ARV1 Gene: A Novel Cause of Autosomal Recessive Cerebellar Ataxia with Elevated Alpha-Fetoprotein

Thanuja Basavanagowda, Mahesh Kamate

Department of Paediatric Neurology, Jawaharlal Nehru Medical College, KAHER Deemed-to-be University, India.

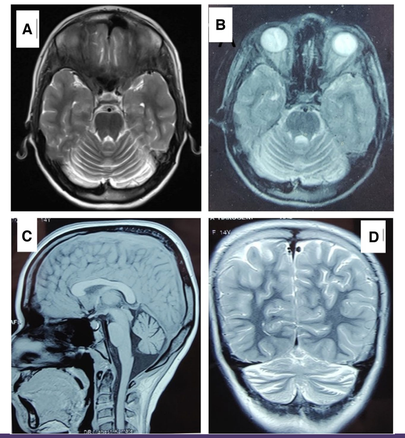
INTRODUCTION

Many novel presentations are described with increased use of whole exome sequencing. ARV1- mutation with developmental and epileptic encephalopathy (DEE)-38, is one such gene with phenotypic pleiotropy.

Only 28 cases of DEE-38 are reported so far since 2016. Ataxia has been described in 8 cases.

Apart from epilepsy and developmental delay, unique features include ocular abnormalities and movement disorders in the form of ataxia or dystonia.

Ataxia telangiectasia (AT), a common inherited childhood-onset ataxia, is characterized by ataxia, oculomotor apraxia, choreoathetosis, and elevated alpha-fetoprotein (AFP) levels. Increased levels of AFP can be noted in other autosomal recessive cerebellar ataxias ARCAs such as ataxia-oculomotor apraxia (AOA). Elevated AFP level in ARV1 mutation has not been described.



MRI Brain [initial (A) and follow-up scan after 2 years (B–D)] showing prominent cerebellar foliae suggestive of cerebellar atrophy

CASE REPORT

- 14 yr girl, born to 2nd degree consanguineous couple with a normal birth history, had seizures from the age of 5 months (once in 3-4 days initially, reduced from 6 yrs age with valproic acid).
- Developmental delay, poor cognition present. Ataxia noticed from the age of 3 yrs, which has progressively increased- now needs assistance for even activities of daily living.
- No history of recurrent infections, hypotonia, dystonia, or skeletal abnormalities.
- On examination, ataxia, oculo-motor apraxia, and flat feet present. Suspecting AT/ AOA, serum **AFP** levels were done, which was elevated (32.2 ng/mL) (laboratory reference: 0–7). Repeat value one year later was 36 ng/mL.
- Liver function, echocardiography, renal ultrasonography, EEG - normal. MRI - cerebellar atrophy. **WES**: homozygous pathogenic missense mutation in ARV1 gene NM_022786.3 (ARV1): c.565G>a/A (p.Gly189Arg).

DISCUSSION

Common features of DEE-38: developmental delay, intellectual disability, and infantile onset seizures.

ARV1 (ACAT related enzyme 2 required for viability-1) gene located at 1q42.2 encodes a 271 amino acid protein. Studies on yeast cell have shown that deletion of ARV1 results in multiple growth and viability defects, abnormal sterol trafficking, membrane disorganization and hypersensitivity to fatty acids.

Most children presenting as DEE have a splice site or frameshift mutation → loss of function. Of the reported 28 cases, 10 have succumbed to death before 5 yrs age (8 due to splice site mutation).

Movement disorders in the form of dystonia and ataxia can be present along with ocular abnormalities. Ataxia has been reported in 8 cases thus far, with a missense mutation. Cerebellar atrophy was present in 3 cases with ataxia.

The index case had oculomotor apraxia and persistently elevated AFP levels. These are novel findings. Ophthalmicl involvement- visual inattention, roving eye movements, hypermetropia, retinal dystrophy, and nystagmus. With regard to elevated AFP, whole exome sequencing in our case ruled out other ARCAs as ATM, APTX, PNKP, and SETX (AT, AOA-1, 4, and 2, respectively) were checked.

Elevated AFP level (>20 ng/mL), is an important diagnostic marker of AT. This elevation in ARCAs is suggested to be secondary to an epi-phenomenon due to dysregulation in hepatic transcription. Whether AFP levels can help in treatment, follow-up, or predicting prognosis remains to be determined in future studies.

With renal involvement in 5, dilated cardiomyopathy in 3, skeletal abnormalities in 5, and hearing loss and facial dysmorphisms in 2 each, ARV1 mutation can cause multisystemic involvement. Movement disorders are commonly found, with dystonia reported in 10 and ataxia in 8.

CONCLUSION

- In a child with ataxia and increased AFP levels, think of ARV1 mutation when genetic testing for the more common ataxia telangiectasia and ataxia with oculomotor apraxia is negative, and the child has epilepsy with developmental delay/ intellectual disability.
- Evaluation of AFP levels must be done in all DEE38 cases, more so in those having ataxia.
- ARV1 missense mutations may have a tendency towards ataxia and mild epilepsy, splice site mutations may have mortality.
- DEE with features of ocular abnormality, movement disorder (ataxia, dystonia), and cerebellar atrophy on imaging can be clues to help in suspecting ARV1-associated DEE-38.

REFERENCES

1. Scala M, Bianchi A, Bisulli F, Coppola A, Elia M, Trivisano M, et al. Advances in genetic testing and optimization of clinical management in children and adults with epilepsy. Expert Rev Neurother. 2020;20(3):251–69.

2. Alazami AM, Patel N, Shamseldin HE, Anazi S, Al-Dosari MS, Alzahrani F, et al. Accelerating novel candidate gene discover in neurogenetic disorders via whole exome sequencing of prescreened multiplex consanguineous families. Cell Rep. 2015;10:148–61.

3. Palmer EE, Jarrett KE, Sachdev RK, al Zahrani F, Hashem MO, Ibrahim N, et al. Neuronal deficiency of ARV1 causes an autosomal recessive epileptic encephalopathy. Hum Mol Genet. 2016;25:3042–54.

4. Paucar M, Taylor AMR, Hadjivassiliou M, Fogel BL, Svenningsson P. Progressive ataxia with elevated alpha-fetoprotein: diagnostic issues and review of the literature. Tremor Other Hyperkinet Mov (N Y). 2019;10:9.

CONTACT

Dr. Thanuja. B: thanu.bg@gmail.com

Dr. Mahesh kamate: drmaheshkamate@gmail.com