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TAY SACH'S DISEASE, A GENETIC MUTATION: MECHANISM OF ONSET OF DISEASE AND PHYNOTYPIC CHARACTERIZATION

Sikander Ali*, Maleeha Hanif and Jawad Siddique

Institute of Industrial Biotechnology, GC University Lahore-54000, Pakistan.

***Corresponding Author: Dr. Sikander Ali**

Institute of Industrial Biotechnology, GC University Lahore-54000, Pakistan.

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ABSTRACT

Tay sach disease is a genetic disorder. It is a storage disease in which due to mutation in gene present on chromosome no 15 called HexA gene. This gene is responsible for production of hexoaminidase enzyme. This enzyme help in lipid metabolism present in cell. Due to lack of this enzyme the GM2 ganglioside does not metabolize thus ultimately store into the brain neurons lead to the accumulation of lipids in brain and cause tay sach disease. This disease is fatal as brain stop working and receiving and transporting signals thus death occur. The disease is simply diagnose by blood test in which level of hexoaminidase enzyme is being checked in the blood, children having this disease can be identify by cherry red spot in their eyes while carrier testing is also done in newly married couples to prevent the risks of pregnancies of tay sach diseased baby. As there is no permanent prevention or treatment for this disease nut the ways can be adopt to make the lives of patients comfortable such as massage therapy to make their muscles relax , treating with feed tubes to those who have lost the ability of swallowing, providing them wheel chairs and walkers to facilitate in mobility. Completely loss of enzyme leads to the severe condition called sandhoff disease in which a patient cannot survive for more time.

Introduction to tay-sach disease as metabolic disease

Tay-Sachs disease (TSD) is a neurodegenerative storage disorder, related to lysosomal sphingolipidosis. It is characterised by deficiency of enzyme present in lysosome which is required for degeneration of sphingolipids **(Fig 2)** such as: gangliosides, shingomylein and cerebrosides. This is fatal in result. It is a genetic disorder which is autosomal recessive in inheritance. TSD is caused by mutations of hexosaminidase A (Hex A, structure aβ) on chromosome 15. Beta-hexosaminidase is an important hydrolytic enzyme, present in the central nervous system cell lysosomes, and breaks down lipids known as GM2 gangliosides. When the enzyme beta-hexosaminidase no longer function properly, the sphingolipid GM2 trihexosylceramide does not metabolize and accumulate in neurocytes and cause lessions in the brain and nerve tissues **(Fig 1)** ultimately loss of function occur. Rapid formation and biodegradation of Gangliosides occur in early life when brain is in developing stage, otherwise the condition becomes a fatal disease in the age of 2 or 3 years. Level of residual HexA activity in brain directly relates to the severity of the disease (Gravel, 1991).

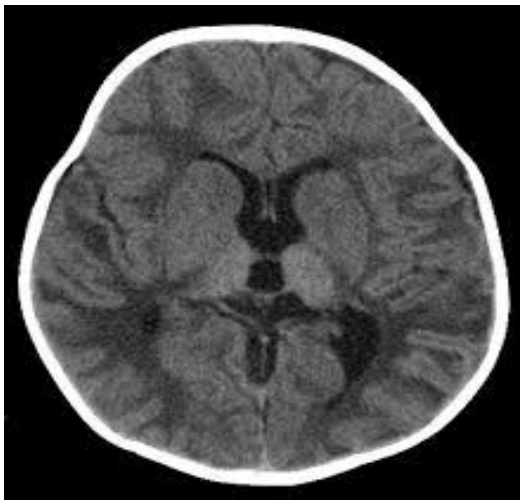

Fig 1: Accumulation of ganglioside in brain nerve

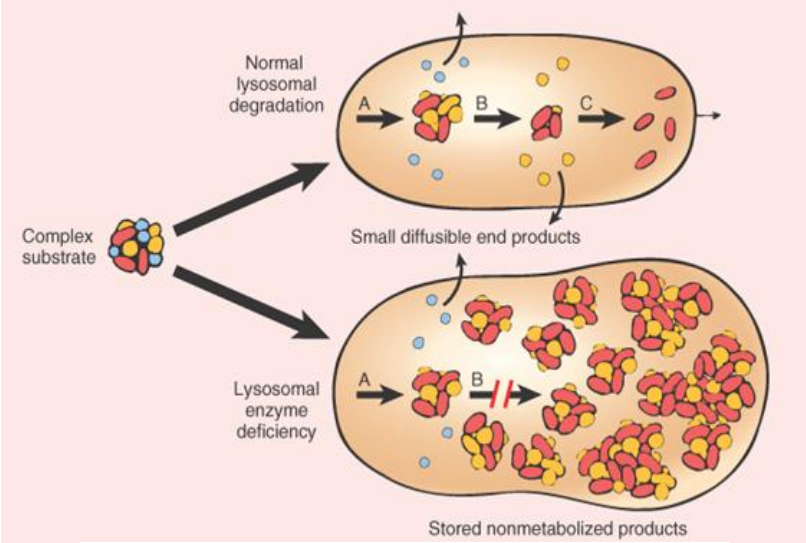

Fig 2: Accumulation of ganglioside due to lack of enzyme

Functioning of hexosaminidase

Hexosaminidase breaks the glycosidic bond present at the nonreducing end of β-N-acetylgalactosamine moieties of glycoconjugates. The two forms of enzyme play an important role in cleavage of linkage. Hex A and Hex B forms of enzymes are able to hydrolyze many of the same substrates other than ganglioside. Ganglioside **(Fig 3)** in negatively charge in nature thus only HexA has the capacity to utilize this negatively charged substrate and hydrolyze it (Myerowitz, 1997).

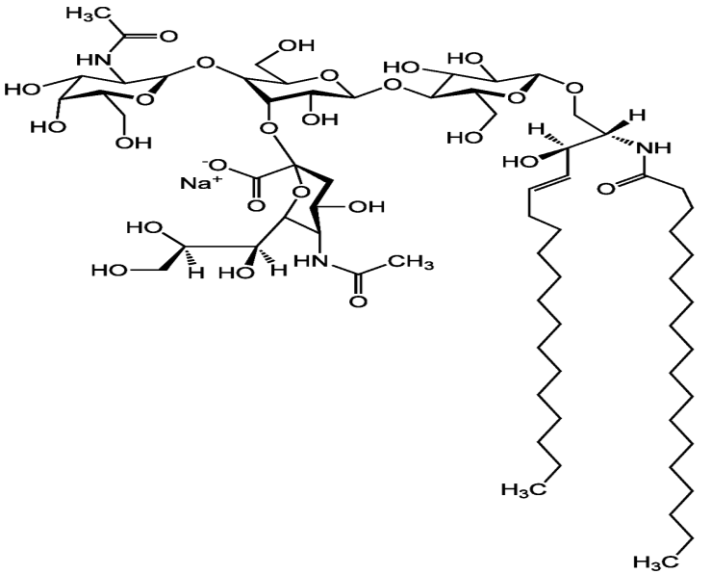

Fig 3: structure of GM2 ganglioside

GM2 activator

It is a lipid-binding protein cofactor which is water soluble. GM2 ganglioside needs the presence of this cofactor and form a complex with it in 1:1 in result whole complex become water soluble. This complex act as a transport protein that deliver the ganglioside substrate to the lysosome where degradation occur. This complex interacts with the Hex A to allow breakage of the glycosidic linkage by α subunit. Lysosomal hexosaminidase enzyme produce in two forms which are Hex A and Hex B which are similar in structural organization also.

Form1	**Form 2**
Hex A	HEX B
Made up of one α and one β subunit	Made up of two β subunits.
Gene present on chromosome no **15 (Fig 4)**	Gene present on chromosome no **5**

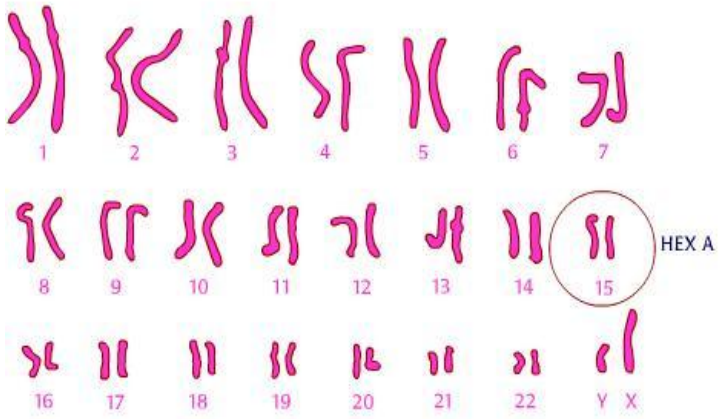

Fig 4: In tay sach disease defect in gene occur at chromosome no 15

After transcription and translation there is 60 percent similarity in the predicted sequence of amino acids and cDNA of α and β subunits. Thus, the genes of both hexA and hexB seems to share a common ancestral origin. Hexosaminidase is synthesized by a sequenced subcellular pathway which includes the formation at endoplasmic reticulum (ER) and packing at Golgi apparatus and terminates in the lysosome where it perform function. Synthesis of protein at endoplasmic reticulum is mediated by signal peptide (hydrophobic in nature) present at amino terminus of prepropolypeptide. This signal mainly helps in the translocation of newly form polypeptide into the lumen of endoplasmic reticulum (Drucker, 1993).The α signal peptide is 22 amino acid residues long,The β signal peptide is 42 amino acids residue longThe signal peptides are cut on entry into the Endplasmic reticulum thus permitting the synthesis of the remaining, freely soluble α and β propolypeptides.

In Infantile Tay-Sachs disease normal growth and development occur until 4 to 5 months of age after that psychomotor obstruction increase, blindness and cherry red spot on retina also appear. The patient can hardly survive to the age of 3 to 5 years.

Cherry red spot as symptom

The termenology "cherry red spot" explains metabolic disorder related to neurons called as tay sach (GM2 type I) disease. It is describe by **Warren Tay** first in **1881.** These patients have quite healthy optic discs in eyes apparently, but in the region of yellow spots present in their eyes there was a large well defined large white patch which is obvious and tolerable **(Fig 5)**. And easy to notice and more or less circular in shape, this spot is display in a brownish-red color nearly circular spot at its center which is contrasting strongly with the white patch surrounding it. The characteristic pale hue is due to intensive deposition of lipid, sphingolipid, or oligosaccharide material in ganglion cells of ratina at the macula, where cells are present in several layers (Suvarna, 2008; Hajela, 2008).

Fig 5: Flat chalk white area with Cherry red spot at center present in both eyes

White area is due to lipid infiltration in ganglion cells

Defective gene include in tay sach disease

The biochemical defect is basically the deficiency of the hydrolase b-hexosaminidase A (a lysosomal enzyme). HexA enzyme is needed for the break-down of the ganglioside GM2 present in the plasma membrane but due to defective gene breakdown does not occur and

disease occur. Cherry red spot appear not only in tay sach disease but it is also related to many other diseases which are also due to deficiency or complete absence of enzyme such as sandfoff disease (GM2 type II), fabry disease, gaucher disease etc **(Fig 6).**

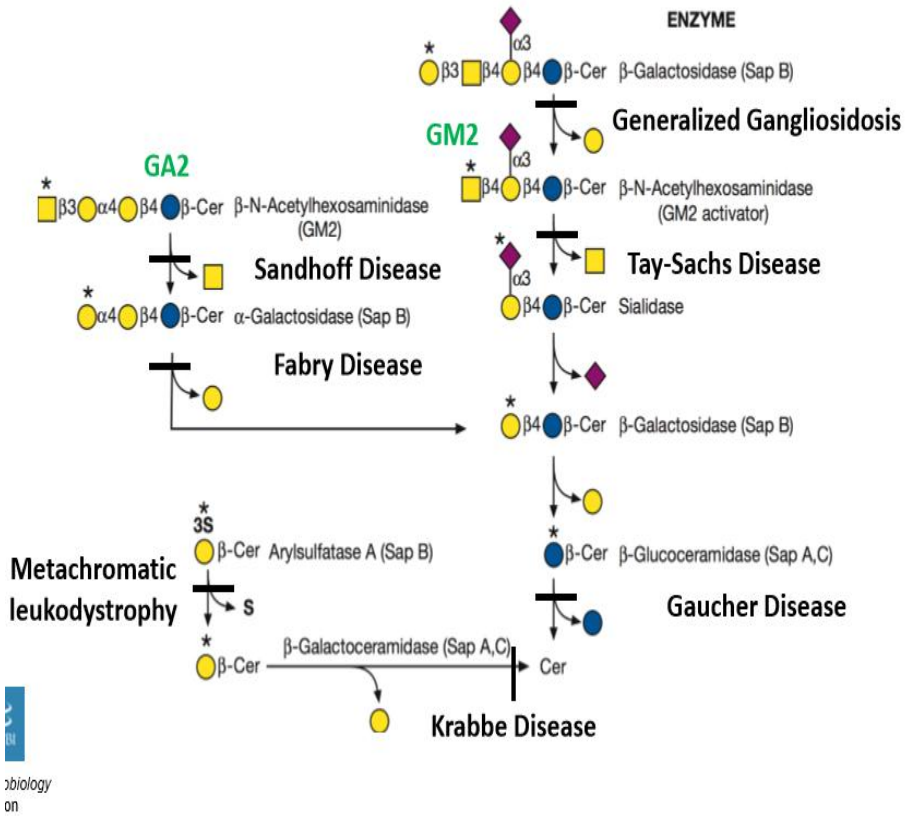

Fig6: Tay-sach disease is the deficiency of enzyme while sandhoff is a severe condition in which enzyme totally stop to produce while fabry disease is also due to deficiency of galactosidase and it inherited in X linked to the next generation (Biase, 2007).

Defective gene location in genome

The biochemical defect is basically the deficiency of the hydrolase b-hexosaminidase A (a lysosomal enzyme). HexA enzyme is needed for the break-down of the ganglioside GM2 present in the plasma membrane. Gene for this enzyme is present on chromosome no 15 **(Fig 7)** It is a hereditary disease due to mutation on gene. In order to get both parents must be the carrier of genes **(Fig 8)**

Three gene system require for hex a activity

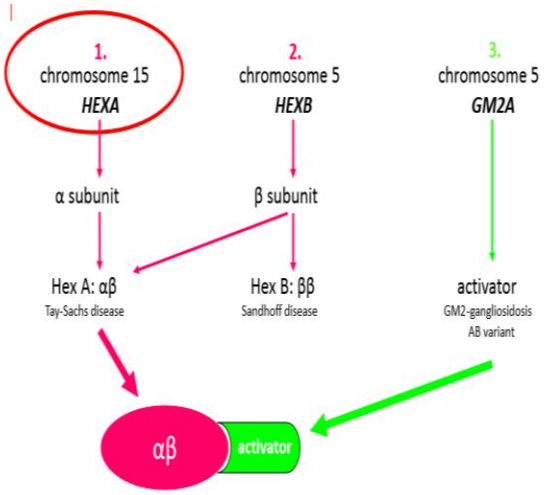

Fig 7: GM2 is an activator which is require to solubilize the ganglioside and to interact with HEX A when genetic disorder occur on chromosome no 15 the hex A production stop or decrease thus ganglioside accumulate and tay sach disease occur(Biase, 2007).

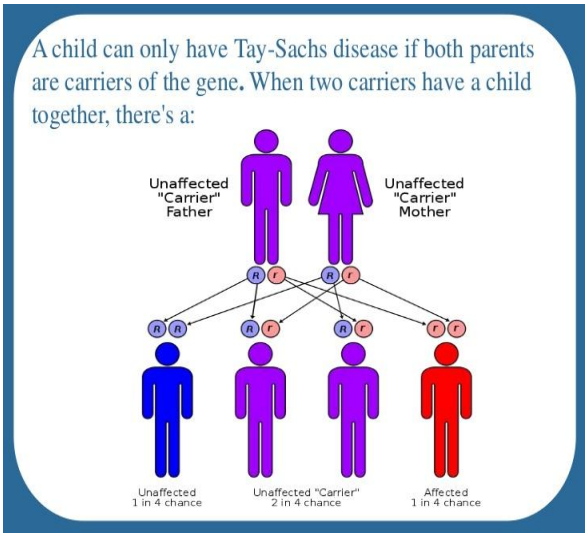

Fig 8: Inheritance of tay sach disease

Onset of disease in different age groups

Infantile TSD	**Juvenile TSD**	**Late Onset TSD**
Infants who have tay-sach disease develop normally in first six months after their birth. Then neurons become swollen with gangliosides accumulation and, a disability of mental and physical abilities begins. The child becomes deaf, blind, unable to swallow anything, paralytic and atrophied. The child can hardly survive till the age of 4and death occur.	Juvenile Tay–Sachs disease is rare than other forms of this disease. Juvenile TSD is normally seen in the children who are two to ten year old. People with juvenile TSD disease develop cognitive Death of the patient usually occur in the age of five to fifteen years.	Late onset TSD is rare form of disease, known as Adult-Onset or Late-Onset Tay–Sachs disease, Symptoms of disease began to appear in the age of 30s or 40s. This type is not fatal because effects of the disease can stop to spread rare.
Symptoms Progressive dystonia, choreoathetosis, ataxia Cognitive, dysfunction and dementia Psychosis, depression, bipolar	**Symptoms** Early death Ataxia (beginning at 2-10 years of age) Cognitive decline Spasticity and seizures Loss of vision	**Symptoms** Suffer from Loss of motor skills(failure to walk) Macrocephaly Twitchy eye vision movement Gradual deafness

Diagnoistic tests

Tay sachs disease is due to the mutation in the isoenzyme HEXA A gene which present in the nerve cells gangliosides of brain. It is due to mutation in the alpha chain (bach, 2001). So the disease can be studied by the enzyme activity and mutation studies, it is more in the jewish and the Canadian French people (Petersen, 1983). There are many tests which are available for the diagnosis of Tay sach disease. All of these tests basic purpose is to measure the amount of an enzyme known as hexosaminidase A mainly. But they can also find out the amount of hexosaminidase B in the blood. The amount of this enzyme in the blood tells whether the person has the disease or not. Blood is required for the diagnostic test of tay sach disease which can be taken from the veins and also from the umbilical cord of baby immediately after it is born.

Importance

Diagnostic tests are important in order to find out that the baby has disease or it is the carrier of the disease. Population of Ashkenazi Jewish has a renowned history of this disease so they should be tested before starting their marital life. Through blood testing it is checked whether any of the partners have HEXA mutation. If the test result for both partners comes out to be positive then there are 25% chances that they will have a baby with Tay sach disease. Similarly those people who live in a population which has many cases of this disease should also get themselves tested. This test is also carried out during the pregnancy but it should be done early in the pregnancy.

Tay sach diasese has high molecular diversity. Due to this it is difficult to find out mutations. That is why for finding out the carriers of this disease the amount of Hex A in the blood is measured. We can easily diagnose whether the person is the carrier of disease or not

through the amount of enzyme present in the blood (Jama, 1993)

B-hexosaminidase A (Hex A) enzymatic activity

One of the diagnostic tests which is carried out is to find out the activity of enzyme Hex A in the serum sample or white blood cells of a person. The substrates which are used are synthetic. The common synthetic substrate which is used is 4MUG. Hex B is more stable than Hex A to heat and this feature helps to distingish people which are carriers or non-carriers of the disease or they have the disease.

In B hexosaminidase enzymatic assay, a specific synthetic substrate known as 4MUG is used for testing. A flourometer is used to find out the amount of 4 MU which is released. The substrate which is released measures the activity of both Hex A and Hex B enzymes. The activity of both enzymes reflects the total activity. As it is known that hex A is sensitive to heat. Due to heat inactivation of hexA we can quantify the activity of hex A as the ration of activity of Hex B (Grabowski, 2006).

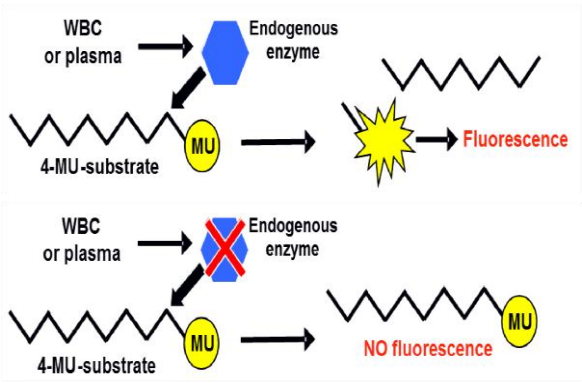

Figure 9: Enzymatic activity test

Enzyme level in an affected individual can be elevated by giving oral contraceptives.

Limitations of test

lthough this test is useful but it also has limitations. One of the limitations is it cannot differentiate between the disease occurring in babies or adults. For example it was discovered that the results of diagnostic tests for both the adult tay sach disaese carriers having Gly269Ser mutation and severe form of Tay sach disease in baby carriers were same. However this issue can easily be resolved by carrying out DNA test.

In some cases only enzymatic assay is not enough. Further molecular analysis is required for correct diagnosis. Like individuals who have an allele of pseudodeficiency gives the test negative but they are the carriers of disease. Similarly the test will also be negative for individuals which are the carriers of B1 variant phenotype (Varki, 2009).

In the year 1971, an assay was developed which measures the amount of HEXA protein in the blood. This assay leads to the diagnosis of the disease in baby before birth. However, the enzyme assay for the disease is still the best known method. It is discovered that the individuals which are the carriers of the disease have 52% enzyme activity and those which are normal individuals have 60% enzyme activity. So it is very difficult to distinguish between these two due to small activity difference. Testing also requires with drawl of blood from the veins due to this people hesitate to carry out this test. In addition, false or wrong diagnosis can be done if molecular analysis is not carried out.

Molecular testing

Molecular testing is useful because: It can confirm whether the person has the disease or it is a carrier or not. It can detect mutation in a gene known as Hex o and can also detect pseudodeficiency alleles which otherwise cannot be detected through enzyme assay.The families which have high risk of acquiring the disease have mutations in their genes which can be detected through molecular testing.It can also find out whether the baby has disease or it is a carrier before the birth. In embryo stage, it is not possible to carry out enzyme test because the amount of material present is less than required for testing. Gene amplification through PCR is done on biopsied fertilized oocytes which are at four to eight cell stage. It is done for the screening of embryo for 4-bp homozygosity (Bell, 2011).

Mutations responsible for late-onset tay sachs disease

While testing and studies about the disease it is seen that there are some mutations which causes late onset of tay sach disease and it is some years delay from other forms. Some case of late-onset disease have also been reported. So disease is late 1-2 years from other strict infantile forms. These reported mutations are as follows;

In Exon 1 there is a missense mutation pro 25Ser (Harmon, 1993).In Exon 8 deletion of 3bp which codes for glycine (Mules, 1992).In Exon 9 there is a nonsense mutation (Mules, 1992). These are the mutations but these patients have normal enzyme activity upto 2.5 percent.In Exon 5 leu190leu (Akli, 1990).In Exon 5 adenine residue replaces guanine which was at end and so that mRNA have incomplete Exon 5.In Exon 7 mutation is Gly250Asp (Trop, 1992). It is also missense mutation.Two missense mutation in Exon 13 Arg499His and Arg504His (Paw, 1990).In adult mostly reported mutation is in Exon 7 Gly269Ser (Navon, 1990).

Table 1. Mutations in the *HEXA* Gene.

Mutation	Location	Result	Class	Origin
G→T	-1 IVS-4	abnormal splicing	Infantile	Black
G_{509}→A	Exon 5	Arg170→Gln	Infantile	Japanese
C_{532}→T	Exon 5	Arg178→Cys	Infantile	Czechoslovakian
G_{533}→A	Exon 5	Arg178→His	Infantile	Diverse
G_{570}→A	Exon 5	abnormal splicing	Juvenile	Tunisian
G_{749}→A	Exon 7	Gly250→Asp	Juvenile	Lebanese
G_{805}→A	Exon 7	Gly269→Ser	Adult	Diverse
$\Delta TTC_{910-912}$	Exon 8	ΔPhe304 or Phe305	Infantile	Moroccan Jewish
G_{1260}→C	Exon 11	Trp420→Cys	Infantile	Irish/German
$+TATC_{1278}$	Exon 11	Frameshift	Infantile	Ashkenazi Jewish
G→C	+1 IVS-12	abnormal splicing	Infantile	Ashkenazi Jewish
G_{1444}→A	Exon 13	Glu482→Lys	Infantile	Italian
G_{1496}→A	Exon 13	Arg499→His	Juvenile	Scottish/Irish
ΔC_{1510}	Exon 13	Fram eshift	Infantile	Italian
G_{1511}→A	Exon 13	Arg504→His	Juvenile	Assyrian
Δ7.6 Kb	5' end	no mRNA	Infantile	French Canadian

Symptoms of tay-sachs in infants include

Person suffers with deafness,It also includes the progressive blindness to some extent,It decreases the muscle strength of that person,The startle response increase,It result in loss of function of muscles,Person suffers with seizure,Person feels muscular stiffness,Major problem is delaye in mental and social development,Usually slow growth is observed,Irritabilit,Listlessnes,Loss of motor skills (Jama, 1993).

Symptoms of other forms of tay-sachs

It is seen that there is very chronic and late onset. In elders the chances are very less but it shows severity. People suffers with this diseases usually in age of 2 to 10 and died at 15 because it is less among elders and majorly children are effected. It is chronic for children.

The other chronic forms of tay sach disease usually shows symptoms at age 10 due to the slow progress rate. They have other issues like the child not speak with flow and also shows muscle cramps. The expectancy differs in different forms, in some cases some spent normal life or some died at early ages. The adult tay sach disease is less common and have less symptoms and very less threat about life. The symptoms may be (Jama, 1993).Person suffers with muscle weakness, Have speech problems, The gait are unsteady, Usually they face with memory problems.

Prevention

We have not any proper way by which we can fight with this problem. By the methods of genetic testing or with new tools we can check about the carriers of the genes and check the risk level for tay sach disease. So now a days most people prefer genetic testing before starting their family because they relax their mind that there is not any problem in the future. For testing we have different approaches. We can use amniotic water for testing or any other strategy. But now a days there is not any proper treatment.

We can also go for gene therapy in which one injection can restore the activity of this isoenzyme but to some extent Children suffer with tay sach should made easy and comfortable because they have very short span. So give them great care and love. We can care them by different strategies: They provide with good nutrition which are good and they like. Take great care that they not face any other disease. Provide them with good environment and fresh air to avoid any respiratory disorder. If they have any problem, give them great care and provide with proper medication. Children must have not any psychological problem or any depression.

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