CASE REPORT

Hunter syndrome with late age of presentation: clinical description of a case and review of the literature

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SUMMARY

Hunter syndrome is an X linked recessive mucopolysaccharidosis (type II) caused by the deficiency of iduronate 2-sulfatase. This in turn leads to the accumulation of glycosaminoglycans, dermatan and heparan sulfate. The intracellular and extracellular accumulation of these substances lead to multisystemic organ abnormality. It is a rare syndrome with a very low prevalence of 1.3:100 000 male live births. Usual presentation is in early childhood although milder variants have been documented to present at a later age. We present a rare case of Hunter syndrome in a 24-year-old male patient who presented with joint contractures and recent onset hoarseness of voice. X-rays were suggestive of dysostosis multiplex. Clinical diagnosis of Hunter syndrome was confirmed by enzyme assay and further by mutational analysis.

BACKGROUND

Although very rare, its awareness among clinicians is warranted. We present this case for its rarity and to highlight the unusual feature of late age of presentation.

CASE PRESENTATION

A 24-year-old male patient presented with a 5-year history of contractures of the small joints of the upper limbs and hoarseness of voice. Symptoms were insidious in onset and gradually progressive. There were no other significant symptoms. He was born to non-consanguineous parents. There was no history of developmental delay. No other family member had similar symptoms. On examination, the patient was of short stature, had coarse facial features, mild scoliosis, genu valgum, short stubby fingers with distal joint contractures, hepatosplenomegaly and umbilical hernia; he had average intelligence (figure 1A–C). He had no restriction of mobility or difficulty in articulation. His hands and radiographs provided clues to the diagnosis of mucopolysaccharidoses (MPS) (making a diagnosis of Hunter syndrome or Hurler-Scheie syndrome possible). Diagnosis of Hunter syndrome was confirmed by enzyme assay and mutational analysis.

INVESTIGATIONS

Echocardiography was suggestive of thickened mitral and aortic leaflets, with mild mitral and aortic regurgitation without evidence of mitral and aortic stenosis; and normal biventricular function. X-rays were suggestive of dysostosis multiplex

(figure 1D–F). A urine test for MPS showed heparan sulfate and dermatan sulfate bands. On enzyme assay, iduronate 2-sulfatase level was reduced to 52 nmol/4 h/mL (normal level 169–475 nmol/4 h/mL). On mutational analysis of IDS gene, a known hemizygous mutation A85T (alanine to threonine at amino acid 85) caused by a G to A substitution at nucleotide position c.253 in the exon 3 of IDS was found (figure 1G). (An apparent heterozygous peak in the electropherogram in the picture is due to the simultaneous amplification of pseudogene).

DIFFERENTIAL DIAGNOSIS

Hurler-Scheie syndrome.

TREATMENT

Enzyme replacement therapy (ERT).

DISCUSSION

Hunter syndrome is a rare X linked recessive MPS (type II) with a very low prevalence of 1.3:100 000 male live births.¹ It was named after Charles Hunter, who first described the condition as an X linked recessive disease in the year 1917.² Nearly all affected patients are male, but, rarely, symptomatic females have been described.³ The disease is caused by a deficiency of iduronate 2-sulfatase, a lysosomal enzyme. Hunter syndrome is characterised by progressive pathological lysosomal storage of glycosaminoglycans (GAGs) in nearly all cell types, tissues and organs. The recognition pattern as described in the literature includes coarse facial features, short stature, joint contractures, visceromegaly, intellectual disability and dysostosis multiplex. Other important associated features are severe airway obstruction due to macroglossia, supraglottic narrowing and tracheomalacia, sleep apnoea, cardiomyopathy, cardiac valve dysplasia, and dental and dermatological manifestations along with progressive neurological decline. Death usually occurs in the first or second decade of life, although the milder variants may survive up to the fifth and sixth decades.^{4 5}

Hunter syndrome is a heterogeneous disorder both in age of onset of the symptoms and their severity. It is classified into mild and severe types, based on the length of survival and presence or absence of neurological symptoms. Patients are normal at birth in both the types. In its severe form, the clinical features, including severe mental retardation and loss of skills, appear by 2–4 years

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Figure 1 The patient demonstrated coarse facial features (A), claw hand deformity due to contractures (B), protuberant abdomen with umbilical hernia (C), vertebral dysplasia mainly affecting L2 (D), broad ribs (E) and comma-shaped pelvic bone (F). Electropherogram shows substitution (G).

of age. However, the milder form, an attenuated phenotype, is compatible with survival into adulthood with fewer clinical features, mild mental retardation and near normal stature.⁶ The majority of those affected with the attenuated form still succumb in early adulthood due to complications. A few cases with mild features may even remain undiagnosed. Literature documents survival up to the age of 87 years and capacity to procreate in these cases.⁷ Our patient has the mild form of this disorder. Residual enzyme activity (30%) may explain the milder phenotype in our case.

Hunter syndrome is the only known X linked MPS disorder. The human gene encoding *IDS* has been mapped to Xq28. It contains nine exons spread over 24 kb. An *IDS*-like pseudogene, comprising copies of exons 2 and 3 and intron 7, is located about 20 kb from the active gene.⁴ Over 300 mutations have been described, the majority being point mutations or small deletions. However, up to 10% of MPS II is the result of large intragenic deletions and/or chromosomal rearrangements, typically associated with the severe phenotype.⁸

Urinary GAGs (heparan and dermatan sulfates), in either a quantitative or qualitative estimation, make up the primary screening test. Definitive diagnosis is established by enzyme assay in leucocytes, fibroblasts or plasma, using substrates specific for *IDS*. However, mutational analysis of the *IDS* gene is the most confirmatory technique. Prenatal testing can be performed if the mutation is known in the family.

Management is multidisciplinary and a holistic approach to the patient is required, especially for patients with severe neurological involvement. Supportive management and the anticipation of possible complications can greatly improve the

quality of life of affected individuals and their families. Family members should be offered genetic counselling, and contact with other affected families, patients and support groups can be helpful. ERT is an important new therapy that has the potential to help many patients, provided it is started early in the course of the disease. Idursulfase (elaprase) is a recombinant form of human iduronate 2-sulfatase and has been approved for treatment in developed countries.⁴

Early diagnosis and initiating early treatment, particularly ERT, may reduce possible disease complications and can greatly improve quality of life. In this regard, newborn screening can detect presymptomatic cases and helps in early establishment of diagnosis. An essential component for a screening programme includes an experienced laboratory for rapid and accurate enzymatic and molecular testing. The laboratory must incorporate appropriate quality assurance and proficiency testing programmes.³

Learning points

- ▶ Although very rare, awareness of Hunter syndrome among clinicians is warranted.
- ▶ This condition is now treatable with enzyme replacement therapy and hence early detection before complications set in is very crucial.
- ▶ Newborn screening also offers hope of detection in the asymptomatic period.

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Contributors KMG conceived the idea and supervised the entire work. AG wrote the manuscript. AU carried out the molecular work under the supervision of AD. All the authors have read and approved the manuscript. KMG is the guarantor.

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