CHEDDA syndrome associated with epileptic encephalopathy and hand stereotypies

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INTRODUCTION

ATN1-related CHEDDA syndrome is a newly described syndromic neurodevelopmental disorder characterized by severe global developmental delay, language deficiency, marked motor disability, dysmorphic facial features, skeletal abnormalities and variable congenital anomalies including heart and genitourinary system. The first case was reported by Mosca et al.in 2007 and only 18 patients have been reported in the literature.

OBJECTIVES

Herein we report the first Turkish case with CHEDDA syndrome, As well as, describe the identification of the first reported recessive variant in the ATN1 gene in literature.

CASE

A 3-year-old boy born from consanguineous parents presented with a complaint of speech and cognitive delay, unsteady gait and seizure. His medical history is consistent with truncal hypotonia, autistic features and epilepsy. Physical examination revealed mild facial dysmorphism, autistic features and stereotyped hand movements(figure1, video 1). All laboratory, metabolic screening tests, and genetic tests including microarray, karyotype analysis, CDKL15, SLC2A1, and FOXG1 gene analysis were normal. Electroencephalography was compatible with epileptic encephalopathy (figure 2). The WES (whole exome sequencing) revealed a homozygous four triplets deletion in exon 5 of the ATN1 gene as c.1476_1508del(p.Q492_Q502del). Parental screening also showed heterozygosity in both parents for the same variant.

DISCUSSION

CHEDDA syndrome is caused by heterozygous mutation in the ATN1 gene on chromosome 12p13. Common manifestations include congenital hypotonia, epilepsy, developmental delay, growth retardation, visual and hearing impairment, brain abnormalities, feeding difficulties, digital, cardiac, renal and vertebral congenital anomalies. Hyperkinetic movement disorders can be seen with some of the genetic early-onset epileptic encephalopathies such as ARX, GNAO1, GRIN1, GABRA2, HECW2, STXBP1, and FOXG1 variants which are also called epileptic dyskinetic encephalopathies. Although our patient had stereotypic hand movement, his genetic studies for Rett and Rett-like syndromes were all normal. Since this patient is the first CHEDDA syndrome with epileptic encephalopathy and movement disorder, it expands the differential diagnosis of epileptic dyskinetic encephalopathies. Our patient has also facial dysmorphism including bitemporal narrowing, long philtrum, minimal retrognathism, low-set ear, and a bulbous nasal tip which are consistent with notable facial appearance of CHEDDA syndrome (figure 1, video 1). He did not have any visual, hearing impairment or any other congenital anomalies. **ATN1-related CHEDDA syndrome is due to a heterozygous pathogenic mutation in a 16-amino-acid sequence of exon 7 in ATN1 in which histidine is in every other position. CHEDDA syndrome is an autosomal dominant condition typically caused by a de novo pathogenic variant. However our patient has homozygous four triplets deletion in exon 5 of ATN1 gene which is different from CAG expansions in exon 5 and missense or insertion repeats within a histidine-rich motif in exon 7.**

Figure 1; facial dysmorphism including bitemporal narrowing, long philtrum, minimal retrognathism, low-set ear, bulbous nasal tip

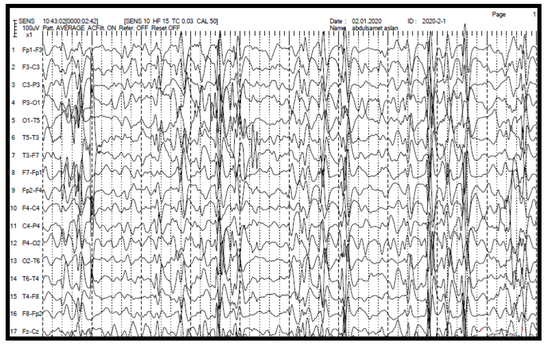

Figure 2; EEG is characterized by significant generalized spike waves, multiple spike waves and suppression periods originating from the bilateral frontotemporal region .

CONCLUSION

To the best of our knowledge, this report is the first of a Turkish patient with CHEDDA syndrome. Besides this, our patient had CHEDDA syndrome together with drug-resistant epilepsy, epileptic encephalopathy and Rett-like hand stereotypies which further expanded the clinical spectrum of CHEDDA syndrome as dyskinetic epileptic encephalopathy. In a disease where only dominant diseases related to the critical region of ATN1 exon 7 have been reported, identification of the recessive variant shown in exon 5, will provide a better understanding of ATN1-related diseases.

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