipase Cγ(2) – an enzyme expressed in B cells, natural killer cells and mast cells –, present with cold urticaria, immunodeficiency and autoimmunity (Ombrello et al 2012).

Conclusion

This review attempts to give a clinical overview of disorders affecting the synthesis and remodeling of phospholipids and other complex lipids. Many metabolic and genetic factors may account for the clinical diversity of these disorders. The quantitative importance of lipids in the nervous system makes the brain and peripheral nerves a privileged target for these lipids synthetic defects. Mitochondrial membranes that are very rich in cardiolipin and phosphoethanolamine should be particularly vulnerable to mutations affecting these molecules. The tissue specificity of some complex lipid molecules also probably accounts for some specific clinical presentations. Hence the high concentration of cardiolipin in muscle and its very small content in the brain may underlie the predominant muscle/cardiac presentation of Barth syndrome with no or minimal involvement of the nervous system. Similarly, the confinement to skeletal muscles of clinical manifestations of Lipin-1 mutations might be related to the nearly ubiquitous expression of the 2 other LPIN genes (LPIN2 and LPIN3). The constant CNS involvement observed in phospholipase A2 deficiency is probably related to the major and predominant expression of this enzyme in the brain even if the clinical heterogeneity is still poorly understood. It is noteworthy that identical mutations affecting the same enzyme can give rise to very different phenotypes like in *ELOVL4* mutations which may present as an autosomal dominant spinocerebellar ataxia with erythrokeratodermia (Cadieux-Dion 2014), a dominant form of Stargardt disease type 3 or a recessive neuro-ichthyotic syndrome resembling a severe presentation of Sjögren-Larsson disease. Another example of such an intriguing phenotypic heterogeneity are mutations in *PCYT1A*, encoding choline-phosphate cytidylyltransferase A, which may present as a spondylometaphyseal dysplasia with cone rod dysfunction or as a congenital lipodystrophy with fatty liver disease but any bone or retina involvement (Payne et al 2014). Tissue specificity might also be responsible for many non syndromic phenotypes, like (i) immune deficiencies syndromes related to mutations in genes specifically expressed in lymphocytes; (ii) congenital ichthyosis related to mutations in genes specifically expressed in keratinocytes such as LIPN encoding epidermal lipase N (Israeli et al. 2011) and PNPLA1 encoding a PNPLA protein involved in glycerophospholipid synthesis (Grall et al. 2012); (iii) retinal dystrophies; or (iv) renal presentations. It must be stressed that many apparently well clinically defined

syndromes are not distinct entities, but rather clusters on a continuous spectrum like for the *PNPLA6*-associated diseases, ranging from Boucher-Neuhauser syndrome, Gordon Holmes syndrome, spastic ataxia and pure HSP. Similarly, LCA, EORD and RP may be considered as a continuum spectrum of retinal dystrophies. Likewise, mutations in *ABCA4* result in a spectrum of related retinal dystrophies including some forms of Stargardt disease.

Awaiting for a more comprehensive overview of this very complex part of cellular metabolism, a clinical approach based on the preponderant presenting symptoms remains therefore the only available one at bedside. The careful grouping of patients in well-defined clinical entities may provide algorithms for orientating metabolic (e.g., lipidomic approaches) and genetic (e.g., exome sequencing) investigations. Of note, these complex molecules synthesis defects are at the crossroad of classical IEM due to an enzymatic block on a catabolic pathway and IEM affecting the synthesis and stability of structural molecules. The concept of complex molecules synthesis defects also opens the window to promising therapeutic trials for example by providing the distal missing compound as it has been successfully done in cerebrotendinous xanthomatosis (Berginer et al 1984), coenzyme Q synthesis defects (Salviati this issue), serine synthesis defects (Méneret et al 2012) and serine metabolism defects involved in *de novo* biosynthesis of glycosphingolipids (Garofalo et al 2011).

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Table

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PREDOMINANT NEUROLOGICAL SYNDROME	AGE AT ONSET	MAJOR SYMPTOMS and BRAIN IMAGE	DEFECTIVE ENZYME	DEFECTIVE GENE (Inheritance)	BIBLIOGRAPHIC REFERENCES
HEREDITARY SPASTIC PARAPARESIS (SP)	Infantile <2 years	**HSP related to "INAD" phenotype**: truncal hypotonia, psychomotor deterioration, cerebellar ataxia, early onset optic atrophy, abnormal EEG pattern (fast rhythms). Brain MRI: cerebellar atrophy, high intensity cerebellar cortex; hypointensities pallidum and SN.	Calcium independent phospholipase A2γ	PLA2G6 (AR)	Morgan et al, 2006
		HSP with ichthyosis:			
		- **Sjögren-Larsson syndrome**: mild to moderate DD, retinopathy, pseudobulbar dysarthria. Brain MRI: Delayed myelination and abnormal lipid peak on MRS (white matter)	Fatty acid aldehyde dehydrogenase	ALDH3A2 (AR)	Rogers et al, 1997
		-HSP with ichthyosis resembling Sjögren-Larsson syndrome. Severe DD, refractory seizures and cataracts.	Fatty acid elongase ELOVL4	ELOVL4 (AR)	Aldamesh et al, 2011
		HSP with variable degrees of cognitive involvement and brain MRI findings:			
		- **SPG56**: "Pure" HSP or associated with variable degree of DD and infraclinic axonal neuropathy. Brain MRI: normal or thin CC with basal ganglia calcifications.	Cytochrome P450 hydroxylase	CYP2U1 (AR)	Tesson et al, 2012
		-HSP with CC agenesis and normal cognition. Brain MRI: CC agenesis, vermis hypoplasia and defective myelination (1 early-onset case described; first symptoms at 9 months of life)	GPI-Anchor synthesis pathway	PGAP1 (AR)	Novarino et al, 2014
		HSP with severe spasticity and severe DD, **SPG54**. Brain MRI: PVWMH, thin CC. Abnormal lipid peak on MRS (basal ganglia)	Phospholipase A1	DDHD2 (AR)	Schuurs-Hoeijmakers et al,

					2012
	Childhood to adulthood	**HSP with severe sensorymotor polyneuropathy**, abnormal gait, pes equinovarus and borderline intelligence. Brain MRI: thin CC and cerebellar hypoplasia (1 single case described)	Arylsulfatase family member I	ARSI (AR)	Novarino et al, 2014
		+/- "Pure" HSP, **SPG28**; slowly progressive (variable association with axonal neuropathy, distal sensory loss, and cerebellar eye movement disturbance)	Phospholipase A1	DDHD1 (AR)	Bouslam et al, 2005
		HSP and cerebellar dysfunction:			
		- **SPG35**: HSP that may associate cognitive decline, epilepsy, mild to severe dystonia, mild to severe optic atrophy. Brain MRI: bilateral T2 pallidum hypointensities, PVWMH, thin CC, pontocerebellar atrophy	Fatty acid-2 hydroxylase	FA2H (AR)	Dick et al, 2010; Kruer et al, 2010
		- HSP that may associate ataxia and hypogonadism	Neuropathy target esterase (NTE)	PNPLA6 (AR)	Synofzik et al, 2014
		- **SPG46**: HSP that may associate variable degree of DD, axonal neuropathy, cataract, hearing loss. Brain MRI may show thin CC and cerebellar atrophy.	Non-lysosomal b-glucosidase 2	GBA2 (AR)	Martin et al, 2013; Hammer at al, 2013
		HSP and distal muscle wasting with spinal cord atrophy, SPG39. Progressive disease	Neuropathy target enterase (NTE)	PNPLA6 (AR)	Rainier et al, 2008

		HSP with variable degrees of cognitive involvement and brain MRI findings: -HSP with border line intelligence and abnormal hand movements. Brain MRI: prominent cortical sulci and widened sylvian fissures (1 case described)	GPI-Anchor synthesis pathway	PGAP1 (AR)	Novarino et al, 2014
		- **SPG26**: HSP that may associate cognitive impairment, cerebellar ataxia, dystonia, muscle wasting, axonal neuropathy and psychiatric signs. Normal brain MRI.	GM2 synthase deficiency	B46ALNT1 (AR)	Boukhris et al, 2013; Harlalka et al, 2013
NBIA	Childhood to adolescence and adulthood	Static encephalopathy in childhood with milder signs than in the INAD phenotype and late onset neurodegeneration in adolescence. Brain MRI: T2 hypointensity of the pallidum and cerebellar atrophy are not an universal feature. MRI may be normal or show cortical atrophy +/- white matter changes	Calcium independent phospholipase A2γ	PLA2G6 (AR) (PLAN, NBIA2)	Kurian and Hayflick 2013; Schneider et al, 2013
		Classical PKAN (mean age: 3.4 years). Dystonia (mainly face and limbs) is always present. Pigmentary retinopathy. Atypical PKAN (mean age: 14 years). Gait abnormality, dystonia, dysarthria, neuropsychiatric manifestations and cognitive decline. Pyramidal signs. Brain MRI: T2 hypointensity of the pallidum centered by T2 hyperintensity: “Eye-of-the-tiger” sign (may appear later)	Pantothenate kinase 2	PANK2 (AR)	Kurian and Hayflick 2013; Schneider et al, 2013
		Childhood onset gait impairment, spastic quadriparesis, severe ataxia and dystonia. Seizures and divergent strabismus may also be present. Similar to INAD. Brain MRI: T2 hypointensity of the pallidum, prominent pontocerebellar atrophy, mild cortical atrophy, white matter abnormalities and CC thinning.	Fatty acid-2 hydroxylase	FA2H (AR)	Kruer et al, 2010

		Childhood onset HSP and DD and later dystonia, dysarthria and spastic-dystonic tetraparesis Brain MRI: T2 hyperintensity and swelling of both caudate nuclei and putamen, mild hyperintensity of both thalami. T2 hypointensity of the pallidum may appear later.	CoA synthase deficiency	COASY (AR)	Dusi et al, 2014
ATAXIA	Infantile to adolescence	**ARCA with hypogonadotropic hypogonadism**: – Boucher-Neuhäuser syndrome (MIM 215470), with chorioretinal dystrophy. – Gordon Holmes syndrome (MIM 215470), with brisk reflexes. Sensory motor axonal neuropathy may be present but not constant. Brain MRI: cerebellar atrophy. Pons and pituitary may be atrophic.	Neuropathy target enterase (NTE)	PNPLA6 (AR)	Synofzik et al, 2014
	Childhood to adulthood	ARCA +/- other manifestations such as migraines, seizures, psychiatric symptoms	Coenzyme Q10 deficiency	COQ8-ADCK3 (AR)	Lagier-Tourenne 2008; Blumkin et al 2014
		Ataxia and gait impairment may be present as an associated sign in diverse disorders that cause **HSP or NBIA** as predominant phenotypes.			
MOVEMENT DISORDERS	Infantile	**Leigh-like** syndrome due to MEGDEL (3-*me*thyl*g*lutaconic aciduria with *d*eafness, *e*ncephalopathy and *L*eigh-like) syndrome. Neonatal hypoglycemia followed by transient hepatic failure. By age 2 years progressive deafness, dystonia, spasticity and psychomotor stagnation. Brain MRI: Leigh-like bilateral basal ganglia involvement	Protein localized at (MAM) mitochondrial associated proteins	SERAC1 (AR)	Wortmann et al, 2012
		Leigh syndrome with multisystem involvement (nephropathy and cardiomyopathy)	Coenzyme Q deficiency	COQ1-PDSS2 (AR)	Rotig et al, 2000

	Adolescence to adulthood	**Choreoathetosis** associated with early onset epilepsy, DD, optic atrophy and hyperpigmented lesions. **Dystonia-Parkinsonism** (PARK14). Dyskinesia associated with tremor including a pill-rolling rest component, rigidity and severe bradykinesia with a good response to L-Dopa; Levy body pathology. Psychiatric symptoms may precede motor signs. Brain MRI: may be normal or show cortical atrophy +/- white matter changes. Dystonia-Parkinsonism may be present in any cause of **NBIA syndrome**. Dystonia may be present in complex forms of HSP, especially SPG26 (B4GALNT1), SPG35 (FA2H) and SPG56 (CYP2U1). **Parkinsonism** may appear very often at late stages of neurodegenerative diseases regardless of the molecular origin	Lactosylceramide α-2,3 sialyl transferase (GM3 synthase) Calcium independent phospholipase A2γ	ST3GAL5 (AR) PLA2G6 (AR)	Simpson et al, 2004; Fragaki et al, 2013 Kurian and Hayflick, 2013
COMPLEX OR SYNDROMIC DEVELOPMENTAL DELAY/ INTELECTUAL DISABILITY	Infantile	**DD and/or ID** may be present as an associated sign in diverse disorders that cause **HSP, NBIA** or **movement disorders** as predominant phenotypes. **HPMRS: Hyperphosphatasia and Mental Retardation** Syndrome. Global developmental delay with marked involvement of expressive language. Coarse facial features. Epilepsy may be present. Anorectal abnormalities and other malformations may be present. In PIGW (1 case described) the	Defects in the GPI-anchor-biosynthesis pathway	PGAP2, PGAP3, PIGV PIGO , PIGW	Krawitz et al, 2012, 2013 Chiyonobou et al, 2013

		patient developed West syndrome. **Mental Retardation/DD and multiple abnormalities:** -Coloboma, ear abnormalities, congenital heart disease and icthyosiform dermatosis, also known as Zurich neuroectodermal syndrome -Severe DD, hypotonia, seizures and multiple congenital abnormalities (MCAHS 1 due to PIGN and MCHAS due to PIGA)		PIGL PIGN, PIGA	Ng et al, 2012 Krawitz et al, 2013
EPILEPSY	Infantile	Early severe epileptic encephalopathy, pharmacoresistant, with choreoathetosis, DD, optic atrophy and hyperpigmented lesions. Venous thrombosis and absence seizures (PIGM) MCAHS1 and 2. Diverse GPI-anchor deficiencies may be associated with epilepsy and intellectual disability.	Lactosylceramide α-2,3 sialyl transferase (GM3 synthase) Defects in the GPI-anchor-biosynthesis pathway	ST3GAL5 (AR) PIGM, PIGN, PIGA	Simpson et al, 2004; Boccuto et al, 2014 Almeida et al, 2006, Krawitz et al, 2013

		Early refractory seizures may appear also in PLA2G6, FA2H and ELOVL4 mutations			

Table 1 Neurological presentations: central nervous system involvement

Abbreviations:

AR: autosomal recessive; ARCA: autosomal recessive cerebellar ataxia. CC: corpus callosum. DD: Developmental delay; ELOVL4: elongase/elongation of very long chain fatty acids deficiency; FA2H: Fatty acid 2-hydroxylase deficiency. FALDH: Fatty aldehyde dehydrogenase deficiency; GM3S: gangliosidosis type 3 synthase deficiency; GP: globus pallidum; GPI: glycosylphosphatidylinositol. HPMRS: Hyperphosphatasia and Mental Retardation Syndrome. HSP: hereditary spastic paraparesis; ID: Intellectual disability; iPLA1: intracellular phospholipase A1. INAD: infantile neuroaxonal dystrophy; LeukoD: leukodystrophy; MCAHS: multiple congenital abnormalities, hypotonia and seizures. NBIA: neurodegeneration associated with brain iron accumulation (type 1 refers to NBIA produced by PKAN deficiency whereas type 2 is due to PLA2G6 deficiency or PLAN: PLA2G6 associated neurodegeneration); NTE: neuropathy target enterase deficiency; PANK2: pantothenate kinase 2 deficiency; PLA2G6: phospholipase A2 deficiency. PVWMH: periventricular White matter hyperintensities; SLS: Sjöegren Larsson syndrome; SN: substantia nigra.

Table

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PERIPHERAL NEUROPATHY and SPINAL CORD involvement	AGE AT ONSET	MAJOR SYMPTOMS	DEFECTIVE ENZYME	DEFECTIVE GENE (Inheritance)	BIBLIOGRAPHIC REFERENCES
SENSORY, AUTONOMIC NEUROPATHY		Progressive loss of pain and temperature sensation spreading from the distal limbs.			
	Adolescence to adulthood	**HSAN type 1** is the most common form. Most cases: autosomal dominant, late onset (typically between the 2nd and 4th decade), slow progression, distal sensory involvement (plantar ulcers predominantly affecting the lower limbs and lancinating pain attacks). Muscle weakness and cataract. Motor neuron degeneration can occur. Considerable clinical heterogeneity in the time of onset and the severity of the symptoms. SPTLC1 and SPTCL2 are the most common mutations.	Serine palmitoyltransferase (SPT) is the most common (corresponding to SPTLC1 and SPTCL2 genes)	AD. Genes: SPTLC1, SPTLC2, ATL1, RAB7A and DNMT1	Dick 1993 Rotthier, et al. 2012
	Early childhood	**Severe early hypotonia and muscle weakness with sensory and autonomic neuropathy** associated with global hypotrophy, developmental retardation, vocal cord paresis, anhydrosis, cataract, and severe respiratory problems. Mutation p.S331 at SPTLC1 is associated with a very severe phenotype.		SPTLC1 and SPTLC2,unknown inheritance, de novo, isolated cases	Murphy et al, 2013. Shu et al, 2013, 2014

DEMYELINATING NEUROPATHY	From early childhood to adulthood	**Refsum disease** characterized by retinitis pigmentosa, anosmia, variable combinations of polyneuropathy (but mostly demyelinating), deafness, ataxia, and ichthyosis. Racemase deficiency is mostly associated with sensory-motor neuropathy	Phytanoyl-CoA hydroxylase (>90% of patients) PTS2 receptor (<10% of patients Racemase: α-Methyl-acyl-CoA-racemase	PHYH (AR) PEX7 (AR) AMACR (AR)	Wanders et al, 2006, 2010 Ferdinandusse et al, 2000; Smith et al, 2010
	Late childhood Childhood	**Refsum -like: PHARC syndrome:** demyelinating polyneuropathy, hearing loss, ataxia, retinitis pigmentosa. Other symptoms that may appear: ataxia, ID, myoclonic seizures. **X-linked adrenoleukodystrophy:** although the most prominent findings are cerebral demyelination associated with a severe neurological regression and progressive spastic	α/β-Hydrolase 12 ALDP deficiency	ABHD12 (AR) ABCD1 (X-linked)	Eisenberg et al, 2012; Fiskerstrand et al, 2010 Steinberg et al, 2012

	Adolescence to adulthood	quadriparesis with cognitive decline, demyelinating (and motor) polyneuropathy may also be present. **Adrenomyeloneuropathy**: although the spinal cord involvement and SP are the most prominent signs, axonal and/or demyelinating neuropathy are frequent.	ALDP deficiency	ABCD1 (X-linked)	Steinberg et al, 2012
AXONAL NEUROPATHY	Infantile to childhood	**Associated with Spastic Paraparesis (SP)** -SP and cognitive regression. Symptoms such as hearing impairment, facial dysmorphism, hepatic involvement and renal cysts may be present. -Severe sensory motor polyneuropathy with spastic paraparesis, abnormal gait, pes equinovarus and borderline intelligence. Brain MRI: CC and cerebellar hypoplasia (1 single case described) - Other causes of sensory motor neuropathy and SP : PLA2G6, CYP2U1 (SPG56), GBA2 (SPG46) and B4GALNT1 (SPG26) (see table that refers to central nervous system involvement)	Different proteins related to PBD Arylsulfatase family member 1	PEX genes (AR) ARSI (AR)	Waterham et al, 2012 Novarino et al, 2014

	Childhood to adulthood	-SP that may associate ataxia and hypogonadism	Neuropathy target enterase (NTE)	PNPLA6 (AR)	Synofzik et al, 2014,
		- SPG26: SP that may associate cognitive impairment, cerebellar ataxia, dystonia, muscle wasting, axonal neuropathy and psychiatric signs. Normal brain MRI.	GM2 synthase deficiency	B46ALNT1 (AR)	Boukhris et al, 2013; Harlalka et al, 2013
		-dHMN: distal hereditary motor neuronopathy. HMN-VII. Electrophysiology and electromyography studies reveal normal motor and sensory conduction velocities with reduced compound-motor-action-potential amplitudes and neurogenic changes, suggesting that pathology is at the level of the anterior horn cell. Patients showed fatigability and decremental EMG Response	Presynaptic choline transporter (CHT)	SLC5A7 (AR)	Barwick et al, 2012
	Adolescence to adulthood	**Associated with retinopathy and episodes of rhabdomyolysis.** Other symptoms characteristics of fatty acid beta oxidation defects may also be present	LCHAD TFP	HADHA (AR) HADHA/B (AR)	Olpin et al, 2005 Smith et al, 2010
		As a single clinical manifestation or associated with symptoms found in Refsum disease (see above)	Racemase: α-Methyl-acyl-CoA-	AMACR (AR)	Ferdinandusse et

		Adrenomyeloneuropathy: involvement of long ascending and descending tracts of the spinal cord , progressive SP, usually associated with peripheral neuropathy. Adrenal insufficiency. Axonal and/or demyelinating neuropathy are frequent	racemase ALDP deficiency	 ABCD1 (X-linked)	al, 2000 Steinberg et al, 2012

Abbreviations:

AR: autosomal recessive. AD: autosomal dominant. CHT: choline transporter. dHMNs: distal hereditary motor neuronopathies. HSAN: inherited sensory and autonomic neuropathy. HSAN1, OMIM#605712 and #605713. ID: Intellectual disability. LCHAD: long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. NTE: neuropathy target enterase deficiency. PBD: peroxisomal biogenesis disorders. SP: spastic paraparesis. SPT: Serine palmitoyltransferase. TFP: trifunctional protein deficiency

Table
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SKELETAL AND CARDIAC MUSCLE involvement	AGE AT ONSET	MAJOR ASSOCIATED SYMPTOMS	DEFECTIVE ENZYME	DEFECTIVE GENE (Inheritance)	BIBLIOGRAPHIC REFERENCES
RECURRENT RHABDOMYOLISIS, MYOGLOBINURIA, MYALGIA	Childhood (2-7 years)	Frequent episodes of myoglobinuria, lasting from 7 to 10 days and induced by infections, febrile illnesses, fasting or anesthesia. Between episodes patients are asymptomatic. The central nervous system is usually non affected, however, mild learning disability has been reported in one patient, and generalized muscle hypotonia at age 18 months, has been reported in another case.	Phosphatidate-phosphatase-1 (Lipin 1)	LPIN1 (AR)	Zeharia et al, 2008. Michot et al, 2010
	Childhood to adulthood	Episodes of rhabdomyolisis and myalgia may appear. Retinopathy and sensory motor neuropathy are also characteristic. Other symptoms characteristics of fatty acid beta oxidation defects may also be present.	LCHAD TFP	HADHA (AR) HADHA/B (AR	Olpin et al, 2005
	Adulthood	Recurrent rhabdomyolisis and stroke like episodes has been described in a single patient. Sensory motor neuropathy and other Refsum-like symptoms have been described in several patients.	Racemase: α-Methyl-acyl-CoA-racemase	AMACR (AR)	Kapina et al, 2010
MYOPATHY (muscular dystrophy, weakness, elevated CK)	Infantile	Severe myopathic phenotype at birth that gradually Improves. Early infantile: severe hypotonia, absent deep tendon reflexes, weak cry, recurrent apnea of newborn. Later on: facial weakness, decreased muscle tone, delayed motor milestones, positive Gower sign. One patient evolved towards normal gait and residual pes cavus at adult age.	3-hydroxyacyl-CoA dehydratase 1 (HACD1)	PTPLA (AR)	Muhammad et al, 2013

	Infantile to childhood	Chanarin-Dorfman syndrome: Myopathy (elevated CK), liver steatosis with hepatomegaly, ataxia, neurosensory hearing loss, cataracts, nystagmus, strabismus and ID with icthyosis.. Intracellular accumulation of triacylglycerol droplets in tissues	Alpha/beta hydrolase 5 (ABHD5)	ABHD5 (AR)	Lefèvre et al, 2001
MYOPATHY (muscular dystrophy, weakness, elevated CK) +/- CARDIOMYOPATHY	Infantile	Early.onset muscle wasting, mental retardation and abnormal mitochondrial morphology (enlarged mitochondria). Some patients may have dilated cardiomyopathy and seizures	Choline kinase beta (CHKB) deficiency	CHKB (AR)	Mitsuhashi et al, 2011
	Infantile	**Severe hypotonia with elevated CK, seizures and other associated signs +/- cardiomyopathy**	IEM of the dolichols. All lead to hypoglycosylated target proteins and belong to the CDG syndromes.		
		-Severe hypotonia with elevated CK, intractable seizures, ichthyosis with loss of hair, severe liver dysfunction and progressive dilated cardiomyopathy. Mild coagulopathy icthyosis and mild ID may be also present.	DK1	DK1 (AR)	Lefeber et al., 2011
		-Acquired microcephaly, severe hypotonia with elevated CK, and early-onset myoclonic epilepsy and cerebellar hypoplasia elevated transaminases and low ATIII mild ID, muscular dystrophy. Stroke-like episodes and dilated cardiomiopathy	DPM 1-3	DPM1-3 (AR)	Barone et al., 2012

		may be associated.			
		-Early-onset seizure, ichthyosis, hypotonia with elevated CK, global developmental delay, failure to thrive and recurrent vomiting. Brain MRI revealed generalized atrophy.	MPDU1	MPDU1 (AR)	Schenk et al., 2001
	Infantile	Sengers syndrome: skeletal myopathy, hypertrophic cardiomyopathy, congenital cataract and lactic acidosis. Mental development is normal but patients may day from early cardiomyopathy. In the severe neonatal form, abnormal basal ganglia, brainstem and cerebellar hypoplasia as well as cortical infarction have been reported. Abnormalities of mitochondria and storage of glycogen and lipids are found in skeletal and cardiac muscle.	AGK: acylglycerol kinase	AGK (AR)	Sengers et al, 1975; Mayr et al, 2012.
	Infantile	Encephalomyopathy with: -Weakness, hypotonia, mental retardation (COQ3) -With hypertrophic cardiomyopathy and renal tubulopathy (COQ9) -With hypertrophic cardiomyopathy and complex encephalopathy (MELAS-like) (COQ2)	Coenzyme Q10 deficiencies	COQ3, COQ9, COQ2 (AR)	Salviati et al, 2005, 2012 Duncan et al, 2009, Jackobs et al, 2013
	Adulthood	Myopathy and cardiomyovasculopathy due to neutral lipid storage disease (NLSD) or triglyceride deposit. Myopathy is mostly proximal (although distal predominance is also possible), may be asymmetric and frequently-affected muscles are posterior compartment of leg, shoulder girdle to upper arm, and paraspinal. Cardiomyopathy may be dilated or hypertrophic. Muscle biopsies shows lipid accumulationand rimmed vacuoles. Comorbidities such as	Patatin-like phospholipase domain-containing 2	PNPLA2 (AR)	Kaneko et al, 2014

		hyperlipidemia, diabetes mellitus, and pancreatitis have been described.			
PRIMARY CARDIAC PRESENTATIONS		**Dilated cardiomyopathy**			
	Infantile	Primary cardiac presentation without seizures, dysmorphic features, ichthyosis or intellectual disability. Dilated cardiomyopathy that leads to life-threatening dysrhythmias, persistent transaminase elevations with decreased Factors XI and ATIII, and microcytic anemia, and the ensuing neutropenia.	IEM of the dolichols. All lead to hypoglycosylated target proteins and belong to the CDG syndromes.	DK1 (AR)	Kapusta et al, 2012
	Any age, antenatal to adulthood	Barth syndrome: the classical presentation includes cardiomyopathy, skeletal muscle weakness, neutropenia and growth retardation. Cardiomyopathy is the most severe presentation (biventricular dilatation or left-ventricular non-compactation are the initial signs). Excretion of 3-methylglutaconic acid is characteristic but not constant.	Cardiolipin (CL)	TAZ (X-linked)	Bione et al, 1996 Barth et al, 2004; Clarke et al. 2013
	Infantile	**Hypertrophic cardiomyopathy**			
		Sengers syndrome: described above. Important to highlight that the clinical course is dominated by the cardiac problems and is variable, ranging from a late onset chronic progressive form with survival into the fourth decade, over patients receiving heart transplantation in childhood to a fatal neonatal onset form.	AGK: acylglycerol kinase	AGK (AR)	Mayr et al, 2012; Sengers et al, 1975.

TABLE 3 Muscular and cardiac symptoms

Abbreviations:

ABDH5: Alpha/beta hydrolase 5. AR: autosomal recessive. AD: autosomal dominant. CL: Cardiolipin. ID: Intellectual disability. HSAN: inherited sensory and autonomic neuropathy. CK: Creatine Kinase. HACD1: 3-hydroxyacyl-CoA dehydratase 1. DPM; dolichyl-phosphate-D-mannose: protein *O*-D-mannosyltransferase. ID: Intellectual disability. MPDU1: Mannose-P-Dolichol Utilization Defect 1. NLSDM: neutral lipid storage disease miopathy. NTE: neuropathy target enterase deficiency. PNPLA2: Patatin-like phospholipase domain-containing 2. SP: spastic paraparesis. SPT: Serine palmitoyltransferase.

Table
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Syndrome/ enzyme defect (gene defect)	Cataract	Retinal dystrophies	Optic nerve degeneration	Major symptoms	
Sengers syndrome (AR) (*AGK*)	**+ may be isolated**			**Hypertrophic cardiomyopathy, myopathy, lactic acidosis, 3-methylglutaconic acid excretion. Cataract may be isolated.**	**Sengers et al, 1975**
Lowe Syndrome (X-linked) *(OCRL, encoding phosphatidylinositol 4,5 bisphosphate 5-phosphatase)*	**+**			**Renal Fanconi syndrome, mental retardation. (PS: OCRL1 mutations are also found in some forms of Dent disease without any cataract (Hoopes 2005)**	**Attree, et al 1992, Suchy et al, 2002.**
Chanarin-Dorfman (AR) (*ABHD5.CGI58)*	**+**			**Congenital ichthyosis, hepatomegaly with liver steatosis, mental retardation, myopathy, decreased hearing**	**Lefèvre et al, 2001**
Glucocerebrosidase 2 (AR) *(GBA2)*	**+**			**Early onset spastic ataxia, developmental delay, axonal sensory neuropathy, hearing loss. Brain MRI corpus callosum and cerebellar atrophy (Hammer et al 2013)**	**Hammer et al, 2013**
Acetyl-CoA carrier (AR) (*SLC33A1)*	**+**			**Lethal disorder with hearing loss, developmental delay, cerebellar atrophy and severe hypomyelination with low serum copper and ceruloplasmin (Huppkee 2012)**	**Huppke et al, 2012**
N-acetylgalactosaminyl transferase 1 (AR) (*B4GALNT1)*	**+ (rare)**			**Early onset spastic paraplegia, developmental delay, cerebellar symptoms, dystonia, muscle wasting, axonal neuropathy.**	**Harlalka et al, 2013**
3-phosphoglycerate dehydrogenase deficiency (AR) (*PHGDH)*	**+**			**Congenital cataract with microcephaly, profound mental retardation, severe spastic paraplegia, nystagmus and intractable seizures. One late onset form described with congenital cataract followed by atypical neuropathy.**	**Meneret et al, 2012**

Smith Lemli Opitz syndrome (AR) (*DHCR7*)	**+ (incidental)**			**Large and variable spectrum of congenital anomalies including distinctive facial features, microcephaly, intellectual disability, behavioral problems, malformations of the heart, lungs, kidneys, gastrointestinal tract, and genitalia.**	**Waterham et al, 2006**
Conradi Hunermann syndrome (dominant X-linked) (*EBP)*	**+**			**X-linked dominant chondrodysplasia type II (asymmetric rhizomelic shortening, epiphyseal calcific stippling) with ichthyosiform erythrodermia**	**Waterham et al, 2006**
Mevalonate kinase deficiency (classic form)(AR) *(MVK)*	**+ (incidental)**	**RP may be isolated (incidental)**		**Multisystemic disease with recurrent inflammatory crisis, hepatosplenomegaly, lymphadenopathy and recurrent severe anemia** **Clinical evaluation of 3 Dutsch patients diagnosed as classic form of RP showed variable extra-ocular symptoms (recurrent childhood febrile crises , mild ataxia , and renal failure). All 3 affected individuals showed a low MK activity and high levels of urinary mevalonic acid (Siemiatkowska 2013)**	**Siemiatkowska et al, 2013**
Cerebrotendinous xanthomatosis (AR) *(CYP27A1)*	**+**			**Neonatal jaundice, diarrhea, mental retardation, late infantile cataract, Late onset tendon xanthomata (2nd decade), progressive neurological dysfunction (spastic paraplegia, ataxia), psychiatric symptoms**	**Berginer et al, 1984**
Fatty acid elongase (AR) (AD) *(ELOVL4*)	**+ recessive**	**Stargardt type Iii dominant**		**Congenital ichthyosis and neurological symptoms resembling Sjögren-Larsson disease (Aldamesh 2011)** **Heterozygous ELOVL4 mutations display an autosomal dominant juvenile form of isolated macular degeneration (Zhang et al 2001)**	**Zhang et al, 2001**
Sjogren Larsson (AR) (*ALDH3A2)*	**+ may be isolated**	**RP**		**Hypertrophic cardiomyopathy, myopathy, lactic acidosis, 3-methylglutaconic acid excretion (Willemsen 2001)**	**Willemsen et al, 2001**
Refsum disease (AR) *(PHYH)*	**+**	**RP cardinal sign**		**Retinitis pigmentosa, cerebellar ataxia, chronic polyneuropathy, sensorineural hearing loss, anosmia, skeletal malformations, ichthyosis**	**Wanders et al, 2011**

PHARC syndrome (AR) *(ABHD12*)	**+**	**RP may be isolated**		**Cataract, hearing loss and predominantly demyelinating peripheral neuropathy. RP develops in the second or third decade. RP may be isolated. (Wotrmann this issue)**	**Nishiguchi et al, 2014**
PZO Biogenesis defects (AR) (*several PEX*)	**+**	**RP**	**OA**	**Various phenotypes ranging from typical Zellweger syndrome to neonatal ALD, infantile Refsum disease and late onset polyneuropathy resembling Charcot Marie Tooth disease**	**Wanders et al, 2011**
Phospholipase A2 group V (AR) *(PNPLA5)*		**Benign fleck retina**		**Benign yellow-white retinal lesions or flecks with otherwise normal retinal findings (Sergouniotis 2011)**	**Sergouniotis et al, 2011**
Retinal pigment epithelium-65 kD protein isomerase *(RPE65)*		**AR RP AD RP LCA**		**LCA, recessive RP, and dominant RP with choroidal involvement (Hanein S et al 2004)**	**Hanein et al, 2004**
ABCA4 transporter of the retinal phospholipid compound, N-retinylidene-phosphatidylethanolamine		**AR Stargardt AR CRD AR RP 19**		**CRD individuals experience severe loss in visual acuity and color vision and display significant atrophy of the central retina or macula. This is followed by progressive loss in peripheral vision and night blindness. Unlike typical RP, affected individuals with RP 19 show an early loss in central vision and atrophy of the macula in addition to the characteristic features of RP (Zhang et al 2013)**	**Sparrow et al, 2010 Zhang et al, 1999**
PITPNM3, **phosphatidylinositol transfer membrane-associated family member 3**		**AD cone dystrophy**		**Patients display subnormal visual acuity and light sensitivity from childhood. Early signs of macular degeneration then appear with a progressive decrease in visual acuity leading to blindness in early adulthood. ERG testing shows a progressive loss of photoreceptor function restricted to the cones. (Köhn,et al 2007)**	**Köhn et al, 2007**
RBP3 , interphotoreceptor binding protein *(IRBP)*		**AR RP66**		**IRBP protein binds and transports retinoids in the interphotoreceptor matrix between the retinal pigmentary epithelium and photoreceptors (den Hollander 2009)**	**den Hollander et al, 2009**

CYP4V2 *(CYP4V2)* may have important roles in eicosanoid metabolism. Catalysts of ω-3 and ω-6 oxidations of polyunsaturated fatty acids		**Bietti's crystalline dystrophy AR**		**BCD is characterized by the presence of yellow-white crystals and/or complex lipid deposits in the cornea and retina, atrophy and degeneration of the retinal pigmented epithelium and sclerosis of the choroidal capillaries. These symptoms progress from visual field constriction to eventual night blindness. BCD is a progressive disease, but patients as young as 16 to 17 years of age have been diagnosed (Nakano et al 2012),**	**Nakano et al, 2012**
RBP 4 (serum retinol binding protein) (AR)		**RP**		**Affected siblings had no detectable serum RBP, one sixth of normal retinol levels, and normal retinyl esters. The retinal pigment epithelium was severely affected, but there were no changes to other organs. This gives evidence for an alternative tissue source of vitamin A, presumably retinyl esters from chylomicron remnants (Seeliger MW et al 1999)**	**den Hollander et al, 2009 Seeliger et al, 1999**
Lecithin retinol acyltransferase (AR) *(LRAT)*		**RP LCA**		**Recessive RP, severe early-onset; recessive LCA (Thompson 2001)**	**Thompson et al, 2001**
RDH11 (AR) RDH11 protein is a widely-expressed enzyme with a role in oxidizing 11-*cis*-retinol to 11-*cis*-retinal similar to RDH 1,5 and 12		**RP syndromic**		**RP with facial dysmorphology, developmental delay, and short stature; RP-associated ophthalmological findings included salt-and-pepper retinopathy, attenuation of the arterioles and generalized rod-cone dysfunction with almost extinguished electroretinogram (Xie et al 2014)**	**Fingert et al, 2008 Xie et al, 2014**
RDH12 (AR and AD) 11-*cis* retinol dehydrogenase 12		**AR LCA with severe childhood retinal dystrophy; AD RP**		**Symptoms include severe progressive rod-cone dystrophy and macular atrophy; may account for 4% of recessive LCA (Fingert et al 2008, Perrault et al 2004)**	**Perrault et al, 2004 Yamamoto et al, 1999**

RDH5 (AR) **11-*cis* retinol dehydrogenase 5** **(same pathway as in RDH11 and 12)**		**Cone dystrophy, late onset**		**Stationary night blindness with subretinal spots and delayed dark adaptation; extremely delayed rod and cone resensitization in null mutation (AV Cideciyan et al 1999, H Yamamoto et al 1999)**	**Cideciyan et, 1999**
Ceramide kinase like(AR) (*CERKL*)		**RP non syndromic**		**Primary dysfunction or loss of cone photoreceptors and then of rod photoreceptors. Patients present with a progressive loss of central vision, visual field constriction and nyctalopia. (Aleman TS 2009)**	**Aleman et al, 2009**
Dehydrodolichyl diphosphate synthase (AR) (*DHDDS)*		**RP non syndromic**		***DHDDS* K42E and T206A missense mutations have been linked to non syndromal RP(Züchner S et al 2011, Zelinger L et al 2011)**	**Zelinger et al, 2011** **Züchner et al, 2011**
Joubert syndrome (AR) *(INPP5E,* encoding inositol polyphosphate-5-phosphatase E)		**RP**		**Absence or underdevelopment of the cerebellar vermis and a malformed brain stem (molar tooth sign). Most common features include ataxia, hyperpnea, sleep apnea, abnormal eye and tongue movements, and hypotonia., with variably associated retinitis pigmentos, nephronophthisis,liver fibrosis and polydactyly .It is included in the newly emerging group of 'ciliopathies' (Bielas 2009)**	**Bielas et al, 2009**
Phosphocholine citidylyl transferase (AR) *(PCYT1A)*		**CRD**		**Spondylometaphyseal dysplasia, short stature with rhizomelia, platyspondyly, early-onset visual impairment with pigmentary maculopathy and cone-rod dysfunction (Wortmann this issue)**	**Yamamoto et al, 2014**
Boucher-Neuhauser syndrome (AR) *(PNPLA6)*		**RP**		**Ataxia with cerebellar atrophy, chorioretinal degeneration, hypogonadotropic hypogonadism (Wortmann this issue)**	**Synofzik et al, 2014**

Pantothenate kinase 2 (**AR**) *(PANK2)*		**RP**		**Dystonia, dysarthria, rigidity and RP. MRI : bilateral T2 hypointense deposits in the pallidum centered by T2 hyperintensities "eye-of-tiger". Acanthocytosis (Tiranti this issue)**	**Gregory and Hayflick 2011**
Fatty acid hydroxylase (AR) *(FA2H*)		**RP**	**OA**	**Spastic paraparesis, dystonia, cognitive decline, epilepsy. MRI : white matter T2 hyperintensities (Tiranti this issue)**	**Rizzo et al, 2014**
2-methyl-CoA racemase (AR) (*AMACR)*		**RP**		**Peripheral neuropathy (demyelinating and axonal), RP; may present as relapsing rhabdomyolysis or relapsing encephalopathy.MRI: thalamus and brain stem T2 hyperintensities**	**Kapina et al, 2010**
LCHAD /Trifunctional (AR) (*HADHA/HADHB**)***		**RP**		**Hypoglycemia, rhabdomyolysis crisis, myocardiopathy, peripheral neuropathy, retinitis pigmentosa (Spiekerkotter 2004)**	**Spiekerkoetter et al, 2004**
Abetalipoproteinemia (AR)(*MTP)* **Homozygou*s* hypobetalipoproteinemia (AR)** *(APOB***)**		**RP**		**Infantile steatorrhea from fat malabsorption, failure to thrive and hepatic steatosis. Malabsorption of fat soluble vitamins leads to retinal degeneration, neuropathy and coagulopathy (Rader 1993)**	**Rader et al, 1993**

Tocopherol carrier deficiency (AR) (*TTPA)*		**RP**		**Cerebellar ataxia and sensory neuronopathy sometimes associated with cardiomyopathy and retinitis pigmentosa. Resembles Friedreich ataxia.**	**Pang et al, 2001**
Dolichol synthesis (AR) *(SRD5A3)* (*DHDDS)*			**OA**	**Developmental delay, ataxia and early visual impairment with optic atrophy, occasional ichthyosiform dermatitis and liver dysfunction (Lefeber this issue)**	**Millon et al, 2011**
Dolichol recycling (AR) (*DPM1 :* CDG1e) *(MPDU1 :*CDG 1f*)*			**OA** **OA**	**DPM1phenotype : acquired microcephaly, dysmorphic facial features, visual loss with optic atrophy, frontal cortical atrophy and delayed myelination, intractable seizures, hypotonia with elevated CK .** **MPDU1 deficiency : early onset nystagmus and optic atrophy with early visual loss together with early-onset seizures, ichthyosis, hypotonia with elevated CK, global developmental delay, failure to thrive and recurrent vomiting (Lefeber this issue)**	**Lefeber et al, 2011**
Amish epilepsy syndrome (AR) (*ST3GAL5)*			**OA**	**Early severe epileptic encephalopathy, pharmacorresistant, with developmental delay and blindness (Levade this issue)**	**Fragaki et al, 2013**

Mitochondrial membrane protein-associated neurodegeneration (MPAN) (AR) *(C19orf12)*			**OA**	**The onset is typically between 4 and 20 years of age, and the progression is generally slower than PKAN and INAD. The clinical presentation comprises dysarthria and gait difficulties followed by spasticity, dystonia, parkinsonism, psychiatric symptoms, motor axonal neuropathy and optic atrophy. MRI: T2 hypointensities in pallida and substantia nigra**	**Tiranti this issue**
Infantile neuroaxonal dystrophy (INAD) (AR) *(PLA2G6)*			**OA**	**Motor and mental deterioration, cerebellar ataxia, marked hypotonia, spastic tetraplegia, and early visual disturbances. MRI: T2 hypointensities in pallida and substantia nigra**	**Tiranti this issue**
Phospholipase A1 (AR) *(DDHD2)*			**+ Optic nerve hypoplasia**	**Early onset spastic paraplegia, strabismus, dysarthria ± dysphagia, developmental delay. MRI: thin corpus callosum, abnormal NMR lipid peak on MRS**	**Wortmann this issue**
Charcot-Marie-Tooth Disease associated with early-onset glaucoma (AR) (*SBF2*)			**Glaucoma**	**Demyelinating CMT, mainly characterized by myelin outfoldings on nerve biopsies, and early-onset glaucoma. MTMR13 is involved in phosphoinositide metabolism**	**Azzedine 2003**

TABLE 4 Ophtalmological presentations

Abbreviations: AR: autosomal recessive; AD: autosomal dominant; LCHAD: 3-hydroxy long chain acyl CoA dehydrogenase; PZO: Peroxisome; RP: retinitis pigmentosa; LCA: Leber congenital amaurosis; CRD: cone rod dystrophy; OA: optic atrophy

Table
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MAIN SYMPTOM	AGE AT ONSET	MAJOR ASSOCIATED SYMPTOMS	DEFECTIVE ENZYME	DEFECTIVE GENE (Inheritance)	REFERENCES
ICHTHYOSIS (ARCI)	Congenital to early infantile <4months	**Non syndromic autosomal recessive congenital ichthyosis (ARCI)**			
		-**ABCA12 lipid transporter defects** may present with Harlequin ichthyosis (HI), congenital ichthyosiform erythroderma (CIE) or lamellar ichthyosis type 2 **(**LI). LI patients are born as collodion babies and present a generalized lamellar ichthyosis with large adherent dark pigmented scales, with ectropion and palmoplantar keratoderma.	ABCA12 lipid transporter	*ABCA12 (AR)*	Lefèvre et al, 2003 Akiyama et al, 2010
		-**ALOX3 /ALOX 12B defects** present with non bullous congenital ichthyosiform erythrodermia (NCIE). Patients are born as collodion baby.	Lipoxygenase-3 12(R)- Lipoxygenase	*ALOXE3 (AR)* *ALOX12 (AR)*	Jobard et al, 2002
		-**CYP4F2** Most of the patients are not born as collodion babies but present a more erythrodermal status of the skin at birth. After birth, they present with generalized LI mostly on the periumbilical region, the lower part of the body and on the buttocks. Hyperlinearity of palms and soles similar to that found in ichthyosis vulgaris is constant. There are scales on the scalps in all patients.	CYP4F2 (leukotriene B4-v-hydroxylase)	*FLJ39501 (AR)*	Lefèvre et al, 2006
		-**Phospholipase A1 deficiency** born as collodion babies, later having generalized ichthyosis with fine white scales and moderate erythroderma and palmoplantar keratoderma**.** No lipid vacuoles.	Phospholipase A1	*PNPLA1* (AR)	Grall et al, 2012

ICHTHYOSIS SYNDROMIC	Congenital to early infantile <4months	**Syndromic congenital ichthyosis** -**Acute neuronopathic Gaucher disease perinatal form:** Transient collodion baby with severe multivisceral failure, hydrops foetalis, hepatosplenomegaly, pancytopenia, arthrogryposis (40%), brainstem dysfunction, pyramidal signs, opisthotonos.	Acid B Glucosidase (Glucocerebrosidase)	*GBA* (AR)	Mignot et al, 2006
		-**Ceramide synthetase 3 deficiency:** One of the affected girls presented at birth an extreme ectropion at eclabium with collodion membrane followed by a moderate lamellar ichthyosis, scaling of the scalp and a pronounced keratotic lichenification with prematurely aged appearance. Four additional Tunisian patients were affected with a contiguous gene deletion syndrome involving exon 13 of *CERS3* and *ADAMTS17*. These patients presented a combination of the above ichthyosiform phenotype and the symptoms of Weill-Marchesini-like syndrome due to *ADAMTS17* mutations.	Ceramide synthase 3	*CERS3 (AR)*	Eckl et al, 2013 Radner et al, 2013
		Ichthyosis with spastic paraplegia (SP) - **Sjögren-Larsson syndrome** : ichthyosis with severe pruritis, early hypotonia, generalized scaling sparing the face, yellow lichenification of neck, flexures, and abdomen, hypohidrosis, HSP over the first 2y, cataracts, macular dystrophy, mild DD. Brain MRI: delayed myelination and abnormal lipid peak. Pruritis improved by Zileuton.	Fatty acid aldehyde dehydrogenase	*ALDH3A2* (AR)	Willemsen et al, 2001
		- **Neuro-ichythyotic syndrome** resembling severe Sjögren-Larsson syndrome: collodion babies, later having generalized ichthyosis with predilection to the neck and diaper areas then to the hands and feet, severe DD,	Fatty acid elongase	*ELOVL4* (AR)	Aldahmesh et al, 2011

		refractory seizures and HSP.			
		-**Mucosulfatidosis (Austin disease**) Moderate ichthyosis (especially over joints) with metachromatic leukodystrophy and mucopolysaccharidosis-like phenotype.	Lysosomal sulfatase Factor	*SUMF1 (AR)*	
		Syndromic ichthyosis with neutral lipid storage disease Chanarin-Dorfman syndrome: congenital erythrodermic ichthyosis ,hepatomegaly with liver steatosis (70%) nystagmus, cataracts, decreased hearing ,mental retardation myopathy and lipid vacuoles in tissues and lymphocytes.	a/b-hydrolase domain containing 5	*ABHD5* (also known as *CGI-58*) (AR)	Lefévre et al, 2001
		Syndromic ichthyosis with chondrodysplasia punctata			
		-**X-linked syndromic ichthyosis**: severe generalized non-pruritic ichthyosis ,palms and soles spared (most cases) pigmented desquamation, corneal opacities, DD, small stature, hypogonadism, chondrodysplasia punctata.	Aryl sulfatase C (Steroid sulfatase)	*STS (X-linked)*	Happle, 1979
		- **X-linked dominant chondrodysplasia punctata** Diffuse cutaneous lesions (may be transient), chondrodysplasia punctate, rhizomelic asymmetric dwarfism, cataracts, DD, only in girls (Conradi-Hunermann syndrome). Resemble Child syndrome and RCDP.	Δ^8, Δ^7 Sterol isomerase	*EBP (X-linked)*	Happle, 1979
		- **RCDP type II and III** :Ichythyosis with severe proximal shortening of limbs,typical facies dysmorphism,cataracts, calcific stippling of epiphyses,coronal cleftsof vertebral bodies,multiple join contractures,severe growth and DD.	DHAPAT:RCDP II Alkyl-DHAP synthase :RCDP III	*GNPAT (AR)* *AGPS (AR)*	Brites this issue
		Ichthyosis and dry skin with multiple congenital anomalies			

		-**CDG syndromes** due to disorders in the synthesis, utilization or recycling of dolichol :DDHDS (DehydrodolichylDiphosphate Synthase), CDG1m (Dolichol kinase), 1q (Steroid 5-a reductase), CDG1f (mannose-P-Dolichol utilization 1), IIb (glucosidase 1), and glycosylphosphatidylinositol (GPI anchor synthesis defect).	Mannose-P-Dolichol utilization I Dolichol Kinase Steroid 5-Reductase Dehydrodolichyl diphosphate synthase Glucosidase 1	*MPDU1, DOLK, SRD5A3, DHDDS, GCS1, PIGL (AR)*	Wolfe et al, 2012 Lefeber this issue
		Neu-Laxova Syndrome (NLS) : lethal multiple congenital anomaly: defective somatic growth, CNS and skin development. There is a generalized ichthyosis with marked hyperkeratosis that can resemble the colloidon membrane. Growth restriction in the second trimester, with profound microcephaly and lissencephaly. The face is highly characteristic with proptotic eyes, ectropion, eclabion, and a severely hypoplastic nose.	3-phosphoglycerate dehydrogenase	*PHGDH (AR)*	Shaheen et al, 2014
	Late infancy to childhood >4 years to adolescence	**Non syndromic autosomal recessive congenital ichthyosis (late onset ARCI).** At birth, skin looks normal; widespread ichthyosis develops at 5y. The entire surface of skin is covered with fine whitish scales whereas face is slightly erythematous. At skin biopsy, hyperkeratosis and acanthosis without evidence for epidermolytic changes or intracytoplasmic vacuoles.	Epidermal lipase N	*LIPN (AR)*	Israeli et al, 2011
		Syndromic late onset generalized ichthyosis sparing palms. Severe ichthyosiform erythroderma affecting the entire body but sparing the palms and plants. No dermatitis at birth. Ichthyosis developed around umbilicus at 2y, progressed to back, trunk, and then the remainder of body by age 6. Dermatitis worsened in the	Sterol methyl-C4 oxidase	*MSMO1 (AR)*	He et al, 2011

		winter, and once almost completely normalized. Patient also displays congenital cataracts, mild DD, microcephaly and failure to thrive. Spectacular improvement with statin and cholesterol supplement. **Late onset neuro-ichthyotic syndromes:** **-Refsum disease:** Cardinal manifestations include retinitis pigmentosa, cerebellar ataxia, chronic polyneuropathy and hyperproteinorachia. Less constant features are sensorineural hearing loss, anosmia, skeletal malformations. Involvement of skin is highly variable, sometimes a presenting sign (children) or absent. Cutaneous signs range from slightly dry skin especially on the trunk to florid ichthyosis. Diagnostic based on phytanic acid accumulation in plasma. **-Serine deficiency with ichthyosis and polyneuropathy** Unique patient who had ichthyosis from the 1st year of life and growth retardation from the age of 6y and presented at the age of 14y with an axonal polyneuropathy. No brain involvement at MRI. Fasting plasma and CSF serine levels were decreased and the CSF Glycine slightly increased. Oral ingestion of serine (400mg/kg/d) cured the skin lesions and polyneuropathy.	Phytanic acid oxidase Unknown (hyperactivity of serine hydroxyl-methyltransferase)	*PHYH (AR)* *Unknown*	Skjeldal et al, 1987 De Klerk et al, 1996 Meneret et al, 2012
HYPER AND HYPO-PIGMENTED SKIN		**Ceramide synthase 2** Neuro-cutaneous syndrome combining hyper and hypo-pigmented skin maculae called 'salt-and-pepper' syndrome, facial dysmorphism (mid-face hypoplasia, microcephalia, prominent lower face), scoliosis, severe DD, seizures, choreoathetosis, spasticity and abnormal electrocardiogram (non specific conduction changes).	Ceramide synthase 2 (loss of function GM3 synthase)	*ST3GAL5 (AR)* (*SIAT9*)	Boccuto et al, 2014
ERYTHRO KERATODERMIA	Early infancy (skin signs)	**ELOVL4 dominant disease: EKV and SCA** 2 types of skin lesions may be observed in early	Fatty acid elongase	*ELOVL4 (AD) Heterozygous*	Cadieux-Dion et al, 2014

VARIABILIS (EKV)	4^{th} to 5^{th} decades (neurologic signs)	infancy .First, erythematous and hyperkeratotic plaques over the dorsal aspects of the hands and feet, the elbows, the ankles, and the external ears. The hyperkeratosis usually is more prominent than the erythema. Second, transient, figurate, and erythematous patches are observed over the legs, thighs, and buttocks. Both types of lesions are symmetrically distributed and vary in severity. The lesions disappear after the patient is 25 years of age. The onset of gait ataxia usually occurred in the fourth or fifth decade of life. The progression of gait disturbance is very slow.			
CONGENITAL GENERALIZED LIPODYSTROPHY	Congenital	**Berardinelli Seip Syndrome** Congenital generalized lipodystrophy, lack of body fat since birth, striking muscular appearance, hyperinsulinemia, hypertriglyceridemia, accelerated growth, hepatomegaly with liver steatosis, diabetes mellitus at puberty, acanthosis nigricans, acromegaloid appearance and occasional cardiomyopathy.	1-acylglycerol-3-phosphate O-acyltransferase	*AGPAT2 (AR)*	Debray et al 2013
INFLAMMATORY DERMATOSIS	Infancy to childhood	**Majeed syndrome:** Autoinflammatory disorder characterized by an Inflammatory dermatosis (pustulosis palmoplantaris, Sweet syndrome, psoriasis), chronic recurrent multifocal aseptic osteomyelitis, periodic fever and congenital dyserythropoietic anemia (microcytosis both peripherally and in the bone marrow).May resemble Gaucher disease.	Phosphatidate phosphatase 2 (Lipin2)	*LPIN2 (AR)*	Ferguson PJ et al J Med Genet 2005

TABLE 5 **Dermatological presentations**

Abbreviations:

AR: autosomal recessive; AD: autosomal dominant; ARCI: autosomal recessive congenital ichthyosis. DD: Developmental delay; ELOVL: elongase/elongation of very long chain fatty acids deficiency. FALDH: Fatty aldehyde dehydrogenase deficiency. GPI: glycosylphosphatidylinositol. HSP: hereditary spastic paraparesis; SLS: Sjögren-Larsson syndrome.

Table
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Syndrome enzyme defect	Major symptoms	Enzyme	Gene	Reference
Majeed syndrome (AR)	**Onset in infancy to childhood: auto-inflammatory disorder, chronic recurrent multifocal aseptic osteomyelitis with osteolytic and sclerotic lesions, periodic fever,inflammatory dermatosis, dyserythropoietic anemia**	**Phosphatidic phosphatase (Lipin 2)**	***LPN2***	Ferguson et al. 2005
Gaucher disease type 1 (AR)	**Bone involvement is an important concern in late childhood to adulthood. Medullary infarction of long bones may cause excruciating pain ("bone crisis"). Aseptic necrosis of femoral head and spontaneous fractures due to osteopenia are common findings and can be inaugural.**	**Glucocerebrosidase type 1**	***GBA***	Vanier 2012
Phosphocholine Citidylyl transferase deficiency (AR)	**Spondylometaphyseal dysplasia (short stature with rhizomelia, platyspondyly, metaphyseal irregularity, bowing of long bones) with cone-rod dystrophy.**	**Phosphocholine citidylyl transferase (alpha isoform)**	***PCYT1A***	Wortmann this issue
Lenz Majewski hyperostotic dwarfism syndrome (AD)	**Progressive generalized hyperostosis leading to severe growth restriction, typical craniofacial dysmorphic features (thickness of the jaw, clavicles and ribs), distal-limb abnormalities (proximal symphalangism), cutis laxa, intellectual disability.**	**Phosphatidylserine synthase 1 gain-of-function**	***PTDSS1***	Wortmann this issue
Opsismodysplasia (AR)	**Chondrodysplasia characterized by pre- and postnatal micromelia with extremely short hands and feet. The main radiological features are severe platyspondyly, squared metacarpals, extreme delayed skeletal ossification and metaphyseal cupping.**	**Inositol polyphosphate phosphatase-like 1**	***INPPL1***	Cormier-Daire 2003 Huber 2013 Below 2013
Yunis-Varon syndrome (AR)	**Wide fontanels with calvarial dysostosis, aplasia or hypoplasia of the clavicles and phalanges in the hands and feet, absence of thumbs and halluces. Pelvic bone dysplasia, absent sternal ossification centers and fractures are also frequent. Common features include diffuse brain atrophy, sparse and pale hair, facial dysmorphism.**	**Phosphoinositide phosphatase (FIG4)** (required for the regulation of PI(3,5)P2 levels)	***PIK3R2***	Campeau 2013

SHORT syndrome (AD)	**Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay.**	**Phosphoinositide kinase (PIK)**	***PIK3R1***	Thauvin-Robinet 2013
Phosphoinositide kinase 3	**Megalencephaly, polymicrogeria, polydactyly, hydrocephalus syndrome .**	**Phosphoinositide kinase (PIK)**	***FIG4***	Gross 2014
PIK3CA-related segmental overgrowth disorders. (Somatic mutations in the phosphatidylinositol/AKT/ mTOR pathway)	**Congenital asymmetric disproportionate overgrowth – mild with little postnatal progression in most, severe and progressive requiring multiple surgeries in others. Overgrowth affects the lower extremities more than the upper extremities and progresses in a distal to proximal pattern. Congenital lipomatosis is present in all patients and, in the most severely affected patients, is associated with marked paucity of adipose tissue in unaffected areas.**		***PIK3CA (somatic mutations)***	Keppler-Noreuil 2014
Rhizomelic chondrodysplasia punctata (RCDP) type I-II-III (AR)	**Severe proximal shortening of limbs, facial dysmorphism, cataracts, calcific stippling of epiphyses, coronal clefts of vertebral bodies, multiple joint contractures, growth and psychomotor delays, ichthyosis. The chondrodysplasia punctata may involve extra-skeletal tissues.**	**PTS2 (type I) DHAPAT (type 2) Alkyl-DHAP synthase (type 3)**	***PEX7 GNPAT AGPS***	Poll The 2012
PZO Biogenesis defects (AR)	**Classical Zellweger syndrome may present with chondrodysplasia punctata less widespread than in RCDP.**	**Several peroxins**	***PEX* genes**	Poll The 2012
Refsum disease (AR)	**Skeletal malformations in 50% of patients: symmetric epiphyseal dysplasia in the knee, joints, elbows and shoulders; bilateral shortening or elongation of the 3rd and 4th metatarsal bones, syndactyly and shortened digits.**	**Phytanic acid hydroxylase**	***PHYH***	Skjeldal 1987
Conradi-Hünermann (X-linked dominant) (CDPX 2)	**Patients (girls) with short stature, asymmetric rhizomelic shortening of the limbs, calcific stippling of the epiphyseal regions and craniofacial defects. Associated with ichthyosiform erythroderma in the neonate, atrophic and pigmentary lesions in childhood, and coarse lusterless hair and alopecia in adults, and cataracts.**	**Sterol Δ^8-Δ^7 isomerase**	***EBP***	Waterham 2006 Braverman 1999 Derry 1999

Child syndrome (X-linked dominant))	**CHILD syndrome (congenital hemidysplasia with ichtyosiform erythroderma and limb defects) presents with skin and skeletal abnormalities similar to those observed in CDPX2 patients but with a striking unilateral distribution affecting the right side of the body more often than the left. Alopecia, nail involvement and limb reduction defects with calcific stippling of the epiphysis are common on the affected side. There is no cataract.**	**3β-hydroxysterol dehydrogenase**	***NSDHL***	Waterham 2006
Smith Lemli Opitz (SLOS syndrome) (AR)	**Variable spectrum of morphogenic and congenital anomalies: characteristic craniofacial appearance and limb abnormalities including cutaneous syndactyly of the 2nd and 3rd toes, postaxial polydactyly and short proximally placed thumbs.**	**7-dehydro cholesterol reductase**	***DHCR7***	Waterham 2006
Desmosterolosis (AR)	**Short limb, osteosclerosis, dysmorphic facial features, microcephaly, profound developmental delay and brain malformations including agenesis of the corpus callosum.**	**3β-hydroxysterol Δ^{24}-reductase**	***DHCR24***	Waterham 2006
Lathosterolosis (AR)	**Only two patients reported who presented at birth with postaxial hexadactyly, syndactyly, craniofacial dysmorphism, severe microcephaly and SLOS-like features.**	**sterol Δ^{5}-desaturase**	***SC5D***	Waterham 2006
Greenberg skeletal dysplasia (AR)	**Severe fetal hydrops, short-limb dwarfism, unusual 'moth-eaten' appearance of the markedly shortened long bones, bizarre ectopic ossification centers and marked disorganization of chondro-osseous histology. May present with polydactyly and non skeletal malformations (HEM skeletal dysplasia)**	**3β-hydroxysterol sterol Δ^{14}-reductase**	***LBR***	Waterham 2006

TABLE 6 **Orthopedic presentations**

Abbreviations:

AR: autosomal recessive; AD :autosomal dominant;;PZO :Peroxisome

Table
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HEPATIC involvement	AGE AT ONSET	MAJOR ASSOCIATED SYMPTOMS	DEFECTIVE ENZYME	DEFECTIVE GENE	REFERENCES
Transient neonatal cholestatic jaundice and/or liver failure followed by neurodegenerative disorder	Neonatal to first 6 months	**Niemann Pick disease type C** About 1/3 of the NP-C patients have a prolonged neonatal cholestatic icterus with hepatosplenomegaly. In most patients, the icterus resolves spontaneously, and only hepatosplenomegaly remains, but in a few patients, the liver disease worsens and they die from hepatic failure before 6 months. Isolated hepatosplenomegaly or splenomegaly can also develop at this age. Filipin staining test is positive	NPC1-NPC2	*NPC1-NPC2)*	Vanier 2013
		MEG(H)DEL syndrome (H=Hepatic) At 24–48 hr of life, patients present with hypotonia and liver dysfunction including symptomatic hypoglycemia, lactic acidosis ,elevated serum transaminase and γ-GT levels, coagulopathy, hyperammonemia and markedly elevated serum a -fetoprotein. Filipin staining test is positive. During the 1st year of life, a few episodes of liver dysfunction may occur. At 6 months of age, failure to thrive and hypotonia become prominent. From age 13 to 22 months, neurological abnormalities characteristic of the MEGDEL syndrome develop.		*SERAC1*	Wortmann 2012 Sarig 2013 Wortmann this issue
	First 6 months	**Infantile Refsum disease and peroxisomal biogenesis defects** During this period of life, the predominant symptoms may be hepatomegaly associated (or not associated) with prolonged jaundice, liver failure and nonspecific digestive problems (anorexia, vomiting, diarrhea) leading to failure to thrive and osteoporosis. Hypocholesterolemia, hypolipoproteinemia and decreased levels of fat-soluble vitamins, symptoms that resemble a malabsorption syndrome, are frequently observed. These patients can be erroneously diagnosed as having a congenital defect of glycosylation or a defect of the OXPHOS respiratory chain.	Several Peroxins	Several *PEX*	Poll-The BT 1987

		Cerebrotendinous xanthomatosis (CTX) Cholestatic jaundice in infancy may be the first manifestation of CTX . However, it usually improves spontaneously. The next (or the first) symptom of CTX is often psychomotor delay detected during the first decade of life. Cataract may also be present as early as 5 years of age. Some patients present with persistent diarrhea from early childhood. Motor dysfunction (spastic paresis, cerebellar ataxia) frequently develops in the second or third decade of life. Xanthomata are observed within the second decade.	Sterol 27-hydroxylase	*CYP27A1*	Clayton 2002
		á-Methylacyl-CoA Racemase Deficiency (AMACR) Neonatal cholestatic liver disease was documented in an infant with AMACR deficiency who presented with a coagulopathy due to vitamin K deficiency; a sibling had died of a major bleed with the same cause. The infant had mild cholestatic jaundice with raised aspartate aminotransferase and, in contrast to 3â-dehydrogenase deficiency, 5â-reductase deficiency and CTX, elevated ã-GT.	α Methylacyl -CoA Racemase	*AMACR*	Van Veldhoven 2001 Setchell 2003
		Oxysterol 7á-Hydroxylase Deficiency Oxysterol 7á-hydroxylase may present in the first 3 months of life with severe cholestasis, cirrhosis and liver synthetic failure. One infant presented with liver failure and hypoglycaemia at 3 months but recovered completely with chenodeoxycholic acid treatment. Oxysterol 7á-hydroxylase deficiency has also been identified as a cause of a recessive form of hereditary spastic paraplegia (SPG type 5).	Oxysterol 7α-Hydroxylase	*CYP7B1*	Setchell 1998 Tsaousidou 2008
		LCHAD deficiency. A few patients with LCHAD deficiency present in the first 3 months of life with transient cholestatic jaundice followed by the classic manifestation of LCHAD disease (recurrent attacks of hypoglycemia and myoglobinuria, cardiac features, peripheral neuropathy and retinitis pigmentosa)	3-Hydroxy long chain acyl-coA dehydrogenase	*HADHA/HADHB*	

					Odievre 2002
Hepatosplenomegaly With storage signs (lysosomal disorders)	Neonatal to late infancy	**Gaucher disease.** The perinatal lethal form is associated with hepatosplenomegaly, pancytopenia and skin changes with hydrops fetalis in many cases. Children often show severe splenomegaly, generally associated with hepatomegaly, . This may lead to anemia, thrombocytopenia and bleeding tendency. Children may show delayed growth and menarche. Subcapsular splenic infarctions may cause attacks of acute abdominal pain and medullary infarction of long bones, excruciating pain often referred to as bone crises.	Glucocerebrosidase	*GBA*	Vanier 2012
		Niemann Pick disease type C. Isolated hepatosplenomegaly or **s**plenomegaly can start at this age. In the severe early infantile neurological onset form, infants with a pre-existing hepato splenomegaly (often with a history of neonatal icterus) show an early delay in motor milestones that becomes evident between the age of 9 months and 2 years, and hypotonia. Most never learn to walk. A loss of acquired motor skills is followed by spasticity with pyramidal tract involvement and mental regression.	NPC1-NPC2	*NPC1-NPC2*	Vanier 2013
	First weeks of life	**Wolman disease** presents in the 1st week of life with poor feeding, vomiting, diarrhea, severe failure to thrive**,** abdominal distension, hepatosplenomegaly with mesenteric adenopathy and bilateral adrenal calcifications at abdominal ultrasound. The psychomotor development is normal.	Acid Lipase	*LIPA*	
		Classic Niemann-Pick Disease Type A. Presents with vomiting and diarrhea, failure to thrive, prominent and progressive hepatosplenomegaly and lymphadenopathy, in most cases before 3-4 months of age and sometimes earlier. Hypotrophy is a frequent finding. Neurological examination is essentially normal until the age	Acid Sphingomyelinase	*SMPD1*	Vanier 2013

		of 5-10 months, when the child shows hypotonia, progressive loss of acquired motor skills, lack of interest in the surroundings and reduction of spontaneous movements.			Hanh 1997
	Neonatal to first days	**GM1 gangliosidosis** (Landing disease) The typical early infantile form (or type 1) presents with hypotonia in the first days or weeks of life, with poor head control. The arrest in neurological development is observed at 3-6 months of age. Feeding difficulties and failure to thrive are common. Many infants have facial and peripheral edema. In typical cases, dysmorphic features resembling Hurler syndrome may be present. Hepatomegaly and later splenomegaly are almost always present. Dorsolumbar kyphoscoliosis is common.	Acid β-galactosidase,	*GLB1 (AR)*	
		Prosaposin deficiency presents as a severe neurovisceral storage disease manifesting immediately after birth with rapidly fatal course and death between 4 and 17 weeks of age. The patients have hepatosplenomegaly, hypotonia, massive myoclonic bursts, abnormal ocular movements, dystonia and seizures.	Prosaposin	*PSAP*	Vaccaro et al, 2010
	Late infancy to adulthood	**Niemann Pick disease type B** chronic, non-neuronopathic disease presents typically with splenomegaly or hepatosplenomegaly in late infancy or childhood but discovery may occur at any point from birth until late adulthood. Bruising and epistaxis are frequent. Hypersplenism may occur. The most constant associated signs are radiographic abnormalities of the lung (diffuse, reticulonodular infiltrations) and interstitial lung disease with variable impairment of pulmonary function.	Acid Sphingomyelinase	*SMPD1*	Vanier 2013
With inflammatory crisis and anemia	First year	**Mevalonate kinase deficiency** present with characteristic episodes of high fever and inflammation with abdominal pain, vomiting, diarrhea, lymphadenopathy, hepatosplenomegaly, skin rash and recurrent non regenerative anemia.	Mevalonate kinase	*MVK*	Houten 2003

Hepatic steatosis	Early infantile	**Chanarin-Dorfman Syndrome** Congenital erythrodermic ichthyosis, hepatomegaly with liver steatosis (70%), nystagmus, cataracts, decreased hearing, mental retardation, myopathy, non-lysosomal lipid storage disease .Tissular accumulation of neutral lipids (vacuoles).	a/b-hydrolase domain containing 5	*ABHD5*	Mitchell this issue
		Berardinelli Seip Syndrome. Congenital generalized lipodystrophy Striking muscular appearance, hyperinsulinemia (insulin resistance), hypertriglyceridemia, accelerated growth, hepatomegaly with liver steatosis.	1-acylglycerol-3-phosphateO-acyltransferase	*AGPAT2*	Mitchell this issue
		Triglyceride lipase deficiency. Neutral lipid storage with myopathy of proximal and distal muscles, asymmetric muscle atrophy, hepatomegaly and liver steatosis (50%).	Patatin-like Phospholipase	*PNPLA2*	Mitchell this issue
		Glycerol-3-phosphate dehydrogenase deficiency Early infantile moderate to massive hepatomegaly and steatosis, abnormal liver function tests, transient infantile hypertriglyceridemia ,and development of hepatic fibrosis. Normal neurologic examination. One patient with microcephaly.	Glycerol-3-phosphate dehydrogenase 1	*GPD1*	Basel-Vanagaite 2012 Joshi 2014 Mitchell this issue
		Phosphate cytidylyltransferase 1 alpha deficiency. Late childhood presentation with severe nonalcoholic fatty liver disease, low HDL cholesterol levels, lipodystrophy, severe insulin resistance, diabetes and short stature without any spondylometaphyseal dysplasia and visual impairment (no cone-rod retinal dystrophy).	Phosphate cytidylyltransferase 1 alpha	*PCYT1A*	Payne 2014

TABLE 7 Hepatic presentations

Table

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CNS	PNS	Muscle	Ophthal.	Skin	Orthop.	Hepatic	Others
ALDH3A2	ABCD1	ABHD5	ABCA4	ABCA12	AGPS	ABHD5	COQ2
ARSI	ABHD12	AGK	ABHD12	ABHD5	DHCR24	AGPAT2	COQ9
B4GALNT1	AMACR	AMACR	ABHD5	AGPAT2	DHCR7	AMACR	DGKE
COASY	ARSI	CHKB	AGK	AGPS	EBP	CYP27A1	INPP5E
COQ1	ATL1	COQ4	ALDH3A2	ALDH3A2	FIG4	CYP7B1	OCRL
COQ2	B4GALNT1	COQ9	AMACR	ALOX12	GBA	GBA	PEX genes
COQ4	COQ1	DK1	APOB	ALOXE3	GNPAT	GLB1	PIK3R1
COQ6	DNMT1	DPM1	B4GALNT1	CERS3	INPPL1	GPD1	PLCE1
COQ8	HADHA	DPM2	C19orf12	CYP4F22	LBR	HADHA	PLCG2
COQ9	HADHB	DPM3	CERKL	DHDDS	LPIN2	HADHB	
CYP2U1	PEX genes	HADHA	CYP27A1	DOLK	NSDHL	LIPA	
DDHD1	PEX7	HADHB	CYP4V2	EBP	PCYT1A	MVK	
DDHD2	PHYH	LPIN1	COQ1	ELOVL4	PEX genes	NPC1	
ELOVL4	PNPLA6	MPDU1	DDHD2	GBA	PEX7	NPC2	
FA2H	RAB7A	PNPLA2	DHCR7	GNPAT	PHYH	PCYT1A	
GBA2	SLC5A7	PTPLA	DHDDS	LIPN	PIK3CA	PEX genes	
PANK2	SPTLC1	TAZ	DPM1	LPIN2	PIK3R1	PNPLA2	
PGAP1	SPTLC2		EBP	MPDU1	PIK3R2	PSAP	
PGAP2			ELOVL4	MSMO1	PTDSS1	SERAC1	
PGAP3			FA2H	PHGDH	SC5D	SMPD1	
PIGA			GBA2	PHYH			
PIGL			HADHA	PIGL			
PIGM			HADHB	PNPLA1			
PIGN			INPP5E	SRD5A3			
PIGO			LRAT	ST3GAL5			
PIGV			MPDU1	STS			
PIGW			MVK	SUMF1			
PLA2G6			OCRL				
PNPLA6			PANK2				
SERAC1			PCYT1A				
ST3GAL5			PEX genes				
			PHGDH				
			PHYH				
			PITPNM3				
			PLA2G6				
			PNPLA5				
			RBP3				
			RBP4				
			RDH11				
			RDH12				
			RDH5				
			RPE65				
			SBF2				
			SLC33A1				
			SRD5A3				
			ST3GAL5				
			TTPA				

Supplementary Table: Gene defects in the lipid metabolism and their predominant clinical manifestation.