Inherited Metabolic Diseases

Radha Ramachandran

Inherited Metabolic Diseases (IMD) (or inborn errors of metabolism) are a group of monogenic disorders that occur as a result of impairment in enzyme activity in one or more metabolic pathways. Although individually rare, collectively they are not that uncommon, with reported prevalence ranging from 1 in 800 to 1/2500 live births. Prevalence may be even higher in populations where consanguinity is common or in relatively isolated societies with a small ancestral pool.

Hundreds of disorders exist, with the number of known individual disorders reported to be increasing yearly. Whilst the majority of IMDs present in childhood, there is an increasing recognition that they may present for the first time in adulthood, and that presenting features may differ from those seen in the paediatric setting.

IMDs can present for the first time in adulthood as a metabolic emergency. A diagnosis of an IMD should therefore be considered in patients presenting with atypical seizure or stroke, encephalopathy, acid–base disturbance, neuropsychiatric symptoms, rhabdomyolysis, if a more common alternative diagnosis is not forthcoming. Presentation is however, often chronic, with non-specific symptoms and with multisystem involvement. A diagnosis of IMD should therefore also be considered in patients with multisystem involvement where more common aetiologies have been excluded.

Autonomic dysfunction and impaired glucose homeostasis, leading to features suggestive of PoTS may be a feature of some IMDs. In these patients, a diagnosis of an IMD should be considered if

(i) There is documented hypoglycaemia where insulin excess has been excluded
(ii) Apparently unrelated multisystem involvement including one or more of the following: cardiomyopathy, myopathy, renal disease, liver disease
(iii) Central nervous system (CNS) manifestations—particularly neurodegenerative/neuropathic disorders and abnormalities on brain imaging
(iv) Dysmorphia
(v) Family history of similar complaints/consanguinity/death.

R. Ramachandran (✉)
Departments of Chemical Pathology/Metabolic Medicine, Guy's and St Thomas' Hospitals NHS Foundation Trust, London SE1 7EH, UK
e-mail: radha.ramachandran@gstt.nhs.uk

R. Ramachandran Adult Inherited Metabolic Diseases, Centre for Inherited Metabolic Diseases, Guy's and St Thomas' Hospitals NHS Foundation Trust, Lambeth Palace Road, London SE1 7EH, UK

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Some IMDs Where Orthostatic Hypotension Is a Common Feature Are Described Below

Dopamine Beta-Hydroxylase Deficiency (DBH Deficiency)

DBH deficiency is an autosomal recessive condition occurring as a result of mutations in the *DBH* gene. Very few cases have been reported in the literature, and prevalence is very rare, reported to be less than 1 in 1,000,000. In the CNS, dopamine is hydroxylated to noradrenaline by DBH. Noradrenaline is subsequently methylated to form adrenaline. Therefore deficiency of DBH enzyme leads to very high levels of dopamine and very low levels of adrenaline and noradrenaline.

The disease is characterised by a lack of sympathetic noradrenergic function but intact parasympathetic and sympathetic cholinergic function. Presentation is usually at birth with temperature dysregulation, hypotonia, ptosis, dehydration and hypoglycaemia. However, diagnosis is often delayed until late childhood or adolescence when patients present with severe orthostatic hypotension (systolic blood pressure falling to less than 80 mmHg and compensatory tachycardia on standing); nasal stuffiness is reported in 100% of patients. There is often a history of a complicated peri-natal course. Ptosis, high arched palate, joint hypermobility and profoundly reduced exercise tolerance are other commonly reported features in this group of patients. Sweating is normal in these patients and pupils are small but reactive to light and accommodation.

Diagnosis

- Plasma catecholamine measurement—minimal or absent adrenaline and noradrenaline with 5–tenfold increase in dopamine levels.
- Molecular genetic testing for pathogenic mutations in the *DBH* gene.

Treatment

Treatment is mainly supportive. Standard therapies for autonomic failure are not very helpful. Drug of choice is L-threo-3,4-dihydroxyphenylserine (Droxidopa), a synthetic precursor of noradrenaline.

Prognosis

Prognosis is largely unknown, although survival beyond 60 years in some individuals has been previously reported.

Menkes Disease

Menkes disease is a rare X-linked disorder caused by mutations in the *ATP7A* gene. The incidence of Menke's disease has been reported to range between 1:40,000 to 1:350,000. The clinical features are due to severe copper deficiency. DBH is a copper dependent enzyme and therefore patients often have partial DBH deficiency. Plasma catecholamine analysis shows high levels of dopamine with low levels of dihydroxyphenylglycol.

Clinical features are characteristic. Patients with classical Menke's present with severe neurological and marked connective tissue dysfunction, often leading to death in early childhood. Patients often present with sparse, hypopigmented, kinky hair. A less severe form presenting in adulthood, is characterised mainly by connective tissue dysfunction including skin laxity and hyperelasticity, and characteristic occipital horns on imaging resulting from calcification of the trapezius and sternocleidomastoid joints. Neurological manifestations in adult presenting patients may be mild or even absent.

Cytochrome B561 Deficiency (CYB561)

4 patients in 2 families with severe orthostatic hypotension, due to CYB561 protein defect have recently been described. The diagnosis was made following exome sequencing,

homozygosity mapping and subsequent Sanger sequencing.

The CYB561 protein defect leads to a disruption in ascorbate-hydroxyascorbate recycling within the catecholamine secretory vesicles. This in turn results is impaired conversion of dopamine to epinephrine, in effect, leading to a functional DBH deficiency.

Patients presented with severe life-threatening orthostatic hypotension. In contrast to patients with DBH deficiency, compensatory tachycardia, ptosis and generalised hypotonia were not noted to be present.

Patients responded to treatment with L-threo-3,4-dihydroxyphenylserine.

Other Disorders Associated with Orthostatic Hypotension

Other disorders that present with orthostatic hypotension as a feature include.

1. Familial dysautonomia (Riley-Day syndrome), an autosomal recessive condition due to pathogenic mutations in the *ELP1* gene.
2. Familial transthyretin amyloidosis, resulting from autosomal dominant mutations in the *TTR* gene.
3. Shy-Drager syndrome due to mutations in the *COQ2* gene.

The following references provide further details on clinical features, investigations and management [1–3].

References

1. Garland EM, Biaggioni I. Dopamine Beta-Hydroxylase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al, editors. GeneReviews (R) Seattle (WA): University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle; 1993.
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