Clinical Neurophysiology 130 (2019) 2134–2136

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Letter to the Editor

Photosensitive epilepsy and long QT: expanding Timothy syndrome phenotype

Timothy syndrome (TS) is an autosomal dominant disorder caused by mutations of *CACNA1C* gene, encoding the CaV 1.2 L-type channel gene (Gillis et al., 2012). Clinical phenotype includes prolonged-QT, hands and feet syndactyly, facial dysmorphisms, congenital heart defects, intellectual disability, seizures and autism spectrum disorder (Napolitano et al., 2006).

We report a child affected by TS and epilepsy, diagnosed with a novel *CACNA1C* gene mutation.

The child was born at term after uneventful pregnancy to healthy non-consanguineous parents. He presented with bilateral, complete cutaneous syndactyly of the last three hand fingers and congenital talipes equinovarus.

During development, the child showed mild hypotonia and joint laxity, clumsiness, intention tremor, dyspraxia, autistic spectrum disorder, and dysmorphic features (brittle, curly hair, a round face with relatively large eyes and small nose and mouth, a thin upper lip, down slanting palpebral fissures, and anteverted nares).

At the age of 2 years, he started to suffer absences with eyelid myoclonia. Electroencephalogram (EEG) (age 3) showed multifocal and sometimes diffuse spike-polyspike and waves, electro-clinical pattern of absence with eyelid myoclonia, and photoparoxysmal response (PPR). Valproic acid failed to control seizures, which disappeared at the age of 4 years after initiation of ethosuximide and clonazepam therapy.

At the age of 7 years, he began to present episodes characterized by sudden loss of consciousness, apnea, cyanosis and hypotonia, lasting 1–5 min, followed by hypotonia and somnolence. Each episode had a trigger (loud, frightening noises, or other frightening stimuli). Valproic acid was resumed suspecting epilepsy relapse.

Diagnostic workup included: TORCH serology, abdominal and cardiac ultrasounds, brain magnetic resonance imaging (MRI: age 4 and 10 years), electrocardiogram (EKG: age 6 years), molecular tests (array-CGH; *PTPN11*, *SHOC2*, *GJA1*, *CUL4B*, CACNA1C exons 8 and 8A *sequencing*), with normal results in all tests.

At the age of 12 years, while awake, after a sudden noise, the child had a cardiac arrest due to ventricular fibrillation, requiring three rounds of electric defibrillation. The child was intubated, transferred to our pediatric ICU and underwent hypothermia (for 36 h). Upon arrival, long QT syndrome (LQTS, 760 ms) was diagnosed (L.L.) based on EKG findings (Fig. 1A. Re-evaluation of previous EKGs by a pediatric cardiologist (L.L.) confirmed the presence of LQTS (550 ms) already in early childhood. The child received beta-blockers and mexiletine and finally underwent implantation of a cardioverter defibrillator.

In the months following cardiac arrest, the child progressively improved up to complete recovery. EEG showed normal background activity and persistence of PPR.

At the last follow-up (age 15 years), the patient, under valproic acid, presented rare photo-induced seizures; the EEG showed normal background activity and a photomyogenic response (Fig. 1B). The cardiac pacemaker was well functioning, no arrhythmic events had been registered since its implantation.

Sequencing of the entire coding region of the *CACNA1C* gene revealed a *de novo* heterozygous missense mutation in exon 9 of the gene c.1220A > G p.(Glu407Gly) (nomenclature is identical for both *CACNA1C* reference sequences NM_000719.6 and NM_001167625.1) (Fig. S1A–B, Supplementary Material). The mutation is not reported in variant databases (ExAC, dbSNP, 1000 genomes) and affects a highly conserved amino acid (Fig. S1C, Supplementary Material). No mutations were detected in other genes associated with LQTS (*ANK2*, *CALM1, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1).*

The unusual association between epilepsy and TS in our patient suggests a possible phenotype-genotype correlation.

Generally, seizures are uncommon in TS patients and usually symptomatic of cerebral damage (Gillis et al., 2012; Napolitano et al., 2006). Conversely, our patient experienced seizures without a history of acute cardiac events and with a normal cerebral MRI.

At onset, our patient's electroclinical pattern was consistent with generalized epilepsy of childhood (eyelid myoclonia with absences). Differently from the classical presentation of this epilepsy (Poleon and Szaflarski, 2017), he had an early onset and a poor response to valproic acid. Moreover, he presented photosensitivity since the first EEG. Some years after epilepsy onset, he presented also photoinduced seizures, inconstantly associated with PPR in EEGs.

PPR appears typically between 5 and 15 years in various epilepsies (Poleon and Szaflarski, 2017). Its appearance before 5 years of age could occur in Dravet syndrome, epileptic encephalopathies, neurodegenerative disorders, and benign idiopathic epilepsies (Binelli et al., 2015). Among children with early PPR appearance, about 30% suffer from a static disorder with a known or suspected genetic origin (Binelli et al, 2015), and genes encoding ion channels could be implicated (Poleon and Szaflarski, 2017).

In our patient a direct link between *CACNA1C* mutation and epilepsy is likely; mutations in voltage-gated calcium channels (VGCCs) genes have been linked to different types of epilepsy (Rajakulendran and Hanna, 2016). Our patient's p.Glu407Gly mutation is *de novo*, its minor allele frequency is less than 1:100,000, and it affects a highly conserved residue, adjacent to the two recurrent mutations causing either classical or atypical TS. All *CACNA1C* mutations manifesting as TS phenotype affect residues that are clustered near the end of several transmembrane alpha helixes that surround the lumen of the channel on the intracellular side of the protein (Fig. S1D–E, Supplementary Material). Both the classical p.Gly406Arg exon 8 and the p.Glu407Gly are predicted to increase by +1 unit the net charge of this protein region,

https://doi.org/10.1016/j.clinph.2019.09.003

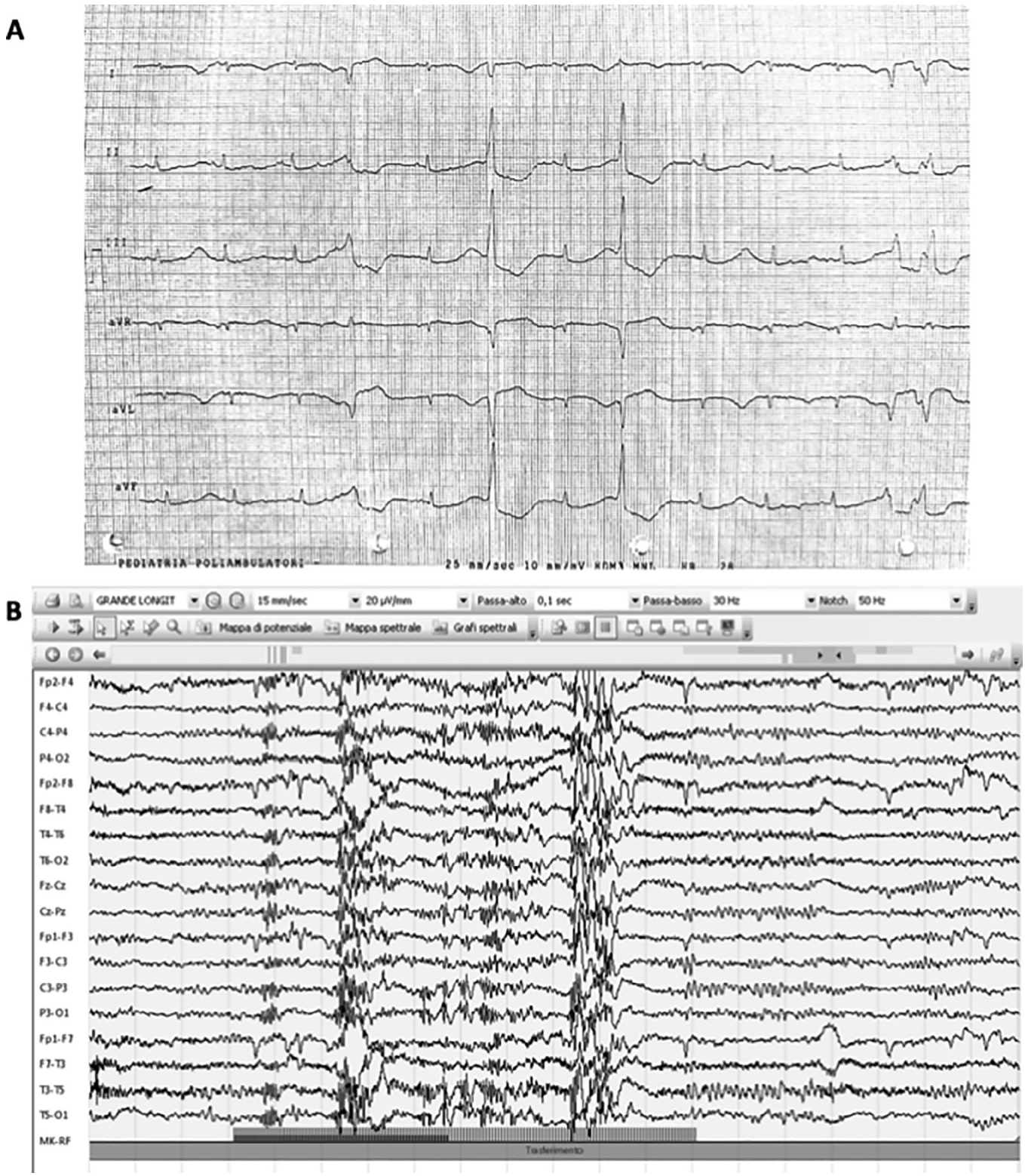

Fig. 1. (A–B): ECG and EEG data of the patient. (A) ECG recorded upon arrival in the pediatric ICU after cardiac arrest, showing very long QT (760 msec) in sinus rhythm and ventricular bigeminy rhythm. (B) EEG recorded during follow up after cardiac arrest, showing photoparoxysmal and photomyogenic response (15 mm/s; 20 µv/mm; high-frequency filter: 30 Hz).

therefore we can hypothesize a similar effect of voltage-dependent inactivation of the channel. However, it is not possible to determine whether the peculiar epileptogenic phenotype of this amino acid change is due to additional effects of the mutation, to the different expression pattern compared to the typical exon 8A p. Gly406Arg mutation, or to modifier genes/environmental factors. More studies are needed to clarify these aspects.

In conclusion, epilepsy and PPR could be a new genetic-based neurophysiological marker of Timothy syndrome. Children with autistic spectrum disorder, epilepsy with photoparoxysmal

response and long QT should undergo gene sequencing of the entire coding region of *CACNA1C* gene.

Disclosures

None of the authors have potential conflicts of interest to be disclosed.

All authors contributed materially the research and/or article preparation. All authors approved the final article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.09.003.

References

Binelli S, Ragona F, Canafoglia L, Freri E, Saletti V, Casazza M, et al. Electroencephalographic (EEG) photoparoxysmal reponses under 5 years of age: diagnostic implications and peculiarities. JCN 2015;30:1824–30. https://doi.org/10.1177/0883073815583687.

Gillis J, Burashnikov E, Antzelevitch C, Blaser S, Gross G, Turner L, et al. Long QT, syndactyly, stroke and novel CACNA1C mutation: expanding the spectrum of Timothy syndrome. Am J Med Gen 2012;158A(1):182–7. https://doi.org/10.1002/ajmg.a.34355.

Napolitano C, Splawski I, Timothy KW, Bloise R, Priori SG. Timothy syndrome. 2006 Feb 15 [Updated 2015 Jul 16]. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2006 [accessed December 17, 2017].

Poleon S, Szaflarski JP. Photosensitivity in generalized epilepsies. Epilepsy Behav 2017;68:225–33. https://doi.org/10.1016/j.yebeh.2016.10.040.

Rajakulendran S, Hanna MG. The role of calcium channels in epilepsy. Cold Spring Harb Perspect Med 2016;6(1):a022723. https://doi.org/10.1101/cshperspect.a022723.

Chiara Po' [a,1]
Roberta Zordan [b,1]
Marilena Vecchi [a]
Alessia Cerutti [a]
Stefano Sartori [a]
Eva Trevisson [b]
Kathrin Ludwig [b]
Biagio Castaldi [a]
Leonardo Salviati [b]
Loira Leoni [c]
Irene Toldo [a,*]

[a] *Department of Woman's and Child's Health, University Hospital of Padua, via Giustiniani, 3 – 35128 Padua, Italy*
[b] *Clinical Genetics Unit, Department of Women's and Children's Health, University of Padua, and IRP Città della Speranza, Corso Stati Uniti, 4 – 35129 Padua, Italy*
[c] *Department of Cardiac, Thoracic and Vascular Sciences, University Hospital of Padua, via Giustiniani, 2 – 35128 Padua, Italy*
* Corresponding author.
E-mail address: irene.toldo@unipd.it (I. Toldo)
Accepted 10 September 2019

Available online 17 September 2019

[1] These authors contributed equally to the work.