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Clinical and biochemical footprints of inherited metabolic disorders. XI. Gastrointestinal symptoms

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Abstract

Inherited metabolic disorders presenting with gastrointestinal (GI) symptoms are characterized by the dysfunction of the esophagus, stomach, small and large intestines, and pancreas. We have summarized associations of signs and symptoms in 339 inherited metabolic diseases presenting with GI symptoms. Feeding difficulties represent the most common abnormality reported for IMDs with GI involvement (37%) followed by intestinal problems (30%), vomiting (22%), stomach and pancreas involvement (8% each), and esophagus involvement (4%). This represents the eleventh of a series of articles attempting to create and maintain a comprehensive list of clinical and metabolic differential diagnoses according to system involvement.

1. Introduction

Inherited metabolic diseases (IMDs) are a heterogeneous group of disorders in which pathogenic variants related to metabolic genes lead to an enzymatic deficiency, a defect in a transporter or molecular chaperone, channel dysregulation, or trafficking molecule dysfunction. Single enzyme defects are the most common. While individually rare, the incidence of inherited metabolic diseases collectively is about 1 in 2,000 live births [1] and many can be identified through mass spectrometry-based expanded newborn screening. The clinical phenotype in these disorders is due to an abnormal accumulation of substrate and/or a subsequent deficiency of the product of the blocked metabolic step. Many inherited metabolic disorders present with gastrointestinal (GI) manifestations, which should be taken into consideration when evaluating a patient. IMDs should be included in the differential

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diagnosis for patients with GI symptoms, particularly when these symptoms occur in conjunction with dietary changes.

A comprehensive overview of IMDs associated with specific organ involvement was provided in the previous issues, including IMDs associated with movement disorders, liver disorders, psychiatric presentations, cardiovascular diseases, cerebral palsy, skin manifestations, ocular phenotypes, neoplasias, ear disease and myopathies [2–14]. This article focuses on GI phenotypes. The list follows the classification in the knowledgebase of IMDs (IEMbase; http://www.iembase.org) with the proposed nosology of IMDs [15] and the International Classification of IMDs (ICIMD) [16]. IEMbase is the data source.

2. Classification of gastrointestinal symptoms

GI manifestations are frequent, non-specific findings in many common diseases, and their presence alone does not point toward an underlying IMD. However, the combination of metabolic manifestations accompanied by persistent and difficult-to-mitigate GI symptoms should prompt the evaluating physician to include IMD when considering differential diagnoses. GI symptoms can affect any portion of the GI tract; some symptoms are more prevalent in certain classes of IMD. The esophagus, stomach, and small and large intestines can be affected. Symptoms can also derive from the organs of the digestive tract, including the pancreas. More generalized symptoms such as feeding difficulties, vomiting, nausea, and drooling are also found. We have identified 339 IMDs associated with various types of GI involvement which we classified into seven groups according to the lesion site of the GI system (Supplemental Table S1): 1) esophagus, 2) stomach, 3) intestines, 4), pancreas, 5) feeding difficulties, 6) vomiting, and 7) other.

Feeding difficulties represent the most common abnormality reported for IMDs with GI involvement (127/339; 37%) followed by intestinal problems (103/339; 30%), vomiting (75/339; 22%), stomach and pancreas involvement (28/339; 8% each), and esophagus involvement (15/339; 4%) (Figure 1 and Supplemental Table S2). Of the GI symptoms in the ‘Other’ group, the most common are abdominal pain and nausea (17% each), dysmotility (15%), drooling and malabsorption (9% each) and macroglossia (7%) (Supplemental Table S2).

Intestinal symptoms are most seen in ‘Lipid Disorders’, ‘Carbohydrate disorders’, and ‘Peroxisomal/Oxalate disorders’, while feeding difficulties are common in ‘Disorders of nitrogen-containing compounds’, ‘Mitochondrial disorders of energy metabolism’, ‘Disorders of vitamins, cofactors, metals and minerals’, ‘Congenital disorders of glycosylation’ and ‘Metabolism of heterocyclic compounds’. Esophagus involvement was more common in ‘Storage disorders’ and stomach and pancreas involvement in ‘Lipid disorders’.

3. Specific disorder groups

3.1. Disorders of nitrogen-containing compounds

Failure to thrive is common among individuals with an IMD involving nitrogen-containing compounds. These disorders include defects of amino acid metabolism (such as urea cycle defects or branched-chain amino acidopathies) and creatine transporter deficiency. Vomiting and feeding difficulties are also commonly observed, as many affected individuals cannot tolerate protein ingestion and must follow a protein restricted diet. Chronic vomiting is a characteristic feature among branched-chain organic acidurias and urea cycle disorders in which hyperammonemia occurs. During acidotic episodes of propionic aciduria, methylmalonic aciduria, and isovaleric aciduria, competitive inhibition of N-acetylglutamate synthase (NAGS) [17, 18] (the first step in the urea cycle) by isovaleryl-CoA, which accumulates in isovaleric acidemia, or by propionyl-CoA, which accumulates in methylmalonic and propionic acidemias, leads to secondary hyperammonemia [19–22]. Some studies have also shown inhibition of carbamylphosphate synthase (CPS), the second step of the urea cycle, by propionyl-CoA [23]. Additionally, urea cycle disorders such as ornithine transcarbamylase deficiency and argininosuccinic aciduria have increased levels of ammonia due to ineffective clearance by the kidneys. In cases where acidosis is detected in an infant or child with cyclical vomiting, the possibility of an underlying organic aciduria should be investigated.

Pancreatitis can be a complication in citrin deficiency, maple syrup urine disease (types 1a, 1b, and 2), isovaleric acidemia, hydroxymethylglutaric aciduria, propionic acidemia, methylmalonic aciduria, and β-ketothiolase deficiency, disorders in which acidosis, ketosis, vomiting, and abdominal pain are common during crises of metabolic decompensation [24–26] [27]. During symptomatic episodes, amylase and lipase are typically elevated. The pathogenesis of the pancreatitis observed in organic acidurias is unclear, although theories include mitochondrial dysfunction, cellular acidosis within the pancreatic acinar cell, and oxidative damage by reactive oxygen species [28–30]. Less common GI symptoms encountered in inborn errors of metabolism involving nitrogen-containing compounds include dysphagia, gastroesophageal reflux disease, midgut malrotation, pyloric stenosis, constipation, diarrhea, and GI dysmotility.

3.2. Disorders of vitamin, cofactors, metals, and minerals

While GI symptoms are not typically hallmark presentations for disorders of lipoic acid and iron-sulfur metabolism, they are found to varying degrees. Multiple mitochondrial dysfunction syndromes may present with feeding difficulties either during the newborn period (NFU1 deficiency and BOLA3 deficiency) [31] or infancy (IBA57 deficiency and ISCA1 deficiency). Gastroesophageal reflux may occur during infancy in cases of ISCA2 deficiency. Other disorders of lipoic acid or iron-sulfur metabolism may also have feeding difficulties during the newborn period, which can continue into adulthood in the case of lipoic acid synthetase deficiency or may be combined with GERD as seen in ISD11 deficiency. Vomiting can occur across multiple age groups: during infancy (lipoyltransferase 1 deficiency), during childhood (along with hemorrhagic pancreatitis in NFS1 deficiency) or induced by exercise in childhood and adolescence (ferredoxin 2 deficiency), extending

into adulthood in ISCU deficiency, which is characteristic of this disorder [32]. In Friedreich ataxia or frataxin deficiency, sphincter control problems and swallowing difficulties may be present in adolescence and adulthood [33].

Cobalamin (vitamin B_{12}) is an essential cofactor for methylmalonyl CoA-mutase in the form of adenosylcobalamin (AdoCbl), and for methionine synthase (also known as methyltetrahydrofolate:homocysteine methyltransferase (MTR) in the form of methylcobalamin (MeCbl). CblA and cblB both result from defects in AdoCbl synthesis. Vomiting is characteristic in these disorders and presents during the neonatal period. Pancreatitis may appear later in the disease progression. Both disorders are responsive to cobalamin therapy (cyanocobalamin or hydroxocobalamin) in many, though not all patients [34] . CblC, cblD, cblF, and cblJ disorders lead to impaired synthesis of both AdoCbl and MeCbl. Failure to thrive is characteristic of these diseases, with feeding difficulties pervasive throughout life. Treatment relies not only on pharmacologic doses of hydroxocobalamin, but also on protein restriction, sometimes in combination with betaine supplementation. Deficiency of transcobalamin II, the principal transport carrier protein of Cbl, has an onset in early infancy with characteristic failure to thrive along with megaloblastic anemia. Vomiting and chronic diarrhea are additional clinical features that present during this time [35] .

Hereditary folate malabsorption due to proton-coupled folate transporter deficiency also presents clinically with severe megaloblastic anemia in the neonatal period. Diarrhea, along with failure to thrive, are also common findings [31]. Other disorders of folate metabolism, including 5,10-methylenetetrahydofolate reductase and 5,10-methenyltetrahydrofolate synthetase deficiency, may lead to feeding difficulties in newborns or infants [31].

Symptoms of biotinidase deficiency derive from the patient’s inability to reutilize biotin. Feeding difficulties, vomiting, diarrhea, glossitis, and stomatitis may be seen. Age of onset and clinical phenotype vary among individuals. This disorder is included in most newborn screening programs, as treatment with biotin is successful in the prevention and reversal of clinical features [36] .

Other inherited disorders of vitamin metabolism, including riboflavin, pyridoxine, and vitamin D metabolic defects, may see vomiting as a part of the clinical presentation. Exercise intolerance with nausea or vomiting is characteristic of mitochondrial flavin adenine dinucleotide (FAD) transporter deficiency [37], which is responsive to riboflavin supplementation. Feeding difficulties are prominent and persistent in disorders of molybdenum metabolism. These present early and are pervasive throughout life. Individuals with molybdenum cofactor deficiency (gephyrin deficiency) rarely survive past infancy [38]. Feeding difficulties are also seen in claudin 16 deficiency, a disorder of magnesium metabolism, as is failure to thrive and abdominal pain.

Diarrhea may be seen in occipital horn syndrome, a rare connective tissue disorder caused by abnormal copper transporter proteins [39]. MEDNIK (mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma) syndrome patients can also experience severe diarrhea [40] at the onset of disease. Wilson disease, one of the best described disorders of copper metabolism, may include abdominal pain and drooling as a part of the

clinical presentation, although these are not hallmark symptoms. Abdominal pain is also found in hereditary hemochromatosis types 1 and 3 (the latter also known as transferrin receptor 2 deficiency), in which iron accumulates in the patient's liver, heart, and pancreas. Acrodermatitis enteropathica, a very rare zinc deficiency, is characterized by diarrhea, along with its other clinical symptoms [41].

3.3. Disorders of carbohydrates

The most common types of inborn errors of carbohydrate metabolism are glycogen storage diseases (GSD) and inborn errors of galactose and fructose metabolism [42]. Patients with GSD with liver involvement present in infancy with a tendency toward hypoglycemia, which can be severe in fasting, and marked hepatomegaly. Symptoms are due to the inability to release glucose from the liver and severely impaired glycogenolysis and glucogenesis [42] . Patients may also have a protuberant abdomen and diarrhea, as seen in von Gierke disease (GSD 1a) and glucose-6-phosphate transporter deficiency (GSD 1b). Irritable bowel syndrome may develop in cases of GSD 1b as well.

Unsurprisingly, disorders of insulin secretion and signaling have pancreatic symptoms varying from hypoplasia in Beckwith-Wiedemann syndrome to endocrine pancreatic dysfunction in RFX6 deficiency. These disorders typically present with hyperglycemia. In the case of RFX6 deficiency, there is also pancreatic hypoplasia, intestinal atresia or malrotation, gallbladder hypoplasia or aplasia, and chronic diarrhea [43, 44] . Pancreatitis, on the other hand, is a finding in von Gierke disease (GSD 1a), glucose-6-phosphate transporter deficiency (GSD 1b), and triokinase/FMN cyclase deficiency.

Hereditary fructose intolerance, or aldolase B deficiency, is characterized by hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, and hyperalaninemia following dietary exposure to fructose, sucrose, or sorbitol. Symptoms typically occur when weaning an infant off breast milk or formula that does not contain fructose or sucrose. However, sucrose-containing formula has been implicated in at least 4 cases of multi-organ failure in patients with undiagnosed hereditary fructose intolerance [45]. Clinically, these patients present with abdominal pain, nausea, and vomiting, followed by steatorrhea and malnutrition. Lethargy, seizures, or progressive coma and/or kidney or hepatic failure can occur if not treated promptly. If a diagnosis is made prior to permanent organ injury, initiation of treatment can theoretically allow the patient to experience a normal quality of life [46, 47] . However, even when fructose intake is strictly controlled through dietary restriction, chronic fructose intoxication can occur, leading to failure to thrive and growth restriction. Additionally, the potential danger from accidental fructose ingestion remains a life-long consideration [48].

3.4. Mitochondrial disorders of energy metabolism

Primary mitochondrial disorders (PMD)) represent a group of defects of mitochondrial biogenesis or function, caused by inherited or sporadic variants in mitochondrial DNA (mtDNA) or in nuclear-encoded genes necessary for mitochondrial function, such as the enzymes of the respiratory chain. Because mitochondria are critical for cellular energy production, organ systems with a high energy demand, like the muscular and central nervous

systems, are most often affected in these diseases. However, GI symptoms are a relatively common yet often overlooked feature of many primary mitochondrial disorders, affecting approximately 15% of patients with MtDNA disease [49]. Nonspecific findings including nausea, feeding difficulties, dysphagia, gut dysmotility, gastroesophageal reflux, vomiting, constipation, and diarrhea occur as part of a constellation of symptoms affecting multiple organ systems in many mitochondrial defects [50–52]. Often beginning in childhood, these symptoms can present before other, more recognizable symptoms of mitochondrial disease are evident.

Although GI manifestations are not the primary feature of most MIDs, gut dysmotility predominates the clinical presentation in most cases of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), an autosomal recessive disorder caused by variants in the thymidine phosphorylase (*TYMP*) gene [52] that presents with ptosis, peripheral neuropathy, ophthalmoparesis, and various GI manifestations. While motility issues due to mitochondrial DNA depletion are the most frequent GI findings in MNGIE, any portion of the GI tract can be affected, leading to symptoms that range from abdominal pain and cramping to nausea, vomiting, bloating, and diverticula [52–55].Cachexia is also seen, and affected individuals tend to be extremely thin, their poor weight gain sometimes falsely attributed to anorexia nervosa [56] . Onset of symptoms can occur between early childhood and late adulthood, although most patients present before 20 years of age.

Cyclic vomiting, constipation, diarrhea, impaired gut motility, and failure to thrive are observed in Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS), a maternally inherited disorder in which mtDNA point variants are found, primarily in the tRNA-Leu gene. The most prominent presenting features in MELAS are those for which the disorder is named. A stroke-like episode occurring prior to age 40 is the hallmark, but GI symptoms are also relatively common, with chronic diarrhea occurring in 65–70% of MELAS patients [57]. Acute onset of intestinal obstruction requiring surgical intervention has been described in siblings with no prior clinical findings suggestive of mitochondrial disease [57]. Symptoms of MELAS usually begin in childhood, but late-onset cases have also been found. The severity of clinical symptoms as well as the age of onset are largely influenced by the degree of mitochondrial DNA heteroplasmy.

Ethylmalonic encephalopathy (EE) is a rare autosomal recessive mitochondrial disorder affecting multiple organ systems. CNS involvement is the most prevalent, but peripheral vasculature and the GI tract are also affected [58]. EE is caused by variants in *ETHE1* [59] , which encodes a persulfide dioxygenase involved in the mitochondrial sulfide oxidation pathway. Symptoms are typically present shortly after birth; neurologic and vascular damage is progressive, resulting in death in the first decade in many cases. An early symptom is chronic hemorrhagic diarrhea, but other characteristic features are worsening neurological symptoms that typically begin with hypotonia and seizures as well as recurrent petechial lesions and orthostatic acrocyanosis of the extremities [60]. Difficulty swallowing and failure to thrive are also found. GI microvascular damage may occur secondary to accumulation of excess sulfide or other toxic metabolites.

Leigh disease (also known as subacute necrotizing encephalopathy) describes a genetically heterogenous group of defects including mitochondrial DNA variants, nuclear-encoded components of the mitochondrial respiratory chain, Surf 1, and pyruvate dehydrogenase deficiency. More than 89 different disease genes have been identified, many in the past decade alone [61]. The most up-to-date information regarding mutations and genotype/phenotype correlation can be accessed from the so-called Leigh Map, an online resource for diagnosis of mitochondrial disease that can be found at http://vmh.uni.lu/#leighmap [62]. Leigh disease usually presents in infancy or early childhood with CNS symptoms and characteristic symmetrical findings in the basal ganglia and brain stem seen on brain imaging; adult cases are rare, but have been reported [63]. Acute respiratory failure is a frequent outcome, observed in approximately 70% of cases. Although neurological symptoms are the hallmark of the disease, GI dysfunction is common, leading to feeding difficulties, failure to thrive, vomiting, and diarrhea. A subset of patients with the so-called Leigh-like syndrome has been described with a different clinical presentation that is predominantly non-neurological, including diabetes, cardiomyopathy, renal failure, and diarrhea. The combined incidence of Leigh and Leigh-like syndrome is estimated to be about 1 in 40,000 live births [64]. Although the etiology of the GI dysfunction in Leigh syndrome is unknown, it has been postulated that the autonomic nerve supply to the GI tract could be affected by necrosis in the brain stem and spinal cord [65].

3.5. Disorders of lipids and steroids

Malabsorption, failure to thrive, abdominal pain, and pancreatitis are characteristic of disorders of lipoprotein metabolism. Chylomicron retention disease, an autosomal recessive disorder of severe fat malabsorption, is associated with failure to thrive in infancy. Malnutrition accompanied by severe diarrhea and steatorrhea is common. Patients with abetalipoproteinemia also have fat malabsorption, some resulting in clinical manifestations secondary to vitamin E deficiency [66]. Intestinal absorption of lipids is defective in this disorder, with very low serum cholesterol levels and absent serum beta lipoprotein. Recurrent acute pancreatitis is characteristic of some hypertriglyceridemias, including apolipoprotein C-II (APOC2) deficiency and lipoprotein lipase (LPL) deficiency [67] , with abdominal pain also noted on clinical exam. The abdominal pain can vary from mild to incapacitating and is usually mid-epigastric in cases of LPL deficiency. Clinically and biochemically, APOC2 deficiency resembles LPL deficiency, as APOC2 is a necessary cofactor for activation of LPL [68]. Mevalonate kinase deficiency, a disorder of sterol biosynthesis, may also present with malabsorption, abdominal pain, vomiting, and diarrhea during recurrent febrile attacks, with attacks typically occurring every 4 to 8 weeks [69].

Disorders of fatty acid oxidation can also have GI manifestations. Intermittent symptoms, most often triggered by infections, intercurrent illness, or periods of prolonged fasting, are typical of these disorders. Familial/congenital hyperinsulinism, or 3-hydroxyacyl-CoA dehydrogenase deficiency, can have a severe presentation during the neonatal period or a milder presentation during childhood. Along with hypoglycemia, the patient may exhibit poor feeding or have a sudden onset of symptoms due to decreased nutritional intake during an acute illness [51]. Feeding difficulties in infancy due to severe hypotonia at birth are observed in 3-hydroxyacyl-CoA dehydratase 1 deficiency, a disorder of fatty acid

synthesis [70]. Hypoglycemia is also seen in patients with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase deficiency, a defect of ketone metabolism. Vomiting and diarrhea may be seen during infancy and early childhood along with mild to severe bouts of gastroenteritis [71].

Steroid metabolic defects can also present with a range of GI symptoms. Episodic vomiting may be seen as early as infancy in cases of 17-alpha-hydroxylase deficiency and 11-beta-hydroxylase type 1 deficiency, forms of congenital adrenal hyperplasia, although is more common in adolescence and beyond. During times of adrenal crisis, nausea, vomiting, and abdominal pain are some of the nonspecific symptoms seen. GI disease, other infectious diseases, and stressful events may precipitate these episodes and immediate therapeutic action is required [72]. MIRAGE syndrome, a form of syndromic adrenal hypoplasia, is characterized by myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy with chronic diarrhea with colonic dilation starting in the neonatal period. This condition is often fatal, usually due to an invasive infection during the first decade of life [73]. Dysphagia may be seen in adults with X-linked spinal and bulbar muscular atrophy, also known as Kennedy disease. This disorder is usually seen in men in the third to fifth decade of life [74]. Severe and chronic intractable diarrhea, failure to thrive, and vomiting are symptoms of diacylglycerol acyltransferase deficiency, also known as congenital diarrhea type 7. Both patients reported with this disorder presented within the first week of life, and both had hyperlipidemia [75]. GI ulceration with dysfunctional platelets (GURDP) is found in cases of cytosolic phospholipase A2α deficiency [76]. Occult GI blood loss and frequent bouts of abdominal pain have been reported during childhood and adolescence. Endoscopy revealed multiple recurrent ulcerations [77].

Disorders of bile acid synthesis commonly present with neonatal cholestasis followed by diarrhea, steatorrhea, and malabsorption of the fat-soluble vitamins A, D, E and K [78]. They can be classified as primary or secondary depending on whether they directly or indirectly impact the synthesis of bile acids. One of the most common disorders is sterols 27-hydroxylase deficiency, also known as cerebrotendinous xanthomatosis (CTX), is a hereditary metabolic disorder characterized by abnormal lipid-storage and is estimated to affect 1 in 70,000 people. Adults with CTX may present with progressive neurologic dysfunction, dementia, ataxia, cataracts, and xanthomata in the brain and tendons. Children with CTX may have indications of neonatal cholestasis, diarrhea during infancy, and juvenile cataracts followed by development of neurologic symptoms and xanthomata in early adulthood (20–30 years). CTX patients have primary enzymatic defects resulting in significantly decreased bile acid synthesis. Other indications of CTX include abnormal elevations in cholestanol, low plasma cholesterol concentration, with deposition of cholesterol and cholestanol in the tissues; increased biliary, urinary, and fecal excretion of bile alcohol glucuronides. The common gastrointestinal symptoms found in bile acids biosynthesis disorders are due to the reduced capability to properly digest and breakdown and absorb lipid macromolecules in the digestive system, leading to a decrease in the stool consistency. This produces diarrhea and a metabolic deficiency of liposoluble compounds due to decreased bioavailability from lack of absorption [78, 79].

3.6 Storage disorders

Lysosomal storage disorders (LSD) are a group of more than 50 inherited defects caused by deficiencies of lysosomal hydrolases or other proteins and enzymes integral to lysosomal function. The majority are inherited in an autosomal recessive manner. In lysosomal enzyme defects, there is a resultant accumulation of the macromolecular substrates of the blocked metabolic steps in the late endosome. LSDs can be further classified based on the chemical nature of their storage products or the nature of the defective protein (for example as sphingolipidoses, mucopolysaccharidoses, glycoproteinoses, neuronal ceroid lipofuscinoses, membrane and transport defects, etc.) [80]. The main organ systems affected by LSDs are the central nervous system, the skeletal system, and the heart. However, GI symptoms are frequently observed in certain LSDs. In Fabry disease, abdominal pain, bloating, diarrhea, nausea, vomiting, and constipation are found in more than half of adult and pediatric patients; these nonspecific GI findings can be among the first clinical symptoms, but diagnosis can be delayed because of overlap with more common disorders such as irritable bowel syndrome [81]. Chronic intestinal pseudo-obstruction (CIPO) is also found in Fabry disease [82] and can significantly affect quality of life. Abdominal pain and diarrhea are the GI symptoms observed most often and occur more frequently in males than in females [83]. In the mucopolysaccharidoses, particularly MPS I and MPS III, GI symptoms can include frequent diarrhea [84, 85]. Other GI findings have also been reported in MPS III patients, including constipation, dysphagia, feeding difficulties, malabsorption, pseudo-obstruction, and ulcerative colitis [86].

3.7. Disorders of peroxisomes

Peroxisomal defects comprise a group of inherited disorders, classified as either defects of peroxisome biogenesis or peroxisome function. In disorders of peroxisome biogenesis, such as Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD), genetic defects in peroxins, proteins encoded by various PEX genes, impair the normal assembly and function of the peroxisome, with a corresponding deficiency of multiple peroxisomal enzymes. Peroxisomes play a role in fatty acid beta oxidation (analogous to the mitochondrial fatty acid oxidative spiral), alpha-oxidation, biosynthesis of etherphospholipids and isoprenoids; they are also involved in fatty acid and bile acid synthesis. Disorders of single peroxisomal enzymes or transporters are also found, and include X-linked adrenoleukodystrophy, 2-methylacyl-CoA racemase deficiency, and Refsum disease. The clinical phenotypes in single enzyme or transporter defects are generally milder than in those disorders where peroxisomes are reduced or absent. Although there is considerable phenotypic variability and severity, peroxisome biogenesis disorders (PBD) typically present with neurological symptoms such as hypotonia and seizures, and affected individuals often have characteristic craniofacial dysmorphic features. In contrast to the typical presentation of PBD, GI symptoms may predominate in early infancy in Infantile Refsum disease (IRD), with diarrhea, steatorrhea, vomiting, and malabsorption. The laboratory findings of hypocholesterolemia and retinitis pigmentosa may falsely suggest a diagnosis of abetalipoproteinemia [87–89]. In X-linked adrenoleukodystrophy (X-ALD) and its adult-onset form X-linked adrenomyeloneuropahy (X-AMN), defects of the ABCD1 peroxisomal transporter which imports very long chain fatty acids and their coenzyme-A esters into the peroxisome, the nervous system and the adrenal glands are

primarily affected. However, neurogenic disturbances resulting in loss of sphincter control are prevalent in affected males as well as in carrier females, with urinary and bowel symptoms occurring before other myelopathic symptoms in about half of patients. Although the sphincter dysfunction is more commonly urinary [90–92], resulting in urinary urgency and incontinence, fecal urgency, fecal incontinence, constipation and diarrhea are also common. In one study of adult X-ALD patients, 67% of patients, regardless of gender, experienced at least one bowel symptom [93]. Together, the urinary and bowel symptoms have a significant effect on patient quality of life.

3.8 Congenital disorders of glycosylation

Congenital disorders of glycosylation (CDG) are a rapidly expanding group of over 170 inherited metabolic disorders affecting the addition of glycan to proteins and lipids. This glycosylation occurs in a complex, stepwise fashion in the endoplasmic reticulum, Golgi apparatus, cytosol and sarcolemmal membrane. Previously, the CDG naming convention was based on its type. CDG Type I were found to have defects in the assembly or transfer of the dolichol-linked glycan, and CDG Type II included defects in the glycan moiety itself. However, there are other types of CDG relating to glycosylphosphatidyl inositol (GPI) anchor protein glycosylation, disorders of O-mannosylation, and deglycosylation defects. As this is a large group of rare disorders that is continually evolving, the nomenclature has been updated to include the gene involved followed by the acronym CDG. The previously denoted CDG type Ia is, therefore, now known as PMM2-CDG [94].

Almost all types of CDG present in infancy, although there are some with milder clinical presentations that are not diagnosed until later in life. Because multiple biological systems can be affected by incorrect synthesis of glycoproteins and glycolipids, there is a broad spectrum of clinical manifestations including, but not limited to, failure to thrive, developmental delay, hepatopathy, hypotonia/neurologic manifestations, hypoglycemia, protein-losing enteropathy, immunologic findings, abnormalities of the skin or eyes, and skeletal findings. For infants and children, GI involvement may involve chronic diarrhea, protein-losing enteropathy, failure to thrive, gastroesophageal reflux, ascites, liver failure, and portal hypertension [95].

3.9 Metabolism of heterocyclic compounds

3.9.1 Disorders of tetrapyrroles—The acute hepatic porphyrias, inborn errors of heme metabolism, result from deficiencies in one of several enzymes involved in heme biosynthesis. Although inherited in an autosomal dominant manner, these disorders often remain latent until an aggravating factor, such as alcohol, drugs, illness, or hormonal changes, affect the body’s requirement for heme. Three acute hepatic porphyrias, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), have similar clinical presentations, but AIP is the most common. Acute abdominal pain lasting from a few days to weeks is the hallmark presentation and is seen in up to 95% of cases. It is usually accompanied by other GI complaints such as nausea, vomiting, abdominal distention and guarding, diarrhea or constipation [96, 97]. In the quiescent phase between acute attacks, patients are usually clinically asymptomatic.

3.9.2. Disorders of nucleotide and nucleic acid metabolism—Familial dysautonomia (FD), or Riley-Day syndrome, is an inherited autonomic and sensory neuropathy most often seen in individuals with Ashkenazi Jewish ancestry due to a founder variant in the elongator complex protein 1 (*ELP1*) gene. The elongator complex consists of 6 subunits grouped into two 3-subunit subcomplexes and is involved in various modifications of tRNA. The main clinical presentation of the disorder is with blood pressure instability and decreased sensitivity to pain and temperature. However, GI symptoms are often observed. Vomiting due to severe nausea occurs during a dysautonomic crisis along with rapid heart rate, increased blood pressure, sweating, and blotching of the skin; these crises occur with a periodicity that is patient specific. Gastroesophageal reflux (GER) occurs due to peripheral autonomic dysfunction [98, 99]. Other common symptoms connected to the GI tract include constipation and bloating, with swallowing difficulties, pain, incontinence, and diarrhea reported less frequently.

Aicardi-Goutieres syndrome (AGS) is a clinically and genetically heterogeneous inherited leukodystrophy that results in progressive encephalopathy with basal ganglia calcifications, abnormalities of the white matter, and chronic lymphocytosis in the CSF. In most cases, the encephalopathic phase persists for several months, after which disease progression is relatively stable. In addition to encephalopathy, acquired microcephaly, spasticity, and chilblain-like lesions, feeding difficulties are common. These can include gastroesophageal reflux, vomiting dysphagia, and problems with chewing, and in some cases require naso-gastric tube feeding [100, 101]..

4 Diagnosis and differential diagnosis

The differential diagnosis of IMDs in patients with significant GI symptoms must take the metabolic manifestations into consideration first and foremost. A well-structured laboratory assessment algorithm that utilizes both routine and specialized testing can help to narrow down a potential diagnosis. A listing of laboratory tests that may be useful in ruling out an underlying IMD is summarized in Table 1. In some disorders, no abnormal body fluid metabolites have been identified to aid in diagnosis, although advances in untargeted metabolomics and lipidomics are accelerating the discovery of potential biomarkers for many IMDs. In disorders where metabolite testing is uninformative, diagnosis relies on molecular analysis as well as a thorough clinical history to identify characteristic presenting features. The diagnosis of an underlying IMD can be difficult on account of the number of different inherited disorders described to date and their wide range of non-specific clinical symptoms. Importantly, patient stabilization during any episode of acute metabolic decompensation should be undertaken even before a specific diagnosis is made.

5 Treatment

The treatment of IMDs should be carried out in a multidisciplinary approach taking into consideration all aspects of the diseases such as the nature of the metabolic derangement, potential accumulating substances and how to facilitate their excretion while at the same time addressing any potential associated metabolite deficiency. Management of IMDs has two goals: treatment of episodes of metabolic decompensation as well a long-term

maintenance regimen. Nutrition management to allow for proper growth and development while simultaneously preventing acute episodes is key. In addition, the GI and any other accompanying clinical manifestations should be addressed and mitigated separately, as some may persist even in well-controlled and stabilized patients. The treatment for individual disorders leading to GI manifestations can be found in Supplemental Table S2.

6 Conclusion

IMDs can have a wide spectrum of clinical manifestations that affect multiple organic systems, and GI symptoms are frequently observed. Although most metabolic disorders present in infancy or childhood, advanced patient age should not be used as a justification to exclude these disorders from the differential diagnosis. Late onset cases of many IMDs have been described, often with a significant delay in diagnosis that can affect quality of life. Therefore, this category of disorders should always be considered when a patient's presenting GI symptoms cannot be explained by more common diseases or conditions, regardless of age. The full list of GI symptoms can be freely accessed at http://www.iembase.org/gamuts, and will be curated and updated on a regular basis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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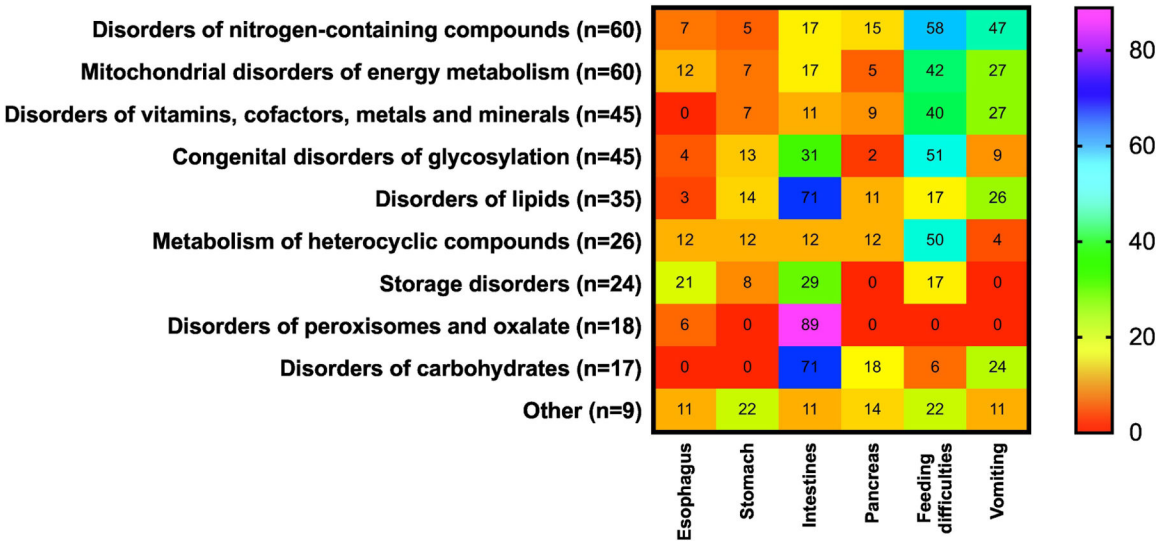

Figure 1.

Occurrence (%) of symptoms associated with disorders presenting with GI symptoms in 6 categories of IMDs. The percentages for GI symptoms were calculated using as the denominator the total number of IMDs in each category presenting with any GI phenotype. Heat scale ranges from red (0%) for diseases with no particular symptoms reported to violet (100%) for diseases with particular symptoms occurring with high frequency within the disorders group. For definition of 6 categories of disorders affecting the GI tract, see Supplemental Table S2. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

Table 1.

Biochemical investigations in IMDs presenting with GI phenotype.

Basic tests	Profiles	Special tests
Blood count	Amino acids (P,U)	Copper (S,U)
ASAT/ALAT (P)	Organic acids (U)	Ceruloplasmin (S)
CK (P)	Acylcarnitines (DBS, P)	Zinc (S)
ALP (P)	Purines and pyrimidines (U, P)	Lysosomal enzymes (S)
Lactate (P)	Sialotransferins (S)	Vitamin B12/A/D/E (S)
Glucose (P)	Oligosaccharides (U)	Glutathione (RBC)
Ammonia (B)	Lipid panel (S)	5-Methyl-THF (CSF)
Bilirubin (P)	Pterins (CSF)	Oxalic acid (U, P)
Calcium (P)	Plasmalogens (RBC)	Interferon signature (B)
Magnesium (P)		IgE (S), IgG (S), IgA (S), IgM (S)
Coagulation factors		