Intractable epilepsy with Rahman Syndrome

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Introduction: Intellectual disability, autism spectrum disorder, epilepsy, congenital heart disease, and other disorders have been reported in patients who have genetic mutations in genes encoding proteins involved in epigenetic machinery. Histone Gene Cluster 1 Member E, HIST1H1E (***H1-4***), encodes Histone H1.4 protein. This protein acts as a linker histone protein and it is involved in the folding and stabilization of chromatin fiber. HIST1H1E syndrome (also known as Rahman syndrome (RS), OMIM #617537) was described in 2017 as an intellectual disability syndrome. Here, we report a patient with Rahman syndrome, who had refractory epilepsy.

Case: 14 year-old girl was being followed up with intractable epilepsy, intellectual disability and behavioral problems. She was born vaginally at full term with a birth weight of 3300 gram (50th percentile). The patient was the sixth child of non-consanguineous healthy parents. Her family history was unremarkable. She had generalized hypotonia in infancy and walked at 3 years and had a speech delay. She was presented with seizures at the age of 2.5 years. Seizures were usually focal, motor seizures with loss of awareness, occasionally evolving into generalized tonic-clonic seizures. During the periods of infection and febrile illness, intensive care hospitalization was required due to status epilepticus. Due to the refractory seizures, she had been using multiple antiseizure medications (levetiracetam, oxcarbazepine, clobazam).

She had dysmorphic facial features, including high anterior hairline, prominent forehead, hypertelorism, downward-slanting palpebral fissures, short filtrum, dental anomalies (Figure A). In addition, she had bilateral clinodactyly and scoliosis (Figure B). At the age of 14 years, her weight was 50 kg (25th percentile), height was 150 cm (10th percentile), and head circumference is 53,5 cm (<3th percentile). Her metabolic evaluation was normal. EEG demonstrated multifocal epileptiform discharges. Brain magnetic resonance imaging revealed corpus callosum agenesis and encephalocele (Figure C,D). Cardiac examination was normal and she had accessory spleen. Her karyotype was 46,XY. Whole exome sequence analysis revealed heterozygous c.190-191insT (**p.Lys64IlefsTer9)** mutation in the HIST1H1E (NM_005321.2) gene, classified as likely pathogenic according to ACMG 2015 criteria. Sanger confirmation was done.

Conclusion: Rahman syndrome is a rare genetic disorder. It is mainly characterized by mild to severe intellectual disability associated with variable somatic overgrowth. The overgrowth is more apparent in infancy and may decrease over time or may persist. Patients also have dysmorphic features. Although seizure is not the major clinical features of this syndrome, patients with recurrent status epilepticus and refractory epilepsy were also reported. In this case presentation, we wanted to draw attention to the coexistence of refractory epilepsy with Rahman syndrome.

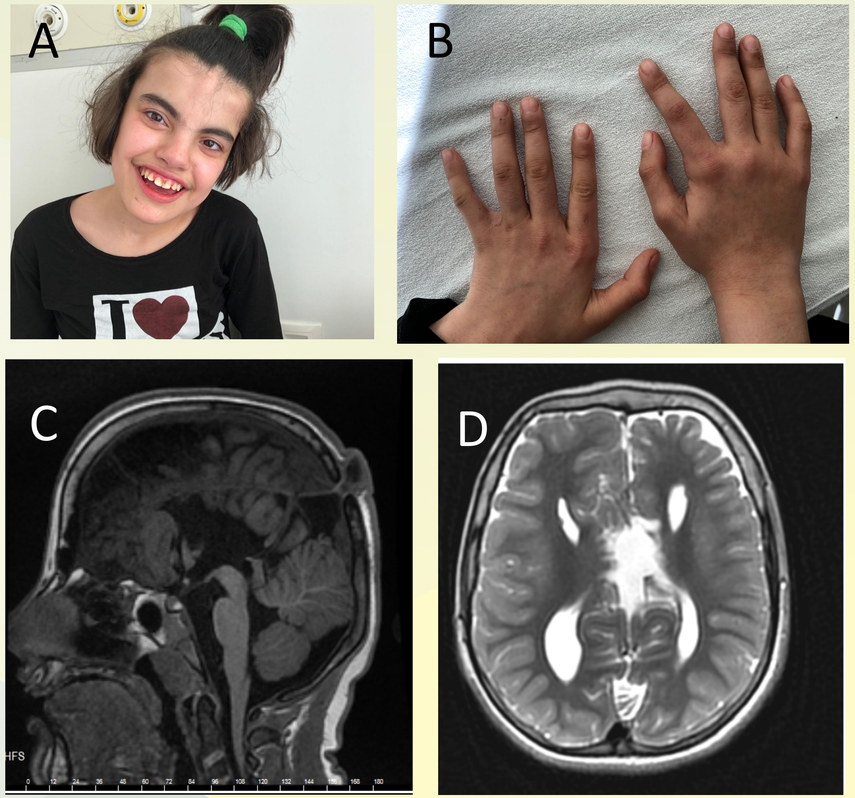

Figure A: high anterior hairline, prominent forehead, hypertelorism, downward-slanting palpebral fissures, short filtrum, dental anomalies
Figure B: She had large hands, clinodactyly.
Figure C and D respectively, sagittal T1- weighted image, axial T2-weighted image showing corpus callosum agenesis and encephalocele.

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