Case Report

Mitochondrial Fission Factor Gene Mutation: A Dilemma for Prenatal Diagnosis

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Abstract

Mitochondrial fission factor (MFF) gene mutations are rare mitochondrial fission disorders, resulting in autosomal recessive neurological disorders. We here report a rare case of MFF gene mutation running in a family which ultimately turned out to be a variant of unknown significance. A 29-year-old multigravida visited at 18-week gestation for prenatal genetic testing as her previous baby had cerebral palsy and global developmental delay. The exome sequencing of the affected baby revealed defective mitochondrial and peroxisomal fission 2 (AR-617086). On Sanger sequencing, the mother was homozygous and the father heterozygous for the same variant. In the current pregnancy, amniocentesis was done and the fetus was also homozygous for a similar mutation. The couple continued the pregnancy and delivered a healthy baby who had normal milestones at 11 months of age. As far as prenatal diagnostic testing is considered, our case is a real-world scenario, where patient expectations befuddle appropriate decision-making.

Keywords: *Autosomal recessive, homozygous, mitochondria, variant of unknown significance*

Introduction

Mitochondrion is an essential organelle in each cell of our body. It has two important functions of fusion and fission, the balance between which is important for the smooth functioning of the body. Fission event ensures the separation of defective genomic material from a functioning one. The fission disorders, although rare, have been predominantly contributed by defective ganglioside-induced differentiation-associated protein 1 and DNM1 L gene leading to various disorders including early-onset mitochondrial encephalopathy.[1] Mitochondrial fission factor (MFF) gene mutation results in encephalopathy due to defective mitochondrial and peroxisomal fission 2 (EMPF2; MIM#617086), thereby resulting in elongation of mitochondria and tubular peroxisomes which cause an autosomal recessive neurological disorder, i.e., encephalopathy. It may present with optic atrophy, peripheral neuropathy, early-onset seizures, hypotonia, and/or delayed psychomotor development.[2]

We could find only six cases of MFF gene mutation reported in the literature.[2-4] We propose to add, ostensibly the first such case to be reported from India.

Case Report

A 29-year-old multigravida visited at 18-week gestation for prenatal genetic counseling. Her first two children delivered by cesarean section have normal developmental milestones till date. The third pregnancy was an unsupervised one when she delivered vaginally at home. The baby did not cry at birth and was kept on ventilator support for 10 days. He was diagnosed with hypoxic-ischemic encephalopathy Grade 3 and developed spastic cerebral palsy and global developmental delay later in life. The parents were not satisfied and went to some fetal medicine center for the evaluation of that baby. They were advised to get clinical exome sequencing of the baby when he was around 4 years of age. On clinical exome sequencing [Figure 1], the child was found to have a deletion "AG" and insertion of "TT" between nucleoside "19" and "20" causing change in amino acid from serine to phenylalanine at codon 7 which was confirmed by Sanger validation. The child had defective mitochondrial and peroxisomal fission 2 (AR-617086) and was homozygous for this mutation. His

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ophthalmic examination and brain stem-evoked response audiometry test were normal. He had no history of seizure till his present age of 5 years. The magnetic resonance imaging of the brain showed symmetrical hyperintensities in bilateral thalami. The biochemical analyses including serum lactate levels were normal.

The pedigree chart is shown in Figure 2. Surprisingly, on testing the parents, the mother came out to be homozygous and the father heterozygous for the same variant [Figure 3a and b]. The mother was phenotypically normal, with normal intelligence quotient and without visual or neurological abnormalities. In the present pregnancy, she came for genetic counseling at 18 weeks and had normal genetic sonogram. The dilemma was whether to go for invasive prenatal diagnosis or not and what if the current fetus also turns out to be homozygous. We counseled the couple that this mutation could be a variant of unknown clinical significance, but they were adamant to get the invasive testing for confirmation. Amniocentesis was, however, done on the patient's request and Sanger sequencing revealed homozygous deletion in exon 3 of the MFF gene [Figure 4].

RESULT SUMMARY

Homozygous variant of uncertain significance was detected in *MFF* gene in the index patient.

Gene and Transcript	Location	Variant	Zygosity	Disease (OMIM)	Classificatio
MFF NM_020194.5	Exon 3	c.19_20delAGinsTT; p.Ser7Phe	Homozygous	Encephalopathy due to defective mitochondrial and peroxisomal fission 2 (AR - 617086).	Variant of Uncertain significance

Figure 1: Phenotype–gene relationship in exome sequencing

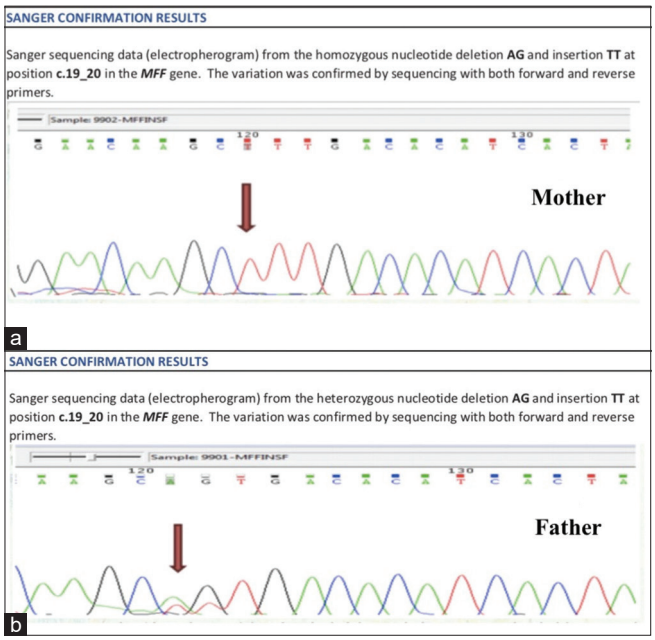

Figure 3: (a) Electropherogram showing deletion AG and insertion TT at position c.19_20 in the mitochondrial fission factor gene in mother; homozygous variant (b) father; heterozygous variant

The couple was again confused and finally decided to continue the pregnancy, and an elective cesarean section was done at 39 weeks, delivering a female child with weight of 3245 g and Apgar score of 8/9 at 1 and 5 min. The baby is under follow-up and has normal milestones at 11 months of life.

Discussion

MFF gene is located on long (q) arm of chromosome 2 at position 36.3. Its mutation is quite rare. In 2012, the first case was reported, where the two siblings born to consanguineous parents, during the course of evaluation for probable mitochondrial encephalopathy, were found to have a gene mutation in MFF gene.[3]

In another study, three cases of MFF gene mutation with features of optic atrophy, peripheral neuropathy, external ophthalmoparesis, neurodevelopmental delay, and microcephaly were documented.[2] The most recent case revealed a homozygous c. 892C>T (p. Arg298) mutation in the *MFF* gene.[4]

Our case is unique because the proband is a 5-year-old boy who presented with cerebral palsy and encephalopathy but no seizures or vision abnormality. He had a history of perinatal asphyxia which can explain cerebral palsy, but interestingly, on exome sequencing, MFF gene mutation was accidentally discovered. The mother is phenotypically normal despite being homozygous for the same variant. Moreover, the last child delivered is also homozygous and is normal at 11 months of life.

We are at crossroads, whether this variant is a variant of unknown significance (VOUS) or is it actually pathogenic?

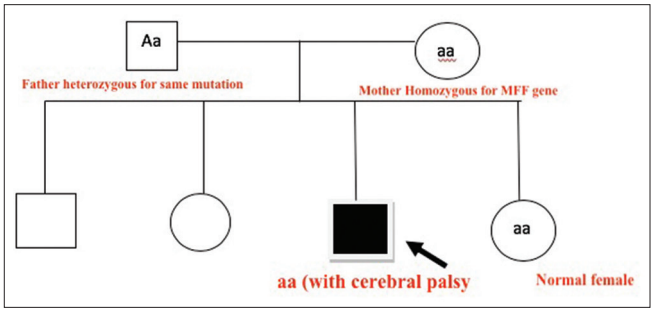

Figure 2: Pedigree chart

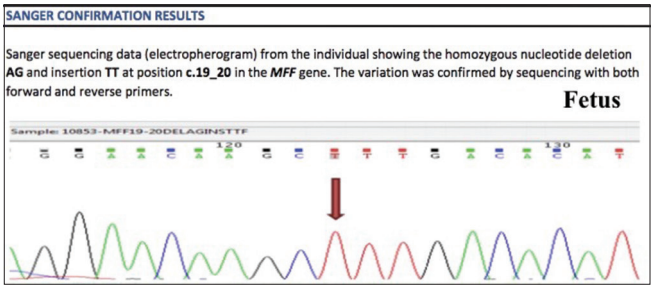

Figure 4: Electropherogram showing deletion AG and insertion TT at position c. 19_20 in the mitochondrial fission factor gene in the fetus; homozygous variant

Follow-up is essential as Chao *et al*. (2016) had reported a boy with EMPF1 who was normal till 5 months of age and developed manifestations later on.[6] Interestingly, all the six cases reported so far had different variants of MFF gene mutation which were all pathogenic. As per the recent American College of Medical Genetics guidelines, our case is likely VOUS.[6] As far as prenatal diagnostic testing is considered, our case is a real-world scenario, where patient expectations befuddle appropriate decision-making.

Consent

Written informed consent was obtained from the patient for publication.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chen L, Winger AJ, Knowlton AA. Mitochondrial dynamic changes in health and genetic diseases. Mol Biol Rep 2014;41:7053-62.
2. Koch J, Feichtinger RG, Freisinger P, Pies M, Schrödl F, Iuso A, *et al.* Disturbed mitochondrial and peroxisomal dynamics due to loss of MFF causes Leigh-like encephalopathy, optic atrophy and peripheral neuropathy. J Med Genet 2016;53:270-8.
3. Shamseldin HE, Alshammari M, Al-Sheddi T, Salih MA, Alkhalidi H, Kentab A, *et al.* Genomic analysis of mitochondrial diseases in a consanguineous population reveals novel candidate disease genes. J Med Genet 2012;49:234-41.
4. Nasca A, Nardecchia F, Commone A, Semeraro M, Legati A, Garavaglia B, *et al*. Clinical and biochemical features in a patient with mitochondrial fission factor gene alteration. Front Genet 2018;9:625.
5. Kniffin CL. Encephalopathy due to defective mitochondrial and peroxisomal fission 2; EMPF2. Available from: https://www.omim.org/entry/617086 [Last Accessed on 2021 March 27].
6. Chao YH, Robak LA, Xia F, Koenig MK, Adesina A, Bacino CA, *et al*. Missense variants in the middle domain of DNM1 L in cases of infantile encephalopathy alter peroxisomes and mitochondria when assayed in Drosophila. Hum Mol Genet 2016;25:1846-56.