

8. Kelly E, Farrell MA, McElvaney NG. Adult-onset nemaline myopathy presenting as respiratory failure. *Respir Care*. 2008;53:1490–4.
9. Kirupaharan P, Kramer D, Gandler A, Kenyon L, Sumner R. 68-year old man with progressive weakness and ventilator dependent respiratory failure: a case report of sporadic late onset nemaline myopathy. *BMC Pulm Med*. 2022;22:97. <http://dx.doi.org/10.1186/s12890-022-01877-4>.
10. Uruha A, Benveniste O. Sporadic late-onset nemaline myopathy with monoclonal gammopathy of undetermined significance. *Curr Opin Neurol*. 2017;30:457–63.
11. Choi B-O, Kang SH, Hyun YS, Kanwal S, Park SW, Koo H, et al. A complex phenotype of peripheral neuropathy, myopathy, hoarseness and hearing loss is linked to an autosomal dominant mutation in MYH14. *Hum Mutat*. 2011;32:669–77.
12. Tanboon J, Uruha A, Arahata Y, Dittmayer C, Schweizer L, Goebel HH, et al. Inflammatory features in sporadic late-onset nemaline myopathy are independent from monoclonal gammopathy. *Brain Pathol*. 2021;31:e12962. <http://dx.doi.org/10.1111/bpa.12962>.

D.A. García Estévez^{a,b,*}, A. Juanatey-García^{a,b},
B. San Millán Tejado^c, F. Barros Angueira^d

^a *Servicio de Neurología, Complejo Hospitalario Universitario de Ourense, Ourense, Spain*

^b *Grupo de investigación Neurociencias Clínicas, Instituto de Investigaciones Sanitarias Galicia-Sur, SERGAS-UVIGO, Vigo, Spain*

^c *Servicio de Anatomía Patológica — Neuropatología, Hospital Álvaro Cunqueiro de Vigo, Vigo, Spain*

^d *Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, A Coruña, Spain*

* Corresponding author.

E-mail address: daniel.apolinar.garcia.estevez@sergas.es (D.A. García Estévez).

<https://doi.org/10.1016/j.nrleng.2023.01.001>
2173-5808/ © 2023 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Epileptic and neurodevelopmental encephalopathy associated to SYNGAP1 mutation: Description of a case and treatment response to cannabidiol



Encefalopatía epiléptica y del desarrollo asociada a mutación del SYNGAP1: descripción de un caso y respuesta al tratamiento con cannabidiol

Dear Editor,

SYNGAP1 mutation was first described in 2009 in patients with nonsyndromic psychomotor retardation and autistic spectrum disorders. Subsequently, in 2013, it was reported to cause developmental and epileptic encephalopathy (DEE).¹ The gene is located on chromosome 6p21.32 and encodes the synaptic Ras GTPase-activating protein 1 (*SYNGAP1*), regulating the excitation/inhibition balance of hippocampal neurons in association with *N*-methyl D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The majority of mutations are de novo mutations, causing a truncated, hypofunctional protein.^{1,2} Up to 98% of patients present epilepsy,^{1,3} showing drug resistance in up to 50% of cases in some series,⁴ with the most frequently described seizures being atypical absence seizures, eyelid myoclonus,

myoclonic-atic seizures with falls, and reflex seizures mainly triggered by eating.¹

Cannabidiol is an approved drug in Europe for treating Lennox–Gastaut syndrome and for Dravet syndrome as an adjuvant treatment with clobazam, in patients older than 2 years, and is approved in the USA for treating tuberous sclerosis complex.⁵ It acts by reducing neuronal hyperexcitability, and also presents anxiolytic and sleep-regulating effects.⁶ Some studies have shown cognitive and behavioural improvements in animal models and human trials,⁷ and effectiveness in other conditions associated with epileptic seizures.⁸

We present the case of a patient diagnosed with encephalopathy associated with *SYNGAP1* mutation at our centre, who was treated with cannabidiol due to drug resistance, achieving a significant clinical improvement.

Case report

We present the case of a 21-year-old woman with no relevant perinatal medical history. From the first days of life, she presented daily episodes of disconnection from the environment, with oral automatism (swallowing), episodes compatible with palpebral and axial myoclonia, and atonic seizures, accompanied by psychomotor retardation. Subsequently, she developed generalised tonic–clonic seizures (GTCS) and gelastic seizures. The patient never acquired language and was diagnosed with autism spectrum disorder, developing episodes of behavioural alterations. Karyotyping, a brain MRI study, and genetic and metabolic studies all yielded normal results. The patient started attending consultations at the adult epilepsy unit at Hospital Regional Universitario de Málaga (HRUM), and showed focal seizures with secondary generalisation and atonic seizures several times per day, in addition to GTCS twice weekly and frequent myoclonus. Several combinations of antiepileptic drugs (AED) were tried, including carbamazepine, perampanel, brivaracetam, and clonazepam, which were suspended due to ineffectiveness; therefore, the patient met criteria for drug resistant epilepsy. She was receiving treatment with valproic acid

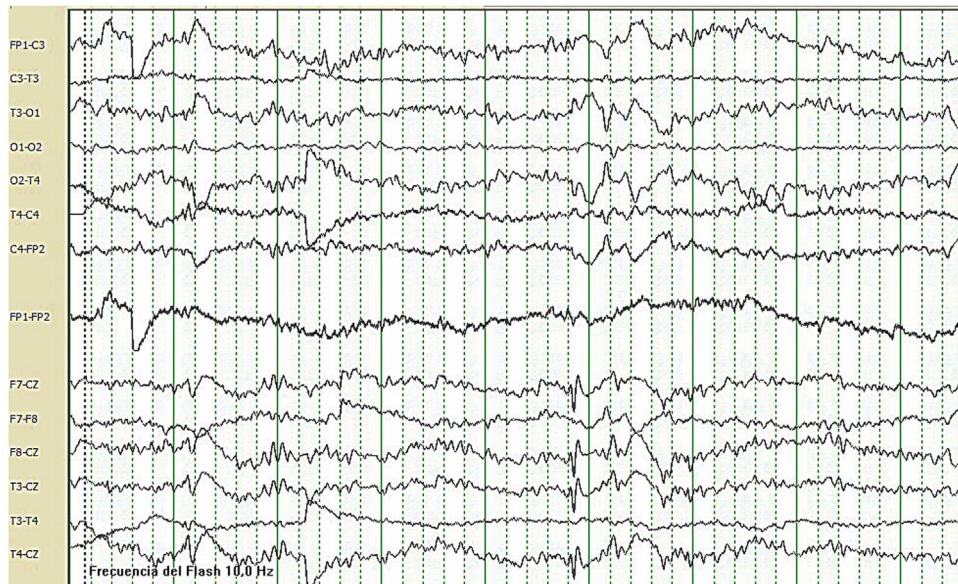


Figure 1 EEG showing diffuse encephalopathy with high-voltage rhythmic delta waves in bilateral central regions and vertex.

(900 mg daily) and lacosamide (400 mg daily). A video-EEG monitoring study recorded no ictal events but did detect background slowing activity compatible with diffuse encephalopathy with high-voltage rhythmic delta waves in bilateral central regions and vertex (Fig. 1). In 2018, an exome sequencing study was performed, revealing heterozygous presence of a de novo nonsense mutation of the *SYNGAP1* gene (c.1861C>T), resulting in replacement of the amino acid Arg621, truncating the protein.

Given the lack of seizure and behavioural control, we decided to start treatment with cannabidiol (300 mg every 12 h) and clobazam (10 mg at night). At 3 months, we observed the effectiveness of the new treatment, with seizure frequency decreasing by more than 50% and a reduction in seizure duration, with atonic seizures disappearing. The effectiveness of the rescue medication also seemed to have improved. Furthermore, improved seizure control led to an improvement in functional status, with the patient recovering the ability to walk autonomously and showing better behavioural control.

Discussion

DEE associated with *SYNGAP1* mutation is a recently described, rare disease, which presents with a characteristic epileptic syndrome characterised by absence seizures, palpebral myoclonus, and myoclonic-atonic seizures. We present the case of a patient with DEE secondary to a pathogenic mutation of the *SYNGAP1* gene, which was described in 2020,⁹ and who, as a peculiar feature, presented gelastic seizures. We are aware of no other case presenting this type of seizures. Another surprising aspect of our patient is her good response to cannabidiol treatment. Mutations in this gene induce an increase in levels of the protein transient receptor potential cation channel subfamily V member 1 (TRPV1), one of the mechanisms causing the excitation/inhibition imbalance, and cannabidiol seems to induce a rapid activation and desensitisation of this receptor.⁸ In fact, some published series report a good clinical response.^{1,10} Based on these data, we decided to prescribe compassionate use of cannabidiol, achieving a clinical improvement, both in terms of seizure control and at the cognitive and behavioural levels.

As cases are increasingly being reported in the literature and genetic studies are becoming more widely available, in the com-

ing years we will probably be able to identify a greater number of patients, which will enable us to better characterise the disease and obtain data regarding treatment effectiveness. Compassionate use of cannabidiol may be an effective treatment for DEE, but further studies are needed on this matter.

References

1. Vlaskamp DRM, Shaw BJ, Burgess R, Mei D, Montomoli M, Xie H, et al. *SYNGAP1* encephalopathy: a distinctive generalized developmental and epileptic encephalopathy. *Neurology*. 2019;93:908.
2. Agarwal M, Johnston MV, Stafstrom CE. *SYNGAP1* mutations: clinical, genetic, and pathophysiological features. *Int J Dev Neurosci*. 2019;78:65–76.
3. Mignot C, von Stülpnagel C, Nava C, Ville D, Sanlaville D, Lesca G, et al. Genetic and neurodevelopmental spectrum of *SYNGAP1*-associated intellectual disability and epilepsy. *J Med Genet*. 2016;53:511–22.
4. Holder JL Jr, Hamdan FF, Michaud JL, et al. *SYNGAP1*-related intellectual disability. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle; 2019. p. 1993–2022.
5. European Medicines Agency [Accessed 20 March 2022] Available from: Epidyolex; 2020 <https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex>
6. Schaiquevich P, Riva N, Maldonado C, Vázquez M, Cáceres-Guido P. Clinical pharmacology of cannabidiol in refractory epilepsy. *Farm Hosp*. 2020;44:222–9.
7. Gaston TE, Martin RC, Szaflarski JP. Cannabidiol (CBD) and cognition in epilepsy. *Epilepsy Behav*. 2021;124:108316, <http://dx.doi.org/10.1016/j.yebeh.2021.108316>.
8. Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, et al. Highly purified cannabidiol for epilepsy treatment: a systematic review of epileptic conditions beyond Dravet syndrome and Lennox-Gastaut syndrome. *CNS Drugs*. 2021;35:265–81.
9. Verma V, Mandora A, Botre A, Clement JP. Identification of an individual with a *SYNGAP1* pathogenic mutation in India. *Mol Biol Rep*. 2020;47:9225–34,

<http://dx.doi.org/10.1007/s11033-020-05915-4>. Erratum
in: Mol Biol Rep. 2021 Sep;48(9):6663. Epub 2020 Oct 22.

10. Kuchenbuch M, D'Onofrio G, Chemaly N, Barcia G, Teng T, Nabbout R. Add-on cannabidiol significantly decreases seizures in 3 patients with SYNGAP1 developmental and epileptic encephalopathy. *Epilepsia Open*. 2020;5:496–500.

Y. López-Moreno^{a,*}, P. Cabezudo-García^{a,b,c},
N.L. Ciano-Petersen^{a,b,c}, G. García-Martín^{a,b,c},
P.J. Serrano-Castro^{a,b,c}

^a *Instituto de Investigación Biomédica de Málaga - IBIMA, Málaga, Spain*

^b *Red Andaluza de Investigación Clínica y Traslacional en Neurología (NeuroRECA), Málaga, Spain*

^c *Servicio de Neurología, Hospital Regional Universitario de Málaga, Málaga, Spain*

* Corresponding author.

E-mail address: YOLANDA.LOPEZMORENO@osakidetza.eus
(Y. López-Moreno).

<https://doi.org/10.1016/j.nrleng.2023.12.002>

2173-5808/ © 2023 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).