European Journal of Paediatric Neurology 48 (2024) 69–77

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Neurological presentations of inborn errors of purine and pyrimidine metabolism

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ARTICLE INFO

Keywords:
Purine
Pyrimidine
Metabolism defects
Neurological presentations

ABSTRACT

Purines and pyrimidines are essential components as they are the building blocks of vital molecules, such as nucleic acids, coenzymes, signalling molecules, as well as energy transfer molecules. Purine and pyrimidine metabolism defects are characterised by abnormal concentrations of purines, pyrimidines and/or their metabolites in cells or body fluids. This phenomenon is due to a decreased or an increased activity of enzymes involved in this metabolism and has been reported in humans for over 60 years. This review provides an overview of neurological presentations of inborn errors of purine and pyrimidine metabolism. These conditions can lead to psychomotor retardation, epilepsy, hypotonia, or microcephaly; sensory involvement, such as deafness and visual disturbances; multiple malformations, as well as muscular symptoms. Clinical signs are often nonspecific and thus overlooked, but some diseases are treatable and early diagnosis may improve the child's future. Although these metabolic hereditary diseases are rare, they are most probably under-diagnosed. When confronted with suggestive clinical or laboratory signs, clinicians should prescribe genetic testing in association with a biochemical screening including thorough purine and pyrimidine metabolites analysis and/or specific enzyme evaluation. This is most likely going to increase the number of confirmed patients.

1. Introduction

Pyrimidines (thymine, cytosine, and uracil) and purines (adenine and guanine) are aromatic heterocyclic compounds containing nitrogen and defined as nucleobases. To be biologically active, nucleobases are attached to a five-carbon sugar: ribose or deoxyribose and called nucleosides. When the nucleoside is phosphorylated, it becomes a nucleotide. Purines and pyrimidines are present in all living creatures. Nucleotides are essential cellular components incorporated in nucleic acids, coenzymes, signalling molecules, and energy transfer molecules [2]. Purine and pyrimidine metabolism is subdivided into three pathways: the *de novo* synthesis pathway from small molecules, the catabolic pathway, and the salvage pathway (which allows nucleotide or nucleoside regeneration by recycling the bases provided by food intake or the catabolic pathway) (Fig. 1). Purine and pyrimidine metabolism defects are characterised by abnormal concentrations of purines, pyrimidines, and/or their metabolites in cells or body fluids. This phenomenon arises due to a decreased or an increased activity of an enzyme involved in this metabolic process and has been documented in humans for over 60 years [1–5]. The clinical manifestations of hereditary conditions impacting this metabolism are heterogenous and may include immunological, haematological, rheumatological, neurological, muscular, sensory impairment like deafness or retinal damage, and renal features (stones and nephropathy) [2–5]. Several enzymes involved in the purine and pyrimidine metabolism (deoxyguanosine kinase, ribonucleotide reductase, thymidine phosphorylase and thymidine kinase 2) are required for maintaining the balance of mitochondrial deoxyribonucleoside triphosphate pool and their congenital deficiencies lead to mitochondrial DNA depletion syndromes. Additionally, polymorphisms in purine and pyrimidine metabolism genes are responsible for drug toxicity and have a major impact on the treatment of some cancers and autoimmune diseases [2]. These disorders may manifest at different times, ranging from patients' prenatal status to advanced age, with patients diagnosed in their 80s [2–4]. Most purine and pyrimidine metabolism defects are

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https://doi.org/10.1016/j.ejpn.2023.11.013
Received 29 August 2023; Received in revised form 25 November 2023; Accepted 30 November 2023
Available online 4 December 2023

autosomal and recessively inherited, except for diseases linked to hypoxanthine phosphoribosyl transferase 1 (*HPRT1*) and phosphoribosyl pyrophosphate synthetase 1 *(PRPS1)* genes (which are X-linked), and some dominant conditions (*IMPDH1*, *ADCY5*, etc.). Neurological symptoms are the most common and prominent clinical presentations associated with inborn errors of purine and pyrimidine metabolism. Several of these diseases may mimic various neurological conditions like cerebral palsy [2–4]. This review focused on neurological presentations of purine and pyrimidine metabolism defects. Some information regarding associated muscular symptoms are also provided. Of note, the mitochondrial depletion syndromes associated to purine and pyrimidine metabolism, although also sharing neurological phenotypes, will not be described in this review [2]. For each disorder described in this paper, a summary of the gene involved, clinical signs, and suggestive biochemical tests are summarised in Table 1.

2. Inborn errors of purine metabolism

Two preliminary remarks are detailed here to clarify this review.

(1) The key precursor for *de novo* purine biosynthesis is phosphoribosyl pyrophosphate (PRPP), synthesised by the PRPP synthetase (PRPS), a highly regulated enzyme, which uses ribose-5-phosphate from the pentose phosphate pathway and adenosine triphosphate (ATP) as substrates (Fig. 1, ①). Three PRPS genes are identified and only one, namely *PRPS1,* which is X-linked, has been associated with two human diseases: PRPS deficiency and PRPS overactivity.

(2) Adenosine monophosphate (AMP) deaminase catalyses the conversion of AMP to inosine monophosphate (IMP) (Fig. 1, ⑤). Three isoforms are encoded by three genes: *AMPD1* (encodes the muscle isoform, see below), *AMPD2* (expressed in the liver and brain, see below), and *AMPD3* (encodes the erythrocyte isoform, whose deficiency is clinically asymptomatic and therefore not described in this review).

2.1. Phosphoribosyl pyrophosphate synthetase (PRPS) deficiency

Three clinical phenotypes due to PRPS deficiency have been initially described (Fig. 1, ①). They are linked to the presence of loss-of-function variants in the *PRPS1* gene and represent a continuum disease spectrum, which is correlated to the residual enzyme activity and to the X-chromosome inactivation pattern in affected females. Arts syndrome is the most severe form, X-linked non-syndromic hearing loss (DFNX1, also called DFN2) is the milder form, and Charcot-Marie-Tooth disease 5

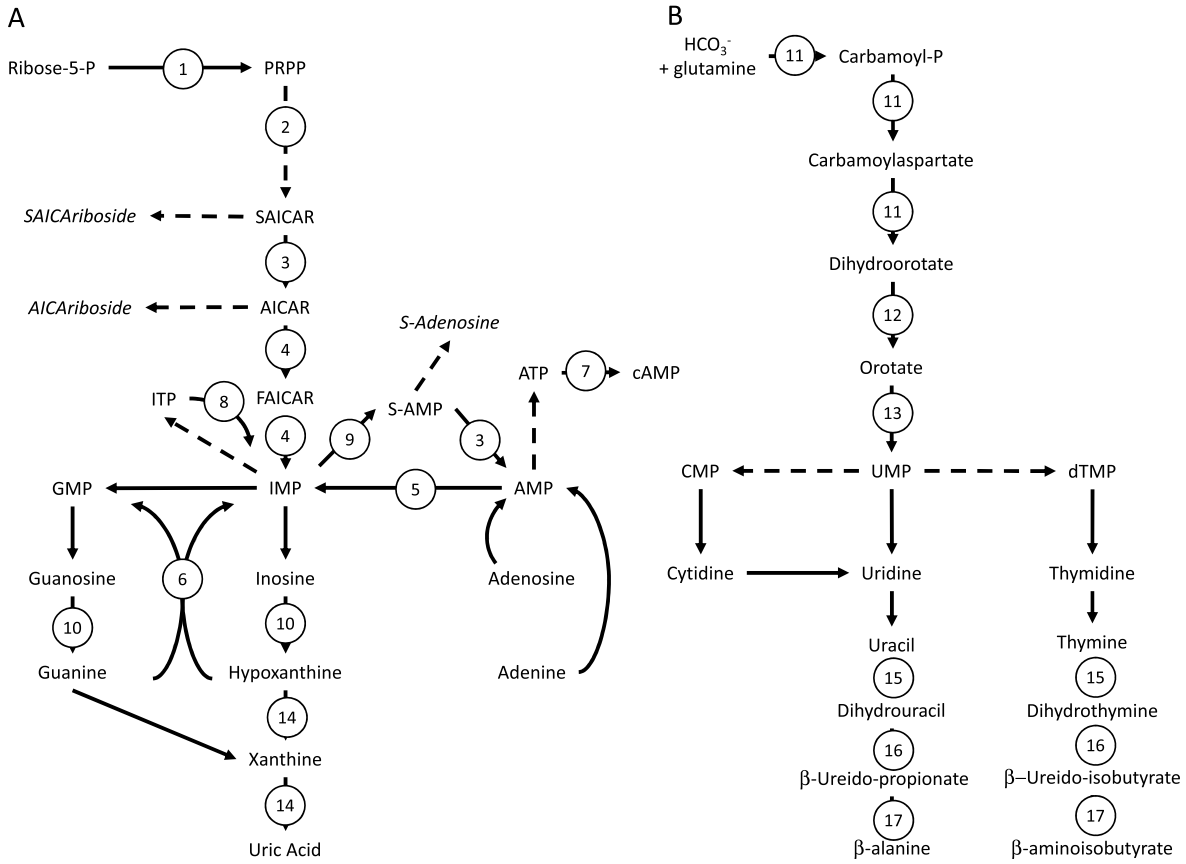

Fig. 1. Simplified pathways of purine (A) and pyrimidine (B) metabolism. Enzyme defects are indicated by a circled number across the arrows. Unusual metabolites consecutive to enzymatic blocks are indicated in italics. (A) AICAR, aminoimidazolecarboxamide ribotide; AMP, adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; FAICAR, formylaminoimidazolecarboxamide ribotide; GMP, guanosine monophosphate; IMP, inosine monophosphate; ITP, inosine triphosphate; P, phosphate; PRPP, phosphoribosyl pyrophosphate; SAICAR, succinylaminoimidazolecarboxamide ribotide; S-AMP, adenylosuccinate. (B) CMP, cytidine monophosphate; dTMP, deoxy-thymidine monophosphate; P, phosphate; UMP, uridine monophosphate.
①Phosphoribosyl pyrophosphate synthetase (PRPS); ② Phosphoribosyl-aminoimidazole carboxylase-Phosphoribosyl-aminoimidazole-succinocarboxamide synthetase (PAICS); ③ Adenylosuccinate lyase (ADSL); ④ AICAr transformylase-IMP cyclohydrolase (ATIC); ⑤ Adenine monophosphate deaminase (AMPD); ⑥ Hypoxanthine-guanine phosphoribosyltransferase (HPRT); ⑦ Adenylate cyclase 5 (ADCY5); ⑧ Inosine triphosphatase (ITPase); ⑨ Adenylosuccinate synthase (ADSS); ⑩ Purine nucleoside phosphorylase (PNP); ⑪ Carbamoylphosphate synthetase 2- Aspartate transcarbamylase-Dihydroorotase (CAD trifunctional protein); ⑫ Dihydroorotate Dehydrogenase (DHODH); ⑬ Uridine monophosphate synthase (UMPS); ⑭ Xanthine oxidase; ⑮ Dihydropyrimidine dehydrogenase; ⑯ Dihydropyrimidinase; ⑰ β-Ureidopropionase.

Table 1
Synthesis of purine and pyrimidine disorders whose clinical presentation is mainly neurological.

Disorder/enzyme defect Gene/Inheritance/ Number	Phenotypes & OMIM number	Clinical features	Main Laboratory/MRI findings
Phosphoribosylpyrophosphate synthetase (PRS) deficiency PRPS1 XLR ①	Arts syndrome (OMIM #301835) Charcot-Marie-Tooth disease-5 CMTX5 (OMIM #311070) X-linked non-syndromic hearing loss DFNX1 (OMIM #304500)	Sensorineural deafness ±Developmental delay±Ataxia ± Peripheral neuropathy±Optic atrophy ±Intellectual disability ±Recurrent respiratory infections	↓ PRS activity (RBC, F, L) n↓Hypoxanthine, adenosine, succinyladenosine, inosine, deoxyinosine (U); n↑ orotic acid (U) n↓ uric acid (P) ↓ ATP, GTP, NAD, and NADP (RBC)
Phosphoribosylpyrophosphate synthetase (PRS) overactivity PRPS1 XLR ①	PRPP synthetase superactivity due to gain-of-function variants: early-onset phenotype (OMIM 300661) Gout, PRS-related, milder phenotype (OMIM 300661)	Nephrolithiasis, gout, and progressive renal failure Early onset phenotype: ± PRPS deficiency clinical features	↑ Uric acid (U, P); ↑ Hypoxanthine (U) ↑ PRPP and nucleotides (RBC, F, L) ↑ PRS activity or lack of allosteric regulation (RBC*, F, L) ↑ PRPS1 mRNA levels
Bifunctional enzyme phosphoribosylaminoimidazole carboxylase/ phosphoribosylaminoimidazole succinocarboxamide synthetase (PAICS) deficiency PAICS AR ②	Phosphoribosylaminoimidazole carboxylase deficiency (PAICSD) (OMIM #619859)	Polyhydramnios and intrauterine growth retardation Multiple malformation: skeletal, facial dysmorphia, choanal atresia, pulmonary hypoplasia, esophagus atresia, and genitourinary abnormalities	↑(?) AI-riboside in body fluids
Adenylosuccinate lyase (ADSL) deficiency ADSL AR ③	Adenylosuccinase deficiency (OMIM #103050)	Developmental delay Epilepsy Autism, stereotypies	↑ S-Adenosine (U, CSF) ↑ SAICA-riboside (U, CSF)
AICAR transformylase/IMP cyclohydrolase (ATIC) deficiency ATIC AR ④	AICA-ribosiduria (OMIM #608688)	Intrauterine growth retardation Severe psychomotor retardation Chorioretinal atrophy Severe scoliosis Facial dysmorphia± Epilepsy ± cardiovascular defects	↑↑ AICA-riboside (U) ↑ S-Adenosine (U) n↑ SAICA-riboside (U)
AMP Deaminase-2 Deficiency AMPD2 AR ⑤	Pontocerebellar hypoplasia type 9 (PCH9) (OMIM #615809) Spastic paraplegia-63 (SPG63) (OMIM #615686)	Microcephaly, profoundly delayed psychomotor development, and spasticity. Seizures	
Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency HPRT1 XLR ⑥	Lesch-Nyhan syndrome (LNS) (OMIM #300322) HPRT-related hyperuricemia (HRH), Kelley-Seegmiller syndrome (OMIM #300323)	Hypotonia, self-injurious behaviour, choreoathetosis, dystonia, spasticity, opisthotonus, mental retardation Nephrolithiasis, gout	Macrocytosis ↑ Uric acid (U, P) ↑ Hypoxanthine, xanthine (U) ↓ HPRT activity (RBC)
Adenylate cyclase 5 (ADCY5)-related dyskinesia ADCY5 AD - AR ⑦	AD dyskinesia with orofacial involvement (DSKOD) (OMIM # 606703) AR dyskinesia with orofacial involvement (DSKOR) (OMIM #619647) Neurodevelopmental disorder with hyperkinetic movements and dyskinesia (NEDHYD) (OMIM #619651)	Facial dyskinesia, motor exacerbations during drowsiness or prominent sleep-related movements, episodic painful dystonic posturing that increases with stress or illness, axial hypotonia, and delayed developmental milestone	
Inosine triphosphatase (ITPase) deficiency ITPA AR ⑧	ITPase encephalopathy Epileptic encephalopathy, early infantile 35 (EIEE35) (OMIM #616647)	Infantile encephalopathy Progressive microcephaly Severe developmental delay Epilepsy±Bilateral cataract ±Cardiomyopathy	↑ ITP and IDP (RBC)
Carbamoylphosphate Synthetase II, Aspartate Transcarbamylase, Dihydroorotase (CAD) Deficiency CAD AR ⑪	Developmental and epileptic encephalopathy-50 (OMIM #616457)	Delayed psychomotor development, early-onset refractory seizures, and severe developmental regression	Normocytic anaemia, anisopoikilocytosis
Dihydroorotate (DHO) Dehydrogenase Deficiency DHODH AR ⑫	Postaxial acrofacial dysostosis (POADS), Miller syndrome (OMIM #263750)	Severe micrognathia, cleft lip and/or palate, hypoplasia or aplasia of the postaxial elements of the limbs, coloboma of the eyelids, and supernumerary nipple	↑ dihydroorotic acid (U,P) ↑ Orotic acid (U)
Dihydropyrimidine Dehydrogenase Deficiency DPD AR ⑮	Dihydropyrimidine dehydrogenase deficiency 5-Fluorouracil toxicity (OMIM #274270)	Controversy for the neurological phenotype: Developmental delay, seizures, asymptomatic Fluoropyrimidines toxicity	↑ uracil, thymine (P, U) ↑ 5-OH-methyluracil (U)
Dihydropyrimidinase deficiency DHP AR ⑯	Dihydropyrimidinuria (OMIM #222748)	Controversy for the neurological phenotype: Dysmorphic features, Intellectual disability asymptomatic Fluoropyrimidines toxicity	↑↑ dihydrouracil, dihydrothymine (P, U) ↑ uracil, thymine (P, U)
Ureidopropionase Deficiency UP AR ⑰	Beta-ureidopropionase deficiency (OMIM # 613161)	Controversy for the neurological phenotype: Developmental delay, seizures, asymptomatic Fluoropyrimidines toxicity ?	↑↑ ureidopropionic acid, ureidoisobutyric acid (P, U) ↑ dihydrouracil, dihydrothymine (P, U)
AMP Deaminase-1 Deficiency AMPD1 AR ⑤	Myopathy due to myoadenylate deaminase deficiency (MMDD) (OMIM #615511)	Easy fatigability, myalgia harmless entity	
Adenylosuccinate synthase (ADSS) muscular isoform deficiency ADSSL1 AR ⑨	Distal myopathy-5 (MPD5) (OMIM #617030)	Distal myopathy predominantly but also possible in proximal and listal leg muscles±respiratory failure ±dysphagia due to masticatory dyfunction±left ventricule hypertrophy	mild ↑ CK Muscle biopsy: Nemaline bodies, increased lipid droplets. Muscle MRI: diffuse fatty infiltration of tongue and masseter muscle
Uridine monophosphate synthase deficiency UMPS AR ⑬	Orotic aciduria (OMIM # 258900)	Immunodeficiency, developmental delay, and failure to thrive	Megaloblastic anaemia unresponsive to vitamin B12, folic

(*continued on next page*)

Table 1 (*continued*)

Disorder/enzyme defect Gene/Inheritance/ Number	Phenotypes & OMIM number	Clinical features	Main Laboratory/MRI findings
			acid, and iron ↑↑↑↑ orotic acid and orotidine (U)
Purine nucleoside phosphorylase deficiency PNP AR ⑩	Immunodeficiency due to purine nucleoside phosphorylase deficiency (OMIM #613179)	Recurrent infections Ataxia, intellectual deficiency, and muscle spasticity	n ↓ Uric acid (U, P) ↑ Inosine, d-Inosine, guanosine, dGuanosine (U) ↓ PNP activity (RBC, L)

XLR, X-linked recessive; AR, autosomal recessive; CK, creatine kinase; IMP, inosine monophosphate; PRPP, phosphoribosyl pyrophosphate; RBCs, red blood cells; U, urine; P, plasma; CSF, cerebrospinal fluid; F, fibroblasts; L, lymphoblasts; n↑ or n↓ refers to normal or slightly elevated or decreased values. * In contrast, PRS activity in RBC is decreased in PRS synthetase superactivity linked to gain-of-function variants, probably because of enzyme lability in post-mitotic cells. For more details about pathophysiological mechanisms and diagnostic methods, please refer to major reviews about these subjects [2–5,45].

(CMTX5, also called Rosenberg-Chutorian syndrome) is in-between. Sensorineural hearing loss is a common feature present alone in DFNX1. It can be associated with ataxia, hypotonia, peripheral neuropathy, and optic neuropathy in CMTX5 and Arts syndrome. The latter is more severe because an intellectual disability and immune system dysfunction characterised by recurrent respiratory infections and early death are also usually described in affected patients [2,3,6]. Female carriers may develop similar symptoms, although they are usually milder, such as hearing loss, retinal dystrophy, or cerebellar ataxia [7,8]. Suggestive laboratory features consist of slightly low blood uric acid, low urinary hypoxanthine levels, a slightly increased urinary orotic acid level and decreased nucleotide levels in red blood cells. Diet supplementation with S-adenosyl-methionine (SAM), a PRPS-independent source of nucleotide precursors that freely crosses the gut and blood-brain barriers, stabilised ataxia and hearing loss in two patients. Likewise, a co-supplementation of SAM with nicotinamide riboside, a PRPS-independent precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), recently displayed encouraging results in a single Arts patient [9]. Additional studies are necessary to corroborate these effects, including in less severe PRPS-deficient phenotypes.

2.2. Phosphoribosyl pyrophosphate synthetase (PRPS) overactivity

Two clinical phenotypes have been described associated with PRPS overactivity: a severe phenotype with neurological early-childhood onset and a milder form, starting during adolescence or early-adulthood [3,4,10]. The severe phenotype, less frequent compared with the milder phenotype, is most often associated with a variable combination of clinical signs usually observed in PRPS deficiency (see previous section) such as sensorineural deafness, hypotonia, developmental delay, short stature, ataxia, recurrent respiratory infections, and facial dysmorphic signs. The milder phenotype is typically only characterised by uric acid overproduction and often results to uric acid lithiasis and gouty arthritis, mostly in male individuals because of the X-chromosomal inheritance. Suggestive laboratory testing relies on hyperuricemia, high urinary uric acid, and hypoxanthine excretion. PRPS overactivity may be caused by two different mechanisms, comprising either the presence of gain-of-function missense mutations affecting enzyme regulations (known as “PRPS superactivity”, described in male severe phenotypes or female phenotypes) or an accelerated *PRPS1* transcription, for which no genetic defect has so far been identified altough a high activity or lack of allosteric regulation of the enzyme and elevated PRPS1 mRNA levels are found (known as “PRPS-related hyperuricemia”). The treatment aims at lowering uric acid levels with xanthine oxidase inhibitors, a low-purine low-fructose diet, high daily fluid intake, and urine alkalinization to increase uric acid solubility. Of note, no beneficial outcome on neurological symptoms has been observed with this treatment in the early-onset form. In that case, it might be helpful to evaluate the supplementation recently proposed to stabilise Arts disease (see previous section).

2.3. Bifunctional phosphoribosyl-aminoimidazole carboxylase/ phosphoribosyl-aminoimidazole-succinocarboxamide synthetase (PAICS) deficiency

Only two affected siblings from the Faroe Islands have been reported with PAICS deficiency (Fig. 1, ②). The clinical picture was characterised by a severe syndrome including multiple malformations and early death. Polyhydramnios and intrauterine growth retardation were detected during pregnancy. Complex malformations, which included multiple skeletal malformations, short neck and short stature, flat face with hypertelorism, nasal hypoplasia and choanal atresia, pulmonary hypoplasia, esophagus atresia, and genitourinary abnormalities were described [11]. Additional reports are necessary to better characterise the clinical picture of this metabolic disorder.

2.4. Adenylosuccinate lyase (ADSL) deficiency

The clinical spectrum of ADSL deficiency is broad, ranging from fatal neonatal presentations to milder forms [3,5,12,13]. The neonatal form presents with encephalopathy, lack of spontaneous movements, respiratory failure, intractable seizures and sometimes vacuolating leukodystrophy [14], all of which result in early death within the first weeks of life. The most common form that was previously described as “Type I” manifests within the first months of life and is characterised by severe psychomotor retardation, early-onset seizures, autistic features, growth retardation, and microcephaly (“Rett-like syndrome”). The moderate form that was previously described as “Type II” is characterised by psychomotor retardation, autistic features, and stereotypies. A fourth, milder phenotype manifesting itself with only isolated psychomotor retardation or ataxia has similarly been reported (3,13, personal unpublished observations). In this phenotype, brain imaging usually reveals unspecific findings, including atrophy of the cerebral cortex, corpus callosum, and cerebellar vermis, as well as white matter anomalies, such as delayed or lack of myelination. Dysmorphic features have been described, namely brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, long, smooth philtrum, and thin upper lip [15]. Around 120 ADSL-deficient patients have been reported, with over 70 different mutations identified [13]. The ADSL enzyme catalyses two different steps pertaining to purine synthesis, including the conversion of succinylaminoimidazole caroxamide ribotide (SAICAR) into aminoimidazole carbozamide ribotide (AICAR), as well as the conversion of succinyl-adenosine monophosphate (S-AMP) into AMP (Fig. 1, ③). The succinylpurines SAICAriboside (SAICAr) and S-adenosine (S-ado) accumulate in body fluids of affected patients. The S-Ado/SAICAr ratio is commonly around one in severe ADSL deficiency forms, and between two and four in milder phenotypes, depending on the pathogenicity of the mutations and the residual enzyme activity. Although the mechanisms underlying the psychomotor retardation remain unexplained, SAICAr is suggested to exert a toxic effect, which is counteracted by S-ado’s protective effect. Treatment is nonspecific and consists primarily in managing epilepsy, by using the beneficial effects of a ketogenic diet for some patients [16].

2.5. Bifunctional aminoimidazole-carboxamide riboside transformylase/IMP cyclohydrolase (ATIC) deficiency

To date, around 10 ATIC deficiency cases have been reported [17,18]. Clinical features comprise intrauterine growth retardation, severe neurodevelopment impairment, visual impairment due to chorioretinal atrophy, severe scoliosis, facial dysmorphia, aortic coarctation, hepatic alteration, and drug-resistant epilepsy. A milder phenotype has recently been described with few dysmorphic features (bulging forehead, depressed nasal bridge, and flat nasal tip), postnatal growth impairment, psychomotor retardation since the second year of life, visual acuity reduction, and mild hepatic dysfunctions [19]. Bifunctional AICAR transformylase/IMP cyclohydrolase (ATIC) catalyses the last two steps of the *de novo* purine synthesis pathway (Fig. 1, ④). High urinary levels of AICAr, which is the dephosphorylated counterpart of AICAR, are a key feature of the disease (Fig. 1).

1.6. AMP Deaminase-2 Deficiency (Fig. 1 ⑤)

Pontocerebellar hypoplasia type 9 (PCH9) and hereditary spastic paraplegia type 63 (HSP63) have been found to be linked to pathogenic variants in *AMPD2*. PCH9 patients display severe intellectual disability, cortical blindness, axonal neuropathy, epilepsy, and microcephaly [20,21]. The course is not progressive. Neuroimaging exhibits a hypoplastic cerebellum and pons with a typical midbrain figure-eight appearance, callosal hypoplasia or agenesis, and periventricular white matter involvement [22].

2.6. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency

The most severe presentation of HPRT deficiency is the well-known Lesch–Nyhan syndrome (LNS) [1–3]. Hypotonia occurring at 3–6 months of age is the first manifestation. Neurological symptoms progress with severe psychomotor retardation by the age of 2–3 years old, accompanied by involuntary movements consisting of dystonia, choreoathetosis, and dysarthria. The hallmark of this disease is a behavioural disorder characterised by aggressiveness and self-mutilation by biting the fingers, lips, and cheeks, causing profound disfigurement. Less severe HPRT variants display hyperuricemia with neurological involvement but no behavioural abnormalities, and some rare patients have isolated hyperuricemia with kidney stones [23]. Macrocytosis is a common feature of HPRT-deficiency [24]. Brain imaging is usually normal, but a volume reduction of grey and white matter has been described [25]. The pathogenesis of the neurological symptoms has still not been explained. Several studies point to a dopaminergic dysfunction, involving a 60–90 % decrease of dopamine concentrations, and to the enzyme activity that is required for its synthesis. However, dopaminergic drugs are not effective. In a recent quantitative analysis of 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging, patients with HPRT deficiency showed a widespread hypometabolism involving several areas of the brain, including the frontal, temporal, parietal and insular cortex, putamen, pallidum, thalamus, brainstem, and cerebellum compared with other genetic or acquired causes of dystonia [26]. HPRT catalyses hypoxanthine and guanine recycling into inosine monophosphate (IMP) and guanosine monophosphate (GMP) (Fig. 1, ⑥). The uric acid overproduction resulting from accelerated *de novo* synthesis, is accompanied by increased serum urate levels up to 18 mg/dL (1 mmol/L), and by increased urinary excretion of uric acid, hypoxanthine, and xanthine. Before puberty, uricemia may be in the normal or high-normal ranges. Determining enzyme activity in red blood cells (RBCs) provides a definitive diagnosis. This disease is X-linked and recessively inherited. Notably, several females with LNS have been reported, due to non-random or skewed inactivation of the X-chromosome. Patients should be treated for hyperuricemia with allopurinol or febuxostat as they inhibit the last enzyme of purine catabolism, xanthine oxidase (Fig. 1, ⑭). This results in decreased uric acid production, which is replaced by more soluble molecules, hypoxanthine and xanthine. Additional measures to prevent crystallisation include a high fluid intake and low-purine diet that is free of red and organ meats, dried beans and peas, and fish-like anchovies, mackerel, sardines, and tuna. Since uric acid and xanthine are more soluble at alkaline pH, alkalinization of urines by administrating sodium bicarbonate, potassium citrate, or citrate mixtures is useful. Adequate uricemia control prevents gouty arthritis and urate nephropathy, but does not correct the neurological symptoms. Although no effective and safe therapy for motor or behavioural symptoms is currently available, some treatments have demonstrated improvements in patients. Among these, diazepam, haloperidol, and barbiturates can sometimes improve choreoathetosis, while S-adenylmethionine (SAM) can improve self-injurious behaviour [27]. Patients should be made more comfortable using appropriate restraints, including elbow splints, lip guards, and even tooth extraction, all of which reduce self-mutilation. Deep brain stimulation (DBS) has also been proposed to treat LNS. In a recent systematic review, DBS was shown to improve dystonia to varying degrees and achieved partial or complete control of self-injurious behaviour, but the results reported thus far have varied widely, especially regarding motor outcomes. DBS-related complications were rather common, which raised questions about the safety of the procedure in LNS. The ultimate clinical benefits in LNS patients are still unpredictable. Further investigations are required to further clarify the safety and effectiveness of this treatment [28].

2.7. Adenylate cyclase 5 (ADCY5)-related dyskinesia

ADCY5 pathogenic variants have been reported in more than 70 patients, with a broad spectrum of hyperkinetic movement phenotypes [29,30]. Common phenotypes of ADCY5-related dyskinesia include facial dyskinesia, motor exacerbations during drowsiness or prominent sleep-related movements, episodic painful dystonic posturing increasing with stress or illness, and axial hypotonia with delayed developmental milestones. Some variants also cause childhood-onset chorea, dystonic movements, and alternating hemiplegia. Intellectual capacity is preserved in most patients. ADCY5 is encoded by the *ADCY5* gene and converts ATP into cyclic AMP (cAMP), which is an intracellular second messenger crucial for several molecular pathways (Fig. 1 ⑦). ADCY5 is mainly expressed in the striatum, a region implicated in the control of movements, where it is inhibited by dopamine through D2 receptors and activated by adenosine through A2A receptors. Most pathogenic variants described in the *ADCY5* gene are monoallelic (*de novo* or autosomal dominant inheritance) and cause a gain-of-function enzyme, as indicated by *in vitro* functional studies demonstrating an intracellular cAMP increase. There is currently no specific treatment for ADCY5-related dyskinesias. Acetazolamide appears to be the most effective way to control chorea and dyskinesia. Caffeine has been reported to improve paroxysmal nocturnal dyskinesia, most likely because of its antagonist effect on A2A receptors. Deep brain stimulation has been also reported to be effective [31].

2.8. Inosine triphosphatase (ITPase) deficiency

Profound ITPase deficiency (Fig. 1 ⑧), an enzyme preventing the accumulation of non-canonical nucleotides, has recently been reported in patients with progressive encephalopathy. This disease typically presents during the first months of life, with severe developmental retardation and bilateral cataracts (Martsolf-like syndrome) [32]. In most cases, this was also associated with early-onset cardiomyopathy. The congenital microcephaly and cardiac involvement are independent clinical predictors of poor outcomes. In the very early stages of the disease, cerebral magnetic resonance imaging (MRI) may not reveal abnormalities. The most typical feature of this disease, which appears after a few months, is a narrow, short segment of T2 hyperintensity in the posterior limb of the internal capsule, which disappears after several months. Over time, delayed myelination progressively becomes more evident. Diffuse weighted imaging sequence is the most useful, revealing

the involvement of structures that are not T2 hyperintense [33]. Reduced ITPase activity results in an accumulation of ITP in RBCs but definitive diagnosis requires molecular investigations.

3. Inborn pyrimidine metabolism errors

3.1. Carbamoylphosphate synthetase II, aspartate transcarbamylase, dihydroorotase (CAD) deficiency

Patients with CAD deficiency present with early infantile epileptic encephalopathy (DEE 50), with epilepsy occurring in early childhood (neonatal period to 2 years old) along with significant global development delay and even psychomotor regression. Anaemia with anisopoikilocytosis is a specific hallmark. The brain volume is initially normal on MRI, which is later followed by progressive cerebral and cerebellar atrophy. However, early diagnosis is important because patients receiving uridine supplementation show obvious benefits manifesting as immediate seizure cessation, resolved anisopoikilocytosis, and improved development [34]. CAD is a trifunctional enzyme performing the first three of the six reactions required for *de novo* pyrimidine biosynthesis, leading to uridine monophosphate (UMP) formation (Fig. 1 ⑪). CAD deficiency is difficult to diagnose because symptoms are non-specific and there is no biomarker. Molecular diagnosis is required [35].

3.2. Dihydroorotate dehydrogenase (DHODH) (Fig. 1, ⑫) deficiency

Pathogenic variants of the *DHODH* gene lead to Miller syndrome, also named Genee–Wiedemann syndrome or Wildervanck-Smith syndrome, which is a very rare genetic condition, also referred to as "postaxial acrofacial dysostosis" [3,36]. This syndrome is characterised by distinctive craniofacial malformations (micrognathia, orofacial clefts, malar hypoplasia, aplasia of the medial lower lid eyelashes, coloboma of the lower eyelid, and cup-shaped ears) combined with postaxial limb deformities, including the apparent absence of either the fifth or both the fourth and fifth rays of the hands and feet, with or without ulnar and fibular hypoplasia. Interestingly, the malformations in Miller syndrome resemble those of foetal exposure to methotrexate, an inhibitor of *de novo* purine synthesis. Thus, purine and pyrimidine biosynthesis defects likely cause similar birth defects. Dihydroorotate (DHO) levels are increased in patients' urine and plasma. Orotic acid in also found surprisingly increased, in urine only, potentially linked to an alternative metabolism upon renal excretion. In theory, dietary supplementation with orotic acid or uridine could bypass the metabolic block. However, as the principal damage occurs in utero, this therapy is unlikely to be effective [37].

3.3. Dihydropyrimidine dehydrogenase (Fig. 1 ⑮), dihydropyrimidinase (Fig. 1 ⑯) and β-ureidopropionase (Fig. 1 ⑰) deficiencies

The pyrimidine bases uracil and thymine are degraded into β-alanine and β-aminoisobutyric acid, respectively through three enzymatic steps catalysed by dihydropyrimidine dehydrogenase (DPD), dihydropyrimidinase (DHP) and β-ureidopropionase (UP). The spectrum of clinical presentations reported in subjects with DPD deficiency ranges from asymptomatic individuals to severely affected patients suffering from seizures, microcephaly, developmental delay and eye abnormalities [38]. Clinical phenotype of patients with DHP deficiency ranges from early infantile onset of severe neurological involvement and dysmorphic features to late onset of mild intellectual disability and even asymptomatic individuals [39]. UP deficiency has also been reported with highly variable phenotypes, ranging from asymptomatic to severe neurological involvement, including intellectual disability, seizures and autism. Yet, a recent review casts doubt on the link between *UPB1* variants, the associated enzyme deficiency and any human phenotype. The high carrier frequency for some variants that have been shown to result in enzyme deficiency strongly suggests that most individuals with a biochemical deficiency do not have a significant neurological phenotype as a result [40]. Additionally, patients identified by newborn screening programs are almost asymptomatic [41]. In conclusion, caution is needed in ascribing clinical significance to the identification of biochemical features (see Table 1) of DPD, DHP or UP deficiency in patients with neurodevelopmental phenotypes, and alternative causes should be sought in such individuals. However, these enzymes, especially DPD, have an important role in pharmacology and drug toxicities. Fluoropyrimidine drugs (FPs), including 5-fluorouracil (5-FU) and its oral prodrugs tegafur, capecitabine, and doxifluridine, are widely used in the treatment of solid tumors. Severe toxicity occurs in around 30 % of patients during or after FPs administration. Patients may rapidly develop severe and potentially fatal toxicities which may manifest as severe forms of common toxicities such as mucositis and cytopenias, and more rarely as central neurotoxicity and acute cardiomyopathy. Clinical signs of encephalopathy include disorders of consciousness, disorientation, lethargy, convulsions and focal deficits. For some, MRI features consist of bilateral and symmetric lesions of deep white matter, corpus callosum and corticospinal tracts, hyperintense in diffusion and FLAIR sequences with diffusion restriction. Hyperammonemia, lactic acidosis and hypocapnia may be associated to the development of encephalopathy. Since FPs are degraded by DPD, DHP and β-UP enzymes, a reduction in their activity results in severe FP-related toxicity. Decreased DPD and DHP enzyme activities have been linked to genetic polymorphisms identified in patients with severe FP toxicity [42,43]. On the other hand, the relationship between β-UP enzyme activity and the development of FP-related toxicity is still unknown. Dihydropyrimidine dehydrogenase (DPD) deficiency is the most important risk factor for developing fluoropyrimidine-related adverse events leading to the implementation of DPD deficiency testing by measuring plasma uracil concentration or by DPYD genotyping before initiation with fluoropyrimidine [44]. Thiopurine S-Methyltransferase, Nudix Hydroxylase 15 and Cytidine deaminase deficiencies constitute other examples of predictive pharmacogenetics but are not detailed in this review.

4. Muscular symptoms

4.1. AMP deaminase 1 deficiency (Fig. 1 ⑤)

The deficiency of muscle AMP deaminase (AMPD1, frequently referred to as myoadenylate deaminase) is observed in 1–2% of the Caucasian population. Most deficient individuals are asymptomatic. Some subjects, classified as having the primary AMPD1 defect, exhibit isolated muscular weakness, cramps, or post-exercise myalgias. This is sometimes accompanied by an increase in serum creatine kinase (CK) and myoglobinuria. AMPD1 deficiency is defined as "double trouble,'' or coincident AMPD1 deficiency, when genetically proven AMPD1 coexists with another disease, generally a metabolic myopathy (*e.g.*, a glycogen storage disease or mitochondrial DNA mutations) or neuromuscular disorder (*e.g.*, amyotrophic lateral sclerosis, facioscapulohumeral myopathy, or polyneuropathies). This emphasises the need to ascertain the absence of another disease when an AMPD1 deficiency is found [2,3].

4.2. Muscle-specific adenylosuccinate synthase deficiency

More recently, a muscular phenotype has been reported associated with an inborn error of purine metabolism and muscular adenylsuccinate synthetase (ADSS) deficiency has been described as a causal factor of adult-onset distal myopathy, which seems more common in Asian populations. Mild facial-muscle weakness and predominant distal muscle weakness appear around the age of 15. Muscle weakness and atrophy progress slowly in the lower legs and, to a lesser extent, distally in the upper limbs [45]. Proximal myopathy with both contractures and muscle atrophy has similarly been reported. A severe phenotype characterised by congenital joint contractures and an even more severe

neurological phenotype (foetal akinesia) have been described in a Turkish patient [46]. Serum CK levels are mildly increased (four to eight times the normal values). In the early disease stage, diffuse fatty infiltrations are observed on MRI of the gastrocnemius muscles, as well as in the soleus or tibialis anterior muscles. Thigh muscles are involved in later stages. Predominant fatty replacement of tongue muscles is a pathognomonic radiological sign. Nemaline bodies in addition to increased lipid droplets and myofibrillar disorganization were commonly observed in muscle biopsy of all patients, suggesting that the disease may be classified as nemaline myopathy [47]. The *ADSSL1* gene encodes the ADSS-like 1-protein, a muscle-specific enzyme responsible for the conversion of IMP to AMP (Fig. 1, ⑨). Compound heterozygous variants in the *ADSSL1* gene are associated with this myopathic presentation.

5. Neurological symptoms associated with predominant immunologic or haematological symptoms

5.1. UMP synthase deficiency (hereditary orotic aciduria)

The hallmarks of the UMP synthase (UMPS) deficiency (also described as hereditary orotic aciduria) are a megaloblastic anaemia that is refractory to iron, folic acid, or vitamin B12. Immunodeficiency, developmental delay, and failure to thrive have been observed. Some patients with epilepsy but without anaemia have also been reported [48]. This orotic aciduria is a rare inborn pyrimidine metabolism error with autosomal recessive inheritance [49]. It results from a deficiency in one or both activities of the bifunctional enzyme uridine-5-monophosphate synthase (Fig. 1, ⑬). UMPS defects lead to the accumulation of orotate and/or of orotidine monophosphate resulting in marked increased urinary orotic acid levels, reaching, 200- to 1000-fold the normal value in infants. These levels are usually much higher than those in urea cycle defects. Orotidine, the dephosphorylated form of OMP is also usually detected in affected individuals. Uridine, which is converted by uridine kinase into UMP, is an efficient treatment if started early in life and induces prompt haematologic response and growth acceleration. In some cases, normal psychomotor development can be achieved, whereas this is not obtained in others, possibly owing to delayed therapy onset.

5.2. Purine nucleoside phosphorylase deficiency (Fig. 1, ⑩)

Purine nucleoside phosphorylase (PNP) deficiency is characterised by a progressive severe combined immunodeficient (SCID) form with profound T-cell deficiency with variable B and natural killer (NK) cell functions. Recurrent infections start from the end of the first year and up to the age of five to six. Neurodevelopmental problems develop toward the end of the second year of life, including ataxia, intellectual deficiency, and spasticity [50]. PNP deficiency leads to the accumulation of guanosine, deoxyguanosine, inosine, and deoxyinosine, which results in intracellular deoxyguanosine triphosphate accumulation, especially in the thymus, where high cell turnover occurs. Low plasma uric acid has been suggested as a marker for PNP deficiency, but this marker is not always reliable. PNP enzyme activity should be measured either in RBC lysates, blood spots, or leukocytes. Diagnosis is confirmed using molecular *PNP* gene analysis. The only successful treatment is autologous haematopoietic stem cell transplantation (aHSCT), but its effectiveness for neurological and autoimmune problems is unclear, due to the small number of transplanted patients. However, no cases reported further neurological deterioration after aHSCT, and improvements were even reported in some patients [51].

6. Biochemical studies

The laboratory diagnosis of inborn errors of purine and pyrimidine metabolism is made by detection of abnormal concentrations of metabolites in urines, plasma, or cerebrospinal fluid (CSF), by enzymatic analysis in RBCs, white blood cells, or fibroblasts, and finally by molecular investigations [2–4,52]. These latter permitted to find new defects during the last decade (PAICS deficiency by example). A few routine simple tests may provide important clues and help for the diagnosis (megaloblastic anaemia, lymphopenia, etc.). Plasma and urine uric acid levels measurements can lead to the suspicion of defects involving HPRT, PNP, and PRPS enzymes. An unexplained elevation of plasma or urine uric acid is not specific, but it should raise suspicion for an inborn purine metabolism error. On the other hand, normal uric acid levels do not eliminate the possibility of this type of disease. There are some potential pitfalls and considerations to keep in mind when interpreting uric acid level results: uric acid levels can vary throughout the day and are often higher in the early morning. It is recommended to measure uric acid levels in the mid-morning or after fasting overnight. Correct diagnosis also requires the establishment of control range values for healthy adult males and females, as well as for children. Diet can significantly impact uric acid levels. High-purine foods, alcohol consumption, and sugary drinks can elevate uric acid levels. Certain medications, such as diuretics and aspirin, can affect uric acid levels as well. In individuals with chronic kidney disease, uric acid levels might be elevated due to reduced clearance by the kidneys. Urinary purine and pyrimidine profiles may be a great value for the diagnosis. The remarkable development of analytical techniques with the use of tandem mass spectrometry has improved the diagnosis of these diseases by the detection of purine, pyrimidine, and nucleoside intermediates in urines, some of them being not detectable using UV detection. However, the analysis of urinary purines and pyrimidines is often not part of the basic metabolic assessment.

7. Discussion

Neurological manifestations are major symptoms in inborn errors of purine and pyrimidine metabolism. These disorders present heterogenous phenotypes characterised by a spectrum of malformations, developmental delay, epilepsy, sensory impairments, and movement disorders. The clinical presentation is broad, but some elements may point to a diagnosis of an inborn error of purine and pyrimidine metabolism and are synthesised in Fig. 2. With the development of extended genetic analyses (whole exome sequencing and whole genome sequencing), new deficits have been discovered (PAICS and muscular ADSS deficiencies [11,45]). Likewise, the clinical phenotype of certain defects has been better described, emphasizing the presentation which is sometimes not very specific for already known diseases (*e.g.*, slight psychomotor retardation in ADSL deficiency) or symptoms in women with X-linked conditions (PRPS or HPRT deficiencies [8,23]). Even if these disorders are ultra-rare metabolic hereditary diseases, they are probably under-diagnosed. In front of suggestive clinical or laboratory signs, genetic testing in association with a biochemical screening including thorough purine and pyrimidine metabolites analysis and/or specific enzyme evaluation will probably increase the number of confirmed patients. Establishing the diagnosis is critical since these disorders are genetic and missing an accurate diagnosis may hinder the possibility of genetic counseling for the family. But most importantly, some of these diseases are treatable and early diagnosis and treatment can be life-changing for the child and the family.

A bulleted outline of the proposed review's structure and main message(s)

This review focused on the main neurological presentations of inborn errors of purine and pyrimidine metabolism. Although these diseases are rare, even ultra-rare, some are treatable or actionable with a better medical outcome of the child. Accurate diagnosis remains as well important for genetic counseling. The major steps of the metabolic pathways are summarised in Fig. 1. The text and the table outlined the

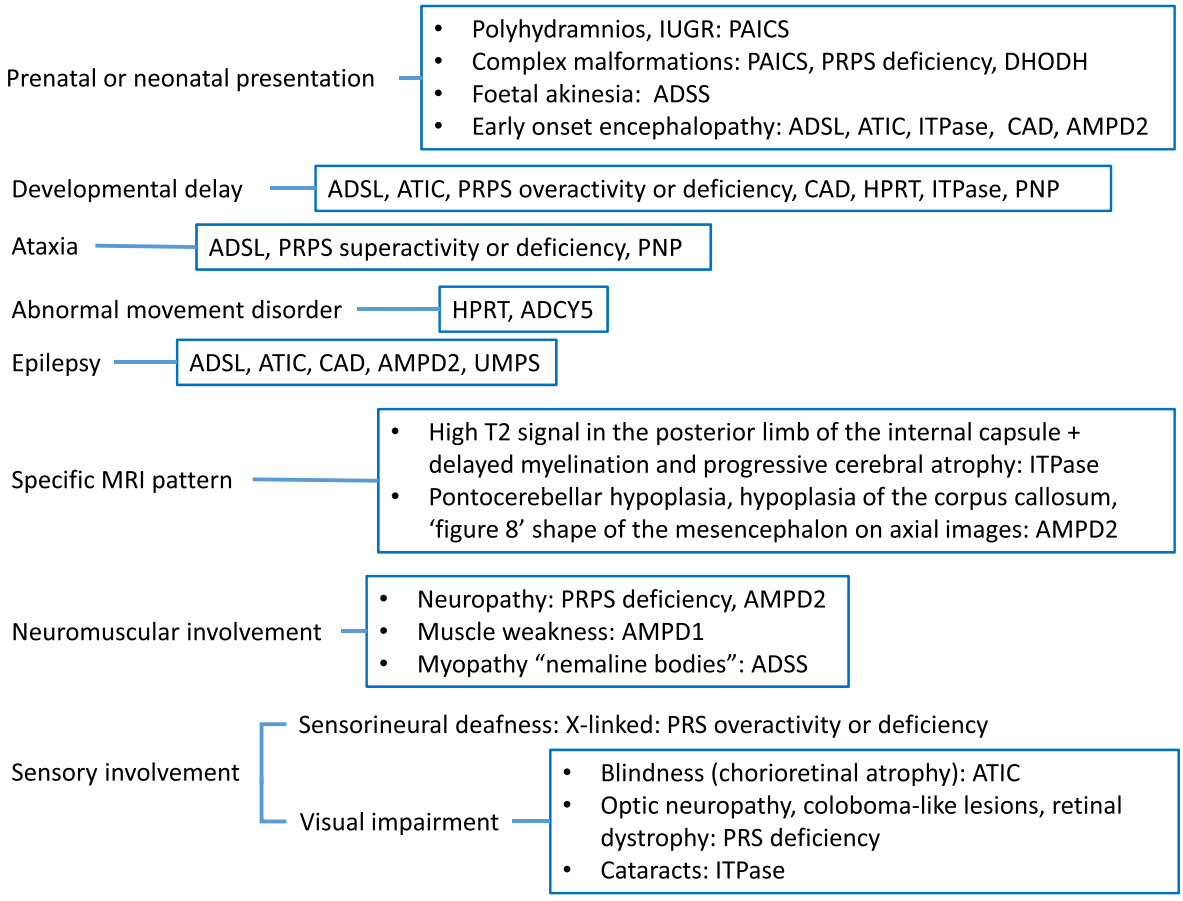

Fig. 2. This flowchart highlights the neurological signs most encountered in inborn errors of purine and pyrimidine metabolism. IUGR, intrauterine growth restriction; PAICS, phosphoribosyl-aminoimidazole carboxylase-phosphoribosyl-aminoimidazole-succinocarboxamide synthetase; PRPS, phosphoribosyl pyrophosphate synthetase; DHODH, dihydroorotate dehydrogenase; ADSS, adenylosuccinate synthase; ADSL, adenylosuccinate lyase; ATIC, aminoimidazolecarboxamide riboside transformylase-inosine monophosphate cyclohydrolase; ITPase, inosine triphosphatase; CAD, carbamoylphosphate synthetase 2-aspartate transcarbamylase-dihydroorotase; AMPD, adenine monophosphate deaminase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; PNP, purine nucleoside phosphorylase; ADCY5, adenylate cyclase 5; UMPS, uridine monophosphate synthase; MRI, magnetic resonance imaging.

clinical signs and diagnostic clues of the major diseases of this metabolic pathway for which neurological signs are prominent. Diseases with muscular symptoms are also included. Finally, Fig. 2 synthesised some important information for the clinician.

Declaration of competing interest

None.

Fundings

J.P. Dewulf is financially supported by the Fons de la Recherche Scientifique FNRS-FSR "F 5/4/150/5".

Acknowledgements

We warmly thank Pr. Georges van den Bergh (who recently passed away in July 2023) and Pr. Marie- Françoise Vincent for sharing their deep knowledge about this topic. We are very grateful to the European Paediatric Neurology Society (EPNS) Board of Directors for trusting us to present this webinar.

References

[1] M. Lesch, W.L. Nyhan, A familial disorder of uric acid metabolism and central nervous system function, Am. J. Med. 36 (1964) 561–570, https://doi.org/10.1016/0002-9343(64)90104-4.
[2] S. Marie, J.P. Dewulf, M.C. Nassogne, Disorders of purine and pyrimidine metabolism, in: J.M. Saudubray, M.R. Baumgartner, A. García-Cazorla, J.H. Walter (Eds.), Inborn Metabolic Diseases Diagnosis and Treatment, seventh ed., Springer, Berlin, 2022, pp. 587–614.
[3] S. Balasubramaniam, J.A. Duley, J. Christodoulou, Inborn errors of purine metabolism: clinical update and therapies, J. Inherit. Metab. Dis. 37 (2014) 669–686, https://doi.org/10.1007/s10545-014-9731-6.
[4] S. Balasubramaniam, J.A. Duley, J. Christodoulou, Inborn errors of pyrimidine metabolism: clinical update and therapy, J. Inherit. Metab. Dis. 37 (2014) 687–698, https://doi.org/10.1007/s10545-014-9742-3.
[5] J.P. Dewulf, S. Marie, M.C. Nassogne, Disorders of purine biosynthesis metabolism, Mol. Genet. Metabol. 136 (2022) 190–198, https://doi.org/10.1016/j.ymgme.2021.12.016.
[6] A.P. de Brouwer, H. van Bokhoven, S.B. Nabuurs, et al., PRPS1 mutations: four distinct syndromes and potential treatment, Am. J. Hum. Genet. 86 (2010) 506–518, https://doi.org/10.1016/j.ajhg.2010.02.024.
[7] B. Almoguera, S. He, M. Corton, et al., Expanding the phenotype of PRPS1 syndromes in females: neuropathy, hearing loss and retinopathy, Orphanet J. Rare Dis. 9 (2014) 190, https://doi.org/10.1186/s13023-014-0190-9.
[8] A. Fiorentino, K. Fujinami, G. Arno, et al., Missense variants in the X-linked gene PRPS1 cause retinal degeneration in females, Hum. Mutat. 39 (2018) 80–91, https://doi.org/10.1002/humu.23349.
[9] N. Lenherr, J. Christodoulou, J. Duley, et al., Co-therapy with S-adenosylmethionine and nicotinamide riboside improves t-cell survival and function in Arts Syndrome (PRPS1 deficiency), Mol. Genet. Metab. Rep. 26 (2021), 100709, https://doi.org/10.1016/j.ymgmr.2021.
[10] A.P.M. de Brouwer, J. Christodoulou, Phosphoribosylpyrophosphate synthetase superactivity, in: M.P. Adam, G.M. Mirzaa, R.A. Pagon, S.E. Wallace, L.J.H. Bean, K.W. Gripp, A. Amemiya (Eds.), GeneReviews® [Internet], University of Washington, Seattle (WA), 2008, pp. 1993–2023 [updated 2022.
[11] A. Pelet, V. Skopova, U. Steuerwald, et al., PAICS deficiency, a new defect of de novo purine synthesis resulting in multiple congenital anomalies and fatal outcome, Hum. Mol. Genet. 28 (2019) 3805–3814, https://doi.org/10.1093/hmg/ddz237.

[12] J. Jaeken, G. Van den Berghe, An infantile autistic syndrome characterised by the presence of succinylpurines in body fluids, Lancet 2 (1984) 1058–1061.
[13] G. Mastrogiorgio, M. Macchiaiolo, P.S. Buonuomo, et al., Clinical and molecular characterization of patients with adenylosuccinate lyase deficiency, Orphanet J. Rare Dis. 16 (2021) 112, https://doi.org/10.1186/s13023-021-01731-6.
[14] S. Sitaram, H.C. Banka, G. Vassallo, et al., Anticipatory banking of samples enables diagnosis of adenylosuccinase deficiency following molecular autopsy in an infant with vacuolating leukoencephalopathy, Am. J. Med. Genet. 191 (2023) 234–237, https://doi.org/10.1002/ajmg.a.62999.
[15] M. Holder-Espinasse, S. Marie, G. Bourrouillou, et al., Towards a suggestive facial dysmorphism in adenylosuccinate lyase deficiency? J. Med. Genet. 39 (2002) 440–442, https://doi.org/10.1136/jmg.39.6.440.
[16] A. Jurecka, V. Opoka-Winiarska, D. Rokicki, A. Tylki-Szymańska, Neurologic presentation, diagnostics, and therapeutic insights in a severe case of adenylosuccinate lyase deficiency, J. Child Neurol. 27 (2012) 645–649, https://doi.org/10.1177/0883073811424465.
[17] S. Marie, B. Heron, P. Bitoun, et al., AICA-ribosiduria: a novel, neurologically devastating inborn error of purine biosynthesis caused by mutation of ATIC, Am. J. Hum. Genet. 74 (2004) 1276–1281, https://doi.org/10.1086/421475.
[18] F. Ramond, M. Rio, B. Héron, et al., AICA-ribosiduria due to ATIC deficiency: delineation of the phenotype with three novel cases, and long-term update on the first case, J. Inherit. Metab. Dis. 43 (2020) 1254–1264, https://doi.org/10.1002/jimd.12274.
[19] J. Galli, E.M. Valente, J. Dewulf, et al., Expanding the spectrum of clinical severity of AICA-ribosiduria: report of two siblings with mild phenotype caused by a novel pathogenic variant in ATIC gene, Am. J. Med. Genet. 191 (2023) 575–581, https://doi.org/10.1002/ajmg.a.63036.
[20] F. Kortüm, R.A. Jamra, M. Alawi, et al., Clinical and genetic spectrum of AMPD2-related pontocerebellar hypoplasia type 9, Eur. J. Hum. Genet. 26 (2018) 695–708, https://doi.org/10.1038/s41431-018-0098-2.
[21] T. Gilboa, N. Elefant, V. Meiner, N. Hacohen, Delineating the phenotype and genetic basis of AMPD2-related pontocerebellar hypoplasia, Neurogenetics 24 (2023) 61–66, https://doi.org/10.1007/s10048-022-00706-4.
[22] M. Severino, F. Zara, A. Rossi, P. Striano, Teaching Neuro*Images*: figure of 8: the clue to the diagnosis of AMPD2 pontocerebellar hypoplasia (PCH9), Neurology 89 (2017) e172–e173, https://doi.org/10.1212/WNL.0000000000004542.
[23] H.A. Jinnah, I. Ceballos-Picot, R.J. Torres, et al., Attenuated variants of Lesch-Nyhan disease, Brain 133 (2010) 671–689, https://doi.org/10.1093/brain/awq013.
[24] H.F. Cakmakli, R.J. Torres, A. Menendez, et al., Macrocytic anemia in Lesch-Nyhan disease and its variants, Genet. Med. 21 (2019) 353–360, https://doi.org/10.1038/s41436-018-0053-1.
[25] D.J. Schretlen, M. Varvaris, T.D. Vannorsdall, et al., Brain white matter volume abnormalities in Lesch-Nyhan disease and its variants, Neurology 84 (2015) 190–196, https://doi.org/10.1212/WNL.0000000000001128.
[26] S. Tsagkaris, E.K.C. Yau, V. McClelland, et al., Metabolic patterns in brain 18F-fluorodeoxyglucose PET relate to aetiology in paediatric dystonia, Brain 146 (2023) 2512–2523, https://doi.org/10.1093/brain/awac439.
[27] R.J. Torres, Current understanding of Lesch-Nyhan disease and potential therapeutic targets, Expert Opinion on Orphan Drugs 7 (2019) 349–361, https://doi.org/10.1080/21678707.2019.1652597.
[28] H. Deng, B.T. Xiong, Y. Wu, W. Wang, Deep brain stimulation in Lesch-Nyhan syndrome: a systematic review, Neurosurg. Rev. 46 (2023) 40, https://doi.org/10.1007/s10143-023-01950-4.
[29] Y.Z. Chen, J.R. Friedman, D.H. Chen, et al., Gain-of-function ADCY5 mutations in familial dyskinesia with facial myokymia, Ann. Neurol. 75 (2014) 542–549, https://doi.org/10.1002/ana.24119.
[30] P.J. Menon, C. Nilles, L. Silveira-Moriyama, et al., Scoping review on ADCY5-related movement disorders, Mov. Disord. Clin. Pract. 10 (2023) 1048–1059, https://doi.org/10.1002/mdc3.13796.
[31] P.J. Menon, C. Nilles, L. Silveira-Moriyama, et al., Scoping review on ADCY5-related movement disorders, Mov. Disord. Clin. Pract. 10 (2023) 1048–1059, https://doi.org/10.1002/mdc3.13796.
[32] S.H. Kevelam, J. Bierau, R. Salvarinova, et al., Recessive ITPA mutations cause an early infantile encephalopathy, Ann. Neurol. 78 (2015) 649–658, https://doi.org/10.1002/ana.24496.
[33] M. Scala, S.B. Wortmann, N. Kaya, et al., Clinico-radiological features, molecular spectrum, and identification of prognostic factors in developmental and epileptic encephalopathy due to inosine triphosphate pyrophosphatase (ITPase) deficiency, Hum. Mutat. 43 (2022) 403–419, https://doi.org/10.1002/humu.24326.
[34] D. Rymen, M. Lindhout, M. Spanou, et al., Expanding the clinical and genetic spectrum of CAD deficiency: an epileptic encephalopathy treatable with uridine supplementation, Genet. Med. 22 (2020) 1589–1597, https://doi.org/10.1038/s41436-020-0933-z.
[35] F. Del Caño-Ochoa, B.G. Ng, A. Rubio-Del-Campo, et al., Beyond genetics: deciphering the impact of missense variants in CAD deficiency, J. Inherit. Metab. Dis. (2023), https://doi.org/10.1002/jimd.12667.
[36] S.B. Ng, K.J. Buckingham, C. Lee, et al., Exome sequencing identifies the cause of a mendelian disorder, Nat. Genet. 42 (2010) 30–35, https://doi.org/10.1038/ng.499.
[37] J.A. Duley, M.G. Henman, K.H. Carpenter, et al., Elevated plasma dihydroorotate in Miller syndrome: biochemical, diagnostic and clinical implications, and treatment with uridine, Mol. Genet. Metabol. 119 (2016) 83–90, https://doi.org/10.1016/j.ymgme.2016.06.008.
[38] M. Fleger, J. Willomitzer, R. Meinsma, et al., Dihydropyrimidine dehydrogenase deficiency: metabolic disease or biochemical phenotype? JIMD Rep. 37 (2017) 49–54, https://doi.org/10.1007/8904_2017_14.
[39] Y. Nakajima, J. Meijer, D. Dobritzsch, et al., Dihydropyrimidinase deficiency in four East Asian patients due to novel and rare *DPYS* mutations affecting protein structural integrity and catalytic activity, Mol. Genet. Metabol. 122 (2017) 216–222, https://doi.org/10.1016/j.ymgme.2017.10.003.
[40] S. Righetti, R.J.N. Allcock, J. Yaplito-Lee, et al., The relationship between beta-ureidopropionase deficiency due to *UPB1* variants and human phenotypes is uncertain, Mol. Genet. Metabol. 137 (2022) 62–67, https://doi.org/10.1016/j.ymgme.2022.07.011.
[41] Y. Nakajima, J. Meijer, D. Dobritzsch, et al., Clinical, biochemical and molecular analysis of 13 Japanese patients with β-ureidopropionase deficiency demonstrates high prevalence of the c.977G > A (p.R326Q) mutation, J. Inherit. Metab. Dis. 37 (2014) 801–812, https://doi.org/10.1007/s10545-014-9682-y.
[42] C.A.T.C. Lunenburg, C.H. van der Wouden, M. Nijenhuis, et al., Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines, Eur. J. Hum. Genet. 28 (2020) 508–517, https://doi.org/10.1038/s41431-019-0540-0.
[43] J. Fidlerova, P. Kleiblova, M. Bilek, et al., Contribution of dihydropyrimidinase gene alterations to the development of serious toxicity in fluoropyrimidine-treated cancer patients, Cancer Chemother. Pharmacol. 65 (2010) 661–669, https://doi.org/10.1007/s00280-009-1071-0.
[44] M. de With, A. Sadlon, E. Cecchin, et al., Implementation of dihydropyrimidine dehydrogenase deficiency testing in Europe, ESMO Open 8 (2023), 101197, https://doi.org/10.1016/j.esmoop.2023.101197.
[45] H.J. Park, Y.B. Hong, Y.C. Choi, et al., ADSSL1 mutation relevant to autosomal recessive adolescent onset distal myopathy, Ann. Neurol. 79 (2016) 231–243, https://doi.org/10.1002/ana.24550.
[46] M. Pergande, S. Motameny, Ö. Özdemir, et al., The genomic and clinical landscape of fetal akinesia, Genet. Med. 22 (2020) 511–523, https://doi.org/10.1038/s41436-019-0680-1.
[47] Y. Saito, A. Nishikawa, A. Iida, et al., ADSSL1 myopathy is the most common nemaline myopathy in Japan with variable clinical features, Neurology 95 (2020) e1500–e1511, https://doi.org/10.1212/WNL.0000000000010237.
[48] K. Grohmann, H. Lauffer, P. Lauenstein, G.F. Hoffmann, G. Seidlitz, Hereditary orotic aciduria with epilepsy and without megaloblastic anemia, Neuropediatrics 46 (2015) 123–125, https://doi.org/10.1055/s-0035-1547341.
[49] M.E. Haggard, L.H. Lockhart, Megaloblastic anemia and orotic aciduria. A hereditary disorder of pyrimidine metabolism responsive to uridine, Am. J. Dis. Child. 113 (1967) 733–740, https://doi.org/10.1001/archpedi.1967.02090210147020.
[50] M.L. Markert, Purine nucleoside phosphorylase deficiency, Immunodefic. Rev. 3 (1991) 45–81.
[51] B. Torun, A. Bilgin, D. Orhan, et al., Combined immunodeficiency due to purine nucleoside phosphorylase deficiency: outcome of three patients, Eur. J. Med. Genet. 65 (2022), 104428, https://doi.org/10.1016/j.ejmg.2022.104428.
[52] A. Jurecka, A. Tylki-Szymanska, Inborn errors of purine and pyrimidine metabolism: a guide to diagnosis, Mol. Genet. Metabol. 136 (2022) 164–176, https://doi.org/10.1016/j.ymgme.2022.02.007.