Introduc
tion

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme arylsulphatase A which catalyses the first step in the degradation of the sphingolipid 3-O-sulphoglucosylceramide (sulphatide). Accumulation of sulphatide in the brain leads to progressive demyelination of the central and peripheral nervous systems causing a variety of neurological symptoms including gait disturbances, ataxias, optical atrophy, dementia, seizures and spastic tetraparesis. Disease severity can range from mild to severe and can be broadly grouped into 3 subtypes (late-infantile, juvenile and adult). The majority of patients with arylsulphatase A deficiency and signs of MLD will have mutations in the ARSA gene however there is a much less common form of MLD caused by deficiency of saposin B, a non-enzymatic sphingolipid activator protein. Arylsulphatase A is also defective in multiple sulphatase deficiency due to mutations in SUMF1. The ARSA gene (22q13.31-qter) comprises 8 exons. Although many novel mutations are known, there are 'common' mutations within the gene, particularly the c.459+1G>A and c.1277C>T, p.(Pro426Leu) mutations, which account for around 50% of disease alleles in the Northern European population.

Pseudodeficiency of arylsulphatase A (PDASA)
Pseudodeficiency of arylsulphatase A is a condition of reduced arylsulphatase A activity (<15% normal) without clinical consequence, which can complicate the biochemical diagnosis of MLD. PDASA is caused by two sequence variants in the ARSA gene, namely PD2 (Poly A / c.*96A>G) and PD1 (NGly / p.(Asn350Ser). PD2 is almost invariably seen on a background with PD1 but PD1 can occur independently of PD2 and its effect on causing PDASA is controversial.

Referrals

PDASA testing is used to assist the interpretation of arylsulphatase A activity results. Referrals are generally via the Enzyme Unit, Great Ormond Street Hospital however referrals may be accepted from other centers who carry out biochemical testing for arylsulphatase A. Biochemical confirmation of arylsulphatase A deficiency can only be confirmed after PDASA testing. In families with PDASA, prenatal testing by enzyme analysis can be complicated and in many cases impossible. For these families genetic testing is particularly useful but this can also mean that in some cases testing for MLD may have to be performed without biochemical confirmation. In these cases a very strong clinical picture of MLD must be present.

Prenatal testing

Prenatal testing is available for families in whom mutations have been identified or in whom appropriate family studies have been undertaken. Prenatal testing for PDASA may also be requested by the Enzyme Unit, Great Ormond Street Hospital.

Service offered

- PDASA: Testing for the presence of PD1 and PD2 by Sanger sequencing.
- MLD Level 1 analysis: testing for the common mutations c.459+1G>A and c.1277C>T, p.(Pro426Leu) by Sanger sequencing.
- MLD Level 2 analysis: Sanger sequencing of all 8 coding exons and intron-exon boundaries.

Target reporting time

4 weeks for PDASA testing and MLD routine level 1 screen in index case, 8 weeks for level 2 screen. 2 weeks for routine testing of specific mutations. Please contact the laboratory for urgent cases.