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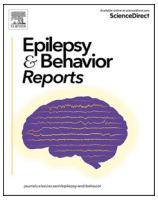

Detection of ictal apnea refines the clinical spectrum of ATRX syndrome

Galal Banat [a], Friedrich G. Woermann [b], Rami Abou Jamra [c], Christian G. Bien [a,*], Christian Brandt [a]

[a] Bielefeld University, Medical School and University Medical Center OWL, Mara Hospital, Department of Epileptology, Maraweg 21, Bielefeld, Germany
[b] Society for Epilepsy Research, Maraweg 21, Bielefeld, Germany
[c] Institute of Human Genetics, University Medical Center Leipzig, Leipzig, Germany

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ABSTRACT

Alpha-thalassemia X-linked intellectual disability syndrome (ATRX) is a rare genetic disorder caused by mutations in the ATRX gene. It is characterized by distinct dysmorphic features, alpha thalassemia, varying degrees of intellectual disability, and the presence of epilepsy in approximately 30 % of affected individuals. We present the case of a 36-year-old patient with severe intellectual disability and epilepsy due to a hemizygous pathogenic variant, c.736c > T, p. (Arg246Cys), in the ATRX gene. During inpatient treatment, numerous respiratory pauses were detected. Repeated video EEG recordings revealed seizure patterns with a left frontocentral origin and an occasional spread to the bifrontal region and episodes of apnea without an EEG correlate. This case report adds to the current literature, as it shows a co-occurrence of ictal and non-ictal apnea in ATRX syndrome, expanding our understanding of respiratory disturbances in this rare genetic disorder.

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 [1,2].

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 [1,2].

Although apnea is not a commonly reported symptom in ATRX syndrome, there have been two documented cases of patients with ATRX experiencing recurrent apnea episodes. Initially, one patient was diagnosed with obstructive apnea due to pharyngeal stenosis and laryngomalacia, but subsequent evaluation revealed the presence of mixed apnea [3]. In another case, the diagnosis was mild-sleep apnea syndrome [4]. We aim to describe a third type of apnea, i.e., ictal apnea, as a novel feature in ATRX syndrome.

2. Case report

We present the case of a 36-year-old patient with severe intellectual disability and epilepsy. He suffered from epilepsy since his first year of life, mainly presenting with bilateral tonic and tonic-clonic seizures. Immediately after delivery, the patient had been intubated and transferred to a pediatric clinic due to insufficient spontaneous breathing caused by birth asphyxia (APGAR scores of 5/7/8). Muscular hypotonia and poor drinking were identified as early as the U2-examination (routine examination between 3rd and 10th day of life). In the first year of life, a comprehensive neuropediatric and genetic examination according to standards at that time (including chromosome analysis, screening examination for congenital metabolic diseases, amino acid chromatogram of blood and cerebrospinal fluid, and exclusion of congenital infections) were carried out, without any significant findings. At the age of 5 years, he underwent an operative correction for bilateral undescended testicles. As seizures occurred only rarely in the first years, anti-seizure medication was not initiated before the age of 14 years. Since puberty, seizure-freedom has not been achieved despite the use of various anti-seizure medications (Valproic acid, carbamazepine, oxcarbazepine, topiramate, zonisamide, perampanel, lamotrigine, sulthiame, and levetiracetam).

Upon admission to our hospital, which is a tertiary referral center for epilepsy, the clinical examination revealed the following facial features: an open mouth, decreased facial movement, large ears with normal insertion, along with severe tetraparesis, microcephaly, scoliosis, and absence of language development.

* Corresponding author at: Bethel Epilepsy Center, University Hospital for Epileptology, Mara Hospital, Maraweg 19-21 / 33617, Bielefeld, Germany.
E-mail address: Christian.Brandt@mara.de (C.G. Bien).

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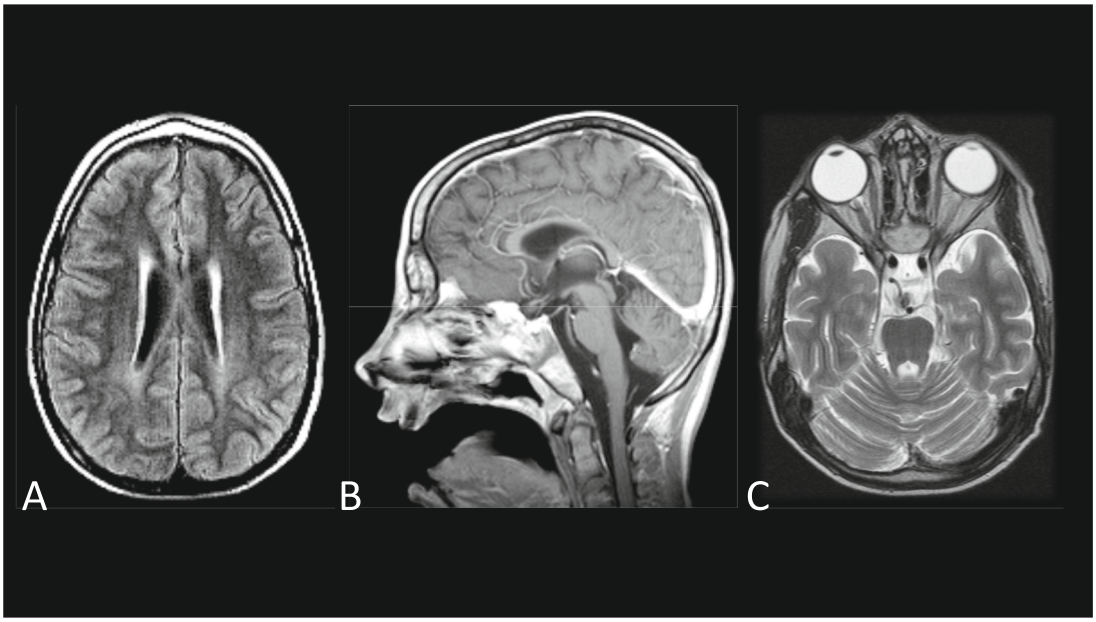


Fig. 1. Cranial 1.5 T MRI at 14 years of age (A: axial FLAIR, B: sagittal T1 after contrast medium, C: axial T2). Subtle signs of periventricular leucomalacia (A) without any signs of brainstem or cerebellar abnormality (B, C) – especially no signs of pontocerebellar hypoplasia or of Joubert syndrome (no molar tooth sign).

An exemption letter has been issued by the ethics committee of Münster, Germany, documenting that no approval by the ethics committee is necessary.

A brain MRI scan at the age of 14 years showed mild periventricular hyperintensities and minimal enlargement of the lateral ventricles, consistent with the spectrum of periventricular leukomalacia (a pattern of injury typically seen in asphyxia-related conditions, especially in preterm births) region (Fig. 1).

During inpatient treatment, numerous respiratory pauses were detected. During an EEG recording with a 2 h and 20 min duration, we recorded 35 events of upward eye deviation to the left, accompanied by mouth opening and breath holding, with no apparent respiratory effort. These apnea episodes lasted from 10 to a maximum of 26 s, accompanied by oxygen desaturation (down to 83 %), measured by pulse oximetry. The EEG revealed a seizure pattern with a left frontocentral origin and an occasional spread to the bifrontal region (Fig. 2). EKG tracing showed tachycardia, which was independent from the seizure patterns.

Notably, 15 apneic episodes occurred without concomitant epileptiform potentials (Fig. 3). Following an otorhinolaryngology consultation, a deviated nasal septum causing complete obstruction on the right side and complete tongue retraction were identified, potentially explaining the occurrence of non-ictal apneic episodes. We referred the patient for a polygraphic recording. However, this was not successful because of his lacking ability to cooperate.

Genetic testing was performed based on exome sequencing (Illumina NovaSeq6000) after enrichment with the Twist Library Preparation EF Kit, and achieved a coverage of over 20x at over 99 % of the targeted sequences. Using the software Varvis (Limbus Medical Technologies, Rostock, Germany), we filtered about 60,000 variants and identified a hemizygous pathogenic variant, c.736c > T, p. (Arg246Cys), in the ATRX gene. As the variant was not observed in the general population, was observed in several affected persons (HGMD: #CM970157 and Clinvar:#11735), other amino acid changes were observed at the same position (e.g. HGMD #CM980196 p.[Arg246Leu]), the variant was functionally validated as pathogenic, and as the gene is not tolerant for missense variants (Z score > 3.09), this variant was clearly classified as pathogenic based on the ACMG criteria PS3, PS4, PM5, PM2_SUP, and PP2 [5]. Laboratory tests (capillary electrophoresis) showed no evidence of hemoglobinopathy.

3. Discussion

Ictal apnea has been described in focal epilepsy as having a temporal and less frequently extra-temporal origin, but also in epileptic encephalopathies [6]. Peri-ictal apnea, especially when occurring during sleep, is seen as a cause of sudden unexpected death in epilepsy (SUDEP) [7]. The apneic symptoms in our patient occurred during wakefulness and resembled apneic seizures, as described by Fogarasy et al. [8]. The EEG (Fig. 2) demonstrates the epileptic nature of the attacks as distinct seizure patterns were recorded with concomitant periods of apnea. In addition, apneic periods without seizure patterns were also recorded as previously described in other patients. This case report adds to the current literature, as it shows a co-occurrence of ictal and non-ictal apnea in ATRX syndrome, expanding our understanding of respiratory disturbances in this rare genetic disorder. Ictal apnea, a self-limiting semiological feature of focal epilepsy, was observed in our patient, preceding the clear onset of EEG seizure patterns [9]. Non-ictal apnea episodes were attributed to anatomical factors, i.e., nasal obstruction and tongue retraction. As a limitation, a comprehensive sleep study could not be performed due to our patient's inability to cooperate. Therefore, the nature of his apnea attacks that were of non-epileptic origin could not be elucidated further.

The management of apnea in ATRX syndrome requires a comprehensive approach, including seizure control, sleep evaluation, and potential interventions for obstructive sleep apnea. Collaboration between epileptologists, sleep medicine specialists, and otorhinolaryngologists is crucial in addressing the complex respiratory issues in these patients.

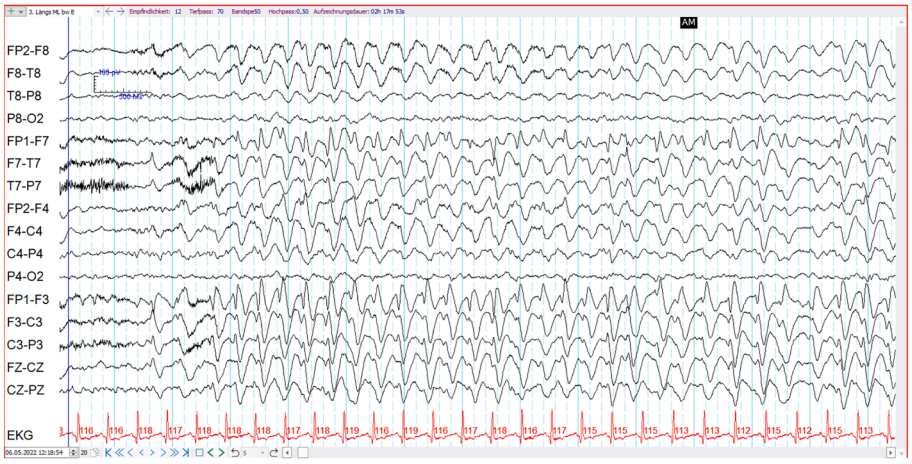
4. Disclosures

CB has received support from and/or has served as a paid consultant for Angelini, Arvelle, Eisai, GW Pharmaceuticals, Jazz Pharmaceuticals, Johnson & Johnson, Marinus, UCB Pharma, and Xenon. The other authors report no disclosures relevant to the manuscript.

Ethical statement

We confirm that all procedures were performed in compliance with relevant laws and institutional guidelines. We received an exemption letter from the local ethics committee stating that ethics approval does

A)



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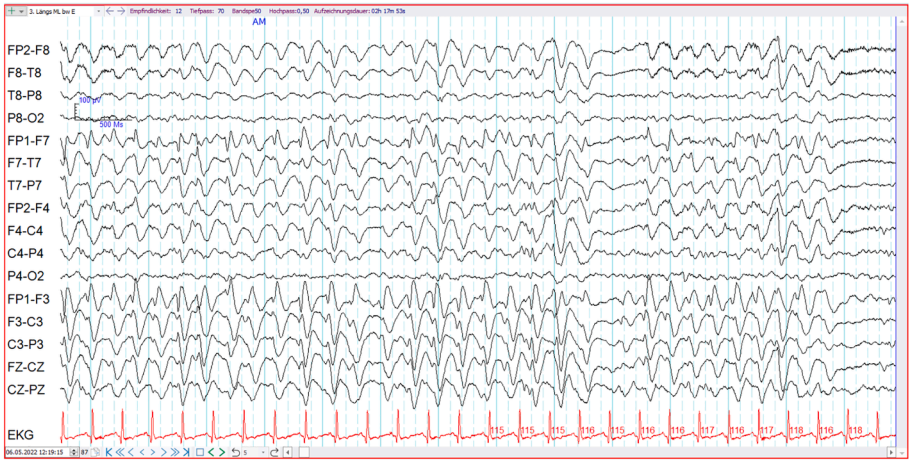
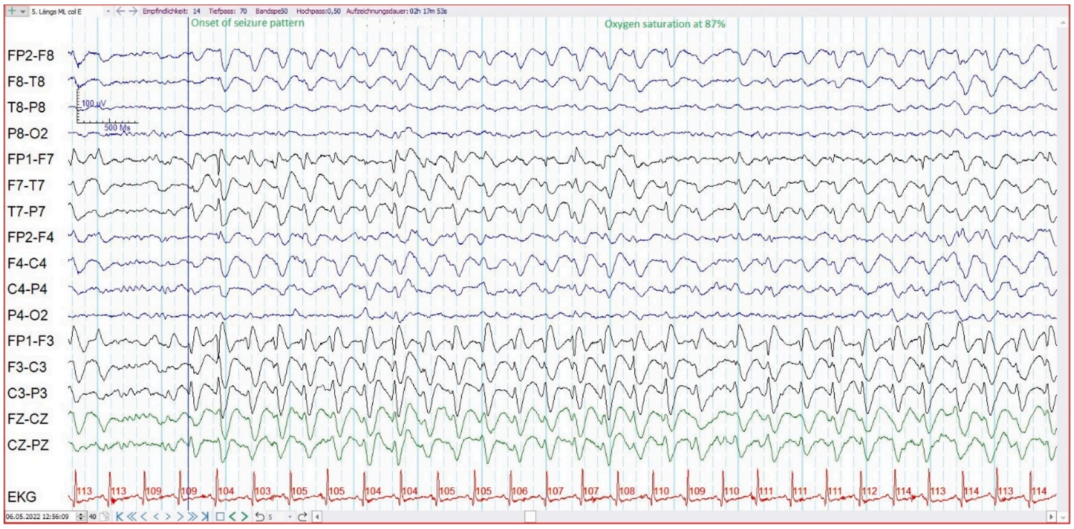


Fig. 2. There were two seizure patterns (A + B without oxymetry and C + D with oxymetry) with a left frontocentral origin and an occasional spread to the bifrontal region, accompanied by ictal apnea (2 channels were hidden because of artifacts at electrode O1).

C)



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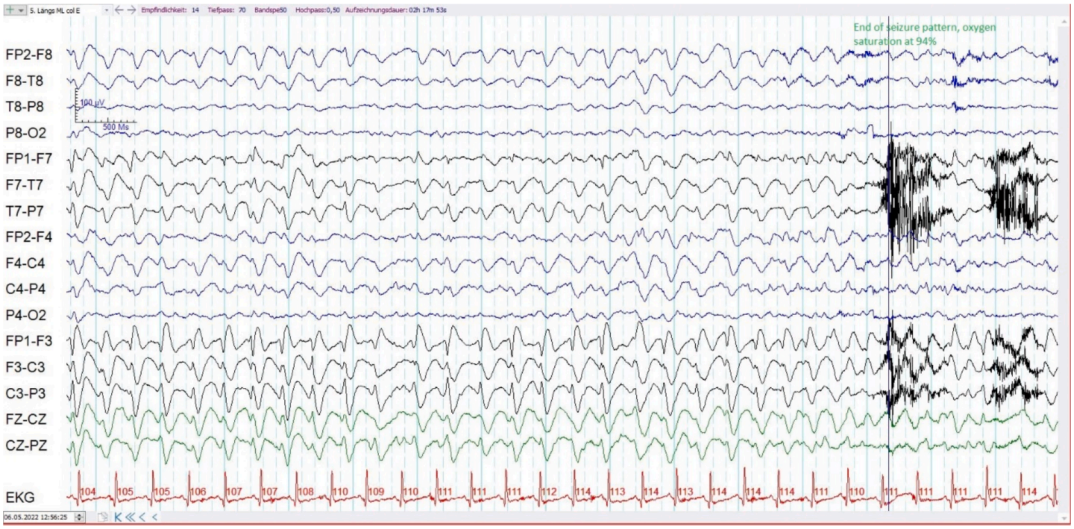

Fig. 2. (*continued*).

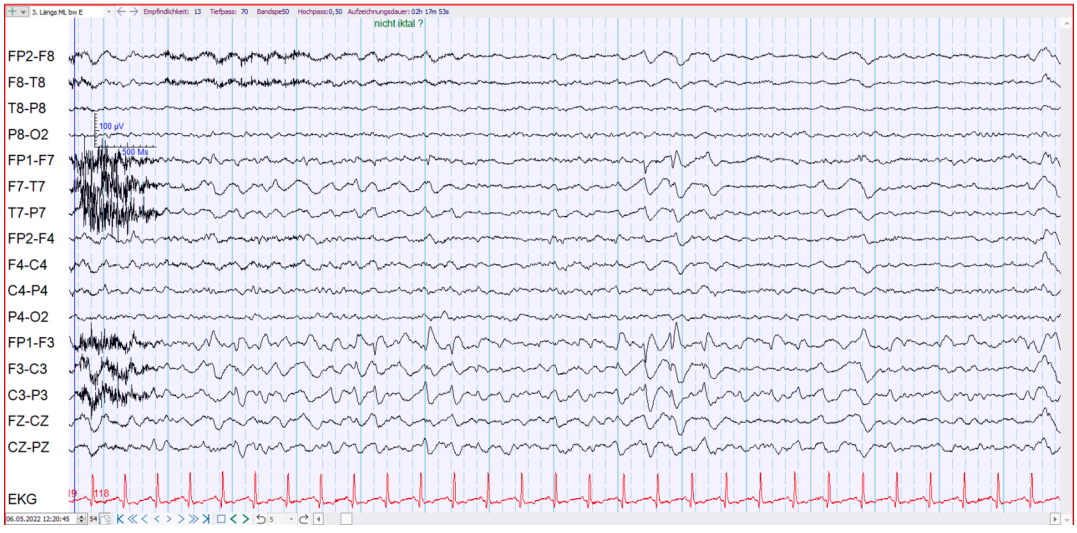

Fig. 3. An apnea attack with no seizure pattern (2 channels were hidden because of artifacts at electrode O1).

not need to be obtained for this case report (Ethics Committee Westfalen-Lippe, 2023–618-f-N, 24-NOV-2023).

CRediT authorship contribution statement

Galal Banat: Writing – original draft, Methodology. **Friedrich G. Woermann:** Writing – review & editing, Methodology. **Rami Abou Jamra:** Writing – review & editing, Methodology. **Christian G. Bien:** Writing – review & editing, Supervision, Methodology. **Christian Brandt:** Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Aiello S, Mancardi MM, Romano A, Santucci M, Scaduto MC, Vari MS, et al. Electroencephalographic findings in ATRX syndrome: a new case series and review of literature. Eur J Paediatr Neurol 2022;40:69–72.
[2] Leon NY, Harley VR. ATR-X syndrome: genetics, clinical spectrum, and management. Hum Genet 2021;140:1625–34.
[3] Ebishima Y, Misaki T, Owa K, Okuno T, Wada T, Suehiro Y. A case of X-linked alpha-thalassemia/mental retardation (ATR-X) syndrome with repeated apnea attacks due to laryngomalacia. No To Hattatsu 2013;45:44–8.
[4] Ogle R, DeSouza M, Cunningham C, Kerr B, Sillence D. X linked mental retardation with non-deletional alpha thalassaemia (ATR-X): further delineation of the phenotype. J Med Genet 1994;31:245–7.
[5] Argentaro A, Yang JC, Chapman L, Kowalczyk MS, Gibbons RJ, Higgs DR, et al. Structural consequences of disease-causing mutations in the ATRX-DNMT3-DNMT3L (ADD) domain of the chromatin-associated protein ATRX. Proc Natl Acad Sci USA 2007;104:11939–44.
[6] Micalizzi E, Vaudano AE, Ballerini A, Talami F, Giovannini G, Turchi G, et al. Ictal apnea: a prospective monocentric study in patients with epilepsy. Eur J Neurol 2022;29:3701–10.
[7] Nadkarni MA, Friedman D, Devinsky O. Central apnea at complex partial seizure onset. Seizure 2012;21:555–8.
[8] Fogarasi A, Janszky J, Tuxhorn I. Autonomic symptoms during childhood partial epileptic seizures. Epilepsia 2006;47:584–8.
[9] Lacuey N, Zonjy B, Hampson JP, Rani MRS, Zaremba A, Sainju RK, et al. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia 2018;59:573–82.