Case Report

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Clinical Features of Infantile GM1 Gangliosidosis: Report of an Iranian Patient

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ABSTRACT

Background: GM1 gangliosidosis is an autosomal recessive lysosomal storage disease due to a lack of β-galactosidase activity, exactly because of mutations in the GLB1 gene. GM1 gangliosidosis is a rare disease that could occur either during infancy (infantile type 1), as a juvenile (type 2), or in adulthood (type 3) in both nervous and skeletal systems. Type 1 is characterized by premature psychomotor deterioration, visceromegaly, macular cherry-red spot, skeletal deformities, and death in the first 2 years of life.

Case Presentation: We reported an Iranian infant who, on initial check-up, had coarse face, visceromegaly, dystonia, and hepatosplenomegaly that increased at 15 months of age. At the initial check-up, a genetic test was performed and GM1 gangliosidosis type 1 was diagnosed.

Conclusion: infant form is characterized by early-onset before the age of 6 months and rapidly progressive psychomotor deterioration, facial abnormalities, and visceromegaly.

Introduction

GM1 gangliosidosis is an autosomal recessive disorder caused by mutation inβ-galactosidase (GLB1).[1,2]Mutation causes GM1-ganglioside to accumulate in the brain as well as in the liver, spleen and kidneys.[3]

It is estimated to be about 1 in 100,000-200,000 newborns.[4] Type1 is the most frequent form of GM1 gangliosidosis.[5]

In this type, a progressive clinical course is observed at the beginning of the neonatal period which is characterized clinically by early psychomotor deterioration, bone abnormalities, coarse facies, cherry-red spot in half the patients, and hepatosplenomegaly.[6-9]

We present a case of infantile GM1-gangliosidosis borne with coarse face.

Case Presentation

The patient, a one-year-old male infant, the only child of parents of a first-degree consanguineous marriage, was born with coarse face, visceromegaly, and dystonia (Figure 1). At age of 6 months, he was a floppy infant with a seizure and the cherry-red spot test was negative but in check-up at 8 months was observed cherry-red spot. Significant psychomotor retardation, abolished tendon reflexes and increased hepatosplenomegaly was found at age of 15 months.

Figure 1. Coarse face

At the initial check-up, a genetic test was performed and GM1 gangliosidosis type1 was diagnosed. MRI test show brain atrophy and ophthalmological examination suggested just cherry red spot and there was no other vision problem.

DNA was extracted from proband peripheral blood for whole exome sequencing and then fragmented by sonication and purification by electrophoresis. The ends of the segments became blunt then ligated with adapter forked oligonucleotides to form paired-end libraries. These libraries were sent for whole genome sequencing

The read sequence was aligned using the human reference genome sequence 37 (hg 19).

Variant including SNPs and INDEL calling and genotyping were used GATK tools (v2.2). Then shortlisted annotated variants were analyzed for detection of pathogenic variants and phenotype genotype correlation. The pathogenicity of the variants is determined by Varsome (https://varsome.com) and UMD predictor (http://umd-predictor.eu).

The results showed a homozygous mutation of the GLB1 (reference sequences: NM_000404.4) gene. We validated SNV identified by WES in proband and his parents using Sanger sequencing of PCR amplified products. PCR primer was designed using perprimer and gene runner software. Primer blast was done in NCBI primer blast (https://www.ncbi.nlm.nih.gov › tools › primer-blast). The sequence of GLB1 forward primer and GLB1 revers are 3'AAACCTCCACCTCAAGCC5' and 3'CCTGTGACGTAGATAGAGAAGAC5', respectively.

Results

Our main goal in this study was to identify the genetic cause of the disease in a 4-month-old child. Analysis of genetic data obtained from whole exome sequencing and examining the relationship between genotype and phenotype homozygote mutation (c.C856T:p.W92X) in GLB1 (reference sequences: NM_000404.4) gene was introduced as a candidate. The variant (c.C856T:p.W92X) is absent in population databases ClinVar (https://www.ncbi.nlm.nih.gov/clinv ar/), LOVD (https://www.lovd.nl/) gnomAD (https://gnomad.broadinsti tute.org/), 1000G and local database. Based on ACMG guidline, this variant can be classified pathogenic variant. Also, this mutation in the database HGMD (http://www.hgmd.cf.ac.uk) has the global report of gangliosidosis type I (GM1)

that was largely consistent with the symptoms of the disease in child. GM1 gangliosidosis and Morquio B are autosomal recessive lysosomal caused by the deficiency of acid β-galactosidase due to mutations in the GLB1 gene.

GM1 deficiency of acid β-galactosidase encompasses both nervous and skeletal systems, but when it involves the skeletal system alone, it is called Morquio's disease. Because of coarse face at birth and cherry-red spot, GM1 is more possible.

Based on this evidence as well as for confirming the role of this gene in the creation of proband disease, the examination of it in the parent was carried out using the Sanger sequencing method.

The results obtained from the Sanger sequencing of the parent showed that both for this variant are healthy heterozygotes and proband is homozygout and the initial diagnosis was confirmed due to the autosomal recessive inheritance gangliosidosis type I (GM1).

Discussion

The onset of this disorder may be in utero (non-immune hydrops fetalis) or by the age of six months. Clinical signs are variable and include arrest/regression of neurological development, hypotonia, visceromegaly, macular cherry-red spots, dysostosis, and coarse facial features.

GM1 gangliosidosis and Morquio B are autosomal recessive lysosomal caused by the deficiency of acid β-galactosidase due to mutations in the GLB1 gene.

In GM1 deficiency of acid β-galactosidase both nervous and skeletal systems are involved, but when it involves the skeletal system alone, it is called Morquio's disease. Because of coarse face at birth and cherry-red spot, GM1 is more possible.

In this patient, we found a coarse face and visceromegaly at birth and dystonia. At age of 6 months had a seizure and at 8 months cherry-red spot was observed. Regression of psychomotor, tendon reflexes, and increased hepatosplenomegaly was found at age of 15 months.

Conclusion

Diagnosis is based on clinical signs although classic signs are not always present at diagnosis. Biochemical and/or molecular genetic tests confirm the diagnosis. Genetic counseling should be provided to affected families.[5]

Conflict of Interests

Authors have no conflict of interests.

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References

1. Rita Fischetto R, Palladino V, Mancardi MM, Giacomini T, Palladino S, Gaeta A, et al. Substrate reduction therapy with Miglustat in pediatric patients with GM1 type 2 gangliosidosis delays neurological involvement: A multicenter experience. Mol Genet Genomic Med 2020; 8(10): e1371.
2. Deodato F, Procopio E, Rampazzo A, Taurisano R, Donati MA, Dionisi-Vici C, et al. The treatment of juvenile/adult GM1-gangliosidosis with Miglustat may reverse disease progression. Metab Brain Dis 2017; 32(5): 1529-36.
3. Przybilla MJ, Ou L, Tăbăran AF, Jiang X, Sidhu R, Kell PJ, et al. Comprehensive behavioral and biochemical outcomes of novel murine models of GM1-gangliosidosis and Morquio syndrome type B. Mol Genet Metab 2019; 126(2): 139-50.
4. Kara DO, Şahpaz A. Pathological findings of central nervous system, two GM1 gangliosidosis autopsy cases. Turk J Pediatr 2019; 61(6): 953-7.

5. Miceli F, Soldovieri MV, Joshi N, Weckhuysen S, Cooper E. KCNQ2 -Related Disorders Summary Genetic counseling Gene Review Scope. Seattle WA: University of Washington 2020; p. 1-25.
6. Muthane U, Chickabasaviah Y, Kaneski C, Shankar SK, Narayanappa G, Christopher R, et al. Clinical features of adult GM1 gangliosidosis: Report of three Indian patients and review of 40 cases. Mov Disord 2004; 19(11): 1334-41.
7. Draïss G, Fouad A, Rada N, Hocar O, Fdil N, Bouskraoui M. Infantile GM1-gangliosidosis revealed by slate-grey mongolian spots. Open Pediatr Med J 2019; 9(1): 1-4.
8. Feng Y, Huang Y, Zhao X, Sheng H, Feng Y, Zhang W, et al. Clinical and molecular characteristics of 11 Chinese probands with GM1 gangliosidosis. Metab Brain Dis 2018; 33(6): 2051-7.
9. Brunetti-Pierri N, Scaglia F. GM 1 gangliosidosis : Review of clinical, molecular, and therapeutic aspects. Mol Genet Metab 2008; 94(4): 391-6.