FOXG1 gene related epileptic diskinetic encephalopathy

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

Forkhead box G1 (FOXG1) related disease was defined as 'congenital Rett syndrome variant' when it was first defined, but since the characteristics of the identified cases were understood it was called 'FOXG1-related syndrome', 'FOXG1-related encephalopathy' or 'FOXG1 gene-related epileptic dyskinetic encephalopathy'. FOXG1 gene plays an important role in the early steps of brain development; from the timing of neurogenesis to the patterning of the cerebral cortex and mutations in this gene have been shown to cause this syndrome. The FOXG1-related syndrome is characterized by dyskinetic encephalopathy, postnatal microcephaly, development delay, speech disorder, early-onset epilepsy and movement disorders. Movement disorders are cardinal signs of the syndrome and stereotypic movements and myoclonic jerks are remarkable. Although FOXG1-related syndrome includes the clinical features of the congenital atypical Rett syndrome variant or typical Rett syndrome, it has also different features such as severity and onset of symptoms, gender, the presence of brain imaging abnormalities and dyskinesias

OBJECTIVES

We present a six-year-old girl with FOXG1 mutation who was preliminarily diagnosed as Rett syndrome.

CASE

A 5-year-old girl presented with growth retardation, small head circumference, seizure and stereotyped hand movements (Video 1). Prenatal history was unremarkable. She was born by spontaneous delivery after an uneventful pregnancy, with normal neonatal parameters with a birth weight of 3,650 g and length of 50 cm, but a relatively small head circumference (32 cm; 10th p). Her medical history was remarkable with hypotonia which was noticed when she was four months old and she started to have seizures at the same time. Her medical history was also remarkable with mental motor retardation, hand stereotypies and epilepsy. She was taking levetiracetam for seizures. Physical examination revealed microcephaly (43.5 cm <3p), retrognathia and almond-shaped eyes (figure 1). Neurological examination revealed, psychomotor delay, uncoordinated head movements and stereotyped hand movements (video 1). Metabolic screening tests and brain MRI were normal, whereas the Denver Development Screening Test was severely retarded at all areas. Her EEG consistent with epileptic encephalopathy (figure 2). Molecular genetic analysis for MECP2 and CDKL15 genes were normal. She was analysed for the possible underlying diagnosis of atypic Rett syndrome and a FOXG1 mutation (rs267606826, de novo heterozigot (forkhead box protein G1 NP_005240.3:p.Tyr208Ter Y (Tyr) was detected by studying the TruSight inherited disease panel (Illumina) containing 555 genes. She was followed up at the out patient clinic with levetiracetam treatment.

RESULTS

Since the core FOXG1-related syndrome fulfills most criteria of the congenital Rett syndrome variant, it was formerly named as 'congenital Rett syndrome variant', however, subsequent studies allowed the definition of the FOXG1-related syndrome, which is now considered a distinct clinical entity with epileptic–dyskinetic encephalopathy. Congenital or early postnatal microcephaly is one of the most important clinical findings of FOXG1-related syndrome which is evident before the age of 4 months. Unlike the classic Rett syndrome, there is no normal development period after birth in FOXG1-related syndrome. The FOXG1-related syndrome is also associated with hyperkinetic movement disorders especially hand stereotypes, mostly hand to mouth with generalized dyskinesia (Video 1). Although movement disorder in infancy can be a sign of neurometabolic disease or basal ganglion disease, FOXG1-related syndrome also should be considered in the differential diagnosis.

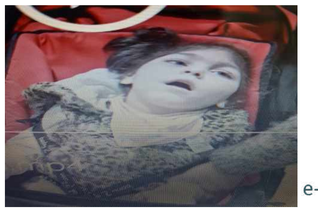

Figure 1. Facial dysmorphism and microcephaly

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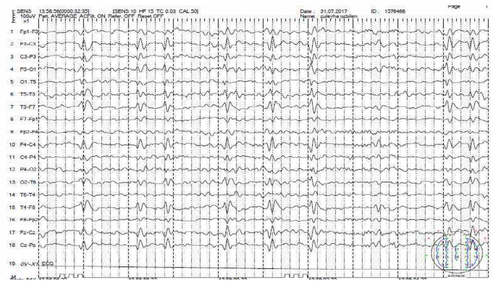

Figure 2. EEG with epileptic encephalopathy

CONCLUSION

Genetic studies in patients with the Retts syndrome variant have broadened the spectrum of underlying genetic etiologies. This case is presented to draw attention to FOXG1-related epileptic-dyskinetic encephalopathy in the differential diagnosis of children with Rett-like phenotype.

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