

## Tay-Sachs Disease in Two Iranian Identical Male Twins; A Case Report

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### Abstract

#### Background

Tay-Sachs disease is an autosomal-recessive lysosomal storage metabolic disorder. The typical symptoms of the disease include ataxia, muscle weakness, and mental disorders. The severity of the clinical symptom relies on the enzymatic activity of residual Hexosaminidase-A.

#### Case Presentation

The patients were two Iranian (Tabriz city, East Azerbaijan Province, Iran) 22-month-old male identical twins of distant consanguineous parents with a high Apgar who score referred to Tabriz Children Hospital, Tabriz, Iran. Both twins had normal growth until 7 months of age. They started regression after 7 months of age and became hypotonic so that they could not keep their neck and control their head. The enzyme analysis of the patients showed the low-level activity of Hexosaminidase-A. A considerable delay in normal myelination process was discovered by brain Magnetic Resonance Imaging in the patients.

#### Conclusion

It can be determined that Tay-Sachs disease can occur in twins of distant consanguineous parents. Further studies are needed for detecting the mutations relating to the disease in the patients as well as their families.

**Key Words:** Hexosaminidase-A; Tay-Sachs Disease; Twins.

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## 1- INTRODUCTION

Tay-Sachs disease is one of the autosomal-recessive lysosomal storage metabolic disorders. It is defined by acute neurodegeneration, unclear macrophage and astrocyte activation, inflammatory mediator production, and activated microglia expansion (1). Physicians Warren Tay (1881), and Bernard Sachs (1887) initially defined the clinical features and signs of Tay - Sachs disease according to the combined reports of the disease. Both physicians reported their first cases among Jewish families (2, 3). It has been revealed that Tay-Sachs disease occurs at high frequency in Ashkenazi Jewish individuals due to a shared genetic background, with an incidence of 1 in 2,500 to 3,900 live births compared to 1 in 320,000 in the general population (4).

Its typical symptoms include ataxia, muscle weakness, and mental and speech disorders (1). The severity of the clinical symptom relies on the enzymatic activity of residual Hexosaminidase-A related to several mutations (1). Based on the clinical presentation, this disease can be classified into three subtypes of acute infantile, juvenile (subacute), and chronic or adult-onset Tay-Sachs disease (2). The acute infantile form of the disease is the most frequent and aggressive type with the signs and death occurring in early infancy (5). It defines the most severe nervous system disorders. Infants' usual neurodegenerative symptoms are augmented startle reflex, hypotonia, eye movement abnormalities, inability to sit or hold their head unsupported, dysphagia, hypomyelination, and spasms. Most patients with infantile Tay-Sachs disease do not survive after 4 years of age (6, 7).

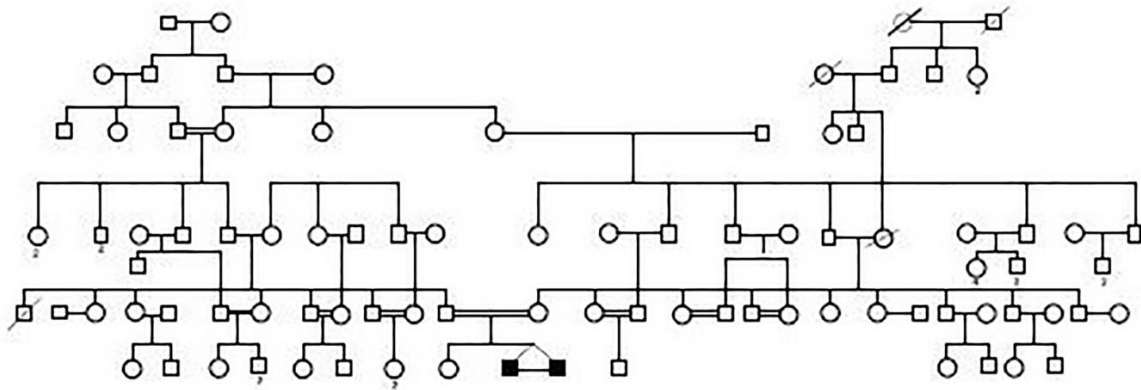
## 2- CASE REPORTS

The patients were two 22-month-old identical male twins of very distant consanguineous parents. **Figure.1** shows

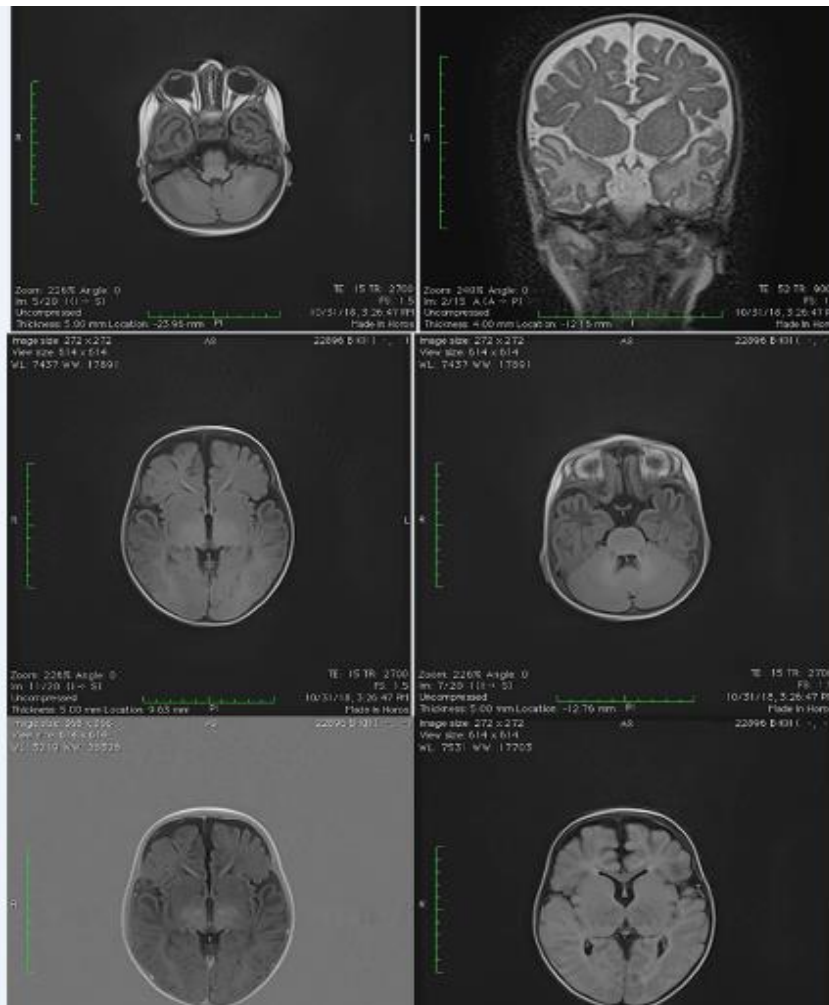
the family pedigree of these two children. Informed consent and permission for publishing the family pedigree were obtained from the parents before including in the study. The children had a high Apgar score and born by cesarean section. They had a normal progression until 7 months of age, so they were able to sit with help, hold things with hands, and turn. In addition, they had social smiles and great attention to the environment. However, they started gradual increasing regression after 7 months of age and became hypotonic, so they were not able to keep their neck and control their head, sit, turn, speak, babble, and smile.

In physical examination, they were entirely hypotonic and had poor head control. They could not perform horizontal and vertical suspension. Also, they seemed to be encephalopathy with no organomegaly and deep tendon reflexes of 3 plus. The head circumference of both infants was 47 cm. Fundus evaluation demonstrated a cherry-red spot in the macula in both infants. The brain Magnetic Resonance Imaging (MRI) discovered increasing signal intensity at hemisphere white matter (which was more severe at both temporal lobes) and considerable delay in normal myelination process (**Figure.2**).

The following results were obtained through the enzymatic analysis. Diminished Hexosaminidase-A activity (0.02; normal range, 0.96-1.78; nmol/ml/min), normal Hexosaminidase-B activity (20.06; normal range, 5.76-15.77; nmol/ml/min), and normal Hexosaminidase-AB activity (21.04; normal range, 18.59-31.33; nmol/ml/min). The alpha-Mannosidase activity was also in the normal range (0.3; normal range, 0.1-0.3; nmol/ml/min). According to these findings, the diagnosis of GM2 gangliosidosis (Tay-Sachs disease) is verified.



**Fig. 1.** Pedigree of the family; squares represent males and circles are females; the filled black symbols indicate individuals with Tay-Sachs; symbols with the diagonal line indicate deceased members; double lines between individuals show consanguinity.



**Fig. 2.** The brain Magnetic Resonance Imaging (MRI) of one of the twins with Tay-Sachs disease; the MRI discovered increasing signal intensity at hemisphere white matter, which was more severe at both temporal lobes, and considerable delay in normal myelination process.

### 3- DISCUSSION

GM2 ganglioside is a glycosphingolipid that exists in the outer layer of mammalian cells and the neuronal surfaces (8). Hexosaminidase-A, a heterodimer lysosomal enzyme, has two subunits including alpha and beta that are encoded by *HEXA* and *HEXB* genes, respectively. This enzyme with its cofactor, GM2 activator protein, can degrade the GM2 gangliosides in lysosomes. Different types of mutations including deletion, nonsense, and missense mutations have been discovered in the *HEXA*, which causes Hexosaminidase-A deficiency. This leads to the accumulation of GM2 gangliosides in the nervous system and the appearance of the Tay-Sachs diseases (B-variant) symptoms.

The mutations in the *HEXB* gene encoding the beta-subunit lead to the deficiency of both Hexosaminidase-A and Hexosaminidase-B (total-Hex) and consequently Sandhoff disease or O-variant, which was initially discovered by Conzelmann and Sandhoff. The third variant, known as AB variant, occurs due to GM2 activator protein deficiency. Hechtmen et al. (1982) firstly diagnosed this very rare variant of GM2 gangliosidosis, in an English child. It has phenotypic similarity with the infantile form of Tay-Sachs disease (9-11).

Although gangliosidoses are more common in Jewish populations, they can also rarely be diagnosed in different cases with a non-Jewish origin. Sheth et al. (12) presented a case with the AB variant of GM2 gangliosidosis (12). The patient was a one-year-old Indian male with global developmental delay, hypotonia, and hypersensitivity to sound (hyperacusis). Ophthalmic examination of the patient presented horizontal nystagmus and cherry-red spot. Thalamic hypointensity, putaminal hyperintensity, and some unmyelinated white matter were also detected in MRI of the brain. As another

non-Jewish case report, Steiner et al. (13) reported late-onset Tay-Sachs disease in a 47-year-old Caucasian man of non-consanguineous parents. The disease signs began in infancy with mild motor and mental retardation. The symptoms including cerebellar ataxia, proximal muscle weakness, atrophy, mild cognitive decline, and incomplete ophthalmoplegia progressively appeared in late adolescence. The man could walk unaided for short distances at the time of the study. MRI detected cerebellar atrophy without white matter abnormalities. Decreased Hexosaminidase-A activity and genetic tests revealing mutations in the *HEXA* eventually confirmed the diagnosis of late-onset Tay-Sachs disease (13).

### 4- CONCLUSION

In the present study, Hexosaminidase A deficiency was revealed in Iranian identical male twins of distant consanguineous parents with apparent Tay-Sachs symptoms. It can be a very rare case of the diseases. However, further and precise evaluations are needed for detecting the mutations relating to the disease not only in the patients but also in their families.

**5- CONFLICT OF INTEREST:** None.

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