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Endocrine system disturbances in children with inherited metabolic diseases: a narrative review

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Inborn metabolic diseases (IMDs) represent a diverse and complex group of rare disorders, typically resulting from variants in genes that encode specific enzymes or cofactors, leading to reduced or absent enzymatic activity. These conditions commonly disrupt one or more metabolic pathways, often impacting multiple organ systems from early childhood. Clinicians should consider the possibility of an IMD when an endocrine abnormality is accompanied by other unexplained clinical signs or in presence of combined endocrinopathies. While some IMDs associated with endocrine dysfunction in children and adolescents are well-documented and supported by established treatment guidelines, others lack clear recommendations or are characterized by inconsistent data. This narrative review aims to summarize the main IMDs that present with endocrine abnormalities in pediatric patients, organized according to affected organ systems and underlying pathophysiological mechanisms. Furthermore, we reviewed the latest recommendations, when available, for monitoring endocrine function in children with these disorders and eventually for providing a tailored treatment, where applicable.

KEYWORDS

adrenal glands, children, endocrine system, gonads, inherited metabolic diseases, pancreas, pituitary gland, thyroid

1 Introduction

Inborn metabolic diseases (IMDs) are a large and heterogeneous group of rare disorders, usually caused by variants in genes encoding specific enzymes or cofactors, leading to an impairment of their activity (1). Since each of these diseases is due to the dysfunction of one or more metabolic pathways, they often affect multiple organs since childhood, although a single endocrinopathy may also occur (2). Figure 1 illustrates the main endocrine systems and organs involved in IMDs.

IMDs should be suspected particularly in children presenting with combined endocrinopathies. Mitochondrial diseases are a typical example of IMDs with frequently reported combined endocrinopathies (3, 4).

The suspicion of an inherited metabolic disease should arise even in case of an endocrinopathy associated with other clinical features which are not explained by the endocrinopathy itself. For instance, diabetes mellitus has been described in several IMDs, such as hemochromatosis, aceruloplasminemia, mitochondrial diseases, and GSD type I and III (3, 5–8). Therefore, even in case of a common endocrine disorder in pediatric patients, a complete clinical examination and critical evaluation of blood and, when appropriate, radiological studies should be performed. In the presence of clinical, radiological, or biochemical findings that are not typical of the diagnosed endocrinological pathology, the appropriate investigations should be carried out in a multidisciplinary context to exclude an underlying rare disease.

While for some IMDs the endocrine system disturbances in children or adolescents are extensively described in the literature, together with

well-defined treatment guidelines, for others data remain controversial or clear management recommendations are lacking.

In this narrative review we specifically address the following research question: which endocrine manifestations are associated with IMDs, and through which underlying pathophysiological mechanism? Therefore, our first aim is to provide an overview of the main IMDs described with a primary endocrine impairment from childhood or adolescence, exploring the underlying pathogenetic mechanisms by organ. Our second aim is to explore the most recent available recommendations for monitoring endocrine organ function in children with these diseases, together with the specific treatments, where applicable.

To the best of our knowledge, this is the first comprehensive overview of the most commonly reported endocrine manifestations of IMDs in children, as well as the available recommendations for their management in the pediatric population.

2 Methods

We conducted a narrative review to explore the main IMDs with reported primary endocrine involvement manifesting in children and adolescents, as well as their follow-up and management. We performed a comprehensive literature search using the PubMed (Medline) and Scopus databases, covering articles published in English between 2000 and 2025. Inclusion criteria were: original research articles, systematic and narrative reviews, guidelines, case reports, and case series describing endocrine involvement in pediatric IMDs; IMDs with

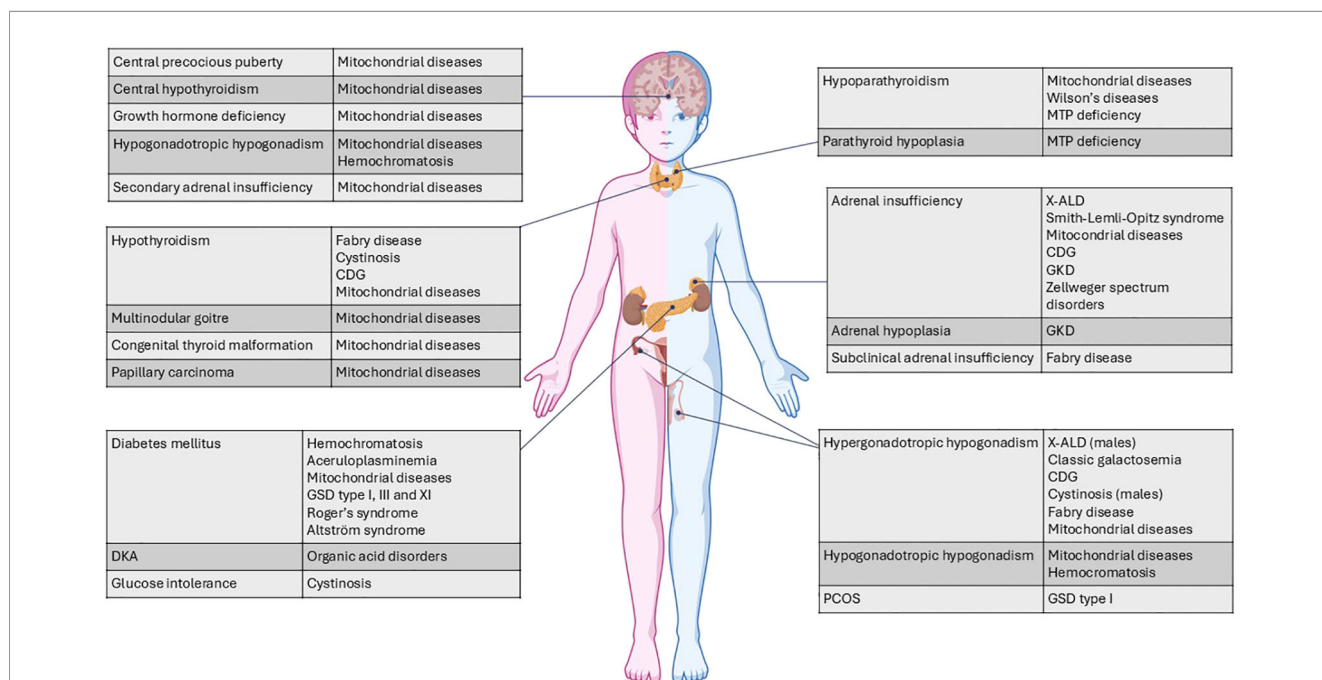


FIGURE 1
Main endocrine systems and organs involved in IMDs and relative clinical manifestations. CDG, congenital disorders of glycosylation; DKA, diabetic ketoacidosis; MTP, mitochondrial trifunctional protein; X-ALD, X-linked adrenoleukodystrophy; GKD, glycerol kinase deficiency; PCOS, polycystic ovary syndrome; POI, premature ovarian insufficiency; GSD, glycogen storage disease. This figure was created using BioRender.com.

documented primary endocrine manifestations (direct effect on endocrine organs). Although the primary focus is on the pediatric population, in a few IMDs we cite evidence derived from adult cohorts only when pediatric data were not available, and these instances are clearly indicated in the text.

Search strategy

As research strategy, we used the following keywords: “inherited metabolic diseases”, “inborn errors of metabolism”, “disorders of fatty acid metabolism”, “disorders of amino acid metabolism”, “disorders of carbohydrate metabolism”, “lysosomal storage disorders”, “congenital disorders of glycosylation”, “mitochondrial diseases”, “organic acidurias”, “disorders of metal metabolism”, “urea cycle disorders”. These were combined with the terms “endocrine system”, “thyroid gland”, “parathyroid glands”, “gonads”, “adrenal glands”, “pancreas”, “pituitary gland” and “etiopathogenesis” for our first aim, or with “management”, “treatment”, “follow-up” for our second aim.

Starting from a total of 312 papers, 71 were excluded after an initial screening based on titles and abstracts. The full texts of the remaining articles were then reviewed, and 147 relevant papers were selected for detailed analysis and critical discussion. References from all selected articles were also checked for additional relevant studies.

A flow diagram illustrating the process of paper selection and exclusion is presented in Figure 2.

3 Results

3.1 Thyroid gland

Thyroid gland function may be impaired in several IMDs, through different pathogenetic mechanisms (Table 1).

Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by variants in the *GLA* gene leading to reduced activity of the encoded lysosomal enzyme alfa-galactosidase A. Consequently, glycosphingolipids (in particular, globotriaosylceramide [Gb3] and globotriaosylsphingosine [lyso-Gb3]) accumulate in lysosomes causing diffuse organ damage. In FD, endocrine organs such as the thyroid gland are among the targets for glycosphingolipid accumulations due to their high vascularization and low proliferation rate. However, the underlying pathophysiology of hypothyroidism observed in patients with FD remains unclear, since it is not known whether these accumulations are responsible for thyroid dysfunction (9, 10). Although no specific follow-up guidelines exist, the relatively high incidence of subclinical hypothyroidism supports regular thyroid function screening from childhood, with initiation of levothyroxine replacement when dysfunction is detected (9, 10). Results from the observational study by Faggiano et al. (2011), conducted on 14 FD patients (7 females, 7 males) aged 21–62 years, suggest that primary hypothyroidism in FD patients may be reversed after long-term enzyme replacement therapy (ERT) (11).

Cystinosis is a rare hereditary disorder resulting from variants in the *CTNS* gene. This gene encodes the carrier protein cystinosis, responsible for transporting cystine out of lysosomes. Defective cystinosis function leads to widespread accumulation of cystine crystals in all body cells and tissues, including the thyroid gland. Progressive storage of cystine in thyroid follicular cells results in fibrosis and atrophy, leading to primary hypothyroidism (12). This endocrine condition affects the majority of patients with cystinosis by the second decade of life (12). Early thyroid changes affecting thyroglobulin synthesis and iodothyroglobulin processing may cause subclinical hypothyroidism, characterized by elevated TSH and normal T3 and T4 levels. Hormone replacement therapy is

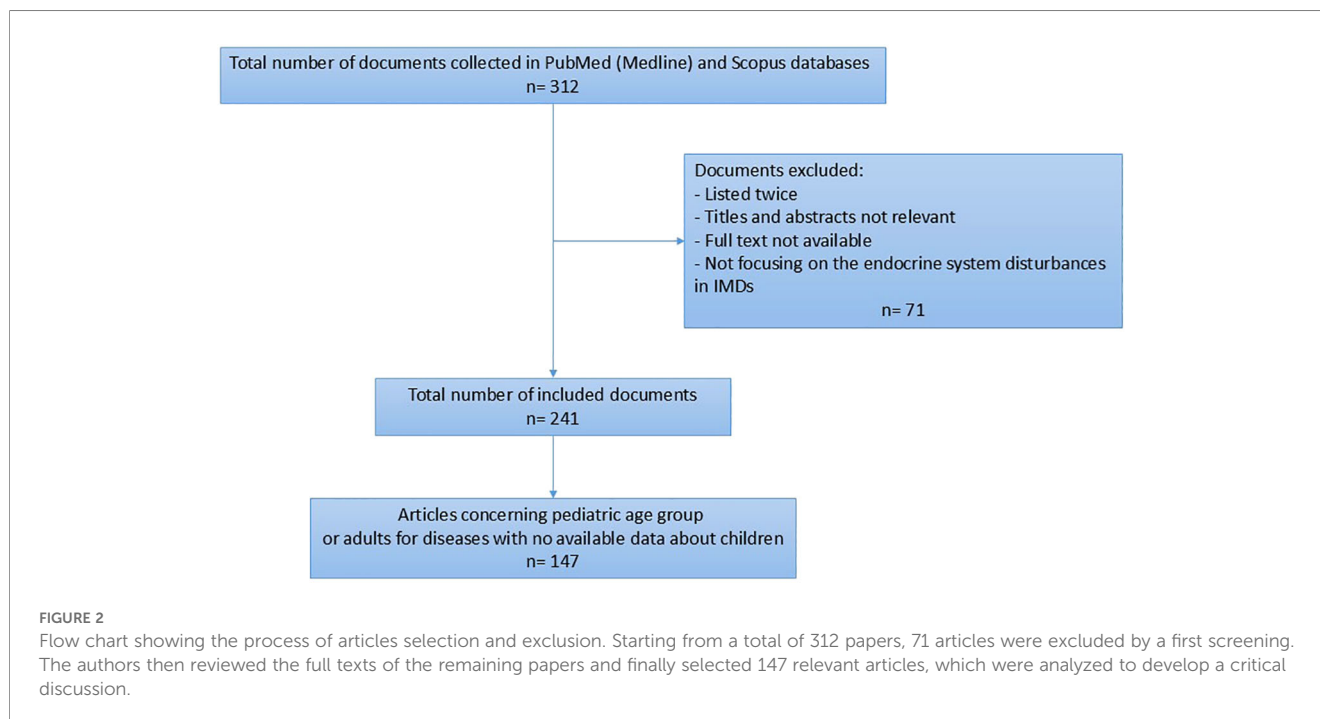


TABLE 1 Reported involvement of the thyroid gland in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
Fabry disease	Primary hypothyroidism (9, 10)	Regular TSH monitoring since childhood (9)	Hormonal replacement (9) Enzyme Replacement Therapy
Cystinosis	Primary hypothyroidism (12–14, 16)	Regular TSH monitoring since early childhood (14, 16)	Hormonal replacement (14, 15) Cysteamine
CDG	Hypothyroidism (17, 18)	Regular TSH and FT4 assessment every six months during the first two years of life and annually thereafter (17, 18) and in critical circumstances (hypoalbuminemia, sepsis, protein-losing enteropathy, etc.) (17, 20)	Thyroid hormone replacement treatment in case of decreased FT4 levels combined with altered TSH levels (17, 18, 20).
Mitochondrial diseases	Primary hypothyroidism (mtDNA) (21–24) (3, 134) Multinodular goitre, congenital thyroid malformation and papillary carcinoma (KSS) (22)	Thyroid function monitoring since childhood (21)	No specific recommendations available

IMD, inherited metabolic disease; CDG, congenital disorders of glycosylation; mtDNA, mitochondrial DNA; KSS, Kearns-Sayre syndrome; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

crucial for managing hypothyroidism in cystinosis; therefore, careful monitoring of thyroid function is mandatory in patients with this disease. Since hypothyroidism may manifest during the first years of life (13), thyroid function monitoring is recommended from early childhood (14). Although levothyroxine dosing guidelines are not available, treatment is generally required (14, 15). The disease-specific treatment, aminothioliol cysteamine, acts by depleting lysosomal cystine, thereby also reducing the need for thyroid hormone replacement therapy (12, 14, 16).

Congenital disorders of glycosylation (CDG) are a group of rare genetic disorders that include defects in synthetic pathways for N-linked oligosaccharides, O-linked oligosaccharides, shared substrates, glycoposphatidylinositol (GPI) anchors, and dolichols. They are characterized by abnormal glycosylation, resulting in multisystem involvement and a heterogeneous clinical presentation (17). Glycosylation is a crucial process in the synthesis and function of various proteins, including those involved in thyroid hormone production and regulation. It has been postulated that disruptions in glycosylation processes may potentially affect thyroid-related proteins and pathways (18). Structural and functional alterations of glycosylated proteins in CDG individuals can make assessment of thyroid function challenging. However, despite decreased thyroid hormone levels, TSH levels are often reported to be normal (19). Clinical symptoms of hypothyroidism might resemble more severe CDG symptoms, especially during acute metabolic decompensation (18). Despite the challenges, early identification and treatment of thyroid dysfunction remain fundamental (20). Therefore, assessing thyroid function, even in critical circumstances, is reasonable, keeping in mind that an euthyroid sick syndrome may coexist. TSH and FT4 levels should be measured regularly, and thyroid hormone replacement therapy should be considered in case of altered values (17, 18, 20).

Mitochondrial diseases constitute a clinically heterogeneous group of disorders that impact mitochondrial function. A significant association between mitochondrial diseases and thyroid dysfunction has been observed, particularly in specific

mitochondrial disorders (3). For example, mitochondrial DNA (mtDNA) deletion disorders, including Kearns-Sayre syndrome (KSS) and polymerase γ (POLG)-related mtDNA depletion syndrome, may present with hypothyroidism (3, 21–23). In KSS, thyroid dysfunction is reported in around 3% of cases, encompassing diverse thyroid abnormalities such as compensated hypothyroidism, multinodular goitre, congenital thyroid malformation, and papillary carcinoma (22). mtDNA depletion disorders, such as POLG-related mtDNA depletion syndrome, have been linked to a broader spectrum of endocrinopathies, including hypothyroidism, adrenal insufficiency, and diabetes (3, 24). While no curative treatment is available, addressing treatable aspects of associated endocrine dysfunctions holds the potential to improve patients' outcomes. For this reason, a comprehensive follow-up strategy, including routine screening for thyroid function and target treatment, is imperative (3), although no specific guidelines are available in this regard.

Overall, despite the heterogeneity of underlying mechanisms, these pediatric IMDs share common challenges, including limited understanding of pathophysiology, lack of standardized screening protocols, and scarcity of pediatric-specific treatment guidelines. Addressing these gaps through focused clinical studies and longitudinal research is essential to optimize early detection, monitoring, and management of endocrine dysfunction in children with IMDs.

3.2 Parathyroid glands

Parathyroid glands dysfunction, particularly hypoparathyroidism, has been described in patients with IMDs (Table 2).

Hypoparathyroidism is notably observed in mitochondrial diseases, especially in severely affected individuals who show multisystemic involvement manifesting during childhood (3, 21). For example, in KSS, approximately 6% of cases exhibit hypoparathyroidism, often accompanied by concurrent renal

TABLE 2 Reported involvement of the parathyroid glands in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
Mitochondrial diseases	Hypoparathyroidism (KSS) (3, 21, 22)	Parathyroid hormone, calcium, magnesium and phosphate ions regular monitoring since childhood (3)	Vitamin D and calcium supplementations (21)
Wilson's disease	Hypoparathyroidism (29–32)	No recommendations available	No specific recommendations available
MTP deficiency	Hypoparathyroidism (33–36) Parathyroid hypoplasia (36)	Periodic assessment of blood calcium, phosphorus, and parathyroid hormone levels since the first months of age (33, 34)	No recommendations available

IMD, inherited metabolic disease; MTP, mitochondrial trifunctional protein; KSS, Kearns-Sayre syndrome.

tubulopathy leading to imbalances in calcium, magnesium, and potassium (22). In mitochondrial diseases, hypoparathyroidism is frequently associated with additional endocrine abnormalities such as diabetes mellitus, short stature, and gonadal dysfunction (22).

In mitochondrial diseases, including KSS, hypoparathyroidism is thought to result from a combination of renal tubular electrolyte losses and direct mitochondrial dysfunction in parathyroid cells, leading to impaired energy-dependent PTH secretion (21, 25, 26). Despite magnesium supplementation, low PTH concentrations may persist (26, 27). Although no specific guidelines are available, these evidence suggest that regular assessment of blood PTH, calcium, magnesium and phosphate levels from childhood, along with supplementation with vitamin D and calcium when needed, may help prevent hypoparathyroidism and its complications in these children (3, 21).

Wilson's disease is a genetic disorder caused by variants in the *ATP7B* gene, located on chromosome 13. These variants lead to impaired copper excretion from the liver into bile and defective incorporation of copper into ceruloplasmin, the protein responsible for copper transport in the blood (28).

The pathogenesis of hypoparathyroidism in Wilson's disease involves the toxic effects of excess copper deposition in various tissues (28). Wilson's disease primarily causes copper accumulation in the liver, brain, kidneys, and other organs, but some authors have reported that excess copper may also be present in the parathyroid glands, particularly in children during the second decade of life and in young adults (29–32). According to the literature, copper deposition in the parathyroid glands may result in parenchymal degeneration, as observed in post-mortem examinations (30). This degeneration of parathyroid tissue may be analogous to iron deposition observed in thalassemia, which leads to granular involution. In Wilson's disease, excess copper can cause hemolytic anemia through inhibition of red blood cell enzymes, and the resulting vascular and parenchymal changes may further impair parathyroid function (30). This process leads to hypoparathyroidism with secondary hypocalcemia, low serum magnesium levels, elevated serum phosphorus, and absent or inappropriately low levels of PTH (31, 32). Further studies and long-term evaluations are needed to determine the reversibility of hypoparathyroidism in Wilson's disease and the potential impact of therapeutic interventions, given the intricate relationship between copper deposition and parathyroid function (30). While calcium

supplementation has been reported to be effective in children and young adults (31, 32), no data are currently available on the effects of copper chelators on parathyroid function.

Mitochondrial trifunctional protein (MTP) is a hetero-octamer composed of four α - and four β -subunits and carries out three distinct enzyme activities that catalyze the final chain-shortening reactions in the β -oxidation of long-chain fatty acids. The *HADHA* gene encodes the α -subunit, which is involved in both long-chain enoyl-CoA hydratase (LCEH) and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) activities, whereas the *HADHB* gene encodes the β -subunit, involved in the Long-chain 3-ketoacyl-CoA thiolase (LCKAT) activity. Variants in *HADHA* or *HADHB* cause MTP deficiency, resulting in decreased activity and levels of all three enzymes because of failed hetero-octamer formation. However, a homozygous variant (1528G>C) in *HADHA* has been reported to cause isolated LCHAD deficiency. Hypoparathyroidism has been reported in four children with MTP deficiency (33–35) and in one child with isolated LCHAD deficiency (36), all manifesting within the first 15 months of life.

The pathogenetic link between MTP deficiency and hypoparathyroidism remains unclear and seems to involve several complex factors. MTP deficiency disrupts the oxidation of long-chain fatty acids within mitochondria, leading to the accumulation of toxic compounds that may affect various tissues, including the parathyroid glands. The resulting mitochondrial dysfunction impacts cellular processes, potentially influencing the secretion of PTH (37). However, hypoparathyroidism has not been reported in other patients with the most common mitochondrial β -oxidation defects, such as carnitine palmitoyl transferase II (CPTII) deficiency and very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD) (34). Another possible explanation for hypoparathyroidism in MTP deficiency is the presence of congenital parathyroid malformations, particularly hypoplasia, which have been described in patients with LCHAD deficiency (36). Although there are no clear guidelines regarding the clinical management of hypoparathyroidism in patients with MTP defects, the available case reports suggest that these patients require periodic evaluation of blood calcium, phosphorus, and PTH levels. A multidisciplinary approach, involving both metabolic and endocrine specialists, is essential to tailor therapy and ensure optimal monitoring (33, 34).

Despite these reports, significant gaps remain in understanding the precise mechanisms linking IMDs to hypoparathyroidism, as well as

the natural history and long-term outcomes of affected children. Further research is needed to clarify disease-specific pathophysiology, assess potential reversibility with treatment, and establish evidence-based monitoring and management protocols for pediatric patients.

3.3 Gonads

Gonadal involvement in metabolic diseases is heterogeneous. The most frequent clinical patterns are characterized by hypogonadism with reduced fertility, ambiguous genitalia, or polycystic ovarian syndrome (PCOS) (Table 3).

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by variants in the *ABCD1* gene, leading to impaired cellular trafficking of very-long-chain fatty acids (VLCFA) (38). Although rare, male patients with X-ALD may present with hypogonadism with normal or reduced testosterone and elevated luteinizing hormone (LH) levels, likely due to VLCFA

toxicity on testicular Sertoli and Leydig cells and potential androgen receptor resistance (39–41). Fertility reduction is uncommon, with only a few cases of declining fertility reported (39, 42, 43). Testosterone replacement therapy should be considered for X-ALD males with clinical signs of hypogonadism and low testosterone levels (39).

Most females with classic galactosemia, even with early diagnosis and good compliance to a lifelong galactose-restricted diet, develop premature ovarian insufficiency (POI), manifesting as delayed puberty, amenorrhea or oligomenorrhea, and infertility (44, 45). These complications are not observed in Duarte variant galactosemia (46). The likely underlying pathogenesis involves altered ovarian granulosa cell function and reduced anti-mullerian hormone (AMH) levels (45), possibly beginning in the prenatal period. International guidelines recommend screening for hypergonadotropic hypogonadism in girls lacking secondary sexual characteristics by the age of 12, or experiencing primary amenorrhea by the age of 14, measuring follicle-stimulating

TABLE 3 Reported involvement of the gonads and reproductive system in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
X-ALD	Hypergonadotropic hypogonadism with normal or reduced testosterone (39–41)	No recommendations available	Testosterone replacement therapy for X-ALD males with hypogonadism signs and low testosterone (39)
Classic galactosemia	Hypergonadotropic hypogonadism in females (44, 45)	Follicle-stimulating hormone and 17-beta-estradiol assessment in girls who reach the age of 12 years with insufficient secondary sex characteristics or the age of 14 years with no regular menses (47) In women with normal pubertal development monitor for POI symptoms, with possible FSH testing (47)	In case of hypergonadotropic hypogonadism puberty induction involving step-wise escalating doses of estrogen and cyclic progesterone administration (47) Hormone replacement therapy in cases of secondary amenorrhea (47)
CDG	Hypergonadotropic hypogonadism (52)	No recommendations available	No recommendations available
Cystinosis	Pubertal delay and hypergonadotropic hypogonadism in males Pubertal delay with normal gonadal function in females (53–55)	Six-monthly assessments of growth, pubertal stage, and bone age in prepubertal males Regular assessment of LH, FSH, testosterone, inhibin B, spermiogram and testicular ultrasound in pubertal males Appropriate pre-pregnancy counselling, with assessment of thyroid function and glucose tolerance in female (53, 54)	In case of hypogonadism referral to a specialist for consideration of fertility preservation therapies In pregnant females treatments to reduce the risk of complications (e.g., acetylsalicylic acid), peripartum and postpartum respiratory support (53, 54) Cysteamine
Fabry disease	Altered LH and SHBG levels in males, menstrual abnormalities in females (10, 56) Infertility debated	Clinical monitoring, annual in boys, every 2–3 years in girls (59)	No recommendations available Enzyme Replacement Therapy
GSD type I	PCOS, dysmenorrhea and menorrhagia in girls (61, 62, 64)	Regular gynecological evaluations and specific questions about the occurrence of menorrhagia or irregular menstrual bleeding (62). In case of menorrhagia, coagulation assessment and referral to a gynecologist or hematologist (64)	For menorrhagia: diet, hemostatic therapies (65, 66), hormonal treatment (67, 68), surgery (64). For PCOS: diet intervention to reduce insulin resistance and hormonal treatments (60, 63).
Mitochondrial diseases	POI (Perrault syndrome, AARS2) Hypogonadotropic hypogonadism (mtDNA, MNGIE, primary coenzyme Q10 deficiency, Leigh syndrome) (3)	No recommendations available	No recommendations available

IMD, inherited metabolic disease; X-ALD, X-linked adrenoleukodystrophy; CDG, congenital disorders of glycosylation; GSD, glycogen storage disease; mtDNA, mitochondrial DNA; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; PCOS, polycystic ovary syndrome; POI, premature ovarian insufficiency.

hormone (FSH), LH and 17-beta-estradiol levels (47). If hypergonadotropic hypogonadism is diagnosed, prompt referral to a pediatric endocrinologist is recommended for puberty induction using stepwise escalating doses of estrogen and cyclic progesterone administration (47). Girls with normal pubertal development should be monitored for POI symptoms, with FSH, LH, and estradiol testing as needed. Hormone replacement therapy should be initiated in cases of amenorrhea due to POI (47). Fertility preservation techniques are not routinely indicated and require individual consideration (48). In contrast, most male patients generally do not exhibit fertility issues, and routine endocrinological follow-up is generally unnecessary (47). Possible explanations for the more severe impact on females reproduction include: higher *GALT* mRNA expression in ovary and liver versus lower in testis, suggesting organ-specific vulnerability (49, 50); the ability of male testes to replenish spermatogonia lost to apoptosis, unlike females; and limited effect of LH hypoglycosylation on male reproductive function and lower reliance on FSH activity (49, 51).

Phosphomannomutase 2 deficiency (PMM2-CDG) may also lead to hypogonadism, as glycosylation is crucial for both spermatogenesis and oogenesis (52). However, literature on this topic is limited, and no standardized follow-up or treatment protocol exist.

Cystinosis can impair gonadal function as well. Males often show low testosterone, elevated FSH and LH, pubertal delay, and azoospermia. Conversely, females typically experience pubertal delay but maintain normal gonadal function, though they have increased risk of pregnancy complications, including pre-eclampsia, preterm delivery, and gestational diabetes (53–55). Prepubertal males should undergo six-monthly assessments of growth, pubertal stage, and bone age. Pubertal males should also have additional evaluations including LH, FSH, testosterone, inhibin B, AMH, and potentially a spermogram and testicular ultrasound. Early detection of hypogonadism and pubertal delay requires referral for fertility preservation (53, 54).

Gonadal involvement in Fabry disease remains controversial. Some authors report azoospermia and infertility in males (9), while others describe alterations in sex hormone-binding globulin (SHBG) and LH in patients with chronic kidney disease (56). In females, menstrual abnormalities and miscarriages have been reported despite a high reproductive success rate (56). Conversely, other authors find no significant fertility abnormalities (10). Proposed mechanisms include glandular deposition of globotriaosylceramide (Gb3) or vascular alterations affecting testicular fluid balance and function (57, 58). Annual clinical monitoring in boys and every 2–3 years in girls is considered appropriate (59).

Glycogen storage disease (GSD) type 1 is characterized by impaired glycogenolysis and gluconeogenesis, with glycogen accumulation in tissues. Clinical manifestations include hepatomegaly, severe hypoglycemia, lactic acidosis, hyperuricemia, and hypertriglyceridemia (60). Female patients may develop PCOS, dysmenorrhea, and menorrhagia, although reproductive rates are typically preserved (61–63). The underlying pathogenesis is unclear (63). Early diagnosis and proper treatment may prevent delayed

puberty (61). Recommended management includes regular gynecological evaluations, documentation of menstrual irregularities (62) and assessment of coagulation if menorrhagia is present, with referral to a gynecologist or hematologist as needed (64). Non-hormonal treatments (dietary intervention to reduce insulin resistance or hemostatic therapies like 1-desamino8-D-arginine vasopressin and antifibrinolytics) may be indicated (65, 66). Regarding hormonal treatment, due to the higher adenoma risk in glycogen storage disease type I, estrogens should be avoided. Progestin-only contraceptives are safer, but long-term medroxyprogesterone use may lower bone density, requiring close monitoring (67, 68). In girls with GSD type 1 experiencing severe menorrhagia not controlled by medical therapy, surgical interventions may be considered (64).

Hypergonadotropic hypogonadism has also been reported in patients with mitochondrial diseases, including mtDNA depletion syndromes (*C10orf2*, *POLG* variants), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), primary coenzyme Q10 deficiency, and Leigh syndrome caused by *LRPPRC* variants (69, 70). POI is also frequent in children with *AARS* variants (71). These endocrine abnormalities seem to be associated with impaired mtDNA maintenance or mitochondrial steroidogenesis (3). In some cases, POI may precede neurological symptoms (3), though no standardized recommendations exist regarding follow-up or treatment in this patient population.

Despite the extensive clinical observations, significant gaps remain in understanding the precise mechanisms leading to gonadal dysfunction across different IMDs, as well as the variability in severity between sexes and among individual diseases. Further research is needed to clarify pathophysiological pathways, assess long-term reproductive outcomes, and establish evidence-based screening and management protocols tailored to each disorder.

3.4 Adrenal glands

Adrenal gland involvement occurs in several congenital errors of metabolism, including X-linked adrenoleukodystrophy (X-ALD), Smith-Lemli-Opitz syndrome, mitochondrial diseases, Glycerol kinase deficiency (GKD), Fabry disease, and Congenital Disorders of Glycosylation (CDG) (Table 4).

Patients with X-ALD frequently develop adrenal insufficiency (AI), characterized by reduced cortisol synthesis and, less commonly, aldosterone deficiency, presenting with asthenia, hypotension, dehydration, hyponatremia, and hypoglycemia (39). Addison's disease is reported as the first clinical manifestation of ALD in 38% of cases, making it the most common presenting symptom of ALD in childhood (72, 73). AI occurs in about 80% of patients and often manifests as early as the age of 3 (74), although cases of onset in infancy have been described. Screening for AI at diagnosis is recommended, keeping in mind the variability of basal cortisol and ACTH in early life (73, 75, 76). Subsequent follow-up should include fasting cortisol, glycaemia, ACTH, renin (in children >2 years), and electrolytes, every 3 to 6 months until age 10, and

TABLE 4 Reported involvement of the adrenal glands in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
X-ALD	Adrenal insufficiency (39, 73–76)	Cortisol, ACTH, renin and electrolytes assessment as soon as possible, then every 3 to 6 months until 10 years of age and annually thereafter (73)	Replacement therapy with glucocorticoids and mineralocorticoids with same schemes as other forms of AI (39)
Smith-Lemli-Opitz syndrome	Adrenal insufficiency (80–82)	Glucose and electrolytes assessment in infants (86, 87)	Corticosteroid replacement during major stressors (e.g., surgery) (86, 87)
Mitochondrial diseases	Adrenal insufficiency (MELAS, Pearson syndrome, KSS and mtDNA) (88–93)	Regularly screen for cortisol and ACTH since infancy (3)	No recommendations available
CDG	Adrenal insufficiency (PMM2-CDG) (94)	Morning cortisol and ACTH levels assessment at least annually, low-dose ACTH stimulation test in patients with abnormal cortisol and ACTH (94)	Steroid replacement therapy in case of abnormal ACTH stimulation test (94)
GKD	Adrenal hypoplasia or adrenal insufficiency (97, 98)	Perform genetic analysis to identify the complex form associated with adrenal alterations (96–98)	In case of adrenal involvement start glucocorticoid and mineralocorticoid replacement therapy as early as possible (96–98)
Fabry disease	Subclinical adrenal insufficiency (9, 10, 77)	No recommendations available	No recommendations for AI Enzyme Replacement Therapy Chaperone Therapy

IMD, inherited metabolic disease; X-ALD, X-linked adrenoleukodystrophy; CDG, congenital disorders of glycosylation; GKD, glycerol kinase deficiency; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; KSS, Kearns-Sayre syndrome; mtDNA, mitochondrial DNA; ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency.

annually thereafter (73). In cases of adrenal dysfunction, glucocorticoid replacement therapy is indicated. Furthermore, mineralocorticoid deficiency affects 40–60% of patients with X-ALD, therefore, mineralocorticoid replacement therapy is required in case of mineralocorticoid deficiency (39, 77–79).

Smith-Lemli-Opitz syndrome is caused by 7-dehydrocholesterol reductase deficiency, leading to impaired cholesterol synthesis and accumulation of 7-dehydrocholesterol (7-DHC). Clinical severity ranges from multiple major malformations to mild phenotypes with minor anomalies and intellectual disability. In severe cases, adrenal dysfunction may occur from the neonatal period (80–82), though the literature is not uniform (83). The etiopathology of adrenal dysfunction likely involves 7-DHC accumulation in adrenal tissue, as demonstrated in autopsy studies (84). However, reported elevated ACTH levels could also be secondary to the altered basal feedback regulation of the HPA axis due to abnormal steroid precursors (83, 85). Some authors recommend screening for AI, with corticosteroid replacement during major stressors (e.g., surgery) using protocols similar to congenital adrenal hypoplasia (CAH) (83, 86, 87).

Adrenal involvement, although rare in childhood, has also been reported in mitochondrial diseases, including MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), Pearson syndrome, KSS, and other mtDNA deletion syndromes (88–93). The mechanism may relate to the high ATP requirements of adrenal glands, with impaired ATP production leading to reduced hormone synthesis (88). However, incidence of AI in these patients appears similar to that of the general population, suggesting mitochondrial defects alone may not be sufficient for adrenal pathology (89). AI age of onset is variable, ranging from infancy to adulthood, and usually occurs in the context of severe mitochondrial disease (77, 89). Some authors

recommend regular cortisol and ACTH measurements (3), though standardized treatment guidelines are lacking.

CDG may affect adrenal function. A multicenter study on 43 PMM2-CDG patients reported AI in approximately 25%, mostly manifesting in childhood, even during the first months of life (94). This dysfunction may result from abnormal N-glycosylation of enzymes, receptors, and transport proteins involved in steroidogenesis (95). Annual assessment of morning cortisol and ACTH is recommended, with ACTH stimulation testing in cases of abnormal results, to enable early detection and initiations of steroid replacement therapy (94).

Glycerol kinase deficiency (GKD), an X-linked disorder causing elevated blood and urinary glycerol levels, can be associated with adrenal abnormalities, particularly in its complex form, involving contiguous gene deletions affecting the *GKD* locus along with *CAH* and/or *Duchenne muscular dystrophy (DMD)* genes (96). Affected patients may present with growth failure and salt-wasting syndrome with convulsions and hyperpigmentation in early infancy (97, 98). Early recognition of adrenal dysfunction is critical to initiate glucocorticoid and mineralocorticoid replacement therapy, with dose adjustments during stressful situations such as infections (96, 97).

Although data are limited and controversial, subclinical adrenal involvement may also occur in Fabry disease (9), with reports of reduced cortisol and elevated ACTH levels, occasionally confirmed by corticotropin stimulation tests (9, 10, 77). However, no formal recommendations exist regarding adrenal monitoring or treatment in these patients.

Zellweger spectrum disorders (ZSD) are genetic peroxisomal biogenesis disorders caused by *PEX* gene variants, leading to impaired peroxisome function and accumulation of very-long-chain fatty acids. In a cohort of 24 ZSD patients (median age

15.4 years), 7 (29%) showed primary adrenal insufficiency on ACTH stimulation testing, of which 4 were asymptomatic. The underlying mechanism is thought to involve toxic effects of elevated VLCFA (especially C26:0) on the adrenal cortex, and lifelong monitoring with regular Synacthen tests plus hydrocortisone (and fludrocortisone when needed) replacement is recommended for management (99).

3.5 Pancreas

Diabetes mellitus (DM) and hyperinsulinemic hypoglycemia are the most common clinical manifestations of pancreas involvement in children with IMDs (Table 5) (8).

In hereditary haemochromatosis, diabetes occurs in approximately 10% of patients and results from progressive insulin resistance due to hepatic oxidative stress and increasing deposition of hemosiderin in pancreatic β -cells (5, 100). Clinically, an initial glucose intolerance precedes insulin insufficiency. The best treatment strategy is represented by insulin and phlebotomies which can delay the need for insulin therapy, required when β -cells are no longer able to maintain glucose homeostasis, while liver transplantation is indicated only in cases of end-stage liver disease due to iron overload and cirrhosis (5, 8, 101).

In aceruloplasminemia, diabetes mellitus (DM) represents one of the main clinical manifestations (68.5%), caused by progressive iron deposition in pancreatic β -cells. Phlebotomies and iron chelation may prevent DM development. In patients with

aceruloplasminemia an annual glucose tolerance test, starting at 15 years of age, is recommended to detect this complication (8). Phlebotomies and iron chelation have been demonstrated to be effective in preventing diabetes (101, 102).

Some organic acidemias may present with hyperglycemia mimicking diabetic ketoacidosis with hyperglycemia, as reported in children with methylmalonic acidemia (MMA) (103–105), propionic acidemia (PA) (106, 107), isovaleric acidemia (IVA) (108–110) and holocarboxylase synthetase deficiency (HCSD) (111). The pathogenesis is unclear, however, the toxic metabolite accumulation in the pancreas seems to impair pancreatic structure or function, causing insulinopenia (8, 112).

Authors suggest that pancreatitis onset should be monitored in cases of organic acid disorders in order to promptly treat their complications (112). In some reported cases diabetic ketoacidosis (DKA) has been treated with intravenous insulin and by reducing intravenous glucose infusion, but with non-univocal results (112, 113); other authors described plasma glucose levels trending towards spontaneous normalization after treatment of the metabolic crisis (114). However, no specific guidelines about DKA in organic acidurias are available.

Several mitochondrial diseases, such as maternally inherited diabetes and deafness (MIDD), MELAS and Kearns-Sayre syndrome, are strongly associated with diabetes (24, 115–118). The pathogenesis is linked to ATP deficiency which leads β -cells to death, as histologically confirmed by a reduction in their number. Furthermore, the lack of ATP is responsible for defective insulin secretion because it prevents the closure of potassium channels and, in addition, insulin sensitivity in

TABLE 5 Reported involvement of the endocrine pancreas in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
Hemochromatosis	Diabetes mellitus (8)	Monitor the onset of insulin insufficiency and liver cirrhosis (5, 8, 100)	Insulin and phlebotomies (5, 8, 100)
Aceruloplasminemia	Diabetes mellitus (8)	Annual glucose tolerance testing, starting at age from 15 years of age (8)	Phlebotomies and iron chelation have been demonstrated to be efficient in preventing diabetes (101, 102)
Organic acid disorders	DKA (MMA, PA, IVA, HCSD) (103, 104, 106–111)	Regular monitoring for pancreatitis onset (112)	No recommendations available
Mitochondrial diseases	Diabetes mellitus (MIDD, MELAS, KSS, Wolfram syndrome) (24, 115–118)	No recommendations available	Insulin insulin-dependent diabetes and insulin-dependent type 2 diabetes, sulphonylurea for non-insulin-dependent type 2 diabetes (3, 115, 116, 119)
GSD	Diabetes mellitus (in GSD type I and type III) (6, 7)	Close monitoring with OGTT (7)	Progressively increasing doses of insulin (7)
Roger's syndrome	Diabetes mellitus (122, 123)	Fasting serum glucose concentration, OGTT, urinalysis and assessment for clinical manifestations of poor glycemic control at least annually (124)	Oral thiamine may allow avoiding insulin therapy (123, 125), but at the onset of puberty oral glucose lowering agents or insulin therapy are usually required (125, 126)
Cystinosis	Glucose intolerance (101, 127, 128)	OGTT, HbA1c and fasting glucose assessment every 5 years	Long-term oral cysteamine administration reduces significantly the risk of developing diabetes mellitus (127)
Alström syndrome	Diabetes mellitus (129, 130)	Annual glucose tolerance test from scholar age (131)	Insulin treatment, although in case of poor glycemic control escalating doses may not be effective (131)
CDG	Hyperinsulinism (132)	No guidelines available	No guidelines available, good response to diazoxide reported (132)

IMD, inherited metabolic disease; GSD, glycogen storage disease; CDG, congenital disorders of glycosylation; MMA, methylmalonic acidemia; PA, propionic acidemia; IVA, isovaleric acidemia; HCSD, holocarboxylase synthetase deficiency; MIDD, maternally inherited diabetes and deafness; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; KSS, Kearns-Sayre syndrome; DKA, diabetic ketoacidosis; OGTT, oral glucose tolerance test; HbA1c, glycated hemoglobin.

skeletal muscles decreases, whereby peripheral insulin sensitivity is affected (3). Mitochondrial dysfunction may cause DM, at any age (3). It is common that patients with mitochondrial diseases and type 2 diabetes need insulin therapy, while in non-insulin-dependent patients sulphonylureas are the first-choice pharmacological treatment (3, 115, 116, 119). Macro- and microvascular complications, especially proteinuria and renal insufficiency, are more common in these patients, due to the pre-existent mitochondrial dysfunction in different organs (3, 101).

Glycogen storage diseases, in particular GSD type I and type III, may evolve into diabetes in adolescence or early adulthood (6, 7). This can be related to recurrent episodes of pancreatitis, due to hypertriglyceridemia, and insulin resistance due to hepatic and muscle dysfunction (101). Therefore, a close follow-up of GSD patients with an oral glucose tolerance test (OGTT) is recommended (7). Gradual insulin titration has been reported to be effective in controlling hyperglycemia without hypoglycemic events (7).

Fanconi–Bickel syndrome (FBS), or glycogen storage disease XI, is a rare genetic disorder caused by variants in the *GLUT2* gene, leading to impaired glucose and galactose transport, glycogen accumulation in liver and kidneys, and proximal renal tubular dysfunction. Recent studies have highlighted pancreatic involvement in children with FBS, where glycogen accumulation in pancreatic β -cells contributes to dysglycemia. The underlying mechanism appears linked to impaired glucose transport and glycogen storage in multiple tissues, including the pancreas (120). Therapeutic approaches remain largely supportive, focusing on careful glucose monitoring, dietary management, however the SGLT2 inhibitor dapagliflozin seems to be effective in reducing glycogen accumulation in the renal proximal tubule, correcting metabolic acidosis and phosphaturia, and improving kidney function in a mouse model and an adult patient (121).

Roger's syndrome, or thiamine-responsive megaloblastic anemia (TRMA), is caused by a defect in the active transport of thiamine (THTR1) in various cells, in particular this defect causes pancreatic β -cell apoptosis and insulin secretion impairment, leading to the development of insulin-dependent diabetes (122, 123). This disease should be suspected especially when diabetes is

associated with megaloblastic anemia and/or neurosensory defects (122). Annual assessment for glucose intolerance, with fasting serum glucose concentration, OGTT and urinalysis, and for clinical manifestations of poor glycemic control is recommended (124). It has been demonstrated that pharmacological treatment with oral thiamine may allow avoidance of insulin therapy (123, 125). However, at the onset of puberty, oral glucose-lowering agents or insulin therapy are usually required (125, 126).

In cystinosis, approximately 25% of patients develop endocrine pancreatic dysfunction (101, 127), with a 50% risk of glucose intolerance by age of 18 (128). Pancreatic fibrosis leads to decreased insulin secretion (8, 101). Gahl et al. (127) demonstrated that long-term oral cysteamine administration significantly reduces the risk of developing DM.

In Alström syndrome, diabetes is common due to *ALMS1* gene-related defects in β -cell function and peripheral insulin signaling (129). Indeed, *ALMS1* is essential at the basal body of primary cilia in β -cells, regulating glucose sensing and controlled insulin release. Loss of *ALMS1* may impair β -cell proliferation, causing inappropriate glucose-independent insulin secretion, and increasing susceptibility to β -cell death under high-glucose stress (129). In a series of 182 patients, hyperinsulinemia developed in early childhood (92%) and progressed to type 2 diabetes mellitus in 82% of those older than 16 years (130). Therefore, an annual glucose tolerance test is recommended, starting from school age (131). Insulin treatment may be effective, however, in case of poor glycemic response to treatment, increasing the insulin dose may not be effective (131).

Hypoglycemia is also a rare manifestation of PMM2-CDG and hyperinsulinism has been identified as its main cause in 43% of patients reported in literature (132). The pathophysiology of hyperinsulinism in CDG has not been defined yet, however, according to a recent systematic review conducted on 933 PMM2-CDG patients, all hyperinsulinemic patients who received diazoxide were reported to respond well (132).

Although numerous clinical presentations of pancreatic involvement have been described in IMDs, many aspects of the underlying molecular mechanisms leading to diabetes or hyperinsulinemic hypoglycemia remain unclear. The progression

TABLE 6 Reported involvement of the pituitary gland in various IMDs, with recommendations for monitoring and treatment.

IMD	Endocrine disturbances	Suggested follow-up	Treatment options
Mitochondrial diseases	Central precocious puberty (133) Central hypothyroidism (MELAS) (3, 134) Growth hormone deficiency (KSS, MELAS) (3, 134–136) Hypogonadotropic hypogonadism (3, 134, 153–155) Secondary adrenal insufficiency (3)	GnRH stimulation test in case of precocious puberty signs (133) GH stimulation test in case of short stature (3, 134, 135) Brain MRI in case of signs of hypothalamus-pituitary dysfunction (3, 133, 134)	GnRH agonist for precocious puberty (133) Hormonal replacement in case of hypothyroidism (134) Growth hormone treatment in patients with GH deficiency (3, 136–138)
Hemochromatosis	Hypogonadotropic hypogonadism (139, 141–148)	No recommendations available	Early phlebotomy, testosterone replacement therapy in males and estrogen in females (139, 149–152)

IMD, inherited metabolic disease; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; KSS, Kearns-Sayre syndrome; GnRH, gonadotropin-releasing hormone; GH, growth hormone; MRI, magnetic resonance imaging.

of pancreatic dysfunction, disease-specific risk factors, and optimal long-term monitoring strategies are still not fully defined, highlighting the need for targeted screening protocols and longitudinal studies to prevent complications and improve patient outcomes.

3.6 Hypothalamus and pituitary gland

The hypothalamus-pituitary system may be impaired in IMDs with various mechanisms (Table 6). Its involvement mainly concerns the pituitary-gonadal axis, but a dysfunction of GH/IGF1 system has also been reported.

Central precocious puberty (PP) appears to occur more often in girls with mitochondrial diseases than in the general population, resulting in increased sex hormone levels (especially estradiol) and advanced bone age compared with chronological age. The etiopathogenic of central

PP in mitochondrial diseases remains unclear, and neuroimaging has not revealed specific anatomic patterns. A hypothalamus-pituitary dysfunction has been suggested, focusing on mitochondrial function and neuronal activity involving glutamate transport: the GnRH pulse generator is inhibited by GABA and stimulated by neurotransmitters such as glutamate; impairment of GABAergic suppression may prematurely activate the GnRH pulse generator, causing PP. Environmental (diet, exercise habit, endocrine-disrupting chemicals, etc.) and disease-specific factors likely contribute as well (133).

In a study by Chae et al. (133), central PP was identified in 10 out of 140 female patients with mitochondrial diseases. All presented with advanced bone age and elevated LH levels on GnRH stimulation testing, and all had normal brain MRI (133). These findings indicate the need for monitoring pubertal development in children with mitochondrial disorders and referring those with signs of PP to a pediatric endocrinologist. In such cases, a GnRH stimulation test, brain MRI to exclude

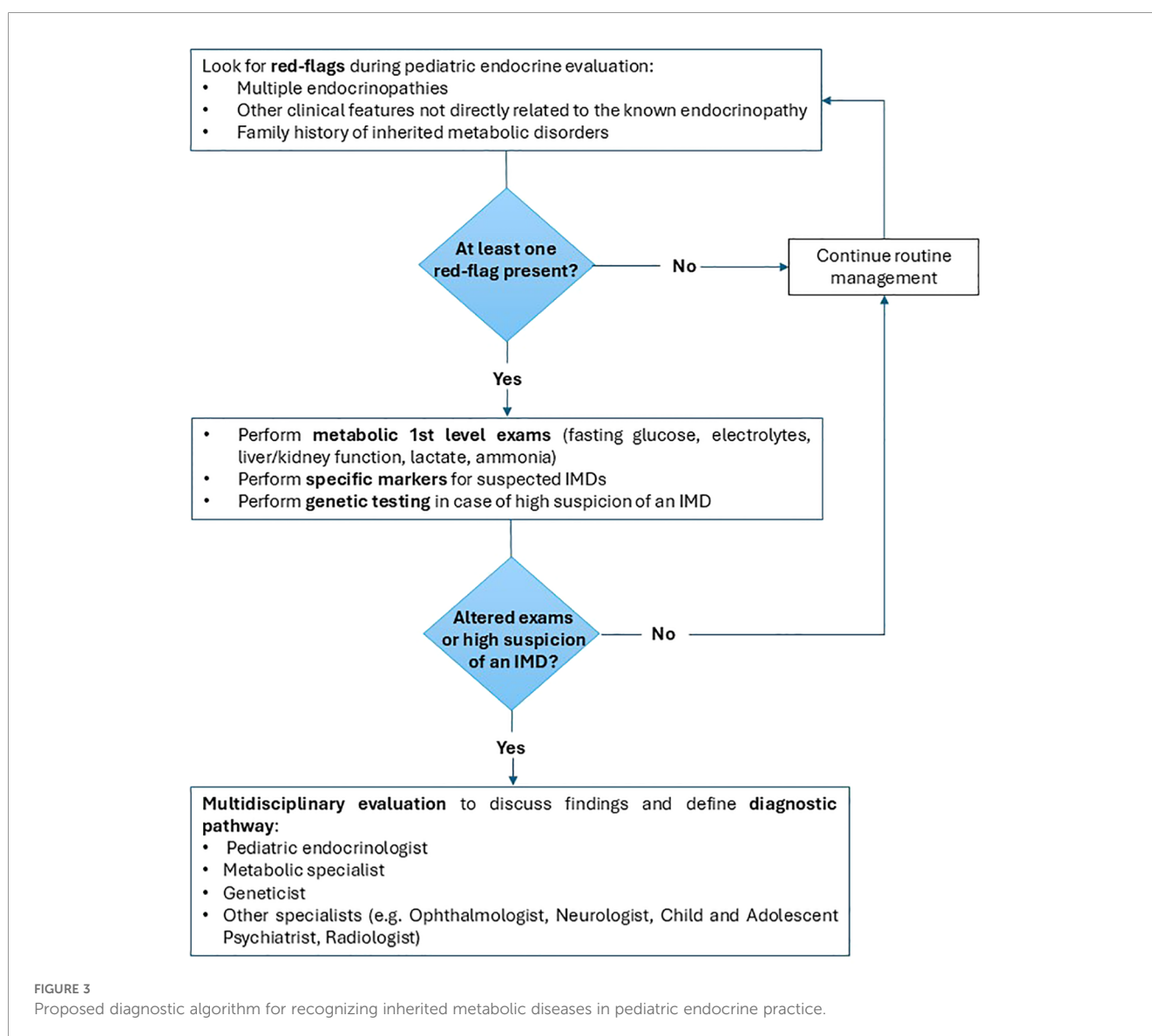


FIGURE 3 Proposed diagnostic algorithm for recognizing inherited metabolic diseases in pediatric endocrine practice.

hypothalamus-pituitary lesions, and therapy with GnRH agonists are important (133).

Central hypothyroidism has also been described, including a 12-year-old girl with MELAS and severe neurological impairment with brain damage on MRI (3, 134).

Involvement of the GH/IGF1 axis is well documented in mitochondrial diseases. In fact, growth retardation is common in these patients, who usually present with short stature and lower body mass index (3, 134, 135). Hypothalamus-pituitary dysfunction has been proposed to explain GH deficiency, but other hypotheses include chronic ischemia and energy deficiency in the diencephalon due to mitochondrial abnormalities, as well as non-specific degenerative changes and cerebral atrophy (3). Delayed or absent puberty is also frequent in patients with short stature, further supporting possible hypothalamic-pituitary dysfunction (3). Patients with confirmed GH deficiency generally respond well to GH therapy, with rapid improvement and few or no adverse effects (3, 136–138).

Patients with hemochromatosis may exhibit hypogonadotropic hypogonadism, primarily attributed to pituitary iron deposition (139, 140). This manifestation is more extensively documented in males, who present with thinning body hair, loss of libido and impotence (141–147). In females, although more rarely described, it may manifest with dysmenorrhea, secondary amenorrhea, reduced fertility, early menopause and decreased libido (147, 148). Early phlebotomy, together with testosterone replacement therapy in males and estrogen in females, appears beneficial in restoring gonadal function (139, 149–152). Despite increasing recognition of hypothalamus-pituitary involvement in IMDs, significant uncertainties remain regarding the precise mechanisms, optimal monitoring strategies, and standardized treatment approaches, highlighting the need for further longitudinal studies and tailored clinical guidelines.

4 Conclusion

Metabolic diseases are multi-organ pathologies that frequently involve the endocrine system. An underlying inherited metabolic disorder should be considered when multiple endocrine abnormalities coexist or when an endocrine condition presents alongside other clinical features not directly related to it.

The pathogenesis of endocrine manifestations in these contexts often remains unclear, highlighting the need for further studies to elucidate the biochemical and biological mechanisms underlying these interactions. A deeper understanding could also guide the development of more targeted therapies.

In certain cases, endocrine disorders secondary to a metabolic disease may respond to specific treatments distinct from the therapy for the primary metabolic condition. Therefore, early recognition of an underlying metabolic disorder can be crucial for improving patient outcomes, particularly in complex cases with endocrine involvement.

Despite evidence of endocrine organ or system involvement in many of the inherited metabolic diseases analyzed, clear guidelines

are lacking regarding the timing of follow-up or the initiation of specific hormonal therapies. Multidisciplinary discussion is essential to develop precise recommendations tailored to each endocrine complication across the various IMDs. To address this gap, we propose a summarized clinical diagnostic and management algorithm for recognizing inherited metabolic disorders in pediatric endocrine practice (Figure 3). Implementation of such an algorithm could facilitate early diagnosis, optimize endocrine care, and ultimately improve outcomes in pediatric patients with IMDs.

Author contributions

VMT: Writing – original draft, Writing – review & editing, Conceptualization, Methodology. LF: Writing – original draft, Writing – review & editing. CM: Writing – original draft, Writing – review & editing. DT: Writing – original draft, Writing – review & editing. MF: Writing – original draft, Writing – review & editing. MG: Writing – original draft, Writing – review & editing. IPG: Writing – original draft, Writing – review & editing. AC: Writing – original draft, Writing – review & editing. VC: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. GZ: Supervision, Writing – original draft, Writing – review & editing. EV: Conceptualization, Funding acquisition, Supervision, Validation, Writing – original draft, Writing – review & editing.

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