On Spinocerebellar Ataxia 21 as a Mimicker of Cerebral Palsy

Johanna van der Put,* Dalia Daugeliene, MD,* Åsa Bergendal, PhD, Malin Kvarnung, MD, PhD, Per Svenningsson, MD, PhD, and Martin Paucar, MD, PhD

Neurol Genet 2022;8:e668. doi:10.1212/NXG.0000000000000668

Abstract

Objectives
Sporadic variants in ataxia genes may mimic cerebral palsy (CP). Spinocerebellar ataxia 21 (SCA21), a very rare autosomal dominant disease, was discovered to be associated with variants in the transmembrane protein 240 (TMEM240) gene in 2014. In this report, we present 2 patients with sporadic SCA21, one of them diagnosed with ataxic CP.

Methods
Patients provided oral and written consent. Comprehensive clinical evaluation, neuroimaging studies, review of previous psychometric evaluations, and whole-genome sequencing were applied in both cases.

Results
Both patients presented with early-onset ataxia and exhibited mild parkinsonian features. Patient 1 experienced motor and speech delay, autism, and dyslexia, whereas patient 2 experienced dyslexia. Neuroimaging was normal in both cases. In patient 1, the previously reported pathogenic c.509C>T (Pro170Leu) variant in TMEM240 was detected, whereas patient 2 harbored the novel c.182_188delinsGGAT (Val61_Pro63delinsGlyMet) variant in the same gene. Both genetic variants were sporadic.

Discussion
Our findings support the notion that SCA21 is a neurodevelopmental syndrome and a mimicker of ataxic CP. Both lack of a family history of ataxia and congenital presentation were reasonable arguments to consider ataxic CP. However, lack of convincing perinatal incidents, progressive symptoms, and the common presence of cerebellar atrophy should alert neurologists about SCA21.

*These authors contributed equally to this work.

From the Department of Clinical Neuroscience (J.v.d.P., Á.B., M.P.), Karolinska Institutet; Department of Pediatric Neurology (D.D.), Sachska Child Hospital; Department of Clinical Genetics (M.K.), and Department of Neurology (P.S., M.P.), Karolinska University Hospital, Stockholm, Sweden.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Massively parallel sequencing has facilitated the diagnostics of neurogenetic syndromes and contributed to reveal mimickers of cerebral palsy (CP). Normal neuroimaging studies in patients with putative ataxic CP may prevent the pursuit of extended workup. Spinocerebellar ataxia 21 (SCA21) is a rare autosomal dominant disease associated with pathogenic variants in the transmembrane protein 240 (TMEM240) gene. In this report, we present 2 patients with sporadic SCA21, one of them diagnosed with ataxic CP.

**Methods**

Patients provided both oral and written consent for this study approved by the Ethical Committee in Stockholm. None of the patients had a family history of neurologic disease. Clinical findings are summarized in Table 1, see also eTable 1 (links.lww.com/NXG/A526).

Patient 1 is a 36-year-old man initially diagnosed with motor and speech developmental delay. He learned to walk at the age of 2 years and started to talk at age 4 years. The patient was able to use sign language before he developed a slurred speech. He was born at term and contracted conjunctival chlamydia infection at birth, but no other perinatal incidents occurred. Coarse postural and action tremor was noticed when the patient was at age 2 years. Subsequently, head titubation, dysphonia, and dysmetria were found; a brain CT scan was normal. During childhood, parents and teachers noticed an impaired ability to communicate and interact socially. At age 6 and 13 years, he went through psychometric evaluation and was diagnosed with atypical autism and dyslexia (eTable 1, links.lww.com/NXG/A526). The patient was diagnosed with ataxic CP, attended a special school, and has been working in a grocery store for a long time. Relatives have perceived a slow motor progression, but because motor scales were not used during childhood, it was difficult to ascertain it. The patient was reevaluated at age 35 years and received a Scale for the Assessment and Rating of Ataxia (SARA) score of 6, which remained unchanged 1.5 years later. Other findings upon an examination include rigidity, hypermetric saccades, left

| Table 1 Main Features in 2 Swedish Men Affected With Sporadic SCA21 and Normal Neuroimaging |
|-----------------------------------------------|-----------------|-----------------|
| **Phenotype features**                        | **Patient 1**   | **Patient 2**   |
| Current age/age at the last examination, y    | 36/36           | 19/18           |
| Axial ataxia                                  | Yes             | Yes             |
| Dysarthria                                    | Yes             | Yes             |
| Age of motor onset, y                         | 2               | 3               |
| First symptom at onset                        | Action and intention tremor | Action and intention tremor |
| Motor and language development                | Motor and speech delay | Normal |
| Attended a special school                      | Attends a regular school |
| Neuropsychiatric features/other psychiatric findings | Autism | Dyslexia |
| MoCA                                          | NA              | 29              |
| Impaired smooth pursuit/nystagmus             | Yes/yes         | Yes/no          |
| Other eye movement abnormalities              | Hypermetric saccades | Hypermetric saccades |
| Strabismus in the left eye                    | SWJ             | SWJ             |
| Other motor features                          | Prominent tremor | Prominent tremor |
| Mild rigidity in the arms*                    | Mirror movements | Reduced arm swing and mild rigidity in the arms* |
| SARA score at the last examination            | 6               | 6               |
| Progressive ataxia                            | Lack of progression in 1.5 y | Over time increased tremor |
| ENeG                                          | Normal          | Normal          |
| MRI of the brain (age when performed)         | Normal (35 y)   | Normal (9 y)    |
| Underlying variant in TMEM240                 | c.509C>T (P170L) | c.182_188delinsGGAT (Val61_Pro63delinsGlyMet) |

Abbreviations: ENeG = electroneurography; MoCA = Montreal Cognitive Assessment; NA = not assessed; SARA = Scale for the Assessment and Rating of Ataxia; SWJ = square wave jerks.

The variant c.182_188delinsGGAT in TMEM240 is novel, whereas c.509C>T is recurrent in patients with different ethnic backgrounds.

*Bradykinesia was absent in both patients.
eye strabismus, foot pronation, and valgus deformity. EEG and electroneurography findings were normal. Brain MRI performed at ages 2, 17, and 35 years were normal. He is currently treated with gabapentin with modest benefit for his tremor.

Patient 2 is a 19-year-old man referred for increasing intention and action tremor, which onset at age 3 years. Impaired dexterity during school made it difficult to write and handle utensils. Brain MRI at age 9 years was normal. At age 10 years, he was diagnosed with dyslexia, and attention-deficit/hyperactivity disorder was suspected but ruled out during the workup. His intellectual ability was evaluated at age 11 years using the Wechsler Intelligence Scale for Children-IV and found to be normal, and screening with Montreal Cognitive Assessment at age 18 years yielded 29 points. On an examination at age 18 years, the patient displayed axial ataxia, coarse postural and action tremor, titubation, reduced arm swing, and rigidity but no bradykinesia. His SARA score was 6 points; other findings included mild posturing, mirror movements, nystagmus, slow, hypermetric saccades, and flat affect. A new brain MRI was proposed, but the patient declined it.

Genetics
Screening for neurometabolic disorders and array comparative genomic hybridization yielded normal findings in both cases. Data from whole-genome sequencing were analyzed with an in silico gene panel for ataxia and related disorders (560 genes) by filtering for rare, potentially pathogenic variants. In patient 1, the previously reported pathogenic c.509C>T (Pro170Leu) variant in TMEM240 was detected, whereas patient 2 harbored the novel c.182_188delinsGGAT (Val61Pro63delinsGlyMet) variant in the same gene. Both variants were verified by Sanger sequencing. None of the variants were present in blood samples from the parents and were thus regarded as de novo.

Discussion
Pro170Leu (P170L) in TMEM240, identified in patient 1, is the most common pathogenic variant found in SCA21 patients with various ethnic backgrounds; the phenotype in patient 1 is in keeping with previous descriptions.3-6,e1,e2 Strabismus, as seen in patient 1, has been reported associated with P170L.41 None of our patients experienced dystonia, chorea, myoclonus, or behavioral abnormalities, as previously reported (eTable 1, links.lww.com/NXG/A526).2-4,6,7,e1,e2 Both our patients exhibited mild parkinsonian features, which is in line with previous reports of parkinsonism in patients with SCA21.2,3 Our findings add support to the notion that SCA21 is a neurodevelopmental syndrome and a mimicker of ataxic CP. Congenital presentation in some cases7,e1 and absence of a family history of ataxia were reasonable arguments to consider ataxic CP. Furthermore, transient improvement in a previous reported case makes an evaluation challenging.6 However, slow progression and lack of convincing perinatal incidents should alert neurologists about SCA21 even when neuro-imaging is normal, as reported in this work and previously.7 In most SCA21 cases, cerebellar atrophy has been described.3-6 Finally, other mimickers of ataxic CP have been reported with de novo variants in SPTBN2, associated with spinocerebellar ataxia 5 and with variants in KCNC3 and ITPRI.e4

Acknowledgment
The authors are truly grateful to the patients and parents for consenting to this publication.

Study Funding
No targeted funding reported.

Disclosure
The authors report no disclosures. Go to Neurology.org/NG for full disclosures.

Publication History
Received by Neurology: Genetics November 17, 2021. Accepted in final form January 28, 2022. Submitted and externally peer reviewed. The handling editor was Stefan M. Pulst, MD, Dr med, FAAN.
References

1. Vuillaume I, Devos D, Schraen-Maschke S, et al. A new locus for spinocerebellar ataxia (SCA21) maps to chromosome 7p21.3-p15.1. Ann Neurol. 2002;52(5):666-670.
2. Delplanque J, Devos D, Vuillaume I, et al. Slowly progressive spinocerebellar ataxia with extrapyramidal signs and mild cognitive impairment (SCA21). Cerebellum. 2008;7(2):179-183.
3. Delplanque J, Devos D, Hain V, et al. TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment. Brain. 2014;137(pt 10):2657-2663.
4. Zeng S, Zeng J, He M, et al. Spinocerebellar ataxia type 21 exists in the Chinese Han population. Sci Rep. 2016;6:19897.
5. Yahikozawa H, Miyatake S, Sakai T, et al. A Japanese family of spinocerebellar ataxia type 21: clinical and neuropathological studies. Cerebellum. 2018;17(5):525-530.
6. Traschütz A, van Gaalen J, Oosterloo M, et al. The movement disorder spectrum of SCA21 (ATX-TMEM240): 3 novel families and systematic review of the literature. Parkinsonism Relat Disord. 2019;62:215-220.
7. Burdekin ED, Fogel BL, Jeste SS, et al. The neurodevelopmental and motor phenotype of SCA21 (ATX-TMEM240). J Child Neurol. 2020;35(14):953-962.

eReferences e1-e5 are available at: http://links.lww.com/NXG/A532.