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# KCNMA1-Related Episodes of Behavioral Arrest and Loss of Postural Reflexes: A Critical Reappraisal

Emmanuel Roze<sup>1</sup>, Laura Silveira-Moriyama<sup>2 3</sup>, Smaranda Leu-Semenescu<sup>4</sup>, Nathalie Villeneuve<sup>5 6</sup>, Bérénice Lecardonnel<sup>7</sup>, Marie-Céline François-Heude<sup>7</sup>, Pierre Meyer<sup>7 8</sup>, Claudio M de Gusmao<sup>9 10</sup>, Agathe Roubertie<sup>7 11</sup>

<sup>1</sup> Sorbonne University, INSERM, CNRS, Paris Brain Institute, AP-HP Salpêtrière Hospital, Paris, France.

<sup>2</sup> Neurology Department, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil.

<sup>3</sup> Teaching Unit, UCL Queen Square Institute of Neurology, London, UK.

<sup>4</sup> Sleep Disorders Clinic, Pitié-Salpêtrière Hospital, APHP-Sorbonne University, National Reference Center for Orphan Diseases, Narcolepsy, Idiopathic Hypersomnia, and Kleine-Levin Syndrome; Paris Brain Institute (ICM), Inserm, CNRS, Paris, France.

<sup>5</sup> Assistance publique-Hôpitaux de Marseille, Reference Centre for Rare Epilepsies (member of the ERN network EPICARE), Marseille, France.

<sup>6</sup> Pediatric Neurology Department, Assistance publique-Hôpitaux de Marseille, Marseille, France.

<sup>7</sup> Service de Neuropédiatrie, CHU Montpellier, Montpellier, France.

<sup>8</sup> Phymedexp, Université de Montpellier, Inserm, CNRS, Montpellier, France.

<sup>9</sup> Pediatric Neurology Department, University of São Paulo, Sao Paulo, Brazil.

<sup>10</sup> Boston Children's Hospital, Boston, USA.

<sup>11</sup> Institute for Neurosciences of Montpellier, INSERM U 1298, University of Montpellier, Montpellier, France.

## **Keywords:**

KCNMA1; cataplexy, stimulant therapy; paroxysmal attacks.

## **\*Correspondence to:**

Dr. Agathe Roubertie, Service de Neuropédiatrie, CHU Gui de Chauliac, 80 Avenue Fliche, 34295 Montpellier, France;

**E-mail:**

a-roubertie@chu-montpellier.fr

# Abstract

## **Background:**

KCNMA1-linked channelopathy is characterized by neurodevelopmental disorder, epileptic seizures and non-epileptic paroxysmal episodes.

## **Objectives:**

To describe the phenotype of paroxysmal non-epileptic episodes related to KCNMA1 pathogenic variants.

## **Methods:**

Videos of paroxysmal episodes were reviewed according to a standardized protocol by a group of movement disorders experts.

## **Results:**

Fourteen videos were reviewed (6 previously published patients and a new patient). The typical pattern of an episode was (i) facial changes including dyskinetic movements of tongue and jaws (ii) behavioral arrest (iii) loss of postural reflexes that could be associated with focal body stiffness, eventually leading to fall (iv) rapid recovery without post-ictal drowsiness. Attacks were brief, with a high daily frequency, occasionally triggered by emotion, and dramatically improved by psychostimulant therapy in three patients.

## **Conclusions:**

KCNMA1-related attacks are clearly distinguishable from paroxysmal dyskinesia, cataplexy or episodic ataxia indicating a unique phenomenological entity whose recognition will enhance accurate diagnosis and treatment.

## **Keywords:**

KCNMA1; cataplexy, stimulant therapy; paroxysmal attacks.

The KCNMA1 gene encodes the pore-forming alpha subunit of a K<sup>+</sup> ion channel, part of the BK family (“Big K<sup>+</sup>”) because of its large conductance and activation by voltage and intracellular Ca<sup>2+</sup> ions.<sup>1,2</sup> KCNMA1 pathogenic heterozygous variants have been associated with a range of phenotypes manifesting developmental delay, epilepsy and/or dyskinesias. Some of these phenotypes have been highlighted as distinctive, such as paroxysmal non-kinesigenic dyskinesia 3, with or without epilepsy (PNKD3, OMIM# 609446) and Liang-Wang syndrome (OMIM# 618729).<sup>1,3–5</sup> While monoallelic variants with gain-of-function (GoF) effect have been associated with PNKD3 and loss-of-function (LoF) variants with Liang-Wang syndrome, the distinction between GoF and LoF phenotypes is not entirely clear as some individuals reported in the literature may have shared features between the two syndromes. Finally, biallelic pathogenic variants in KCNMA1 cause cerebellar atrophy, developmental delay and seizures (OMIM # 617643).<sup>6</sup>

PNKD3 is a condition characterized by the presence of epileptic and/or non-epileptic paroxysmal events and delayed development.<sup>1,3,4</sup> Several authors have suggested that PNKD3 may present with a particular type of non-epileptic episode, but inconsistent classification has prevented the development of a uniform definition. Heterogeneous terms have been used, such as “negative motor episodes”, “cataplexy”, “dystonia-cataplexy”, “dystonic spells”, “paroxysmal non-kinesigenic dyskinesia” and “atonic seizure-like episodes”.<sup>2,7–10</sup> Interestingly, these episodes have been reported in association with the p.N995S variant in KCNMA1 (annotated to reference transcript NM\_002247.4; also referred to in the literature as p.N999S, p.N1036S or p.N1053S), but it is unclear whether this is a specific finding.<sup>4</sup>

We propose a critical reappraisal of the phenomenology of the paroxysmal non-epileptic events associated with KCNMA1, through standardized analysis of previously published videos and report an additional individual with a pathogenic variant in KCNMA1.

## Methods

We reviewed the literature (PubMed, keyword KCNMA1) and selected individual cases who fulfilled the following criteria: (i) harboring pathogenic monoallelic variants of KCNMA1 gene (ii) described as exhibiting paroxysmal non-epileptic episodes, (iii) with available videos of the non-epileptic attacks in the publication. A patient not previously published with a pathogenic KCNMA1 variant and video-recorded paroxysmal non epileptic attacks was also included. This patient gave written informed consent according to the Declaration of Helsinki for review and publication of his clinical, genetic and video recording results.



**VIDEO 1.** Recorded at 5 years of age. There was no triggering factor and the onset was abrupt with loss of facial expression, followed by mouth opening and loss of postural reflexes and fall on the right side 2 s after onset. Behavioral arrest was associated with falling of the head backwards and mild dystonic posturing/stiffness of the upper limbs. There was a rapid recovery: the total duration of the attack was 40 s. This attack was recorded during a 24 h video-EEG monitoring; interictal EEG during awakening and sleep recorded a normal background rhythm with no interictal epileptic abnormality; during the attacks, EEG activity was unchanged and a sharp decrease in muscle activity on the deltoids' myographic electrode was noticeable. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14289>

Clinical and genetic data were collected in the publications and from the medical file of the unpublished patient (case 7). The videos were analyzed during five shared video sessions lasting 90–120 min involving four movement disorders experts (ER, CDG, LSM, AR) and using a standardized protocol (one session to build-up the standardized protocol of analysis, two rounds for clinical description, two rounds for phenomenology categorization, one last session to verify consensual agreement). Appearance of each body region (face, mouth, neck, trunk, limbs) was collected during the course of the attacks, with precise description of each observed sign (for example, staring, jaw opening, limb stiffness); then the collected signs were categorized by their phenomenology according to established neurological guidelines especially movement disorders classification,<sup>11–13</sup> with specific focus on dyskinetic movements/stiffness/loss of tone/loss of motion/behavioral arrest; we also analyzed the progression of each sign using a timer, and their regional extension to investigate craniocaudal progression.

## Results

We identified four publications of individuals harboring heterozygous pathogenic KCNMA1 variants and presenting paroxysmal non-epileptic and available videos. We focused on the medical data and 12 videos of the six cases extracted from these four reports. 7–10, 14 Not previously published case 7 was also included in this study (videos 1 and 2). According to the publications and/or physicians familiar with the patients, videos were highly representative of a typical episode.



**VIDEO 2.** Recorded at 24 years of age. The morning methylphenidate dose was skipped to record an attack, which occurred spontaneously 2 h after the missing dose. The onset of the episode was not recorded; at the beginning of the recording, the family asked and encouraged the patient to stand up; at the beginning of the recording, the patient was unable to move and remained crouched down in a fixed posture, then he could only voluntarily raise his legs; he was unable to answer verbally to the questions of his family and smiled at a brief familial joke at 12 s from recording onset, then his face kept this faint smile although the joke was finished (between the attacks, the patient was usually very smiley). The video showed behavioral arrest with frozen smile with mouth opening, fist, dystonic posture of the hands; the episode lasted more than 1 min 30 s and the end was not recorded. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/ivc.314289>

Clinical characteristics of the patients are summarized in Table 1. Neurodevelopmental disorder was reported in 6/7; absence epilepsy was diagnosed in two individuals. The most commonly reported variant was p.N995S (5/7), additional variants included p.I512V and p.N536H. Functional studies available for 2 of these variants indicated a gain-of-function of the BK channel in p.N995S and p.N536H.<sup>14,15</sup>

**TABLE 1** Characteristics of the patients

Patient number/ gender/reference in the original paper when provided	1/F/RJ7712	2/F/-	3/F/-	4/F/1	5/F/2	6/M/3	7/M/-
Article	Tian et al 2018	Zhang et al 2020	De Gusmao et al 2022	Heim et al 2020	Heim et al 2020	Heim et al 2020	This report
c.DNA HGVS	c.1534A>G p.I512V	c.1606A>C p.N536H	c.2984A>G p.N995S *	c.2984A>G p. p.N995S*	c.2984A>G p p.N995S *	c.2984A>G p.N995S *	c.2984A>G p p.N995S
Variant type	Missense	Missense	Missense	Missense	Missense	Missense	Missense
Functional effect	NK	Gain of function	Gain of function	Gain of function	Gain of function	Gain of function	Gain of function
Age of onset of the first symptoms	15 y	<2 y	8 m	infancy	infancy	infancy	1 y
First symptoms	Paroxysmal attacks	Developmental delay	Spells of axial atonia, limb dystonia, and preserved consciousness	NK	NK	NK	Paroxysmal attacks
Epilepsy	No	No	No	No	absence seizures from 6 y	No	absence seizures from 11 y
Dystonia	No	No	no	No	no	No	No
Cognitive or psychiatric disorders	Normal	autism spectrum disorder, dystonia and intellectual disability.	Speech delay at 2 y	Developmental delay, hypotonia	Developmental delay	intellectual disability, autism spectrum disorder, speech and motor dyspraxia.	Developmental delay, severe dysarthria
Age at onset of the paroxysmal attacks	15 y	2 y	8 m	infancy	infancy	infancy	1 y
Frequency of episodes	10-20/d	100/d	70/d	60/d	12/d	60/d	100/d
Duration of episodes	10 s	15-20 s	10-30 s	seconds to minutes	NK	NK	5 s initially, and then 20-40 s
Triggering factor	Voluntary movements	NK	Emotion, or no trigger	Strong emotions and illness Most of the time: no trigger			None

**TABLE 1** Continued

Patient number/ gender/reference in the original paper when provided	1/F/RJ7712	2/F/-	3/F/-	4/F/1	5/F/2	6/M/3	7/M/-
Effective treatments	carbamazepine 50 mg at night	metamphetamine 15 mg/d at 8 y	Initial: Caffeine 60 mg (~4 mg/kg/day) Subsequent: lisdexamfetamine titrated up to 20 mg qd (1 mg/kg/d)	acetazolamide (250 mg qd)	no treatment	No treatment	methylphenidate 10 mg tid from 7.7 y
Outcome	Good control with carbamazepine, incomplete remission at 19 y with occasional aura	Resolution with metamphetamine; recurrence to 5episodes/d the day after discontinuation up to 200/d the next few days after discontinuation of the treatment	Peak frequency at 18 m; partial improvement with caffeine. Complete resolution with lisdexamphetamine (improvement within hours after the first intake; and relapse within hours after discontinuation), increased compromised by side effects of stimulant use.	Improvement with acetazolamide (30/d); no clear benefit using higher dosage	NK	Frequency slowly decreased over time	Dramatic improvement with methylphenidate (improvement within hours after the first intake, and relapse within hours after discontinuation
Ineffective treatments	NK	valproic acid carbamazepine ethosuximide gabapentin leviteracetam phenobarbital zonisamide temazepam clonazepam ketogenic diet	NK	levetiracetam clonazepam amitriptyline	No treatment	valproic acid carbamazepine levetiracetam pimozide cannabidiol vitamin B complex, docosahexaenoic- acid, 5-HIAA	valproic acid carbamazepine ethosuximide levetiracetam ketogenic diet, topiramate
MRI	Normal	2 y: normal; 18 y: mild cerebellar atrophy	Normal	Normal	NK	NK	Normal (4 y)

(Continues)



TABLE 1 Continued

Patient number/ gender/reference in the original paper when provided	1/F/RJ7712	2/F/-	3/F/-	4/F/1	5/F/2	6/M/3	7/M/-
EEG	Normal (whether the recording was during an episode or not is unknown)	Interictal EEG at 4 y: normal; 14 y: diffuse background slowing; 18 y: rare generalized spike and wave and rare bifrontal sharps, diffuse slowing EEG recording of episodes at 4 y (2 attacks recorded), 15 y (51 attacks recorded), 18 y: no EEG correlate	Captured events without EEG correlate. Background slowing; rare spike and sharp waves during sleep in left frontal and right frontocentral areas.	EEG during attacks without discernible change in the background	EEG during attacks without discernible change in the background	EEG during attacks without discernible change in the background	5 y: Interictal EEG during awakening and sleep recorded a normal background rhythm with no interictal epileptic abnormality; during the attacks EEG activity was unchanged and a sharp decrease in muscle activity on the deltoids' myographic electrode was noticeable.
CSF hypocretin	NK	NK	NK	Normal	NK	NK	Normal

All variants are mapped to the reference *KCNMA1* transcript NM\_002247.4/ENST00000286627.  
Abbreviations: F, female; M, male; y, years; m, months; d, day; s, second; NK, not known.  
\*Originally reported as p.N999S.

Attacks were characterized by onset in infancy in 6/7 patients (at 15 years of age in one), short duration (from 10 to 45 s); and high frequency (ranging from 10 to 100 per day). Triggers were reported in some patients (emotion, voluntary movement), but most often attacks did not have a clear trigger. Episodes were dramatically reduced in 3/3 patients by psychostimulant therapy (case 2, dextroamphetamine, 15 mg; case 3 lisdexamfetamine, initial dose 5 mg/day, titrated to 1 mg/kg/day; case 7: methylphenidate, dose 10 mg tid) (Table 2). Benefit occurred during the few hours following the first psychostimulant intake, with recurrence of the attacks within hours after withdrawal. In case 3, episodes were completely abolished with stimulant treatment, but dosage had to be lowered due to side effects. Carbamazepine (50 mg at night) and acetazolamide (250 mg/day) provided benefit in case 1 and 4 respectively. Case 3 also derived partial benefit from caffeine 4 mg/kg/day (prior to the molecular diagnosis and changing therapy to lisdexamfetamine). Other medications, particularly other anti-epileptic drugs, were ineffective.

Video review is summarized in Table 2. Onset of the attacks (available in 10/14 videos) was characterized by abrupt modification of facial appearance and behavioral arrest. Modification of facial appearance was identifiable in all of the 11 videos with facial recording, occurring from onset of the episode in nine and in the course of the attacks in two; that consisted in starring (from onset in three videos), mouth opening, jaw or tongue movements, drooling, loss or freezing of facial expression. Behavioral arrest associated with loss of postural reflexes was noticed in all of the episodes. Falling was also observed in all recordings, occurring less than 4 s after the onset for the attacks with available information. Stiffness of at least one body part was noticed at onset in two videos and occurred variably during the course of the episodes in three other patients (backwards truncal arching, dystonic hand or feet postures). Although the episodes started with cranial manifestations (face and neck), the progression of the loss of postural reflexes was not cranio-caudal, and often

affected only legs and trunk, sparing the neck. Recovery was rapid and the patients could resume their activity within a couple of seconds.

**TABLE 2** Phenomenological assessment of the videos

Patient number/ gender/reference in the original paper when provided	1/F/RJ7712	2/F/-	3/F/-	4/F/1	5/F/2	6/M/3	7/M/-
Publication	Tian et al 2018	Zhang et al 2020	De Gusmao et al 2022	Heim et al 2020	Heim et al 2020	Heim et al 2020	This report
Number of videos/ age at video	n = 2 (19 y)	n = 1 (25 y)	n = 4 (14, 19, 24 m)	n = 1 (4 y)	n = 2 (13 m, 6 y)	n = 2 (13 y)	n = 2 (5 y, 24 y)
Triggering factor	Kinesigenic	None	Temperature fluctuation; Emotion	NK	Emotion	NK	None
Onset of the attack	V1: NK V2: body stiffening beginning on the right	Staring, body stiffening, mouth opening	Staring, loss of facial expression (V1–V4)	Behavioral arrest, jaw movement	Staring, mouth opening, loss of facial expression (V1, V2)	NK	Loss of facial expression (V1, not available on V2)
Fall to the ground	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time to fall from the onset/duration of episode/recovery	2 s/9 s/rapid recovery	NK (recording started after onset and ends prematurely)	4 s/14 to 30 s/rapid recovery	2 s/45 s/rapid recovery	2–3 s/21–24 s/rapid recovery	ND/ND >8 s/rapid recovery (V2)	2 s/30s/ rapid recovery (V1) NK/>1 min/30/ NK
Behavior arrest	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neck/head drop	No	Yes	Yes	No	No	No	video 5 y: head falls back/video 24 y: no
Loss of postural reflexes*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stiffness including dystonia	Yes	Yes	Yes	No	Yes (V1, V2)	No	Yes
Facial expression	NK	Open mouth; tongue movement	Open mouth; loss of facial expression (V1, V2, V4; face not clearly recorded on V3)	Mouth movements	Open mouth; freezing facial expression (V1, V2)	Open mouth; freezing facial expression; drooling (V1, V2)	Open mouth (V1); frozen smile with opened mouth (V2)

(Continues)

**TABLE 2** Continued

Patient number/ gender/reference in the original paper when provided	1/F/RJ7712	2/F/-	3/F/-	4/F/1	5/F/2	6/M/3	7/M/-
Cranio caudal progression	No	Yes	No	No	No	No	No
Motor symptoms	Arching back	NK	NK	Arms backwards	NK	Abnormal posturing of two hands	Sometimes hands dystonia
Description in the paper	Involuntary dystonia affecting the right or both sides since the age of 15 incomplete remission at the age of 19, with occasional aura attacks.	Falling limp with associated tightened fists, stiffening of the upper extremities, and associated head turning; dystonic events	Spells of axial hypotonia, limb dystonia and preserved consciousness	Behavioral arrest, and a slow lean to the ground, with loss of axial tone and dystonic extremity posturing, lasting seconds to a few minutes, occurring multiple times daily. Eyes typically remain open with the ability to maintain eye contact, suggesting retained consciousness. Repetitive mouth gaping is a common feature. Patients recovered quickly			None
Video legend	Two episodes were recorded at the age of 15, which were induced by voluntary movements affecting symmetric limbs and trunk, lasting for 9– 10 s	Episode of neck facial and right upper extremity dystonia, which leads to abnormal posture of the head, facial grimacing, and posturing of the right upper extremity.	None	Typical attack during an office visit. Note gradual loss of tone, mouth movements, and curled fingers, followed by rapid return to baseline.	Drop attacks in the same patient at different ages. The first portion of the video was taken at age 13 months, the second portion at age 6 years, and represent the patient's typical, stereotyped drop attacks, followed by rapid return to baseline.	2 typical drop attacks. These videos were captured toward the end of the events. Note arm and neck dystonia, unresponsiveness, followed by rapid return to baseline.	See Video legend

Abbreviation: F, female; M, male; y, year; m, month; d, day; s, second; V, video; NK, not known.  
\*Loss of postural reflexes was defined as the inability to show adequate response to loss of balance.

**TABLE 3** Comparison of cataplexy and KCNMA1-related attacks

Symptom	Cataplexy	KCNMA1-episodes
Ptosis	+++	+
Facial hypomimia	+++	+
Lack of facial expression	+++	+++
Mouth opening (gape, yawn)	++	++
Neck Drop	+++	+
Neck extension	+	+++
Hypotonia of upper limbs	+++	++
Hypotonia of lower limbs	+++	+++
Severity of hypotonia	Eyes, face & neck >> trunk & limbs	Eyes, face & neck << trunk & limbs
Progression of hypotonia	Classically cranio-caudal	Trunk and limbs mainly affected, neck preserved

Summary of main features described in cataplexy<sup>19-22</sup> and observed in KCNMA1-non epileptic attacks. Features are rated + if uncommon, ++ if somewhat common, +++ if very common or even characteristic.

## Discussion

The phenomenology of KCNMA1-related non-epileptic paroxysmal motor events was typically consistent. The usual pattern of an episode was as follows: (i) facial changes that can include dyskinetic movements of the tongue and jaws (ii) behavioral arrest (iii) loss of postural reflexes that could be associated with focal body stiffness, eventually leading to fall (iv) rapid recovery without post-ictal drowsiness. The attacks have a short duration, lasting between 5 and 45 s, with an abrupt onset often characterized by modification of facial appearance (starring, mouth opening, jaw or tongue movements, drooling, loss or freezing of facial expression) and a fall occurring less than 10 s after the onset. Occasional triggering factors were reported (emotion, voluntary movement), but most often there was no obvious trigger. Attacks started in infancy in 6/7 patients, and all had a high daily frequency of episodes. The absence of significant interictal abnormalities and above all the high number of EEG-recorded episodes without any EEG correlates, highlight that episodes were not consistent with a diagnosis of epilepsy, as reported by the authors of the six previously published cases; attacks of case 7 also fitted within this category of non-epileptic events.

The distinctive hallmark of the paroxysmal episodes was the combination of behavioral arrest and loss of postural reflexes. Facial dyskinesia and focal body stiffness were frequent associated features but were usually mild and/or of short duration. In some patients, episodes could end with mouth opening or a yawn. The core features of paroxysmal dyskinesia (regardless of the cause) are involuntary hyperkinetic movements (dystonia, chorea, ballism, myoclonus, or a combination thereof) lasting from seconds to hours.<sup>13,16–18</sup> For this reason, we think that KCNMA1-related episodes are not consistent with this phenomenological diagnostic framework. Ataxia or even unsteadiness were not part of the clinical picture in

KCNMA1-related episodes, distinguishing them substantially from episodic ataxia attacks.<sup>16,18</sup> There is significant but incomplete overlap of these attacks with cataplexy. Cataplexy is characterized by sudden loss of skeletal muscle tone, typically triggered by strong positive emotions.<sup>12</sup> Pathognomonic for narcolepsy type 1 (NT1), in which excessive daytime sleepiness is another core symptom, cataplexy is linked to the lack of hypocretin, a hypothalamic neuro-peptide [cerebrospinal fluid hypocretin level was normal in the 2/2 patients tested (Table 2)]. In children with NT1, video-documented “cataplectic facies” are marked by hypotonia (ptosis, jaw tremor/ dropping, mouth opening and tongue protrusion). Hypotonia can be also perceived at postural level leading to head dropping to generalized atonia and fall. Yet, subtle differences between cataplexy in NT1 and KCNMA1-related episodes are highlighted in Table 3. In NT1, uncommon (<15% of children) and transient dyskinesic and/or dystonic movements and stereotyped motor behaviors were reported. Cataplexy in NT1 is triggered by emotional stimuli,<sup>19</sup> unlike KCNMA1-related episodes commonly without clearly trigger.

All patients treated with amphetamine-based stimulants showed dramatic improvement, with benefit after intake or relapse after skipping a dose within hours.<sup>14, 23</sup> Stimulants drugs are standard treatment for narcolepsy, but rarely used to treat paroxysmal movement disorders. However, consistent benefit of caffeine treatment has been reported in paroxysmal dyskinesia related to ADCY5 pathogenic variants.<sup>24</sup> The anecdotal reports of efficacy and safety profile of stimulant use, the short delay of efficacy, and the absence of an effective alternative to treat KCNMA1-related paroxysmal episodes should prompt physicians to consider this option in patients with a genetically-proven diagnosis. Alternatively, in limited resource settings in which genetic testing is delayed or not available, a careful trial of stimulant, or alternatively caffeine, is not entirely unjustifiable.

It is noteworthy that 6/7 patients harbored variants with known gain-of-function effects, while the functional consequence in the remaining patient is unknown. Among them, 5/7 patients harbored the p.N995S pathogenic variant in KCNMA1. These findings provide further evidence for an association between some gain-of-function variants in KCNMA1 and the occurrence of these particular paroxysmal attacks.<sup>3,4</sup> The KCNMA1 gene is highly expressed in the brain, modulates neurotransmitter release and undergoes extensive alternative splicing.<sup>3,4,15</sup> The underlying molecular mechanism has been studied in epilepsy, especially the effect of increased BK channel activity due to GOF variants.<sup>15,25</sup> The pathogenesis of KCNMA1-related paroxysmal episodes is unknown

We advocate that the characteristics of KCNMA1-related attacks are distinguishable from those of paroxysmal dyskinesia, cataplexy or episodic ataxia. We suggest a unique phenomenological entity and we propose to call these attacks “KCNMA1-related behavioral arrest and loss of postural reflexes” reflecting the main and most characteristic manifestations

of the episodes. Recognition of this entity is relevant for clinical practice, abbreviating the diagnostic process and influencing therapeutic strategy.

### **Author Roles**

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Clinical Data: A. Data Collection, B. Data Analysis. (3) Manuscript: A. Writing of the First Draft, B. Review and Critique, C. Editing of Final Version of the Manuscript. E.R.: 1A, 1C, 2B, 3B, 3C L.S-M.: 1C, 2B, 3B, 3C S.L-S: 2B, 3B, 3C N.V.: 2A, 3B B.L.: 1B, 1C, 2B, 3B M-C.F-H.: 3C P.M.: 3C C.M.dG.: 1C, 2B, 3B, 3C A.R.: 1A, 1B, 1B, 2A, 2B, 3A, 3C

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### **Disclosures**

#### **Ethical Compliance Statement:**

Patient 7 gave written informed consent according to the Declaration of Helsinki for review and publication of his clinical, genetic and video recording results. The authors confirm that the approval of an institutional review board was not required for this work. 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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### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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