Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Fever-Induced and Early Morning Paroxysmal Dyskinesia in a Man With *GNB1* Encephalopathy

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The *GNB1* gene encodes the guanine nucleotide-binding protein subunit beta-1 (Gß1), a component of the heterotrimeric G-protein complex that is ubiquitously expressed in the central nervous system and highly enriched in medium spiny neurons (MSNs).

The Gß1 subunit is part of the Gβγ dimer, which primarily interacts with the Gαo subunit. The Gαo subunit is the small G-protein encoded by the best known *GNAO1* gene, which is associated with a complex developmental encephalopathy with severe hyperkinetic movement disorder, with or without epilepsy.

The Gβγ/Gαo complex is part of a still poorly understood network of signal transducing proteins involved in neurotransmitter release and intracellular cAMP homeostasis. A number of recently described genes associated with hyperkinetic and paroxysmal movement disorders (PMDs) belongs to this pathway [e.g., *GNAO1*, *ADCY5*, *GNAL*, *GPR88*, *PDE10A*, and *PDE2A*].

The discovery of *GNAO1* and *ADCY5* pathogenic variants has helped identify the role of this pathway in PMDs. Dyskinetic storms and minor paroxysmal choreic and/or dystonic spells, a baseline hyperkinetic movement disorder characterized by a variable association of dystonia, myoclonus, chorea, prominent orofacial involvement, axial hypotonia, susceptibility to a wide range of triggers, and resistance to standard pharmacological treatments, are shared features of both conditions. Paroxysmal nocturnal dyskinesia, with ballistic bouts in the transition from sleep to awakening, is considered a diagnostic clue to *ADCY5*.[1] Paroxysmal dyskinesia occurring upon morning awakening, although not clearly documented in literature, also occurs in patients with *GNAO1* pathogenic variants [personal observation].

GNB1 pathogenic variants have been described in children with an autosomal dominant condition with variable association of developmental encephalopathy, macrocephaly, craniofacial abnormalities, epilepsy, and hyperkinetic movement disorders including dystonia, ataxia, chorea, stereotypies, and tics.[2] The natural history of the disease and the clinical outcome in adulthood are not well known.

Here we report the prolonged clinical follow up of a man with GNB1 encephalopathy who experienced fever- and awakening-induced paroxysmal dyskinesia in adulthood. This clinical observation further highlights the role of G-protein coupled receptor signaling pathway in diurnal and nocturnal PMDs.[1]

Case Report

This 34-year-old man was born from non-consanguineous healthy parents. Pregnancy and delivery were uneventful, but failure to thrive, hypotonia, and global developmental delay were noticed from the first months. He could sit at 12 months and walk at 5 years, though he never developed verbal language. Absence and atonic seizures appeared with fever at the age of 12 months and subsequently evolved into drug resistant epilepsy with multiple seizure types, including focal, myoclonic, myoclonic-atonic, and tonic–clonic seizures with febrile exacerbation and recurrent episodes of convulsive and non-convulsive status epilepticus. EEG recordings showed multifocal epileptiform discharges with bilateral temporo-occipital and frontocentral predominance. Nonprogressive macrocephaly (OFC >2 SD) was observed from infancy and repeated brain MRI showed non-progressive enlargement of the frontal subarachnoid space and ventriculomegaly. Epilepsy gradually improved and resolved from late adolescence. Generalized dystonia with prominent cranial involvement progressed since early childhood (Video 1) leading to loss of independent walking at the age of 9 years. The patient remained stable up to the age of 20 years when two severe paroxysmal dyskinetic episodes during pneumonia required intensive care admission. After these episodes paroxysmal dyskinetic episodes appeared, typically occurring after awakening in the early morning and lasting 2–4 hours, with a frequency of 2–3 per month (Video 3).

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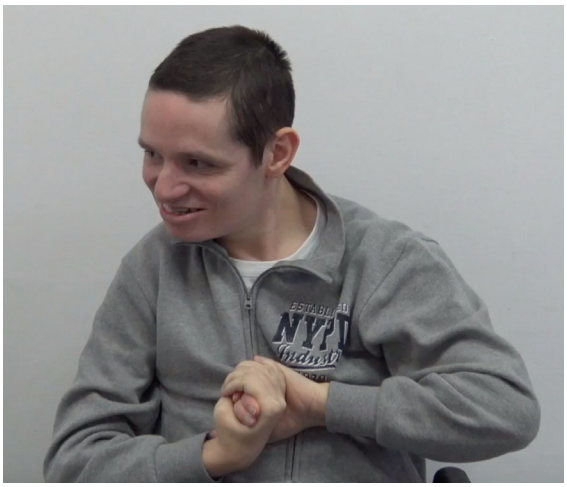
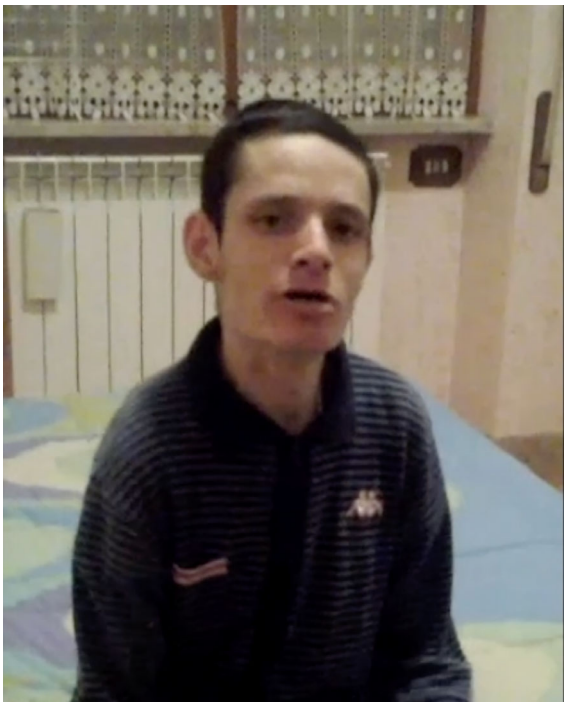


Video 1. Neurological examination at the age of 34. The patient is wheelchair-bound due to progressive generalized dystonia. A dystonic neck lateral shift due to a combination of right laterocollis and laterocaput to the contralateral side is associated with oromandibular dystonia. The tone of the four limbs is significantly increased for the coexistence of dystonia and pyramidal signs, especially in the lower limbs with increased reflexes. Dystonic hands and fingers postures and movements associated with hand wringing stereotypies are observed over the entire examination.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13525



Video 2. An episode of paroxysmal dyskinesia at the age of 32 years characterized by subcontinuous dystonic movements and jerks of upper limbs, hands, and face. Axial jerks are superimposed on dystonic movements.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13525

A combination of Lorazepam (3 mg/day) and tetrabenazine (25 mg/day) dramatically reduced the frequency and severity of these episodes. Trihexyphenidyl (6 mg/day) was helpful in the management of the baseline dystonia. Buccal midazolam (10 mg) was successfully used to treat paroxysmal motor episodes.

A targeted panel for genetic epilepsies disclosed a novel heterozygous variant in the *GNB1* gene (NM_002074.5: c.357C>G, p.Asn119Lys) that occurred de novo (both maternity and paternity confirmed) and was classified as pathogenic according to American College of Medical Genetics and Genomics criteria. The variant was not present in the gnomAD population data set (gnomad.broad institute.org), not reported in the HGMD mutation database (https://portal.biobase-international.com/), and predicted to be damaging by multiple computational tools, with a CADD score of 25.2.

Discussion

Here we describe the case of a young man with *GNB1* encephalopathy and adult-onset episodes of fever- and awakening- triggered PMD, superimposed on generalized dystonia with prominent cranial involvement.

More than one-third of patients with GNB1 encephalopathy have a movement disorder, usually dystonia. Myoclonus-dystonia with prominent facial, axial, and upper limb involvement and exacerbation with activity, fatigue, and illnesses has been reported in patients harboring substitutions at the Asp118 position,[3,4] which is adjacent to the aminoacidic change identified in our patient. These variants cluster in the binding surface involved in Gα interactions, resulting in altered Gβ interactions with its effectors.

The emergence of fever-induced paroxysmal dyskinesias during adulthood and subsequent persistence of paroxysmal episodes upon awakening have not been previously reported in this condition.

This unusual combination of paroxysmal motor events and the phenomenology of the interictal movement disorder observed in this patient, evoke the best characterized *ADCY5* and *GNAO1* phenotypes, and further defines the role of G-protein coupled receptors signaling in the pathophysiology of PMDs.[1,5,7]

More recently, childhood-onset paroxysmal dyskinesia and interictal choreodystonia, with episodes respectively during sleep or upon awakening, have been associated with biallelic *PDE2A*[8] and *PDE10A* pathogenic variants.[9]

Paroxysmal dyskinesia upon morning awakening has been hypothesized to be related to imbalanced dopamine and adenosine interplay, which is modulated by Gα and Gβγ interactions, and to altered adenylyl cyclase 5 activity in MSNs.[6,7] Preclinical models are needed to further explore the role of this network and of cAMP homeostasis in sleep regulation and motor control.

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Author Roles

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

GS: 1A, 1B, 1C, 3A, 3B.
PL: 1A, 1B, 1C, 3A.
NF: 1B, 1C, 3A.
CE: 1B, 1C, 3A.
GR: 3A, 3B.
LV: 3A, 3B.

Disclosures

Ethical Compliance Statement: Written informed consent for offline and online video distribution of the video material was obtained from parents and is available upon request. 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. The authors confirm that the approval of an institutional review board was not required for this work.

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Video 3. Full video from the 2021 Video Challenge discussion of this case.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13525