Tripolitana Medical Journal; 2021, Vol.10, No.2, pp. 28 - 31

CASE REPORT
ISSN 2077-5628

First Report of PIGT Mutant Among the Libyan Population that Cause Multiple Congenital Anomalies, Hypotonia, Seizure Syndrome (MCAHS3) by A New Gene Mutation: A CASE REPORT

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Received 15 April 2021/ Accepted 15 july 2021

ABSTRACT

Multiple congenital anomaly hypotonia seizure syndrome 3(MCAHS3) is a rare inherited neurological disease due to mutation of the PIGT gene (OMIM615398). MCAHS3 is characterized by multiple congenital anomalies (cardiac. Renal and skeletal), severe hypotonia from an early age, and usually is associated with refractory seizures. This study described phenotypic and genotypic findings of a case and compared them to previously described cases. This study also highlighted the importance of Whole-Exome Sequencing in the diagnosis of rare neurological diseases. A severe hypotonic ten-month-old Libyan girl, a product of consanguineous marriage was admitted at the age of one month.Her results of Whole-Exome Sequencing revealed homozygous missense variant c.1519C>T(p. Arg507Trp). The PIGT gene revealed multiple congenital anomaly hypotonia seizure 3 diseases due to the PIGT gene. Comparing our case with the ten previously reported cases, all shared clinical presentation of hypotonia, some dysmorphic features, EEG findings. The congenital anomalies and low alkaline phosphatase are a feature of some cases. Lastly, the seizure is reported in all cases. In our case, she had two attacks of convulsion with fever. Whole-Exome Sequencing is a vital tool for diagnosing this rare neurological disease.c.1519 C>T(p.Arg507Trp) in PIGT has been described 6 times heterozygously in the gnom AD for the control population, but it has not been described in homozygous situation. We considered homozygous c.1519 C>T (p.Arg507Trp) in PIGT as a likely pathogenic variant and causal to the clinical phenotypes observed in our patient. However, the coexistence of developmental delay, hypotonia, and epilepsy together with multiple congenital anomalies, especially anorectal anomalies, should lead a clinician to consider a GPI deficiency-related disorder.

Keywords- *Hypotonia; seizure; Glycosylphosphatidylinositols (GPIs).*

INTRODUCTION

Glycosylphosphatidylinositols (GPIs) works as membrane anchors of a lot of eukaryotic cell surface proteins. GPI anchoring is essential for mammalian embryogenesis, fertilization, development, immune system, and neurogenesis. GPI biosynthesis is affected by pathogenic bi-allelic pathogenic variants in the genes that control it, e.g. PIGA, PIGN, and PIGT. Mutations in genes involved in remodeling of the GPI lipid moiety can lead to diseases characterized by neurological abnormalities.[1] GPI is a glycolipid that anchors more than 150 types of proteins human cell surface. There are at least 26 genes involved in the biosynthesis and remodeling of GPI anchored proteins (GPI-APs). Inherited GPI deficiencies (IGDs) were reported, which cause intellectual disability commonly associated with epilepsy, multiple anomalies, and course features of the face.[2] Multiple congenital anomalies-hypotonia-seizures syndromes (MCAHS) are characterized by early-onset hypotonia, psychomotor developmental delay, dysmorphic features, seizures, and variable congenital anomalies that involve the urinary, cardiac, and gastrointestinal systems.[4] This condition is caused by a defect in glycosylphosphatidylinositol (GPI) biosynthesis. The coexistence of developmental delay, hypotonia, and epilepsy together with multiple congenital anomalies, especially anorectal anomalies, should lead a clinician to consider a GPI deficiency-related disorder.[3] According to the gene mutation of the PIG gene, there are three types of MCAHS: (MCAHS1) resulting from a homozygous mutation in the PIGN gene (606097) on chromosome 18q21. MCAHS2 (300868) is caused by a mutation in the PIGA gene (311770) on chromosome Xp22, and MCAHS3 (615398) is caused by a mutation in the PIGT gene (610272) on chromosome 20q13[OMIM].

CASE REPORT

Clinical features

Ten months old Libyan girl product of a consanguineous first-degree marriage of completely healthy parents. She was admitted at the age of one month due to severe hypotonia. She is a full-term baby following an uncomplicated pregnancy; her birth weight was 3.100gm with a normal head size. She had multiple admissions due to repeated chest infections. She had mild myoclonic

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convulsion during a febrile illness at the age of six months and generalized tonic-clonic convulsion associated with high-grade fever at the age of ten months. There are no abnormal movements between the two attacks. There are no similar illnesses in her family. On physical examination, she was alert, followed objects andturned to sounds, her head size is 44 cm, just below 50th centiles, weight 8 Kg on 25th centiles, and the length 71 cm on 50th centiles, she had incomplete head lag and was unable to sit or crawl. Dysmorphic features include an elongated face, a broad forehead, upward slanting of eyes, bitemporal narrowing, hypotolaresm, and long philtrum (Figure 1). She also had mild pectus excavatum. Neurological examination revealed hypotonia, hyporeflexia both in upper and lower limbs and normal plantar reflex.

***Biochemical and imaging and investigations*:**

The biochemical profile (done at the age of 8 months) showed low alkaline phosphatase (183 U\L, the normal range less than 462), average bone age, no osteopenia. Serum calcium, liver functions, renal functions, complete blood count were all normal. An ultrasound scan of the kidneys was normal. ECHO showed a small patent ductus arteriosus. MRI brain done at the age of one month was normal; MRI at the age of ten months showed mild brain atrophy (Figure 2). Resting electrocardiography showed multiple bilateral outbursts of spike-wave epileptiform activity, compatible with generalized epilepsy (Figure 3).

Family pedigree of family of index case showed both parents carry a PIGT gene in heterozygous state, while their child carry the gene in homozygoues state indicate an autosomal recessive inheritance (Figure 4).

Genetic studies

The family signed informed consent for the gene sequencing and the publication of our case's photos and results. **WES**[9]: More than 20.000 genes of the patient DNA were enriched and sequenced. Filtering of the exome data targeted recessive, X-linked, and dominantly inherited diseases. WES identified the homozygous missense variant c.1519C> T p. (Arg507Trp) -(chr20:44054248; hg19) in the PIGT gene (OMIM*610272; chromosome 20q13.12) (Figure 5). which leads to an amino acid exchange. 12 out of 21-bioinformatic in silico programs predict a pathogenic effect for this variant (Table1). Regarding the literature survey, the variant has not been described (RGMD 2019.4). No allele frequency in the general population has been documented (gnomAD v2.1.1 controls), and this is an unpreceded detection of such 'variant in the internal database. The variant is classified as a "variant of uncertain significance" (Bioscientia Healthcare GmbH).[9]

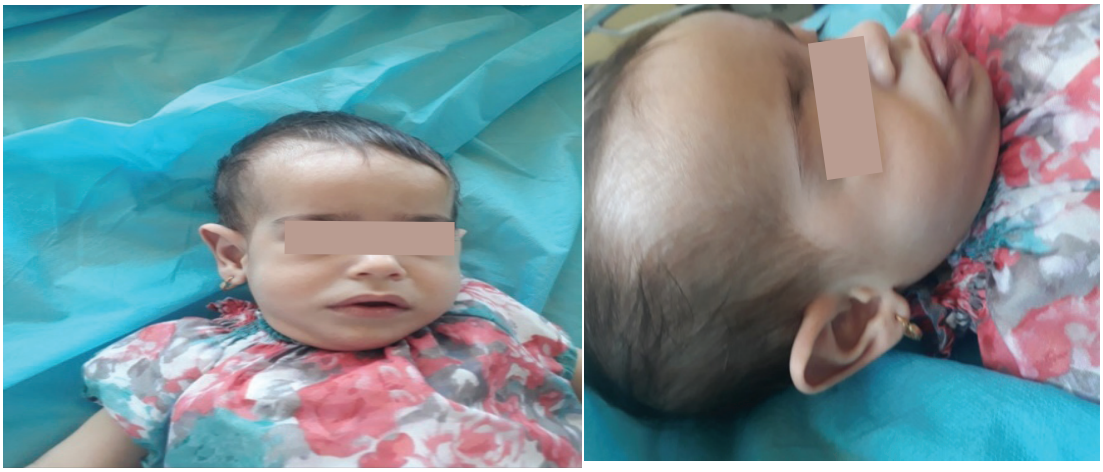

Figure 1: Picture of the proband with some dysmorphic feature going with MCAHS3 syndrome.

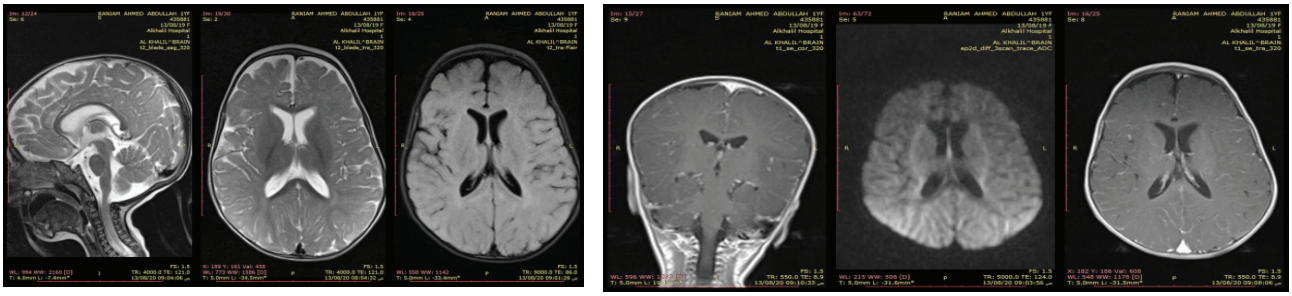

Figure 2 : MRI brain of index case at ten month

Performed using a dedicated head coil a 1.5 Tesla Magnetom Essena Scanner, showed prominent bilateral supra tentorium cortical sulci with mild white matter volume loss consistent with mild brain atrophy.

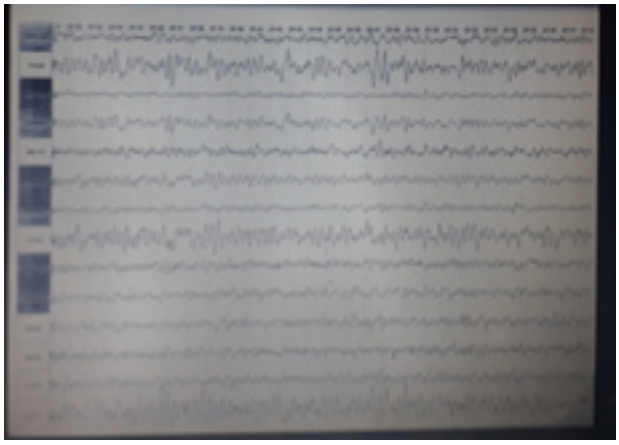

Figure 3: An EEG of the proband revealed an epileptic discharge

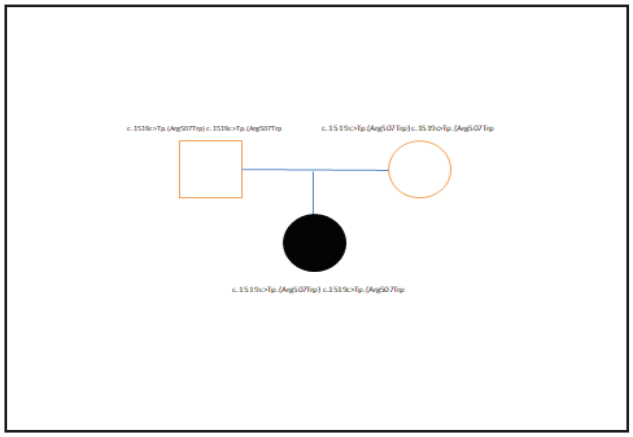

Figure 4: Family pedigree of family of index case.

Both parents carry a PIGT gene in heterozygous state , indicate an autosomal recessive inheritance .

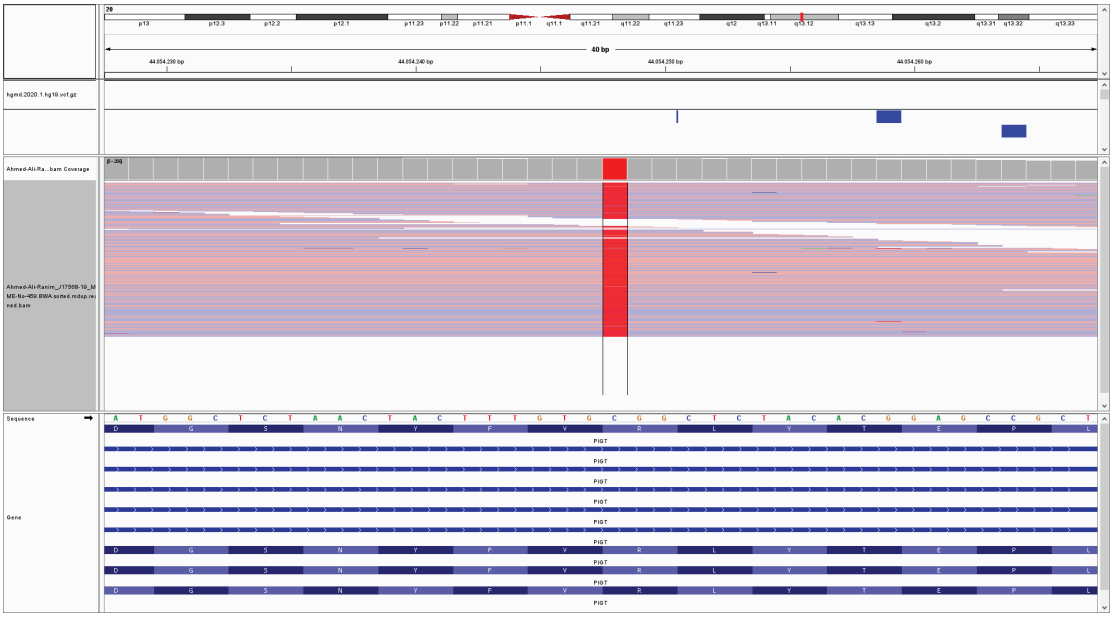

Figure 5: A lignment of PIGT gene.

Which is indicated by the vertical shadow , the PIGT gene is located chromosome.

DISCUSSION

Multiple congenital anomalies-hypotonia-Seizures syndromes (MCAHS) is an autosomal recessive, very rare genetic disorder caused by a genetic mutation of the PIGT gene. A total of ten cases was reported worldwide. The first reported four cases were from a Turkish family Kvarnung et al.[4], one Japanese girl) Nakashima et al. (2014)[5], two from Somalian families Skauli et al. (2016)[6], two from mixed African American families and Caucasian ethnic backgrounds (Lam et al. (2015)[7], finally, one Japanese boy Kohashi et al. (2018).[8] The characteristic feature of all cases, including this study case, is hypotonia, which was reported at an early age of life; but in this case, it was existent from one month of her age. The presence of multiple congenital anomalies in the second feature that varies from case to case. this study case had congenital heart disease in the form of small ductus arteriosus, which does not require any treatment, and mild pectus excavatum. The third feature is the seizure, which is the feature of all cases. In this case, she had two attacks of convulsion, which was associated with fever, and despite her abnormal EEG, she was stable between the two attacks and did not require treatment. The dysmorphic feature is also a feature of this syndrome. The case had an elongated face, a broad forehead, upward slanting of eyes, bitemporal narrowing, hypotolaresm, long philtrum. Also, most cases had low alkaline phosphatase, which was present in this study case as well.

By Whole Exome sequencing, this study identified a novel that is likely pathogenic rather than the uncertain significance of a homozygous PIGT missense variant c.1519c>Tp. (Arg507Trp) in the PIGT gene in a Libyan girl with typical dysmorphic features and some congenital anomaly, low alkaline phosphatase together with severe multi-neurological disorders, supporting the diagnosis of MCAHS3 syndrome.

CONCLUSIONS

This report highlights the variant spectrum of MCAHS3, and this is the first report of PIGT mutant among the Libyan population. c.1519 C>Tp.Arg507Trp in PIGT has been described 6 times heterozygously in the gnom AD for the control population, but it has not been described in a homozygous situation. We considered homozygous c.1519 C>Tp.Arg507Trp in PIGT as a likely pathogenic variant and causal to the clinical phenotypes observed in the patient. Also, we conclude that patients with multiple congenital abnormalities combined with severe psychomotor retardation/regression, seizures, dysmorphic features, and hypotonia, GPI-deficiency should be suspected, and WES must be performed to diagnose this type of rare diseases. The follow-up of the patients diagnosed with MCAHS3 syndrome must be addressed carefully and published up-to-date to know any new aspect as well as the prognosis of this disease.

ACKNOWLEDGMENT

The author would like to thank the family for their cooperation in making this report and Mr. Ali Aboulgasm, who works in the Central Laboratory at Tripoli University Hospital, for their help in sending and receiving the investigation of our patient from Germany.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Compliance with ethical principles

No prior ethical approval is required for single case reports. However, the patient provided consent for publication as stated above.

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