Movement Disorders
CLINICAL PRACTICE

LETTER: GENOTYPE AND PHENOTYPE

Focal Dystonic Tremor as a Prominent Feature in a Child with a CACNA1A-Related Disorder

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Pathogenic variants in the *CACNA1A* gene have been associated to a wide spectrum of neurological disorders including paroxysmal and persistent epileptic or non-epileptic symptoms.[1] Cerebellar phenotype is a relevant clinical features including autosomal-dominant spinocerebellar ataxias, several autosomal recessive ataxias and episodic ataxias.[2]

Herein we describe a Caucasian 14-year-old female, fourth child of non-consanguineous healthy parents, born at term via scheduled caesarean section. Silent medical history for the three siblings. At birth her Apgar score was 7–9, she presented mild respiratory distress requiring a few seconds of nasal oxygen therapy and resulting in fast improvement. Early psychomotor development milestones were achieved normally. Nevertheless, clumsiness in her manual skill, slight imbalance and learning difficulties were noticed during development. At 5 years of age, she started presenting a right arm disabling tremor, non-progressive and not spreading to other body regions over time. At 14 years of age, on examination (Video 1) with no pharmacological therapy, she showed an irregular, medium frequency, focal action tremor of the right upper limb, which worsened with maintenance of posture. Dystonic posturing of the right upper limb appeared especially during task specific movements. She also showed bilateral horizontal nystagmus and hindrance in tandem walking.

Brain MRI showed bilateral alterations of occipital cortex compatible with outcomes of perinatal suffering (Fig. 1), and resulted unchanged from the one she performed at age 9 in another center.

The polygraphic study demonstrated the absence of tremor at rest. During the maintenance of the upper limbs, the appearance of rhythmic bursts at 6 Hz, synchronous on the antagonist muscles, was observed in the right upper limb (Fig. 1). Tactile stimulation enhanced tremor and induced the appearance of a co-contraction of the distal muscles superimposed with mild superimposed myoclonic jerks. The tremor was also increased during target achievement and writing. Distraction maneuvers were ineffective (Video 2).

Formal cognitive evaluation, using Wechsler Intelligence Scale, highlighted mild intellectual disability (IQ: 63). Affective immaturity and marked anxious aspects were reported.

Next generation sequencing gene panel for movement disorders identified in the proband a de novo heterozygous c.1108delG variant in exon 8 of the *CACNA1A* gene (NM_001127222.2), causing a premature stop codon (p.Val370TrpTer7). Sanger sequencing did not detected the variant in the parents. This variant

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Video 1. Video showing examination of the patient. In details irregular, medium frequency, focal action dystonic tremor of the right upper limb worsening with maintenance of posture. Bilateral horizontal nystagmus and hindrance in tandem gait. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13854

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has never been reported in literature but, according to ACMG guidelines, has pathogenic predictions (gnomAD allele frequency 0%, in silico predictions: PaPI scores 0,992 -damaging-, Mutation taster Disease causing, VarSome likely pathogenic -ACMG 9- and Franklin likely pathogenic).

CACNA1A encodes for voltage-dependent P/Q-type calcium channel subunit alpha-1A, which is widely expressed throughout the CNS. The biological roles of the P/Q channel are multiple and crucial in neurotransmitter release.

We report a patient harboring a novel heterozygous pathogenic variant in *CACNA1A*, showing a pediatric onset non-progressive focal dystonic tremor localized in one upper limb occurring in a phenotype of mild intellectual disability and cerebellar signs.

Dystonia have been recently reported associated to *CACNA1A* by two independent group showing activity-induced dystonia[3] and cervical dystonia[4] with mild ataxia. Links between *CACNA1A* and tremor have rarely been reported: head tremor was a presenting feature in two adults with Familial Hemiplegic Migraine[5] and another patient presenting with paroxysmal head tremor and mild cerebellar signs with cerebellar atrophy[6] but, as far as we are concerned, there are no previous reports of focal and non-progressive tremor as the most significant presenting symptom. Focal dystonia with handwriting impairment has been reported as prominent sign in *ADCK3*/COQ8A gene mutation supporting the possibility that childhood-onset focal dystonia may underlie inherited complex movement disorder.[7]

The clinical features we reported may increase the knowledge about *CACNA1A* variants and provide an additional diagnostic tool in the differential diagnosis of tremor in children.

Video 2. Video with polygraphy recordings showing medium frequency, focal action tremor of the right upper limb, worsening with maintenance of posture and dystonic posture. Also subtle dystonic posturing and movements in the left upper limb and some cerebellar sway of the upper limbs. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13854

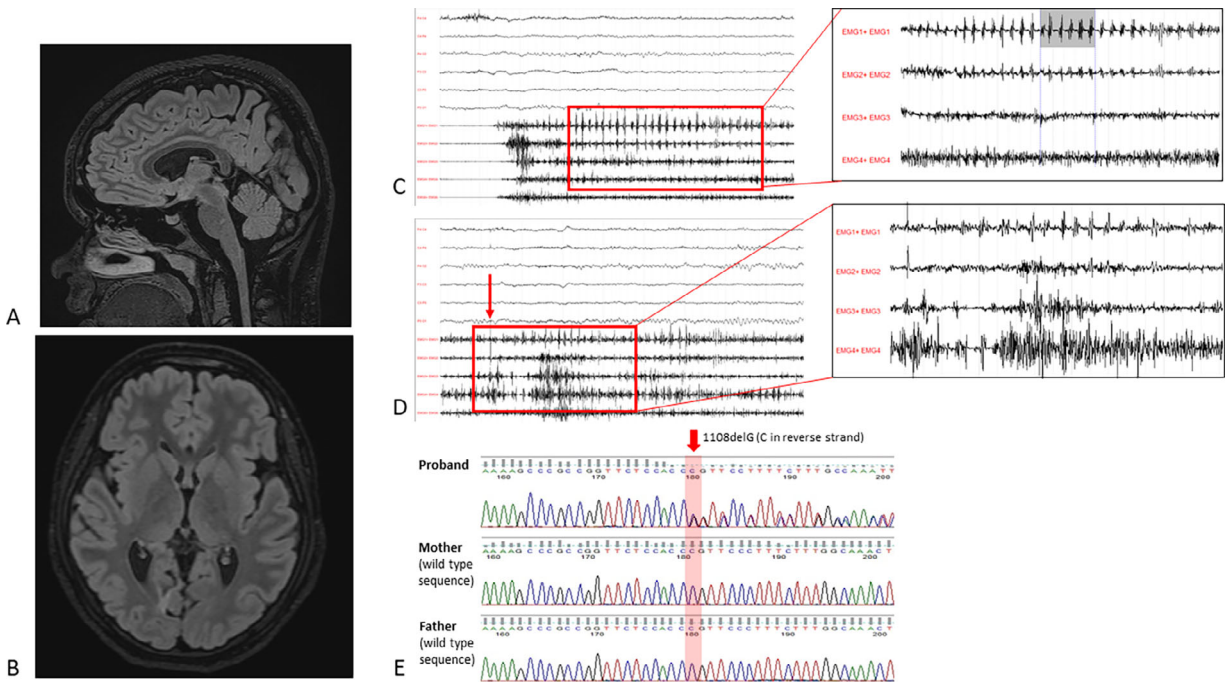

Figure 1. Axial T1-weighted MRI scan showing regular basal ganglia (**A**) and Sagittal T1-weighted MRI scan showing normal cerebellum (**B**). Polygraphic recording showing during upper limb extension a rythmic 6 Hz bursting is observed over the proximal muscles, burst duration is around 100 msec; tremor is enhanced by tactile stimulation (**C**) with evidence of a tonic co-contraction of distal muscles, intermingled with synchronous myoclonic bursts (arrow indicates tactile stimulation), (**D**). Chromatogram of CACNA1A for proband, mother, father (**E**). EMG1, right biceps; EMG2, right triceps; EMG3, right flexor; EMG4, right extensor; EMG6, left extensor.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

M.M.: 1A, 1B, 1C, 2A.
F.G.: 1A, 1B, 1C, 2B.
L.C.: 1C, 2B.
D.C: 1C, 2B.
F.R.D.: 1C, 2B.
C.R.: 1C.
G.Z.: 1A, 1B, 2B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Patient's guardians gave full written consent to publication of anonymized patient's data and video. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Supplemental File 1. Movement Disorders gene panel (NGS performed with Illumina Miseq platform).

Figure S1. Basal EEG ruled out the cortical genesis of the tremor in the right upper limb. Fig. 1A shows a diffuse, brief, burst of high amplitude irregular spike and waves during hyperpnea and Fig. 1B shows Intermittent Photic Stimulation at 10 Hz inducing a diffuse photoparoxysmal response consisting in high amplitude slow waves intermixed with posteriorly dominant small spikes. Both EEG paroxysmal activities are not accompanied by clinical modifications.