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Metabolic disorders of purine metabolism affecting the nervous system

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INTRODUCTION

The purines are a group of molecules used by all cells of the body for many essential biochemical processes. They are synthesized by a multistep pathway known as the *de novo* synthetic pathway, they pass through several steps where they may be interconverted, and ultimately they are degraded and excreted as uric acid (Fig. 187.1). An example purine is adenosine triphosphate (ATP), which is required for many energy-requiring enzymatic reactions. ATP and guanosine triphosphate (GTP) also serve as building blocks for the synthesis of DNA and RNA. Some purine molecules, such as nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD), serve as cofactors that are used in other reactions. The cyclic nucleotides, cAMP and cGMP, play a key role in many intracellular signaling pathways.

In addition to many biochemical processes that are used ubiquitously by all cells, some purines serve more specialized roles in the nervous system (Rathbone et al., 1999; Abbracchio et al., 2009). For example, aden- osine and its phosphorylated nucleotides act as neuro-transmitters or trophic agents in the nervous system. Similar roles exist for guanosine and its nucleotides. Uric acid also has been proposed as an endogenous antioxidant of relevance to multiple sclerosis, stroke, and neurodegenerative diseases.

Defects in some of the enzymes of purine metabolism are known to be associated with specific clinical disorders (Table 187.1). Although purines are essential in all cells of the body, the clinical manifestations of these disorders often suggest the nervous system to be more seriously affected than other organs. This chapter provides detailed summaries for three disorders in which the neurological manifestations have been well characterized, as

well as briefer summaries for several other disorders for which the neurological manifestations are less well characterized. It does not cover putative disorders for which only small numbers of patients have been described in isolated reports.

ADENYLOSUCCINATELYASE DEFICIENCY

Clinical features

The clinical presentations of adenylosuccinate lyase (ADSL) deficiency are very diverse. Most of the initial reported patients, often referred to as type I, display variable associations of psychomotor retardation from birth, followed by epilepsy in infancy, autistic features (absence of eye contact, repetitive gestures, bouts of agitation, temper tantrums, self-injurious behavior) hypotonia, feeding problems, and occasional growth retardation with muscle wasting (Van den Berge and Jaeken, 2001). Later, patients were diagnosed who presented with intractable neonatal convulsions. A very early presentation has been described with intrauterine growth impairment, microcephaly, fetal hypokinesia, and absence of fetal heart rate variability. This was followed after birth by severe hypotonia requiring mechanical ventilation, intractable seizures, and early death (Mouchegh et al., 2007). Microcephaly is often present. As a rule there are no other dysmorphic features, except for two patients with brachycephaly associated with a long, flat philtrum and thin upper lip (Holder-Espinasse et al., 2002).

Rare patients, referred to as type II, are strikingly less intellectually impaired as compared to type I. One patient displayed only delayed motor development and profound hypotonia. Another boy presented with high functioning autism without other symptoms except for two epileptic seizures (Stathis et al., 2000). Recently ADSL deficiency was diagnosed in two sisters with a behavioral phenotype resembling Angelman syndrome (Gitiaux et al., 2009).

Genetics

ADSL deficiency is inherited as an autosomal recessive trait. To date, the defect has been diagnosed in over 70 patients in various European countries and in the USA. The disorder seems to be rare in the UK. More than 50 mutations of the *ADSL* gene, located on chromosome 22q, have been identified. Most are missense mutations, and about half of the patients are compound heterozygotes. A common mutation is R426H, carried by several unrelated patients from various countries, but most other mutations are unique. Most mutations lead to instability of the enzyme, without modifications of its kinetic properties, and result in a parallel decrease of activity towards its substrates, succinyl aminoimidazolecarboxamide ribotide (SAICAR) and adenylosuccinate (S-AMP). The severity of the clinical symptoms tends to correlate with residual activity. A R303C mutation, found in two independent type II patients with much less pronounced psychomotor retardation, is thermostable and displays a markedly lower activity with S-AMP than with SAICAR. This provides an explanation for the markedly higher ratios of S-Ado/SAICA-riboside, the dephosphorylated forms of the enzyme's substrates, in these patients.

Pathogenesis

ADSL (EC 4.3.2.2) catalyzes two steps in the synthesis of the purine nucleotides (Fig. 187.1). These include the conversion of SAICAR into aminoimidazolecarboxamide ribotide (AICAR), and the conversion of S-AMP into AMP. The deficiency results in the accumulation in body fluids, mainly cerebrospinal fluid and urine, of SAICA-riboside and succinyladenosine (S-Ado). These succinyl purines are the products of dephosphorylation, by 5'-nucleotidase(s), of the two substrates of the enzyme, and constitute the hallmark of the disorder. Although ADSL deficiency would be expected to lead to decreased synthesis of adenine and guanine nucleotides, normal levels of both were measured in freeze-clamped liver, kidney, and muscle of patients. This can be explained by residual activity of the enzyme and/or by circumvention of the defect by the purine salvage pathways, involving hypoxanthine-guanine phosphoribosyltransferase (HPRT) and adenine phosphoribosyltransferase (APRT).

The symptoms of ADSL deficiency might be caused by neurotoxic effects of the accumulating succinyl purines. In the majority of patients, who can be classified as type I, S-Ado/SAICA-riboside ratios are below or around 1. In the much less frequent, and markedly less affected, type II patients, levels of SAICA-riboside are similar to those in type I, but those of S-Ado are higher, resulting in S-Ado/SAICAriboside ratios above 2. This suggests that SAICA-riboside is the neurotoxic compound, and that S-Ado could protect against its deleterious effects. However, all attempts to demonstrate neurotoxicity of the succinyl purines have so far failed. Therefore, the exact mechanism by which ADSL deficiency leads to neurobehavioral dysfunction remains uncertain.

Diagnosis

The wide diversity of clinical presentations of ADSL deficiency renders systematic screening for the defect mandatory in all patients presenting with unexplained intractable neonatal convulsions, severe infantile epilepsy, marked or mild psychomotor retardation, hypotonia, microcephaly, autistic features, and neurological disease without clear etiology. Diagnosis is based on the presence in urine and cerebrospinal fluid of the succinyl purines, S-Ado and SAICA-riboside, both normally nearly undetectable. For screening, a modified Bratton-Marshall test (Laikind et al., 1986), performed on urine, appears most practical. False positive results may be observed in patients who receive antibiotics, particularly sulfonamides, and antiepileptic medications. The succinyl purines can also be detected by other techniques, final diagnosis requiring HPLC with UV detection or LC-MS/MS (Ito et al., 2000; Hartmann et al., 2006).

Accumulation of SAICA-riboside was also observed in a female infant with profound intellectual disability, dysmorphic features (prominent forehead, brachycephaly, wide mouth, low-set ears, prominent clitoris) and blindness. It was, however, overshadowed by a massive excretion of AICA-riboside, the dephosphorylated counterpart of AICAR. This reflects a deficiency of AICAR-transformylase/IMP-cyclohydrolase (ATIC), a bifunctional enzyme catalyzing the two last steps of purine biosynthesis (Marie et al., 2004).

Treatment and prognosis

To replenish hypothetically reduced concentrations of adenine nucleotides in ADSL deficient tissues, a number of patients have been treated for several months with oral supplements of adenine and allopurinol, the latter to avoid conversion of adenine by xanthine oxidase into very poorly soluble 2,8-dihydroxyadenine. No clinical or biochemical improvement was recorded, with the exception of some acceleration of growth. More recently, therapeutic trials have been performed with D-ribose (10 mmol/kg per day) and uridine (2 mmol/kg per day). In a single patient a reduction in seizure frequency was observed, but this effect was not sustained. In four other patients, D-ribose treatment was also ineffective (Jurecka et al., 2008).

The prognosis of ADSL-deficient patients is variable. Several of those presenting with neonatal epilepsy have died within the first months of life. In patients with severe intellectual disability, evolution is characterized by absent or minimal progression of psychomotor development and persistence of autistic behavior, except for some improvement of eye contact. Those with less severe cognitive impairment have reached adult age and may perform satisfactorily in a protected environment.

LESCH–NYHAN DISEASE

Clinical features

Patients with classic Lesch–Nyhan disease (LND) have a characteristic clinical phenotype that includes three major elements (Jinnah and Friedmann, 2001). The first is overproduction of uric acid with its consequences of hyperuricemia, nephrolithiasis, gouty arthritis, and subcutaneous tophi. Hyperuricemia may be evident from birth, but it may be mild and is often overlooked. The other consequences of uric acid overproduction most often emerge in late childhood or early adolescence, but may rarely occur within the first months of life.

The second major element of the clinical phenotype is motor disability. The main problem is severe generalized dystonia superimposed on hypotonia, sometimes combined with choreoathetosis or corticospinal signs (Jinnah et al., 2006). The motor disorder is often mistaken as quadriplegic cerebral palsy until other aspects of the clinical phenotype become more apparent. These problems are sufficiently severe that self-care is not feasible.

The third major element of the clinical phenotype is a peculiar neuropsychological profile (Nyhan, 1976; Schretlen et al., 2001, 2005). The most characteristic problem is recurrent self-injurious behavior with biting of the digits, lips, or buccal mucosa. Self-hitting, eye-poking, head-banging, and other forms of self-injury are also common. Many patients also have other difficult behaviors including spitting at or hitting others and use of socially inappropriate language. Intellectual disability is common, but severe cognitive impairment is rare. Global IQ scores most often fall in the 60–70 range, with the most serious difficulties in attention but relatively preserved awareness and language abilities.

In addition to the characteristic clinical phenotype of classic LND, there also are attenuated variants with incomplete or milder phenotypes (Emmerson and Thompson, 1973; Puig et al.,

2001; Jinnah et al., 2010). These LND variants all have overproduction of uric acid, but they lack self-injurious behavior. In addition, their motor disability is often less severe or even absent, and they may have relatively normal global IQ scores. The LND variants currently are divided into two groups. The most mildly affected group is designated HPRT-related hyperuricemia. These patients have overproduction of uric acid, but motor and cognitive difficulties are not evident. An intermediate group is designated HPRT-related neurological dysfunction. These patients have overproduction of uric acid along with some neurological or behavioral problems, but self-injury is absent (Fig. 187.2).

Genetics

LND and its variants are inherited in a sex-linked recessive manner, with virtually all cases being males (Jinnah et al., 2000, 2004). They are caused by mutations on the long arm of the X-chromosome in the *HPRT* gene, which encodes the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT; EC 2.4.2.8). Mutations of the coding region are heterogeneous including missense mutations, nonsense mutations, deletions, insertions, duplications, and other substitutions or rearrangements. Noncoding mutations at splice junctions and regulatory regions also have been described.

Genotype-phenotype studies have indicated that a simple correspondence between specific mutations and specific clinical features does not exist (Jinnah et al., 2000, 2004). Instead, the influence of the mutation on residual HPRT enzyme function appears to be more informative than the mutation itself. Mutations expected to produce a null enzyme, such as nonsense or frame-shifting mutations, are typically associated with the most severe phenotype of classic LND. The milder variant phenotypes typically result from mutations capable of permitting some residual enzyme function, such as conservative missense mutations.

These predictions from genetic studies are supported by biochemical studies of HPRT enzyme function in live fibroblast cultures, where residual enzyme activity correlates with overall clinical severity. However, exceptions exist where enzyme function does not correlate with disease severity, especially when assays are done on blood or cell extracts rather than live cells.

Pathogenesis

The HPRT enzyme plays a role in recycling the purine bases hypoxanthine and guanine back into the purine nucleotide pools (Fig. 187.1). The pathogenesis of uric acid overproduction in HPRT deficiency is well understood. In the absence of HPRT, the purine bases are metabolized into uric acid because they cannot be recycled (Jinnah and Friedmann, 2001). Additionally, regulatory changes in purine synthesis result in increased synthesis of purines via the *de novo* pathway. These two processes cause uric acid overproduction. The excess uric acid tends to precipitate in certain body fluids since it is near its limit of solubility. Stones may form in any portion of the urogenital system where uric acid is concentrated by the kidneys, resulting in nephrolithiasis or crystalluria. It may also precipitate in the synovial fluid of the joints, causing gout.

The pathogenesis of the neurological and neurobehavioral anomalies is less well understood. These problems do not appear to be the direct result of uric acid overproduction. Autopsy studies have not revealed overt morphological defects or signs of neurodegeneration (Jinnah et al., 2006; Del Bigio and Halliday, 2007). Instead, the absence of HPRT appears to influence the maturation of specific neural pathways in the brain. The mesotelencephalic dopamine pathways appear to be most vulnerable. Autopsy studies have shown 60–90% loss of dopamine in the basal ganglia and PET studies have shown similar reductions in dopamine transporters or fluorodopa uptake in the same regions.

The disruption of the developing dopaminergic pathways from the substantia nigra to the putamen is likely to be responsible for the dystonic motor disability, while disruption of the pathways from the ventral tegmentum to the accumbens and prefrontal cortex is likely to be responsible for the behavioral peculiarities (Visser et al., 2000). Dysfunction of dopaminergic pathways from the midbrain to the caudate and frontal cortex may be responsible for the abnormal cognitive profile, though additional direct dysfunction of cerebral cortical neurons may also play a role.

Diagnosis

A presumptive clinical diagnosis of LND is straightforward when all the clinical features of the classic syndrome are apparent. Serum uric acid is usually, but not always, above the upper limits of normal, and serves as a useful screening test. Urinary uric acid values are more often abnormal, especially 24 hour specimens or after correction for creatinine excretion. Definitive diagnosis requires demonstration of reduced HPRT enzyme activity in blood cells or fibroblasts, or documentation of a pathogenic mutation in the *HPRT* gene. Diagnosis is more challenging at a young age before all the clinical features are manifest. The telltale self-injurious behavior emerges at a median age of 2 years, but may be delayed until teenage years. The sometimes slightly elevated serum uric acid is easily overlooked, and kidney stones or gout may be delayed for decades.

Diagnosis also is challenging in the LND variants with attenuated syndromes. Self-injurious behavior is absent in the variants, and cognitive or motor handicaps may be mild. The most useful clues are hyperuricemia, nephrolithiasis, or gout. Although these problems are common in adults, they are uncommon below 40 years of age. Their occurrence should prompt further evaluation for HPRT deficiency, especially if combined with evidence for motor or cognitive impairment. Evaluations are conducted as for classic LND, via biochemical assessment for HPRT enzyme deficiency or molecular confirmation of an *HPRT* gene defect.

Treatment and prognosis

Treatments are organized according to problem symptoms (Jinnah and Friedmann, 2001). The overproduction of uric acid must be treated in all cases. Treatment with allopurinol to inhibit uric acid production along with generous hydration is usually sufficient. If kidney stones continue to develop while on therapy, chemical analysis of the stones and advice from an expert in metabolic disease can be helpful. Stones composed of uric acid may

suggest the dose of allopurinol is too low or that the drug is not effective. Stones composed predominantly of xanthine and oxypurinol may indicate the dose of allopurinol is too high.

The treatment of motor disability involves the use of assistive devices such as a wheelchair as needed. Increased muscle tone is often treated with benzodiazepines or baclofen. In our experience, dystonia in LND does not respond well to anticholinergics, levodopa, dopamine agonists, or dopamine depletors or antagonists.

The treatment of self-injurious behavior requires the use of protective restraints applied to the limbs. They must be positioned to prevent self-hitting or self-biting. Restraints may also be required for the trunk or head. Biting of the lips or tongue requires dental extraction in approximately half of the cases. Self-injurious behavior also responds to behavior modification methods that involve extinction, although these methods usually are not sufficient to eliminate restraints entirely. Neuroleptics may be used during particularly stressful or difficult behavior periods, but they should be used only transiently because they are sedating and they carry substantial risk of side-effects.

MYOADENYLATEDEAMINASE DEFICIENCY

Clinical features

Inherited myoadenylate deaminase (mAMPD) has heterogeneous clinical manifestations (Table 187.2). The vast majority of individuals with mAMPD deficiency are asymptomatic (Norman and Sabina, 2010). Those who develop symptoms typically present with exercise intolerance accompanied by muscle pain and cramping (Table 187.2). Symptoms most commonly begin in adulthood, but they may begin in late childhood. Symptoms typically are nonprogressive. Myoglobinuria following strenuous exercise rarely has been reported. Increased serum creatine kinase has been found in approximately half of symptomatic individuals; however, in many cases this value was normal at rest and increased into the abnormal range only following exercise. Electromyography may be normal, but minor abnormalities have been described in some patients.

Though most individuals with mAMPD deficiency are asymptomatic, they may exhibit measurable physiological abnormalities during exercise. Exercise studies in healthy population samples have revealed functional abnormalities in asymptomatic individuals homozygous for a common mutation in the AMPD1 gene, c.34C>T encoding Q12X (Rico-Sanz et al., 2003), suggesting that these individuals may be at risk of developing symptoms. Notably, mAMPD deficiency has been identified as a genetic risk factor in individuals who develop pain, weakness, and other symptoms of muscle dysfunction while on lipid-lowering drug therapy (Vladutiu et al., 2006).

Owing to its high incidence in the Caucasian population, mAMPD deficiency may also present coincidentally along with a wide array of other neuromuscular and rheumatological conditions, in which cases the contribution of the mAMPD deficiency may be unclear because symptoms are typically dominated by the associated disorder. Nevertheless, there is substantial evidence supporting a cause-and-effect relationship between mAMPD deficiency and myopathy. For example, c.34C>T appears to act synergistically with mutations in other

genes known to be associated with other metabolic disorders of skeletal muscle to promote myopathic symptoms. A subset of these individuals, termed “double trouble,” is characterized by complete deficiencies in both *AMPD1* and a second metabolic gene, which in many cases is associated with a more severe phenotype than what is typically observed with either abnormality alone (Bruno et al., 1998).

In a second subset of individuals with metabolic myopathy, heterozygosity for c.34C>T has been found secondary to complete genetic deficiencies in other metabolic pathways and may also contribute to clinical variability of the primary disorder, and in some cases more profound functional deficits may be evident (Rubio et al., 2008). A third subset of metabolic myopathy comprises individuals who are carriers of mutations in more than one energy-generating pathway, or at multiple steps in the same pathway. Termed “synergistic heterozygosity,” the clinical presentations in these individuals may be similar to those with complete genetic deficiencies of the pathways involved (Vockley et al., 2000). Although there is no evidence for diminished exercise capacity in asymptomatic c.34C>T heterozygotes in the absence of another neuromuscular or rheumatological condition, augmented hyperemia and decreased tissue damage have been reported in response to forearm ischemia in these individuals compared to normal homo-zygotes (Riksen et al., 2007).

Genetics

Deficiency of mAMPD is an inherited autosomal recessive disorder caused by mutations in the *AMPD1* gene, which is located on the short arm of chromosome 1 (Norman and Sabina, 2010). The prominent *AMPD1* mutant allele in the Caucasian population includes a C to T transition at nucleotide (c.34C>T), which creates a nonsense codon, Q12X, in the mRNA resulting in a severely truncated polypeptide devoid of enzymatic activity. Notably, nucleotide is located in mini-exon 2 that is removed from 0.6–2% of processed mRNA transcripts by a cassette-type alternative splicing event. Although other rare mutations have been identified in the *AMPD1* gene, c.34C>T allele frequencies across populations account for differences in the incidence of mAMPD deficiency, which is highest in Caucasians, intermediate in African Americans, and lowest in Asians.

Potential mechanisms underlying variable penetrance in mAMPD deficiency are coinheritance of mutations in other energy-generating pathways and inter-individual differences in an alternative splicing event that removes the nonsense mutation from mRNA produced by the predominant mutant c.34C>T allele.

Pathogenesis

AMP deaminase (AMPD; EC 3.5.4.6) catalyzes the irreversible deamination of AMP to IMP and is one component of the purine nucleotide cycle (Fig. 187.1). AMPD is manifest in human tissues and cells as a multigene family comprising three genes. Myoadenylate deaminase (mAMPD) deficiency affects predominantly skeletal muscle adenine nucleotide catabolism.

Whether symptomatic or asymptomatic, when individuals with mAMPD deficiency exercise, their skeletal muscle does not accumulate IMP and NH₃, as occurs in normal

subjects. This abnormality forms the basis for a commonly used lactate-ammonia test conducted during forearm exercise that is also used to detect glycolytic myopathies. Results of muscle biopsy examined by routine histochemical staining and electron microscopy have varied from no pathologic findings to mild abnormalities in distribution of fiber size.

The mechanisms responsible for myopathic symptoms are thought to arise from interruption of the purine nucleotide cycle from AMP to IMP and back again. These series of reactions may function during exercise to maintain the adenylate energy charge of the myocyte, enhance the rate of glycolysis, and fuel the citric acid cycle (Norman and Sabina, 2010).

The high prevalence of the c.34C>T allele in Caucasians suggests that this genetic variation may confer some selective advantage to the nearly one in four carriers of the mutation in this population. This hypothesis has prompted a number of studies designed to explore correlations between *AMPD1* genotype and clinical outcomes. Initial retrospective studies identified the c.34C>T allele as a marker of improved clinical outcome in patients with heart failure and coronary artery disease. However, subsequent retrospective studies employing larger patient cohorts were unable to confirm these initial associations, with one finding significantly poorer survival for c.34C>T heterozygotes in heart failure and following myocardial infarction. A single prospective study also failed to confirm a survival benefit among heart failure patients carrying the c.34C>T mutation, although a nominal trend was observed when the analysis was restricted to patients with ischemic heart failure. While survival data are conflicting, another retrospective study in both coronary artery disease and heart failure patients found that several indices of the metabolic syndrome (i.e., obesity, hyperglycemia, and diabetes) were reduced in Q12X heterozygotes compared to those values in corresponding normal homozygotes with these clinical disorders (Safranow et al., 2009).

Diagnosis

Deficiency of mAMPD is typically diagnosed with a forearm lactate-ammonia blood test or by histochemical staining of skeletal muscle biopsy material (Sabina and Holmes, 2001). *AMPD1* genotyping and AMPD enzyme assay can also be used to diagnose or confirm mAMPD deficiency.

Treatment and prognosis

While there are no reliable medical therapies for symptomatic mAMPD deficiency, oral ribose has reportedly provided temporary relief in a few cases, but not in others (Norman and Sabina, 2010). Avoidance of triggers such as exercise is generally recommended.

OTHER PURINE DISORDERS

Overview

There are several others disorders of purine metabolism where the neurological features are less well characterized, or available for only a small number of patients (Camici et al., 2009). In some of these disorders, the neurological features are inconsistent, raising

questions regarding their relationship to the metabolic disorder. The most prevalent of these are outlined below and summarized in Table 187.1.

Phosphoribosylpyrophosphate synthase defects

Phosphoribosylpyrophosphate (PRPP) synthase provides an example of how different mutations in the same gene may lead to different clinical phenotypes. Mutations in the *PRPS1* gene that increase the activity of PRPP synthase lead to sensorineural hearing loss. Approximately half of these patients also have psychomotor retardation to varying degrees.

Mutations in the *PRPS1* gene that reduce but do not eliminate PRPP synthase activity have been linked with some cases of the Charcot–Marie–Tooth syndrome, type CMTX5. Affected individuals have sensorineural hearing loss, optic neuropathy, and peripheral sensorimotor neuropathy. Mutations leading to a null PRPP synthase have been linked with Arts syndrome, which is characterized by hearing and visual loss, psychomotor retardation, and recurrent infections.

The mechanisms by which abnormalities in PRPP synthase cause neurological dysfunction are not known. PRPP serves as a cosubstrate for a diverse family of enzymes, only three of which are involved directly in purine metabolism. These include the first and rate-limiting step of *de novo* purine synthesis (amidophosphoribosyltransferase (AMPRT)) as well two recycling enzymes (APRT and HPRT). The clinical syndromes associated with PRPP synthase defects do not resemble the syndromes associated with APRT or HPRT defects. Thus neurological manifestations linked with PRPP synthase may result from alterations in nonpurine pathways.

Purine nucleotide phosphorylase deficiency

Purine nucleotide phosphorylase (PNP) deficiency typically presents with abnormalities related to the immune system. Most patients have varying degrees of immunodeficiency, and one third have autoimmune diseases. Approximately half exhibit neurological features. There is a broad range of severity. More severely affected individuals exhibit severe psychomotor retardation, while less severely affected individuals may have only mild motor or cognitive abnormalities. The reason for the marked variability of neurological difficulties remains uncertain. Some of the neurological problems may result directly from the enzyme defect, while others may be secondary to the immune defects or interaction with other unknown inherited or acquired factors.

Adenosine deaminase deficiency

Adenosine deaminase (ADA) deficiency most often presents with the syndrome of severe combined immunodeficiency, with lethal infections in infancy or early childhood. Children who survive with treatments involving bone marrow transplantation or enzyme replacement occasionally develop neurological difficulties as they grow older. Problems may include psychomotor retardation, seizures, or hearing loss. Some of these problems may result directly from the enzyme defect, while others may be the result of chronic infection or their treatments.

Deoxyguanosine kinase deficiency

The deoxyguanosine kinase (dGK) enzyme is mitochondrial, and its deficiency presents with a severe form of mitochondrial DNA depletion syndromes. Most patients present with liver failure and severe psychomotor retardation shortly after birth. Fatal multiorgan system failure is common in the first year of life.

IMP dehydrogenase deficiency

Mutations in the gene encoding IMP dehydrogenase (IDH) 1 have been linked with retinitis pigmentosa type 10 and some cases of Leber congenital amaurosis.

SUMMARY AND CONCLUSIONS

Although purines are required by all living cells, disorders of purine metabolism often have clinical features suggestive of selective involvement of specific parts of the nervous system. For example, patients with ADSL deficiency exhibit neurocognitive features and epilepsy characteristic of dysfunction of the cerebral cortex, whereas LND patients with HPRT deficiency have a syndrome that has been linked with dysfunction of the basal ganglia. Similarly, deficiency of mAMPD affects only muscle, defects of PRPP metabolism primarily affect nerves, and IMP dehydrogenase deficiency causes retinopathy.

There are many potential reasons for selective dysfunction of specific parts of the nervous system. In some cases, the unique neurological features are attributable to preferential expression of a specific enzyme or isoform to a specific tissue, as in mAMPD deficiency. In other cases, the neurological features suggest selective vulnerability of specific parts of the nervous system. These disorders provide an unusual window on the unique importance of purine metabolism for different parts of the nervous system.

The disorders of purine metabolism are rare, and the spectrum of the clinical phenotype is not yet fully characterized for each one. It therefore is likely that additional clinical manifestations for many known disorders will be forthcoming. It also is likely that novel disorders may be linked with enzymes that are not yet known to be associated with disease.

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Fig. 187.1.

Purine metabolic pathways. Abbreviations: 5'NT, 5'-nucleotidase; AICAR, aminoimidazolecarboxamide ribotide; ADA, adenosine deaminase; AK, adenosine kinase; ADP, adenosine diphosphate; ADSL, adenylosuccinate lyase; AMP, adenosine monophosphate or adenylic acid; AMPD, adenylyate deaminase; AMPRT, amidophosphoribosyltransferase; APRT, adenine phosphoribosyltransferase; ASS, adenylosuccinate synthetase; ATIC, AICAR-transformylase/IMP-cyclohydrolase; ATP, adenosine triphosphate; GA, guanase; GDP, guanosine diphosphate; GMP, guanosine

monophosphate or guanylic acid; GS, GMP-synthase; GTP, guanosine triphosphate; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IDH, IMP-dehydrogenase; IMP, inosine monophosphate or inosinic acid; NDK, nucleoside diphosphate kinase; NMK, nucleoside mono-phosphate kinase; PRPP, phosphoribosylpyrophosphate; SAI-CAR, succinyl-aminoimidazolecarboxamide ribotide; S-AMP, succinyl-AMP or adenylosuccinate; XMP, xanthine monophosphate or xanthylic acid; XOR, xanthine oxidoreductase.

Fig. 187.2.

Schematic of the spectrum of clinical features associated with HPRT deficiency. The three commonly recognized patient subgroups include classic Lesch–Nyhan disease, HPRT-related neurological dysfunction (HND), and HPRT-related hyper-uricemia (HRH). The severity and frequency of each clinical problem is shown by the length and thickness of the tapered arrow.

Table 187.1

Disorders of purine metabolism

Disorder	Enzyme*	Neurological features	Other clinical features
Adenine phosphoribosyltransferase deficiency	APRT	None	Nephrolithiasis
Adenylosuccinate synthase deficiency	ADSL	Intellectual disability, autistic features, epileptic seizures	Growth retardation
AICAR-transformylase/IMP-cyclohydrolase deficiency	ATIC	Intellectual disability, blindness	Dysmorphism
Deoxyguanosine kinase deficiency: mitochondrial	dGK	Psychomotor retardation	Multiorgan system failure
DNA depletion syndromes			
Hereditary xanthinuria	XOR	None	Hypouricemia, nephrolithiasis
Lesch–Nyhan disease	HPRT	Motor disability, self-injurious behavior, intellectual disability	Hyperuricemia, nephrolithiasis, gout, tophi
Myoadenylate deaminase deficiency	mAMPD	Exercise intolerance, myalgia, cramping	None
Phosphoribosylpyrophosphate synthase superactivity	PRPP synthase	Deafness ($\pm$ psychomotor retardation)	Hyperuricemia, nephrolithiasis, gout
Phosphoribosylpyrophosphate synthase deficiency: Charcot–Marie–Tooth CMTX5, or Arts syndrome	PRPP synthase	Deafness, neuropathy, optic neuropathy ($\pm$ psychomotor retardation)	None
Purine nucleoside phosphorylase deficiency	PNP	Uncommon	Immunological defects
Renal hypouricemia	URAT1	None	Hypouricemia, nephrolithiasis, renal failure
Retinitis pigmentosa type 10, or Leber congenital amaurosis	IDH-1	Retinal degeneration	None
Severe combined immunodeficiency syndrome (SCID)	ADA	Variable	Life-threatening infections

* See legend to Figure 187.1 for key to the abbreviations used in the table.

Table 187.2

Variable phenotypes of inherited myoadenylate deaminase deficiency

Classification	Clinical features	Comments	
Asymptomatic	None	1	Functional abnormalities noted in physiological studies
		2	Affected individuals may be at risk of developing symptoms
Symptomatic	Exertional myalgias	1	Typically nonprogressive
		2	Proposed to involve other factors
Coincidental	Heterogeneous	1	Nature and severity dependent on associated disorder
		2	May be synergistic if associated disorder is metabolic