Tay-Sach Disease with "Cherry-Red Spot" - First Reported Case in Malaysia

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SUMMARY

We present a rare case of Tay-Sachs disease with retinal 'cherry-red spots' in a 19-month-old Malay child. Molecular genetic studies confirmed the diagnosis. The case highlights that 'cherry-red spot' is a useful clinical clue in Tay-Sachs disease and several other lysosomal storage disorders. It serves as an ideal illustration of the eye as a window to inborn error of metabolism.

KEY WORDS:
Tay-Sachs disease; Cherry-red spot; Lysosomal storage disorders

INTRODUCTION

Tay-Sachs disease (TSD), also known as GM2 gangliosidosis 1 is an autosomal recessive, progressive neurodegenerative disorder. This results from a deficiency of β-hexosaminidase A enzyme that leads to an accumulation of GM2 gangliosides. In the infantile form, progressive loss of neurological function ensues and is usually fatal by age 4 or 5 years. The 'cherry-red spot' is the hallmark of TSD. It is the result of GM2 accumulation in the retinal ganglion cells, giving the white fundus appearance surrounding the normal tint of the fovea. This is the first reported case of Tay-Sachs disease in Malaysia. The diagnosis was confirmed by molecular genetic testing.

CASE REPORT

A 19-month-old Malay boy was brought to the hospital by his parents for seizures. He presented with a history of neuroregression since 6 months old and seizures since 12 months old.

He was born full-term at 37 weeks with no complications. The patient was developing normally until he was 6 months old when it was observed that the child was listless and lost the ability to move his limbs and roll over. Since then, the loss of motor skills became progressively evident.

The patient is the only child of a healthy non-consanguineous couple. There were no similar manifestations in both parents' families.

Clinically, he was a thriving child, with relative macrocephaly. He had spastic quadriplegia, decreased eye contact and hyperacusis. Neuroimaging revealed leukodystrophic changes.

Ophthalmic assessment confirmed severe visual impairment and fundoscopic examination revealed bilateral retinal 'cherry-red spots' (Figure 1). Anterior segment examination of both eyes were insignificant.

Clinical presentation associated with corroborative fundoscopic findings geared the diagnostic workup towards lysosomal storage disorders, in particular neurolipidoses. The diagnosis of TSD was made by leukocyte lysosomal enzyme assay with analysis of leukocyte β-hexosaminidase A activity (6 nmol/min/mg protein) markedly below the normal range (10-50 nmol/min/mg protein). A similar reduction was also evident in his plasma sample (0.02 nmol/min/mL, normal range 0.5-3.1 nmol/min/mL). Further confirmation was made through molecular analysis whereby two novel pathogenic compound heterozygous mutations of the hexosaminidase A (HEXA) gene were identified. The c.964G>T (p.Asp322Tyr) mutation was inherited from the father, and the c.1395C>G (p.Asp465Glu) mutation from the mother.

Genetic counseling and options of prenatal diagnosis in subsequent pregnancies were provided to the parents. The parents were also counseled regarding appropriate health care for their son and probable outcome which is death occurring by age 4 or 5 years. The patient is still under clinical observation by the ophthalmology and genetic teams.

DISCUSSION

TSD is an autosomal recessive genetic disorder. The most common variant becomes apparent in infancy. Infants with this disorder typically appear normal until the age 3 to 6 months, when their development slows and muscles used for movement weaken. Early milestones are lost and loss of visual attentiveness occurs early. As the disease progresses, progressive neurological deterioration occurs with seizures, intellectual disability and paralysis. It is usually fatal by age 4 or 5 years [1]. Other forms of TSD are very rare. Neurological signs and symptoms can appear in childhood, adolescence and adulthood and are usually milder than those seen in the infantile form [2].

While TSD is very rare in the general population, the genetic mutations that cause this disease are more common in people of Ashkenazi (eastern and central European communities) Jewish heritage than in those with other backgrounds. Approximately 1 in 30 people of Ashkenazi Jewish ancestry is

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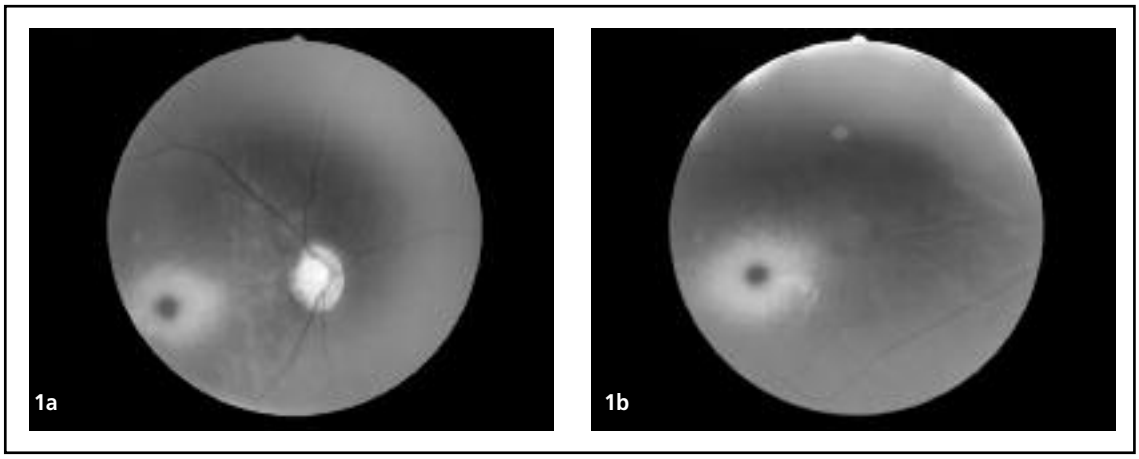

Fig. 1: Fundus photograph showing 'cherry-red spot' of right eye (1a) and left eye (1b).

a recessive carrier. About 1 in 360 000 people in the general population develops TSD compared to 1 in 3 600 people of Ashkenazi Jewish ancestry [3].

The pathogenesis of TSD is attributable to the accumulation of GM2 gangliosides resulting from deficiency of β-hexosaminidase A enzyme caused by a mutation in the alpha subunit of the HEXA gene on chromosome 15q. As a result, GM2 gangliosides accumulate to toxic levels, particularly in neurons in the central nervous system. Progressive damage caused by the buildup of GM2 gangliosides lead to destruction of these cells.

A 'cherry-red spot' at an early stage is one of the dramatic diagnostic clues found on fundus examination [4]. It is due to GM2 gangliosides accumulation in the retinal ganglion cells leading to thickening and loss of transparency of the posterior pole of the retina. The absence of ganglion cells at the fovea gives rise to the red spot surrounded by white diseased cells. Its colour is due to the pigment epithelium and choroid, and therefore may demonstrate colour variability according to the race [5]. As the ganglion cells die, the 'cherry-red spot' fades and optic atrophy becomes apparent.

Although experimental work, such as gene therapy research is underway, there is currently no cure or treatment to slow the progression of TSD. Patients receive palliative and supportive care to ease the symptoms.

'Cherry-red spot' is a useful clinical indicator in TSD and several other lysosomal storage disorders. A useful sign, when associated with key clinical features and a good history, it often guides one to a diagnosis of the disease. It serves as an ideal illustration of the eye as a window to inborn errors of metabolism. This case reaffirms that the eyes may offer vital clues in identifying signs of health conditions. We would also like to highlight that an appropriate multidisciplinary approach by the geneticist, ophthalmologist, neurologist and clinical biochemist is crucial in ensuring diagnostic success in various disorders.

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