Movement Disorders
CLINICAL PRACTICE
LETTERS: NEW OBSERVATIONS

Kinesigenic Triggers in Episodic Ataxia Type 1

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Episodic ataxia type 1 (EA1) (MIM 160120) is an autosomal dominant disorder associated with *KCNA1* mutations, encoding for the alpha subunit of the delayed rectifier potassium ion channel Kv1.1.[1] It usually presents in childhood with intermittent attacks of short-lasting imbalance, dizziness, and sometimes interictal painful cramping and muscle contractions, variably reported as neuromyotonia, myokymia, or dystonia.[2,3] Premonitory sensory symptoms may occur, and attacks may be triggered by startle, vigorous activity, changes in posture, emotion, hunger, alcohol, or intercurrent illness.[4,5] EA1 was described by Van Dyke in 1975 and associated with *KCNA1* mutations in 2004.[6,7] Pre-genetic era reports mentioned kinesigenic triggers and sometimes the co-existence of paroxysmal kinesigenic dyskinesia (PKD).[5,8]

PKD (MIM 128200) is a clinical syndrome characterized by short bouts of dyskinesia triggered by sudden initiation of movement, such as rising from a chair or running after standing for some time.[9] PKD is associated with mutations in the *PRRT2* gene in 27–65% of patients, with other genes involved including *KCNA1*.[10,11] This apparent allelic heterogeneity had been implicated in earlier reports but has not been revisited. We sought to explore the presence of kinesigenic triggers in patients with a clinical and molecular diagnosis of EA1.

Using a database of all EA1 published cases, we retrieved 86 EA1 subjects with confirmed pathogenic *KCNA1* mutations from 20 articles published between 1994 and 2017 (Supporting Information). Demographic and clinical data from this cohort are seen in Table 1. Data analysis was performed with IBM SPSS software; analysis of statistical significance was done using the Chi-square test when comparing categorical variables. Trigger data was available in 87.2% of cases (75/86), with kinesigenic triggers reported in 68% (51/75). These were often described as sudden movements (of a limb or head) or changes in posture, such as standing up from a seated position. Presence of kinesigenic triggers was associated with interictal myokymia (77.3% vs. 38.1%, χ^2 $P = 0.002$), higher attack frequency (daily in 46.8% vs. 18.8%, χ^2 $P = 0.048$), and acetazolamide responsiveness (complete/partial remission 63.2% vs. 12.5%, χ^2 $P = 0.016$).

Generalizability of our findings is limited as data were collected indirectly through a literature review, comprised mostly of retrospective observational studies that are prone to recall and selection bias and may overestimate the presence of kinesigenic triggers in EA1. A smaller prospective study reported sudden movement as a trigger in 9/33 cases (27.3%).[3] Other papers reported "postural changes" as a trigger, but it is unclear from clinical descriptions whether this represented purely a kinesigenic trigger or some other mechanism. Finally, the association with interictal and clinical features is exploratory, and direct causal relationship cannot be inferred.

The limited understanding of pathophysiology of EA1 renders the relationship between phenotype and triggers mysterious. The Kv1.1 channel is expressed in the juxtaparanodal region of peripheral nerves and cerebellar basket cells. *KCNA1* pathogenic mutations exert a dominant-negative effect with channel dysfunction leading to neuronal hyperexcitability, potentially explaining neuromyotonia/myokymia in the peripheral nervous system.[4] Centrally, *KCNA1* mutations in mice lead to increased GABAergic output from basket cells to the Purkinje cell axon hillock, causing deep cerebellar nuclei disinhibition.[12,13] Cerebellar involvement has also been demonstrated in *PRRT2* mutations, causing altered synaptic input from granular cells to Purkinje cells.[14] These findings suggest a shared role of kinesigenic triggers, network excitability and cerebellar dysfunction in *KCNA1* and *PRRT2*.[15,16]

Notwithstanding limitations in our study, our results are informative. The prevalence of kinesigenic triggers in *KCNA1*-EA1 is clinically relevant, particularly in limited resource settings where

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TABLE 1 ***Clinical and demographic characteristics of KCNA1 cases****

Features	
Demographics	
Female sex (%)	52/86 (60.5)
Age at onset (mean ± SD)	8.18 ± 5.48
Information on triggers (% yes)	75/86 (87.2)
Clinical	
Presence of kinesigenic trigger (% yes)	51/75 (68)
Presence of startle trigger (% yes)	38/75 (50.7)
Attack frequency (%)	Daily 25/64 (39.1) Weekly 25/64 (39.1) Monthly 6/64 (9.4) Rare/sporadic 8/64 (12.5)
Interictal myokymia (% yes)	45/72 (62.5)
Acetazolamide responsiveness (% yes)	14/29 (48.3)

*Numbers in denominators change to reflect described data (missing data excluded).

genetic testing is unavailable. Future studies may attempt to describe attack features and triggers in more detail, ascertaining sensitivity and specificity of kinesigenic triggers to differentiate forms of episodic ataxia.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

C.M.G.: 1A, 1B, 1C, 2A
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Supporting Information

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

Supplementary Material 1 - Search methodology
Supplementary Material 2 - Episodic Ataxia type 1 papers
Supplementary Material 3 - Database