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Electroencephalographic findings in ATRX syndrome: A new case series and review of literature

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ABSTRACT

Alpha-thalassemia X-linked intellectual disability syndrome (ATRX) is a rare genetic condition caused by mutations in the *ATRX* gene characterized by distinctive dysmorphic features, alpha thalassemia, mild-to-profound intellectual disability, and epilepsy, reported in nearly 30% of the patients. To date, different types of seizures are reported in patients with ATRX syndrome including either clonic, tonic, myoclonic seizures or myoclonic absences. However, an accurate analysis of electroencephalographic features is lacking in literature. We report on the epileptic and electroencephalographic phenotype of seven unpublished patients with ATRX syndrome, highlighting the presence of a peculiar EEG pattern characterized by diffuse background slowing with superimposed low voltage fast activity. Likewise, we also review the available literature on this topic.

1. Introduction

Alpha-thalassemia X-linked intellectual disability syndrome (ATRX) is a rare genetic condition with an estimated prevalence of 1/58,000 to 1/73,000 in male newborns, caused by pathogenic variants in the *ATRX* gene on Xq13.3 chromosome [1]. The syndrome shows a wide spectrum of clinical manifestations such as distinctive dysmorphic features, alpha thalassemia, genital abnormalities, gastrointestinal disorders, mild-to-profound intellectual disability, together with a risk of early-onset osteosarcoma [1]. Epilepsy occurs in roughly 30% of the patients and it is usually mild and drug responsive. The type of seizures most frequently reported are either clonic, tonic, myoclonic seizures, or myoclonic absences [1]. However, to date, no characteristic electroencephalographic features have been described in ATRX syndrome. Here, we report on seven unpublished patients with ATRX syndrome focusing on the epileptic and electroencephalographic phenotype.

2. Case studies

We described seven male patients (age range: 3–23 years, median 13,5) with a clinical and molecular diagnosis of ATRX syndrome, caused by *de novo* pathogenic variants in *ATRX* gene, identified at 5 Italian Epilepsy Centers (Naples, Bologna, Genoa, Salerno, Troina). All subjects underwent complete general and neurologic examination, awake and sleep video-EEG recordings and brain MRI. Clinical, electroencephalographic, neuroradiological data and age at last evaluation are reported in detail below and summarized in Supplementary Table 1.

2.1. Patient#1

This was an 18-year-old male, carrying the pathogenic *de novo* variant NM_000489.6: c.6392G > A(p.Arg2131Gln), previously described in literature [2]. He showed severe intellectual disability,

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axial hypotonia together with stereotypies and dystonic movements, dysmorphic features, microcephaly, and feeding difficulties requiring artificial nutrition by gastrostomy. At 3 months of life, he presented febrile seizures (FSs) treated with phenobarbital for one year, and at 10 years of age, he developed myoclonic seizures responsive to levetiracetam. Brain MRI at 3 and 11 years showed corpus callosum (CC) agenesis, anterior commissure hypoplasia, decreased volume of the frontal lobes and delayed white matter myelination on the periventricular and fronto-temporal areas. At the age of 11 years, his sleep EEG showed asynchronous spikes or sharp-and-slow wave complexes over the frontal areas of both hemispheres (Fig. 1 A). The background activity was characterized by an unusual low voltage fast activity in the beta range (Fig. 1 B).

2.2. Patient#2

This was a 3-year-old male carrying the pathogenic *de novo* recurrent variant NM_000489.6: c.736C > T (p.Arg246Cys) already reported in literature (ClinVar). From the first months of life, he showed a severe delay in the acquisition of developmental milestones, hypotonia, dysmorphic features with microcephaly and feeding difficulties. He suffered from several respiratory infections and hypothyroidism treated with levothyroxine. He also exhibited autistic-like behavior with expressive language limited to vocalizations. Brain MRI performed at 7 months showed thinned CC. The EEG both in wakefulness and in sleep showed a slow and poorly structured electrical background activity, with a generalized low voltage fast activity (Fig. 1 C). He never suffered from seizures.

2.3. Patient#3

This was a 9-year-old male carrying the pathogenic *de novo* intronic variant NM_000489.6:c.5273-5C > G, (Varsome, ACMG guidelines) [3]. He showed a profound intellectual disability, severe axial hypotonia, gastrointestinal problems with short bowel syndrome and eosinophilic esophagitis, growth impairment with microcephaly, central hypothyroidism, hypospadia. Brain MRI performed at 4 years showed CC and anterior commissure severe hypoplasia, mild cerebellar and pons hypoplasia, enlarged supratentorial subarachnoid spaces and areas of T2-hyperintensity in frontal and parietal subcortical white matter. He never experienced seizures. Instead, he suffered from paroxysmal dystonic episodes triggered by pain and was treated with trihexyphenidyl and diazepam without benefit. The EEG performed during wakefulness showed a diffuse theta low voltage rhythm mixed with a generalized beta low voltage activity (Fig. 1 D).

2.4. Patient#4

This was an 18-year-old male carrying the *de novo* pathogenic recurrent variant NM_000489.6: c.736C > T (p.Arg246Cys). The clinical picture was characterized by severe impairment of psychomotor development, with hypotonia, profound intellectual disability, peculiar craniofacial dysmorphisms, optic atrophy and hypospadia. He suffered from severe feeding difficulties due to gastroesophageal reflux, and he underwent gastric fundoplicatio. Brain MRI performed at the age of 4, 8 and 15 years showed cerebral hypoplasia, with enlarged frontotemporal subarachnoid spaces and dysmorphic CC. The main EEG features were a slow and monomorphic background activity and unusual diffuse fast rhythms; during childhood occipital epileptiform discharges appeared, increased by sleep. He never experienced seizures, but paroxysmal non-epileptic movements of upper limbs occurred during infancy and childhood.

2.5. Patient#5

This 13-year-old-male carries a novel pathogenic frameshift variant NM_000489.6:c.7376del (p.Met2459Sfs*21), not reported in literature. He developed at 12 months FSs and at 10 years of age generalized tonic-clonic seizures treated first with valproic acid and then lamotrigine. He had a mild intellectual disability. The EEG showed diffuse slow activity mixed with low voltage generalized fast activity and epileptiform discharges increased during sleep. Brain MRI, performed at 6 years, showed CC hypoplasia.

2.6. Patient#6

This 11-year-old-male carries the pathogenic recurrent variant NM_000489.6:c.736C > T (p.Arg246Cys), not present in his parents. He did not experience seizures. When he was 7-year-old, a brain MRI showed multiple white matter T2-hyperintensities of gliotic origin in the posterior periventricular and bilateral subcortical fronto-parietal areas and the right cerebellar hemisphere. Sleep EEG was poorly structured and characterized by diffuse theta rhythms.

2.7. Patient#7

This was a 23-year-old male with a novel *de novo* likely pathogenic variant NM_000489.6:c.1046C > G (p.Pro349Arg), following ACMG classification (PM2, PP3)[3]. Psychomotor and language development was severely delayed. Focal seizures started at 4 years of age, 1–2 per month, and were characterized by loss of awareness, hypertonia, perioral cyanosis and were treated by valproic acid. Brain MRI at 3 years showed a diffuse hyperintensity of the periventricular white matter.

3. Discussion

Epilepsy is present in about 30% of patients with ATRX syndrome [1], but no characteristic EEG findings have been associated with this syndrome until now. In our cohort of patients, we found the presence of a typical EEG pattern characterized by diffuse background slow theta-delta rhythms with generalized superimposed fast low-voltage activity.

ATRX is a key gene in the development and organization of the brain, but its role in epileptogenesis is far to be understood. *ATRX* could be indirectly involved in the survival and differentiation of inhibitory interneurons and its mutations could lead to an altered balance between excitatory and inhibitory activity with a consequent epileptic predisposition [1].

In the literature, few articles focus on epilepsy and EEG features of patients with ATRX syndrome (Supplementary Table 2). Moncini et al. [4] described two adult siblings presenting with FSs in the first year of life, followed by myoclonic absences from the two years of age, well-controlled by antiseizure medications (ASMs). The EEG of the elder brother was characterized by multifocal epileptiform discharges, but no further information is provided on the other sibling. In another case series of five unrelated patients with ATRX syndrome, two out of five were reported with FSs, while a third had a diagnosis of epilepsy; unfortunately, no information about EEG pattern was supplied [5].

Guerrini et al. [6] described a family including 4 affected patients: three suffered from generalized convulsive seizures developed during the first year of life; their EEG showed mild diffuse epileptiform discharges during childhood and adolescence. Giacomini et al. [7] reported two affected brothers with profound intellectual disability, hypotonic tetraparesis, myoclonus-dystonic movement disorder, and drug-resistant epileptic encephalopathy: Lennox–Gastaut syndrome in the elder sibling and West syndrome in the younger one. The EEG of the first brother showed slow background activity with continuous multifocal paroxysmal discharges (spikes and spike waves) worsening during sleep; the EEG of the younger sibling showed an hypsarrhythmic pattern.

Neonatal seizures are reported in a patient with severe phenotype who died at 4 months of age because of hypoventilation; he carried an

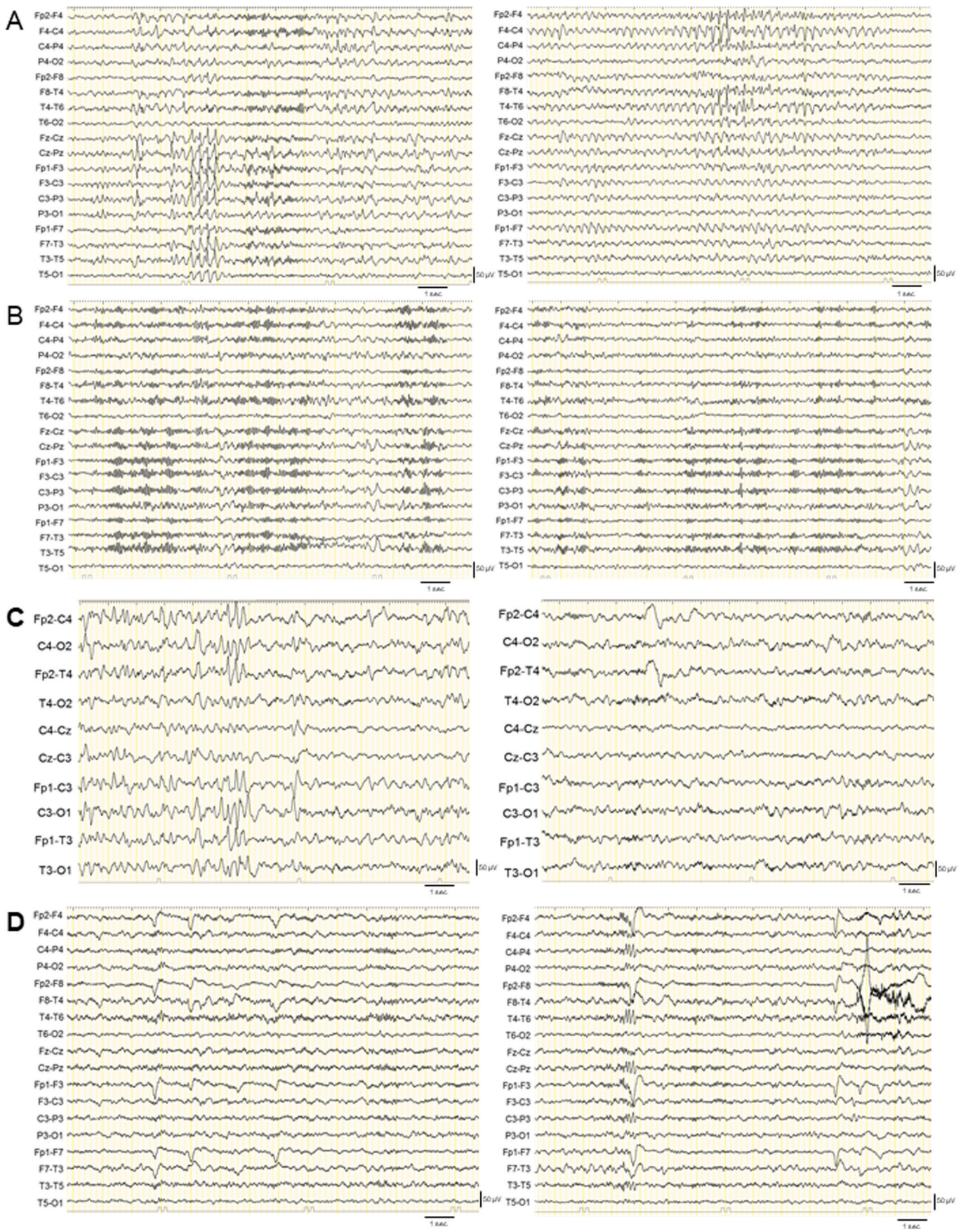

Fig. 1. Awake and sleep EEG of patients 1 (A–B), 2 (C) and 3 (D). (EEG parameters: High pass: 35 Hz, Low pass: 1.5 Hz, Notch filter: 50 Hz, Sensibility 100 mcV).

ATRX partial duplication [8]. In addition, it is also reported a subject with ATRX syndrome who developed tonic-clonic seizures and refractory status epilepticus [9].

In our case series, 3/7 patients had a diagnosis of epilepsy with seizure onset in the first decade of life; one had focal seizures while two patients presented with generalized seizures (myoclonic and tonic-clonic) preceded by FSs: it seems that the occurrence of FSs before the onset of epilepsy is not uncommon in ATRX syndrome [4]. Three out of four patients without epilepsy share the same recurrent c.736C > T(p.Arg246Cys) pathogenic variant.

The EEG background activity was abnormal in all patients with a slow theta-delta activity as predominant rhythm and in 5/7 a peculiar non-ictal generalized fast low voltage activity was evident both in wakefulness and sleep. Interictal epileptiform discharges were present in 4/7 patients, three with epilepsy. The epilepsy in our patients was well controlled by one or two ASMs, as the majority of cases previously reported in literature. The incidence of pharmaco-resistance in ATRX syndrome is not reported, and in addition, there is a lack of information on choosing the most effective ASM.

In our cohort, the brain MRI study confirmed previous neuroimaging data associated with the ATRX syndrome, including mild cerebral atrophy, partial or complete CC agenesis and white matter abnormalities (see Supplementary Table 1) [1]. Interestingly, all patients with CC abnormalities showed the peculiar non-ictal generalized fast low voltage activity; CC malformations could result in considerable changes in brain electrical activity. As concerned a possible genotype-phenotype correlation, especially focusing on the epileptic phenotype, taking into account data from literature and our cohort of patients, FSs seem to be more frequent in patients with the pathogenic variant c.109C > T (p.Arg37Ter) [5], while the pathogenic variant c.736C > T (p.Arg246Cys) is not reported in subjects with epilepsy, as confirmed in 3 of our patients.

To the best of our knowledge, this is the first attempt to describe the electroencephalographic phenotype in patients with ATRX syndrome. We highlighted a low amplitude fast activity as peculiar background activity in five out of seven patients. Further clinical and EEG studies on a larger cohort of patients with ATRX syndrome are needed to better clarify the EEG pattern and to delineate a genotype-phenotype correlation. Our sample is rather small and presumably not representative of the larger population with ATRX syndrome, but patients with this syndrome may share a common EEG pattern.

Declaration of competing interest

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2022.08.002.

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