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Tay- Sachs Disease(TSD)

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Abstract:

Tay-Sachs disease is an autosomal recessive disease characterized by progressive neurologic degeneration, fatal in early childhood. In the Ashkenazi Jewish population the disease incidence is about 1 in every 3,500 newborns and the carrier frequency is 1 in every 29 individuals. Carrier screening programs for Tay-Sachs disease have reduced disease incidence by 90% in high-risk populations in several countries. The Brazilian Jewish population is estimated at 90,000 individuals. Currently, there is no screening program for Tay-Sachs disease in this population. To evaluate the importance of a Tay-Sachs disease carrier screening program in the Brazilian Jewish population by determining the frequency of heterozygotes and the acceptance of the program by the community.

Introduction:

Tay-Sachs disease (TSD) is a fatal genetic disorder, most commonly occurring in children, that results in progressive destruction of the nervous system. This condition is inherited in an autosomal recessive which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Tay-Sachs is caused by the absence of a vital enzyme called hexosaminidase-A (Hex-A). Without Hex-A, a fatty substance, or lipid, called GM2 ganglioside accumulates abnormally in cells, especially in the nerve cells of the brain. This ongoing accumulation causes progressive damage to the cells . In children, the destructive process begins in the fetus early in pregnancy. However, a baby with Tay-Sachs disease appears normal until about six months of age when its development slows. By about two years of age, most children experience recurrent seizures and diminishing mental function. The infant gradually regresses, and is eventually unable to crawl, turn over, sit or reach out. Eventually, the child becomes blind, cognitively impaired, paralyzed and non-responsive. By the time a child with Tay-Sachs is three or four years old, the nervous system is so badly affected that death usually results by age five. A much rarer form of Tay-Sachs, Late-Onset Tay-Sachs disease, affects adults and causes neurological and intellectual impairment.[(1)]

As for the childhood form of Tay-Sachs, there is no cure. So Other names of TSD are B variant GM2 gangliosidosis, GM2 gangliosidosis, type1, HexA deficiency , Hexosaminidase A deficiency, Hexosaminidase alpha-subunit deficiency variant , Sphingolipidosis Tay-Sachs, TSD . TSD is genetic disease and I will be discussing Tay-Sachs disease , its causes , its types and finally its genetic basis[(1)].

TSD also have types and its types are:

1-Juvenile Hexosaminidase A deficiency: Begins with trouble walking (ataxia) and incoordination in early childhood. Symptoms are similar to those of classic Tay-Sachs although the cherry-red spot is not as common. Age of death is usually in teenage years, usually from infections, although some will die much sooner. [(1)]

2-Chronic Hexosaminidase A deficiency: usually develops before age 10 but people do not lose as many motor skills as those with Tay-Sachs. Cognitive and verbal skills are affected later in the course. [(1)]

3-Adult-onset Hexosaminidase A deficiency: causes slow but progressive muscle weakness and wasting, trouble speaking clearly, cognitive problems, and dementia. Up to 40% of people have psychiatric problems (which can be present without dementia). [(1)]

Materials and Methods:

1-Identification of deletion-duplication in HEXA gene in five children with Tay-Sachs disease from India: Multiplex Ligation-dependent Probe Amplification (MLPA) study was carried out in 5 unrelated patients for copy number changes where heterozygous or homozygous disease causing mutations could not be identified in the coding region by sequencing of HEXA gene. [(2)]

2- A total of 18 cases affected byGM2-gangliosidosis disease were assessed in our study from October 2009 to February 2014 in the Neurology Department of Mofid Children's Hospital, which is the referral center for neurometabolic diseases in Iran. The diagnosis was performed based on clinical manifestations, laboratory assessment of decreased total hexosaminidase enzyme activity for Tay Sachs and Sandhoff disease from a

metabolic laboratory in Germany . So the data was collected from the patient depending on their age, gender, past medical history, developmental status, general appearance, and clinical neuro-imaging findings.[3]

Results:

1-The study has identified the presence of a homozygous deletion of exon-2 and exon-3 in two patients, two patient showed compound heterozygosity with exon 1 deletion combined with missense mutation p.E462V and one patient was identified with duplication of exon-1 with novel variants c.1527-2A > T as a second allele.[2]

2- In our study 18 patients with GM2-Gangliosidosis (9 patients with Sandhoff and 9 with Tay Sachs disease) were included. There were 10 males and 8 females with a mean age at time of presentation of15 months and an average age of18 months. Hospitalization history for 2 patients from maternal preeclampsia and for 4 patients from pneumonia (1 patient) and icter (3 patients) . The first and chief complaint in 100% of the patients were neurological disorders, such as developmental delays (6 patients), developmental regression (5 patients), or both (7 patients) and 4 patients complained of simultaneous seizures.[3]

During developmental assessment, 66% of patients showed developmental regression. The average age for developmental regression was 15 months and the mean age was 12 months(3 months before admission and detection time).Four patients had a history of recurrent hospitalization because of respiratory and urinary tract infections. Eight patients had central hypo tonicity (decreased tonicity and increased DTR) and 5 patients had spasticity .55% of patients had visual disorders and fix-follow did not exist during physical examinations. Nine patients had a history of seizure with the most common form of seizure were tonic-myoclonic seizures.

Seven patients had hyperacusis .55% of patients had a dysmorphic face with protruding forehead, depressed nasal bridge, and hypertelorism. Five patients had blond hair. One patient had hepatomegaly and another had hepato splenomegaly. [4] Weight in 6 patients was below the 3 percentile and height in 10% of patients was below the 5 percentile. Three patients had microcephaly, seven patients showed macrocephaly, and the remainder had normal head circumferences .83% of patients were the offspring from consanguineous marriages. Four patients had a family history of seizures and mental

retardation . No abnormality was observed in other physical examinations (chest and abdomen).Cherry-red spots were seen in 88% of patients. In lab data three patients had increased levels of AST and ALT. [3]

Discussion:

Tay-Sachs is an autosomal recessive genetic disorder resulting from mutation of the HEXA gene encoding the alpha-subunit of the lysosomal enzyme, alpha-N-acetylhexosaminidase. This enzyme is necessary for breaking down certain fatty substances, N-galactosamine from GM2 gangliosides, in brain and nerve cells. These fatty substances build up and gradually destroy brain and nerve cells, until the entire central nervous system stops working. There is no known cure for the disease . More than thirty mutations have been identified in the HEXA gene. These mutations consist of base pair insertions, base pair deletions , splice site mutations, and point mutations. All of these mutations alter the protein product. For example, a four base pair insertion in exon 11 results in an altered reading frame for the HEXA gene while a three base pair deletion eliminates the amino acid phenylalinine from the protein product at position 304. The lack of beta-hexosaminidase A results in ganglioside accumulation in the lysosomes causing swelling in many tissues, most notably neurons. Sandhoff disease has symptoms similar to those associated with Tay-Sachs. The genetic basis of Sandhoff disease, like Tay-Sachs, is a mutation in the hexosaminidase A gene. However, Sandhoff disease has a defective beta-chain of beta-hexosaminidase, whereas Tay-Sachs has a defective alpha-chain of beta-hexosaminidase. Tay-Sachs is more prevalent in certain ethnic groups, especially Ashkenazi Jewish populations. One reason why may be due to heterozygote advantage. Ashkenazi Jewish TSD carriers may be less susceptible to tuberculosis. However, it has been estimated that it would take more than 300 generations to reach this level of frequency and the Ashkenazim have only been a separate group for 70 generations (Shaw and Smith, 1969)[4]. Also, one would expect a higher frequency of TSD in other ethnic groups living in the same conditions, which is not the case. Another reason may be due to the fact that parents who have had a child die from TSD will usually have more children than normal to ensure descendants. Since fifty percent of their children will be heterozygous for the TSD gene, its frequency increases among the specific group (Koeslag and Schach 1984 and 1985). [4]

Conclusion:

Tay-Scahs Disease (TSD) is hereditary. A mutation in the Hex-A gene causes the body to have no or very low levels of the Hex-A enzyme. Without Hex-A, cells (espically nerve cells in the brain) . Are unable to break down fatty waste product.

Tay-Sachs like many genetic disease its complex, there are many questions that have been answered, but many remain unanswered. Continuing research and improved techniques may someday answer them.

References:

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