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TAY-SACHS DISEASE IN A CHILD: A RARE CASE REPORT ,GGH KURNOOL

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ABSTRACT

The neurodegenerative condition known as Tay-Sachs disease is inherited in an autosomal recessive pattern and is caused by an abnormal accumulation of the cell membrane glycolipid and GM2 ganglioside within the lysosomes of affected cells. A lack of the isoenzyme -hexosaminidase A, which is synthesised in the endoplasmic reticulum, is the root cause of this condition. In patients who have Tay-Sachs disease, the first few months of life are characterised by normal motor development, followed by gradual weakening and loss of motor abilities beginning around 2 to 6 months of life. Due to the irreversible nature of neurodegeneration, death typically occurs between the ages of 4 and 5 years. The hexosaminidase enzyme assay and DNA analysis of the HEXA gene are two methods that can be used to diagnose Tay-Sachs disease. On the other hand, there is no specific treatment that has been established. We discuss here a case of Tay-Sachs disease found in an 9-month-old male child who presented with loss of milestones and seizure symptoms. Upon examination of the fundus, it was found that this patient had cherry red spot in the macula. In the enzymatic assay, the hexosaminidase A activity was zero percent, and DNA analysis revealed a mutation in which glutamine was replaced by a stop codon at position 390.

Introduction :

Tay-Sachs disease is an autosomal-recessive lysosomal storage metabolic illness. GM2 ganglioside accumulates in nerve cell lysosomes due to □-hexosaminidase A (HexA) enzyme deficiency induced by mutations in the □-subunit gene.[1]

HEXA can be found at locations 15q23. More than 130 mutations have been discovered up to this point; these mutations include single gene deletions, substitutions, insertions, splicing alterations, duplications, and complex gene rearrangements.[2]

The infantile form of the disease is characterised by a gradual decline in neurological function, which typically results in death by the age of 4 or 5 years. TSD is easily identifiable by its telltale 'cherry-red spot.' The buildup of GM2 in the ganglion cells of the retina is the cause of the white fundus that may be seen surrounding the usual colour of the fovea.[3]

Here we Report 18 months male child with Tay sachs Disease presented with loss of milestones and Seizures.

CASE REPORT :A 9 month old boy was brought to hospital with complaining of seizures and with history of loss of milestones some weeks before seizures .

He was born at term by normal Vaginal Delivery at Government Hospital .the child had appropriate developmenral milestones until 6 months old .Parents are observed that loss of neck holding, inability to recognise mother, sit with support, loss of roll over,bysyllables , exaggerated startle reflex, At age of 9 months ,child had one episode of Seizures in the form of tonic posturing of both upper and lower limbs and uprolling of eyeballs that lasted for more than 1 hour which is refractory to anti epileptics intially, later subsided.post ictal drowsiness present for 3-4 hrs .MRI Brain was done after 3-4 days ,which was normal .

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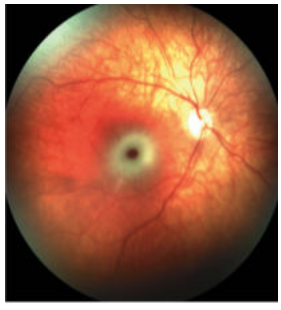
Family History :consangnious marriage ,married maternal cousin ,fourth in birth order with 2 elder sisters (3 and 4 years of age and healthy) and one abortion. History of mental retardation is present in maternal side .

On examination



Fundus showing cherry red spot

Child is conscious ,sparse hair+ ,Head Circumference _47 Cm at 9 months of age no visual tracking,heterochromia present , Fundus Examination shows : macular hyperpigmentation ,cherry rod spot .

CNS:

Tone –Variable ,Doesnot Grasp Anything .
Superficial Reflexes Present ,
Plantors extensors ,
Deep Tendon Reflux Brisk ,
Sensory Examination –Normal.

INVESTIGATIONS

MRI brain normal,plasma ammonia elevated (296mg/dl),CSF analysis –normal.Sleep EEG normal.Newborn screening TMS(7 PANEL) ,Urine for reducing substances and organic acids were Normal

Clinical Exome Sequencing Report :

HEXA chr15:72640399_72640401delAGA Uncertain Significance.
Gene –Hexa NM

Variant – c.1061-1063 DelTCT at Location Exon 9,Homozygosity ,Autosomal Recessive .and diagnosed as Tay Sachs Disease

This variant results in a deletion of a phenylalanine at position

354 of the HEXA gene. However, as this is an in-frame deletion, it is not expected to result in either a truncated protein product or loss of protein through nonsense-mediated mRNA decay. This mutation is predicted to be damaging by Mutation Taster. The p.Phe354del variant is conserved by GERP and PhyloP The nucleotide c1061 in HEXA is predicted conserved by GERP++ and PhyloP across 100 vertebrates. This variant has been reported for Tay Sach's disease by Montalvo A Let al., 2005.

Reclassification of the variant shall be considered on the basis of availability of additional scientific information and segregation analysis. Tay-Sachs disease (TSD) is caused by homozygous or compound heterozygous mutation in the alpha subunit of the hexosaminidase A gene (HEXA) on chromosome 15q23. It is an autosomal recessive. progressive neurodegenerative disorder which, in the classic infantile form, is usually fatal by age their years. Common neurodegenerative symptoms in infants are hypotension, inability to sit or hold their head unsupported, eye movement abnormalities, dysphagia, spasms, psychomotor degeneration, seizures and hypomyelination (Ji H et al., 2018)

OUTCOME AND FOLLOW UP :

Usually child with Tay sach disease will dye at 4-5yrs of age... Genetic Basics and prognosis of Taysach explained to parents .Autosomal Recessive Inheritance explained .25% of recurrence in each off spring of carrier parent .there is no Curative theraphy available at present for Tay sachs disease.advised to continue anti epileptic drug and supportive care . In this study child was died at 2 yrs with refractory seizures and respiratory failure

Discussion :

In 1881, British ophthalmologist Warren Tay first documented the cherry-red patches on the retina, and in 1887, American neurologist Dr. Bernard Sachs detailed the cellular alterations, naming it TSD.[4] HEXA and HEXB genes encode hexosaminidase, a heterodimer of subunits □ and □. The HEXA gene on chromosome 15 causes TSD, while the HEXB gene on chromosome 5 causes Sandhoff disease. HEXA has 150 mutations.[5]

Beta hexosaminidase A (Hex A) deficiency causes Tay Sachs disease by degrading GM2 ganglioside. Endoplasmic reticulum synthesises Hex A alpha and beta subunits. The enzyme enters the Golgi network after glycosylation, intramolecular disulfide bond formation, and dimerization in the endoplasmic reticulum. The most crucial step in lysosome recognition is post-translational enzyme modification with mannose-6-phosphate. An activator protein, GM2A, makes Hex A lipophilic by presenting GM2 ganglioside to its active site.[6]

The condition also causes aberrant endosomal transport, poor autophagy, alpha-synuclein buildup, and anti-ganglioside antibodies.[7]

Depending on symptom onset, Tay-Sachs is classed as infantile, juvenile, or adult. Infantile Tay-Sachs affects most people.[8]

The nerve injury normally starts in the womb. Symptoms typically occur at 3–6 months. The sickness progresses rapidly, and the infant usually dies by 4 or 5. Adult-onset Tay-Sachs disease is rare.[9]

Tay Sachs disease manifests neurologically. Infants are hypotonic from birth and show developmental delays or regression by four to six months. By eight to ten months, symptoms rapidly advance, spontaneous and voluntary movements decrease, and the new-born becomes less responsive.[10]

By twelve months, the patient has seizures, mostly tonic-myoclonic. Spasticity and seizures end the sickness. Massive, refractory myoclonic seizures can occur (more than two-thirds of patients needed more than two anticonvulsants). Generalized, focal, and gelastic seizures can occur. Ataxia, dyskinesia, sleep difficulties, yelling, and irritation emerge around the same age.[11]

Patients develop macrocephaly by 18 months. Reactive cerebral gliosis increases head circumference, not hydrocephalus. Patients develop decerebrate posture, dysphagia, unresponsiveness, and vegetative state by two years old.[12]

Fundus inspection can reveal a conspicuous "cherry-red patch" early on. GM2 gangliosides in retinal ganglion cells cause posterior pole retinal thickening and loss of transparency. The red patch with white sick cells in the fovea is caused by ganglion cell deficiency. The pigment epithelium and choroid determine its colour, which varies by race. The "cherry red patch" disappears when ganglion cells die, causing ocular atrophy.[13]

At this time, TSD carrier detection techniques are only intended to look for the most prevalent mutations in a gene; however, carrier status can be verified using molecular testing that looks for genetic mutations in the hexosaminidase gene sub-unit □.[14]

The sequencing of DNA, as well as focused analysis for potentially harmful variations and deletion/duplication analysis, are both included in molecular genetic testing. The focused analysis is carried out if the initial test reveals that the enzyme activity is either non-existent or very low. There are six different common pathogenic variants included in the panel. The panel consists of three null alleles: p.Tyr427IlefsTer5, c.1421+1G>C, and c.1073+G>A. These three null alleles are related with Tay Sachs in either the homozygous or compound heterozygous form. There is a correlation between the allele p.Gly269Ser and an adult-onset type of Hex. A deficiency.[15]

When Hex A enzyme assay shows parents are heterozygous and molecular genetic testing rules out pseudo deficient allele in either parent, prenatal foetal cell testing can be done by chorionic villus sampling at 10–12 weeks or amniocentesis at 15–18 weeks. Pathogenic variant families can undergo preimplantation genetic testing.[16]

There is no treatment for Tay-Sachs disease.

Tay Sach disease treatment focuses on providing appropriate nutrition, regulating seizures, treating infectious disease, safeguarding the airway, and early vigorous physical and occupational therapy. Seizure management frequently requires numerous antiepileptics. However, seizure patterns fluctuate and require regular dose changes and new drugs. Good bowel management becomes crucial as the youngster with Tay Sachs illness becomes handicapped and impaired.

Cell transplantation, enzyme replacement therapy, substrate reduction therapy, enzyme boosting therapy, and gene therapy are Tay Sachs disease treatments.[17]

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