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Case Report

SCN2A developmental and epileptic encephalopathy in an infant with bilateral polymicrogyria and opercular dysplasia

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ABSTRACT

Introduction: *SCN2A* mutations have been associated with a wide phenotypic spectrum that includes, among others, developmental and epileptic encephalopathy (DEE), usually not associated with any brain structural counterpart.

Case description: We report the occurrence of a super-refractory status epilepticus (SRSE) in a 2-month-old infant, who presented at birth with refractory neonatal seizures attributed to an extensive bilateral polymicrogyria and cortical dysplasia. Upon his SRSE, he responded radically to the sodium-channel blocker phenytoin with complete seizure resolution and has remained seizure free during the 2-year follow-up period. A *SCN2A* pathogenic variant was found with predicted gain-of-function effect. Notably, brain MRI findings during the neonatal ictal phase showed signs of hypoxia with cytotoxic and vasogenic oedema, corresponding to the ictal localisation. These changes were not observed upon repetition of the brain MRI during the SRSE at 2 months of age, perhaps suggesting increased neonatal vulnerability to hypoxia in the presence of an *SCN2A* variant, that modifies over time.

Conclusion: Our case report highlights the importance of challenging our clinical management in the presence of refractory seizures attributed solely to a structural cause, with genetic testing providing a key insight for therapeutic management.

1. Introduction

The sodium channel neuronal type 2 alpha subunit (*SCN2A*) gene encodes the voltage-gated sodium channel $Na_v\alpha1.2$, crucial for neurologic function and expressed throughout the central nervous system, predominantly in excitatory neurons [1,2]. *SCN2A* pathogenic variants cause various neurodevelopmental disorders, accounting for approximately 1 % of all epileptic encephalopathies [3]. Three major phenotypes are associated with pathogenic *SCN2A* variants: 1) Self-limited neonatal/infantile epilepsy, with or without late-onset episodic ataxia; 2) Development and epileptic encephalopathy (DEE) with early-onset (<3 months-old) or late-onset (>3 months-old) and 3) *SCN2A*-related autism spectrum disorder and/or intellectual disability (ASD/ID) with or without late-onset epilepsy. Variant type determines clinical presentation: *SCN2A* gain-of-function (GOF) pathogenic variants lead to self-limited neonatal/infantile epilepsy or early-onset DEE, while loss-of-function (LOF) variants result in late-onset DEE or ASD/ID. In GOF variants, the degree of potentiation of $Na_v\alpha1.2$ activity allows for further distinction between self-limited neonatal/infantile epilepsy (milder variants) and early-onset DEE (severe variants) [3,4].

While most *SCN2A* variant-related epileptic syndromes lack generally a structural counterpart, cases of concomitant associated cortical dysplasia have been reported [5–7]. We describe the case of an infant diagnosed with neonatal seizures initially attributed to an extensive bilateral polymicrogyria and cortical dysplasia, who developed at 2 months of age a super-refractory status epilepticus (SRSE), responding dramatically to the sodium channel blocker phenytoin. Genetic investigations identified a *de novo* *SCN2A* missense pathogenic variant with predicted GOF effect.

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2. Case study

We report the case of a full-term boy born at 40 weeks of gestation after an uneventful pregnancy and uncomplicated vaginal delivery. He was the third child of healthy non-consanguineous parents with two older siblings without prior medical history. His Apgar score was 9/10/10 and birth parameters were within the norm: weight 3700 g (percentile 50–75), height 52 cm (percentile 50–75) and head circumference 35 cm (percentile 50). First clinical evaluation at birth was unremarkable.

On day 1, he experienced focal motor seizures described as brief clonic movements of the right face and hemibody (20–30 s), relapsing within a five-minute period. Seizures ceased after phenobarbital and levetiracetam administration. Clinical exam remained normal between seizures. Routine blood laboratory yielded normal results. Brain MRI on day 2 revealed an extensive bilateral symmetric polymicrogyria in perisylvian and pericentral regions, along with bilateral opercular dysplasia. Additionally, a cytotoxic edema with restricted diffusion, presenting decreased apparent diffusion coefficient (ADC) (Fig. 1.I), involving the left temporo-parieto-occipital cortex and subcortical white matter was observed, with hyperintensity on T2-weighted and hypointensity on T1-weighted images, resembling a "stroke-like" appearance, but without specific arterial distribution, likely reflecting ictal neuronal changes [8]. EEG showed a discrete left hemisphere slowing with a theta pattern and superimposed asynchronous sharp waves predominant in the fronto-central and temporal regions.

On day 5, seizures recurred with subtle clinical events, including sudden apnea, loss of contact, left eye deviation and clonic movements of extremities. EEG monitoring revealed a right central onset rhythmic spike-wave discharges with subsequent bi-central spread and secondary generalization (Fig. 2). Treatment with phenobarbital and levetiracetam, followed by a loading dose of phenytoin, prevented further seizures. Brain MRI repeated on day 9 revealed a new right-sided area of restricted diffusion in the temporo-parieto-occipital cortico-sub-cortical region (mirroring the previous left-sided lesion), with associated T2 hyperintensity and T1 hypointensity (Fig. 1.II). The left-sided injury showed reversible restricted diffusion, with an increased ADC (Fig. 1.II). A comprehensive metabolic work-up was unremarkable. Initial genetic testing conducted during the neonatal period, consisting of whole exome sequencing with bioinformatic analyses of genes implicated in vascular and cerebral malformations, showed negative results.

Clinical evolution was favourable, and he was discharged on phenobarbital maintenance therapy by day 17. On the following weeks, occasional brief focal motor seizures occurred, and levetiracetam was subsequently added. Mild axial hypotonia was described on neurological examination, which was otherwise within the norm.

At 2 months and 19 days old, he presented with seizures recurring hourly, leading to admission to paediatric intensive care. He progressed to SRSE lasting for 5 days despite numerous medications (phenobarbital, levetiracetam, valproic acid, midazolam, clonazepam, propofol, ketamine) and ketogenic diet. EEG confirmed status epilepticus with bi-central ictal onset and secondary generalization. Interictal sharply contoured waves were seen in the left and rarely right temporo-occipital regions. New brain MRI found no new areas of restricted diffusion, neither sequelae of the previous areas involved (Fig. 1.III). Phenytoin was added on day 5 of SRSE, resulting in complete seizure cessation within 12 h. Concurrently, given the clinical context, genetic testing was further extended to include a panel of 871 genes involved in epilepsy and brain malformations. This analysis identified a *de novo* missense heterozygous variant c.4375 T > G, p.(Phe1459Val) in the *SCN2A* gene.

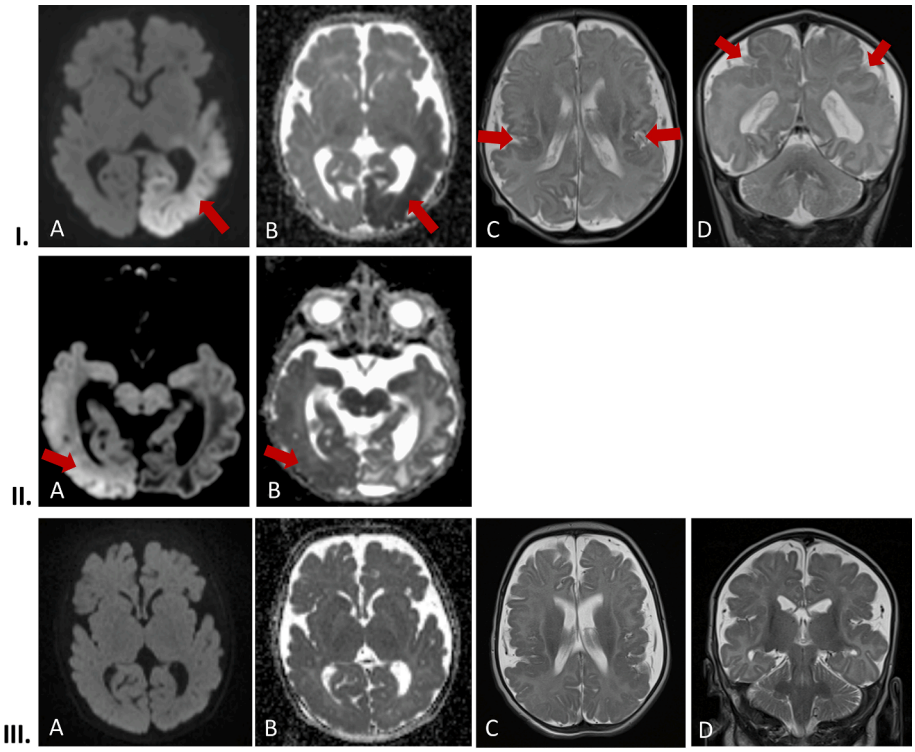

Fig. 1. I. Brain MRI at day 2. A,B. Axial DWI (A), ADC map (B) show restricted diffusion on DWI with low ADC values in the left temporo-parieto-occipital cortex and subcortical white matter, without a specific arterial distribution; C,D. Axial (C) and coronal (D) T2-weighted image demonstrate a bilateral extensive perisylvian polymicrogyria extended to the pericentral region, as well as bilateral opercular dysplasia. **II.** A,B. Brain MRI acquired on day 9, one week after the first brain MRI. Axial DWI (A) image and ADC map (B) show a new area of reduced diffusivity in the right temporo-parieto-occipital cortex without a specific arterial distribution. Note the evolution of the prior left hemisphere injury, seen as a vasogenic oedema with increased ADC values. **III.** Brain MRI at day 2 after onset of status epilepticus at 2 months of age and 19 days. A,B. Axial DWI (A), ADC map (B) show no new restricted diffusion neither parenchyma lesion. C,D. Axial (C) and coronal (D) T2-weighted image demonstrate the known bilateral extensive perisylvian polymicrogyria extended to the pericentral region, as well as bilateral opercular dysplasia.

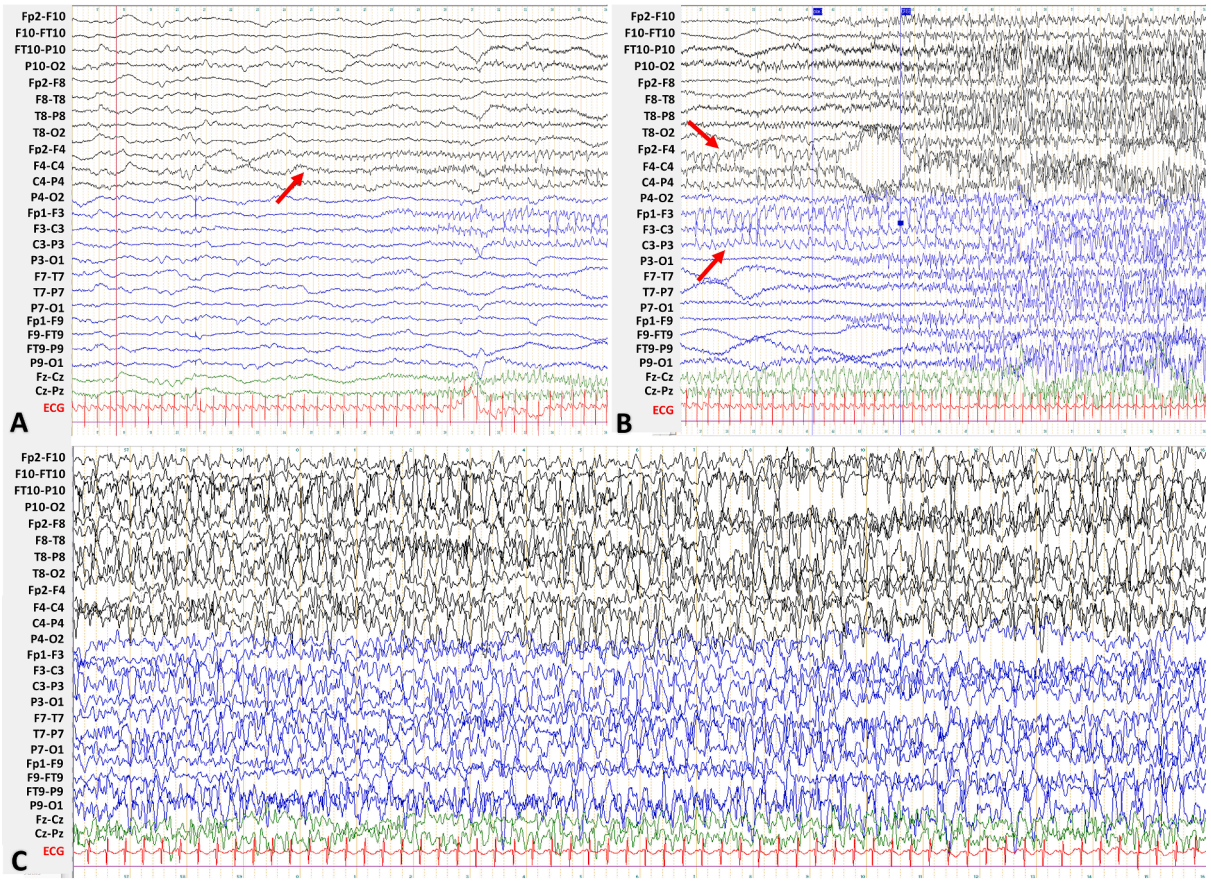

Fig. 2. Ictal EEG at day 5 of life, showing a right central onset of rythmic spike-wave discharges (A), with a subsequent bi-central spread (B) and secondary generalization (C), correlating clinically with sudden apnea, loss of contact, left eye deviation and clonic movements in all 4 extremities (longitudinal bipolar montage, 25 electrodes).

This variant (reference sequence NM_001040143.2) has not been previously reported in the general population database (gnomAD) or in major *SCN2A* gene mutation databases (HGMD, LOVD, ClinVar). The prediction algorithms agree on the pathogenic nature of this variant and with a predicted GOF effect (which correlated with the specific response to phenytoin), but these predictions have not yet been confirmed by functional studies. This variant is located in a missense-depleted region [9,10]. Following current recommendations [11], this variant of the *SCN2A* gene is classified as pathogenic (class 5, criteria retained: PS2, PM1, PM2, PP3, PP4).

He was discharged on phenytoin monotherapy with no further seizure relapse. EEG normalized at 1 and 3 months' follow-up, with no residing epileptiform discharges. At 12 months, his treatment was switched for carbamazepine to minimize long-term effects of treatment. At 24 months, he presented a moderate delay in gross motor skills, having acquired walking at 22 months. He had good receptive skills and a vocabulary of 10–15 words. Cognitive development was within the norm.

3. Discussion

We describe the case of an infant with extensive cortical malformation and early-onset DEE, responding dramatically to sodium channel blockers during SRSE. Further investigations revealed a *de novo SCN2A* pathogenic variant with expected GOF. SRSE was initially attributed to his cortical malformation, but the discovery of a sodium channel genetic defect enabled a targeted therapy, successfully rendering him seizure free.

SCN2A pathogenic variants have been associated with a large phenotype spectrum including different neurodevelopmental disorders with or without epilepsy. GOF *SCN2A* mutations presenting within the first 3 months-of-life are thought to potentiate neuronal excitability, persisting over time and leading to the more severe DEE phenotype. Our patient presented with early-onset neonatal seizures that later progressed SRSE, ceasing upon sodium channel blockers. Given the specific response to phenytoin, further functional testing to confirm the GOF effect was not deemed necessary. His developmental delay has not been as severe, with certain aspects like delayed expressive speech possibly steaming from the bilateral perisylvian polymicrogyria, rather than the genetic component.

Most *SCN2A* variants described aren't linked to brain structural anomalies. However, some have been associated with extensive macroscopic cortical dysplasia, typically concomitant with an epileptic phenotype [5–7]. Indeed, cortical malformations occur in fewer than a quarter of reported *SCN2A* cases. Bernardo et al. documented a newborn diagnosed prenatally with a cortical dysplasia and pachygyria, presenting with status epilepticus at 6 days old, responding to the sodium channel blocker carbamazepine, with subsequent *SCN2A* variant discovery [5]. Vlachou et al. reported an infant with *SCN2A* early-onset DEE and posterior perisylvian and parietal polymicrogyria, presenting seizures from birth, moderately controlled with phenytoin and carbamazepine. Zeng et al. reviewed 72 young patients with *SCN2A* variants, with 22.2 % showing frontal or frontotemporal lobes dysplasia. Amongst them, 81 % presented an early-onset DEE phenotype and all had psychomotor and/or language delay [7].

Association of cortical malformation with a *SCN2A* pathogenic variant does not appear farfetched, given its crucial role in cortical development. *SCN2A* expression begins early in gestation and is

implicated in early brain development stages: neuronal ion channels malfunctions have been shown to underlie brain migration abnormalities [12–15]. Furthermore, various gene variants were shown to relate to bilateral perisylvian polymicrogyria, including neuronal ion channels mutations, such as *SCN1A, SCN2A, SCN3A, KCNQ2, KCNMA1* and *CACNA1C* [16,17]. The severity of DEE with concurrent cortical malformation and *SCN2A* pathogenic variant warrants further consideration. As seen in our patient, optimal seizure control is an achievable outcome at an early age.

In our case, the dramatic response to a class of anti-epileptic drugs suggested an underlying channelopathy. Furthermore, SRSE in the first months of life is considered a relatively atypical presentation for structural epilepsy with cortical malformation; seizures tending to be more frequently observed in childhood [18]. Neonatal MRI findings were also a subject of debate. They may reflect alterations within the *SCN2A* function and a vulnerability of the neonatal brain to seizure-induced hypoxia, as no alterations of diffusion weighted imaging (DWI) signal or on ADC maps were found at 2 months during SRSE. The reversible cerebral edema might be the result of a metabolic insult secondary to neuronal hyperexcitability, induced by the heightened *SCN2A* GOF effect. One limitation in our case is the short follow-up period. Seizures arising in the early period of life responding to sodium channel blockers may recur at a later age, and be less responsive to such a targeted therapy, likely resulting at that point from the structural etiology.

4. Conclusion

Our case highlights the importance of early genetic analysis in the assessment of patients with epilepsy and cortical malformations. Sodium-channel blockers offer an effective personalized gene-therapy for *SCN2A* early-onset DEE. The neonatal diagnosis of one presumed etiology for early-onset DEE does not exclude others. Constant re-evaluation of clinical and paraclinical information guides a tailor-made therapeutic approach.

Ethics statement

We confirm this report is consistent with the journal's ethical guidelines for publication.

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Author contributions

All authors meet the ICMJE authorship criteria. J.S.A. gathered patient data, prepared figures and wrote the full manuscript. J.F. critically revised the manuscript for important intellectual content. M.L. gathered patient data, prepared the figures and critically contributed for the manuscript. L.Q. analysed patient's genetic data and critically contributed for the manuscript. C.K. critically revised the manuscript for important intellectual content and helped conceiving this case report. S. G.T. gathered patient data, prepared the figures, obtained written consent from the patient's legal representatives, critically revised the manuscript for important intellectual content and conceived this case report. All authors reviewed the manuscript.

Consent for publication

Written consent was obtained from patient legal representatives prior to publication, in accordance with our hospital's ethical policy and using our institutional consent form.

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.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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References

[1] Ahmed CM, Ware DH, Lee SC, Patten CD, Ferrer-Montiel AV, Schinder AF, et al. Primary structure, chromosomal localization, and functional expression of a voltage-gated sodium channel from human brain. Proc Natl Acad Sci U S A 1992;89 (17):8220–4.
[2] Hu W, Tian C, Li T, Yang M, Hou H, Shu Y. Distinct contributions of Na(v)1.6 and Na(v)1.2 in action potential initiation and backpropagation. Nat Neurosci 2009;12 (8):996–1002.
[3] Reynolds C, King MD, Gorman KM. The phenotypic spectrum of SCN2A-related epilepsy. Eur J Paediatr Neurol 2020;24:117–22.
[4] Wolff M, Brunklaus A, Zuberi SM. Phenotypic spectrum and genetics of SCN2A-related disorders, treatment options, and outcomes in epilepsy and beyond. Epilepsia 2019;60(Suppl. 3):S59–67.
[5] Bernardo S, Marchionni E, Prudente S, De Liso P, Spalice A, Giancotti A, et al. Unusual association of SCN2A epileptic encephalopathy with severe cortical dysplasia detected by prenatal MRI. Eur J Paediatr Neurol 2017;21(3):587–90.
[6] Vlachou V, Larsen L, Pavlidou E, Ismayilova N, Mazarakis ND, Scala M, et al. SCN2A mutation in an infant with Ohtahara syndrome and neuroimaging findings: expanding the phenotype of neuronal migration disorders. J Genet 2019;98(2):54.
[7] Zeng Q, Yang Y, Duan J, Niu X, Chen Y, Wang D, et al. SCN2A-related epilepsy: the phenotypic spectrum, treatment and prognosis. Front Mol Neurosci 2022;15: 809951.
[8] Alves IS, Coutinho AMN, Vieira APF, Rocha BP, Passos UL, Gonçalves VT, et al. Imaging aspects of the hippocampus. Radiographics 2022;42(3):822–40.
[9] Havrilla JM, Pedersen BS, Layer RM, Quinlan AR. A map of constrained coding regions in the human genome. Nat Genet 2019;51(1):88–95.
[10] Samocha KE, Kosmicki JA, Karczewski KJ, O'Donnell-Luria AH, Pierce-Hoffman E, MacArthur DG, et al. Regional missense constraint improves variant deleteriousness prediction. bioRxiv 148353 [Preprint]. [posted June 12, 2017]. Available from: doi: 10.1101/148353.
[11] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405–24.
[12] Smith RS, Kenny CJ, Ganesh V, Jang A, Borges-Monroy R, Partlow JN, et al. Sodium channel SCN3A (Na(V)1.3) regulation of human cerebral cortical folding and oral motor development. Neuron 2018;99(5):905–913 e7.
[13] Ackman JB, Crair MC. Role of emergent neural activity in visual map development. Curr Opin Neurobiol 2014;24(1):166–75.
[14] Lancaster MA. An electric take on neural fate and cortical development. Dev Cell 2019;48(1):1–2.
[15] Hurni N, Kolodziejczak M, Tomasello U, Badia J, Jacobshagen M, Prados J, et al. Transient cell-intrinsic activity regulates the migration and laminar positioning of cortical projection neurons. Cereb Cortex 2017;27(5):3052–63.
[16] Epilepsia 2021;62(4):973–83.
[17] Cushion TD, Dobyns WB, Mullins JG, Stoodley N, Chung SK, Fry AE, et al. Overlapping cortical malformations and mutations in TUBB2B and TUBA1A. Brain 2013;136(Pt 2):536–48.
[18] Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. Dialogues Clin Neurosci 2008;10(1):47–62.