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COMPOUD HETEROZYGOTE REASON FOR JUVENILE FORM OF TAY-SACHS DISEASE-CASE REPORT

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Abstract

Tay-Sachs diseases are group of rare autosomal recessive lysosomal disorders, GM2-gangliozidoses. They are progressive neurodegenerative diseases, caused by a mutation in the enzyme β-hexosaminidaseA. Depending on the time of presentation of symptoms, there are three forms: infantile, juvenile and adult. We present a 8 year old patient, who is presented at the age of 4 with progressive deterioration in psychomotor and speech skills, pyramidal symptoms, ataxia and muscle weakness. The EEG showed bihemispheric fast spike waves and the MRI showed no findings of organic disease. Finally amolecular genetic testing was made, which proved the diagnosis of juvenile form of Tay-Sachs disease. It was determined that the patient is a compound heterozygote, with two different mutations in the alleles of the HEXA gene, one inherited from the mother and the other one from the father.The juvenile Tay-Sachs disease is characterized with onset between the age of 2 to 10 years old. Clinically it is presented with muscle weakness, incoordination, ataxia, dysarthria, dysphagia and progressive spasticity. It progresses to development of dementia, convulsions, blindness and vegetative state with decerebrate rigidity and death by the age of 15. It is inherited autosomal recessive with one mutation present on both alleles of the HEXA gene. Treatment options for Tay-Sachs disease currently are only symptomatic and supportive. There are ongoing researches for curative treatments for Tay-Sachs, like enzyme replacement, chaperone, substrate reduction and gene therapy.

Keywords: Tay-Sachs disease, juvenile form, compound heterozygote.

Introduction

Tay-Sachs disease belongs to the group of lysosomal storage diseases, GM2-gangliozidoses. It is a rare autosomal recessive disease, caused by mutations in the HEXA gene, which is located on the 15th chromosome and is responsible for encoding of the lysosomal enzyme β-hexosaminidase A. Mutations of the gene lead to excessive accumulation of GM2-gangliozides, mostly in the cells of the central neural system, consequently leading to progressive neurodegeneration. Depending on the time of presentation of the first symptoms, there are three types of Tay-Sachs disease: infantile, juvenile and adult form. The severity of the disease correlates with the level of Hex A activity.

Juvenile form of Tay-Sachs disease is characterized with onset beginning of symptoms in early childhood, between the age of two and ten. The residual Hex A activity in patients with juvenile form is 0.5% of the normal activity. The earlier the symptoms start, the more progressive the disease will be[1].

Some of the first symptoms appearing are clumsiness, muscle weakness and movement incoordination. Children slowly lose their acquired psychomotor, intellectual and speech skills. Ataxia, dysarthria, dysphagia and progressive spasticity develop. Finally it progresses to dementia, convulsions, optic nerve atrophy and vegetative state with decerebrate posturing, and death by the age of fifteen, most commonly caused by respiratory tract infections [2].

First step in the evaluation for making a diagnosis of Tay-Sachs disease is determining the level of the enzyme β-hexosaminidase A activity with enzyme assay.

It measures the hexosaminidase activity in serum, leukocytes or fibroblasts.Individuals with Tay–Sachs have decreased hexosaminidaseA activity[3].

Next step would be a confirmation of the disease with molecular analysis[4].

Case report

A four year old boy was referred to our Pediatric clinic for delay in the development of the speech, left side muscle weakness on upper and lower extremities and regression in his previous psychomotor development.Initially an EEG was made with findings of bihemispheric fast spike waves and contrast-enhanced MRI scans that demonstrated no sign of organic brain disease.

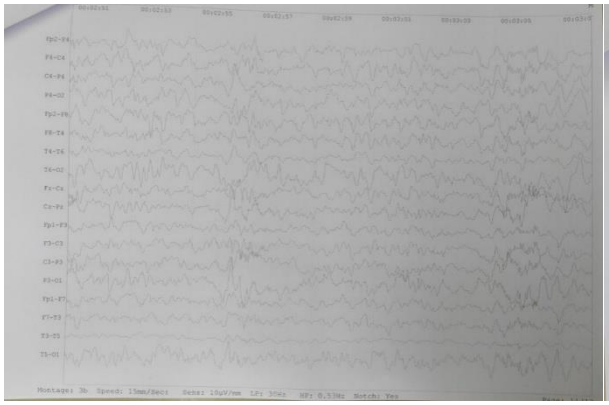

Figure 1.EEG

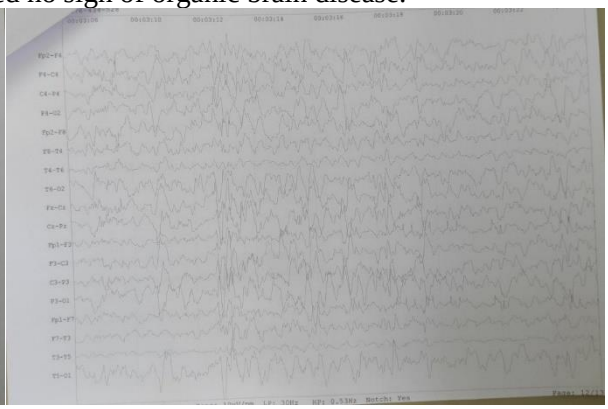

Figure 2.EEG

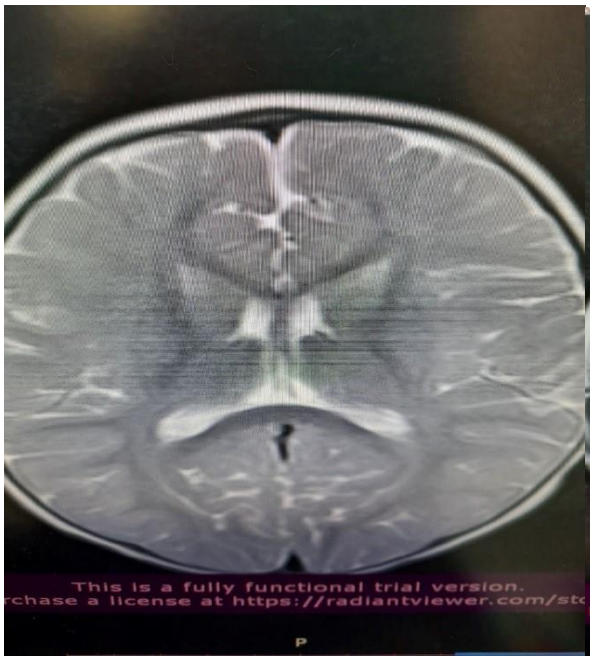

Figure 3.MRI brain of patient-with normal findings.

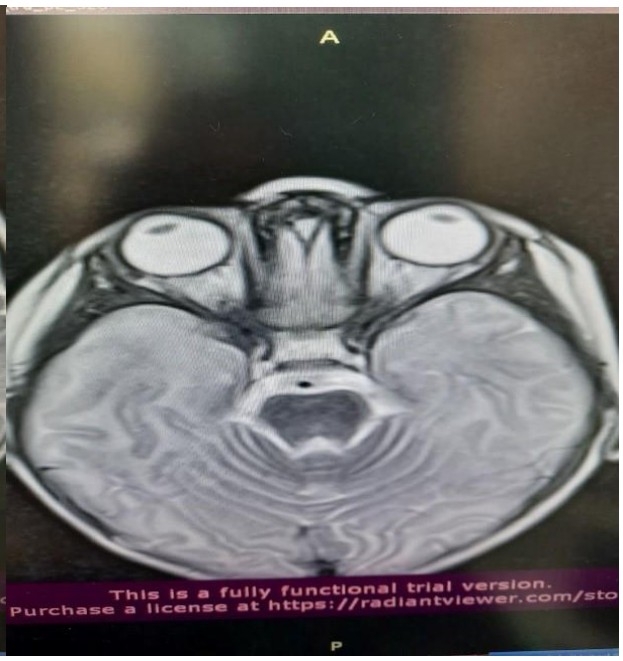

Figure 4.MRI brain of patient-with normal Findings.

Four months after the onset of symptoms, at five years of age, the patient shows pyramidal signs on all four extremities, muscle weakness, incoordination and bilateral deep tendon hyperreflexia, as well as progression in the loss of the psychomotor and speech skills. A consultation with geneticist was made and metabolic screening, molecular genetic testing and screening for spinal muscle atrophy were done.The genetic analysis was done in Academy of Sciences and Arts of Macedonia.

The molecular genetic testing proved the diagnosis of juvenile form of Tay-Sachs disease.

It was determined that the patient is a compound heterozygote, with two different mutations in the alleles of the HEXA gene, one inherited from the mother and the other one from the father. *c.902T>G (p.Met301Arg)* was inherited from the mother and *c.1496G>A (p.Arg499His)* from the father.

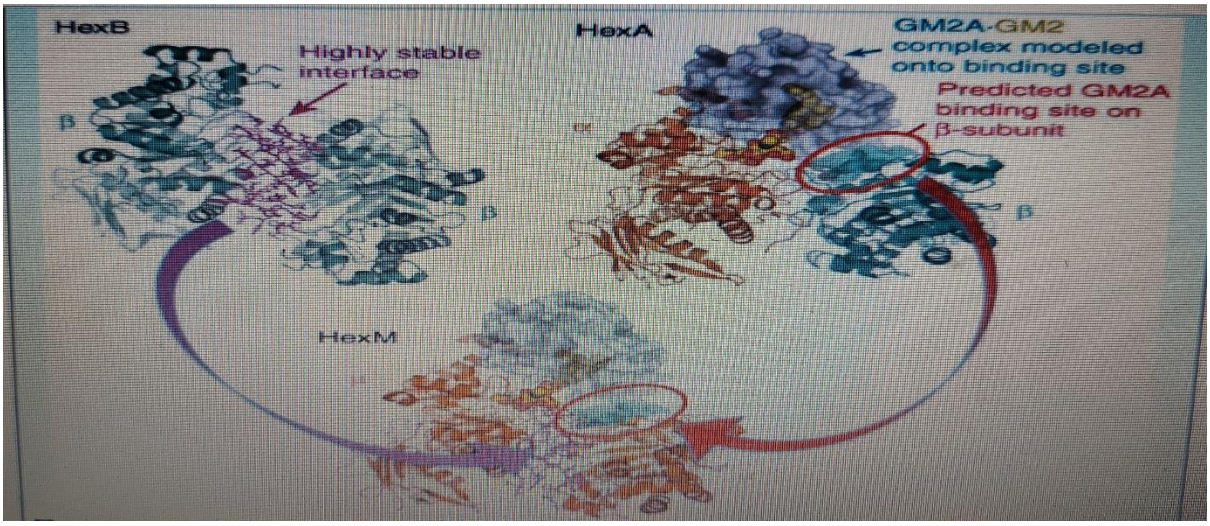

Figure 5. Gene muatation-Schematic view of protein structure HEXA,Hex A and Hex B (Methods and Clinical Developments volume 3,januari 2016).

Discussion

Tay-Sachs disease is caused by around 170 known mutations in the HEXA gene, which is located on the 15th chromosome. [5]Over 70% of them cause infatile acute form, 20% cause the juvenile subacute form and around 9% the adult chronic form of the disease. This is a rare disease with incidence of 1:100.000 live births, in the general population[6]. It is very common among the Ashkenazi Jews, Cajuns and French Canadians.

It is inherited autosomal recessive, with one mutation present on both alleles of the HEXA gene, responsible for the encoding of the lysosomal β-hexosaminidaseA enzyme. These mutations include insertions or deletions of single base, missense mutations and splice space mutations[7]. They alter the gene product and lead to completely or partially inhibited enzyme function. Most common mutation that leads to development of the infantile form of Tay-Sachs among the Ashkenazi Jews is a four base pair insertion in exon 11[8].

Patients with late onset forms of Tay-Sachs disease are usually compound heterozygotes. The disease is a result of two separate mutations in the HEXA gene, inherited one from each parent. In the early onset forms of Tay-Sachs, the child inherits one mutation from both parents, that completely stops the biodegradation of the gangliosides. Compund heterozygotes have two different mutations in the HEXA gene, that will alter, inactivate or inhibit enzyme activity. But in presence of one copy of the HEXA gene that allows for residual activity of hexosaminidase A, the onset of symptoms is usually later. Because of that patients with the adult-chronic form of Tay-Sachs disease are compound heterozygotes.

The incidence of heterozygous carriers for Tay-Sachs is high in the general population and it is 1:300. Heterozygous carriers have one mutant allele of the HEXA gene with abnormal enzyme activity,

but no signs of disease. The level of hexosaminidaseA activity is 50% from the normal activity, and allows for normal functioning of the enzyme and no phenotypic expression of disease.

Screening of heterozygous carriers for Tay-Sachs is made in case of positive family history or with specific ethnic backgrounds. The gold standard is the HEXA enzyme assay, which detects the concentrations of the hexosaminidaseA in serum or leukocytes isolated from the blood.

Molecular genetic screening can also be made, to detect the known mutations of the HEXA gene. Negative result does lower the chance of being a carrier, but it does not exclude it completely. There is still the possibility that there are carriers of mutations that are not yet discovered. Combination of these two methods is the best screening technique for discovering the heterozygous carriers for Tay-Sachs[9].

The treatment for Tay-Sachs is currently only supportive and symptomatic. As well as for the juvenile form, the treatment options are directed towards proper supportive care with adequate nutrition and hydratation, placement of oro or nasogastrig feeding tube in the presence of dysphagia. It is necessary to treat rigorously every infection with antibiotic therapy, especially those of the respiratory tract. Regular chest physiotherapy and aspirations of mucus, are important in the prevention of respiratory tract infections. Also patients with Tay-Sachs need regular physical therapy for preventing the contractures and delaying the onset of spasticity of the extremities. Finally usingmedicamentous therapy for symptom relief- antiepileptic, analgetic drugs,etc.

Curative treatment for Tay-Sachs is currently not available. Enzyme replacement therapy and chaperone pyrimethamine therapy did not bring the expected results. The use of pyrimethamine did increase the activity of hexosaminidase A, but still didn't lead to improvement in the clinical presentation of the disease. At the present moment there is a clinical trial for using supstrate reduction therapy with the medicament Miglustat in the infantile and juvenile forms of Tay-Sachs. Miglustat is currently used for treatment of a form of sphingolipidosis - type I Gaucher disease.

Gene therapy is explored as another option for treatment of Tay-Sachs, with using adeno or adeno-associated viruses like vectors for delivering cDNA for encoding the genes of the α and β HexA subunits [10,11].

In February 2022 the first gene therapy for Tay Sachs diseases is published. Two patients with infantile form of Tay-Sachs received adeno-associated gene therapy (AAVrh8-HEXA and AAVrh8-HEXB), with signs of improvement in the clinical course of the disease 3 months after the application of the therapy and with no vector associated side effects[12].

Conclusion

Juvenile form of Tay-Sachs is a rare and progressive disease which inevitably leads to lethal outcome in the second decade of life. Inheritance is autosomal recessive, but there are examples of compound heterozygosity like our case study here. Incidence of carriers is high in the general population and genetic consultation and carrier screening is needed when the family history for the disease is positive, with the purpose of discovering the heterozygous carriers. Curative treatment for Tay-Sachs is still not available, but ongoing clinical trials for new therapeutic treatments bring hope for the possibility of disease stabilization with halt in the progression of the neurodegeneration and improving the quality of life of these patients.

References

1. Seyrantepe V, Demir SA, Timur ZK, Von Gerichten J, Marsching C, Erdemli E, et al. MurinsialidaseNeu 3 facilitates GM degradation and bypass in mouse model of Tay-Sachs disease. Exp.Neurol.2017:2018 (299):26-41
2. Lawson CA, Martin DR. Animal models of GM2 gangliosidosis: utility and limitations. ApplClin Genet. 2016 Jul 20;9:111-20.
3. Park JH, Ko JM, Kim MS, Kim MJ, Seong MW, Yoo T, Lim BC, Chae JH. Novel HEXA variants in Korean children with Tay-Sachs disease with regression of neurodevelopment from infancy. Mol Genet Genomic Med. 2021 Jun;9(6):e1677.

4. Hechtman P, Kaplan F. Tay-Sachs disease screening and diagnosis: evolving technologies. DNA Cell Biol. 1993 Oct12(8):651-65.
5. Sheth J, Mistri M, Mahadevan L et al. Identification of deletion-duplication in HEXA gene in five children with Tay-Sachs disease from India. BMC Med Genet.2018 Jul 4;19(1):109
6. Lew RM, Burnett L, Proos AL, Delatycki MB. Tay-Sachs disease: current perspectives from Australia. ApplClin Genet. 2015 Jan 21;8:19-25.
7. Myerowitz R. Tay-Sachs disease-causing mutations and neutral polymorphisms in the Hex A gene. Hum Mutat. 1997;9(3):195-208.
8. Boles DJ, Proia RL. The molecular basis of HEXA mRNA deficiency caused by the most common Tay-Sachs disease mutation. Am J Hum Genet. 1995;56(3):716-724.
9. Park N, Morgan C, Sharma R et al. Improving Accuracy of Tay Sachs Carrier Screening of the Non-Jewish Population: Analysis of 34 Carriers and Six Late-Onset Patients With HEXA Enzyme and DNA Sequence Analysis. Pediatr Res.2010 Feb; 67:217–220.
10. Solovyeva VV, Shaimardanova AA, Chulpanova DS, Kitaeva KV, Chakrabarti L, Rizvanov AA. New Approaches to Tay-Sachs Disease Therapy. Front Physiol. 2018 Nov 20;9:1663.
11. Leal AF, Benincore-Flórez E, Solano-Galarza D, Garzón Jaramillo RG, Echeverri-Peña OY, Suarez DA, Alméciga-Díaz CJ, Espejo-Mojica AJ. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. Int J Mol Sci. 2020 Aug 27;21(17):6213.
12. Flotte TR, Cataltepe O, Puri A, Batista AR, Moser R, McKenna-Yasek Det al. AAV gene therapy for Tay-Sachs disease. Nat Med. 2022 Feb;28(2):251-259.