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On Spinocerebellar Ataxia 21 as a Mimicker of Cerebral Palsy

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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.

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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 pursue of extended workup. Spinocerebellar ataxia 21 (SCA21) is a rare autosomal dominant disease associated with pathogenic variants in the transmembrane protein 240 (*TMEM240*) gene.[1-7,e1,e2] 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 Attended a special school	Normal Attends a regular school
Neuropsychiatric features/other psychiatric findings	Autism Dyslexia	Dyslexia Flattened affect
MoCA	NA	29
Impaired smooth pursuit/nystagmus	Yes/yes	Yes/no
Other eye movement abnormalities	Hypermetric saccades Strabismus in the left eye	Hypermetric saccades SWJ
Other motor features	Prominent tremor Mild rigidity in the arms[a]	Prominent tremor Mirror movements Mild posturing Reduced arm swing and mild rigidity in the arms[a]
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.
[a] 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 (Val61_Pro63delinsGlyMet) 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.[e1] 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 cases[7,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 neuroimaging 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[e3] and with variants in *KCNC3* and *ITPR1*.[e4]

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Name	Location	Contribution
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Dalia Daugeliene, MD	Department of Pediatric Neurology, Sachska Child Hospital, Stockholm, Sweden	Major role in the acquisition of data; analysis or interpretation of data
Åsa Bergendal, PhD	Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
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Martin Paucar, MD, PhD	Department of Clinical Neuroscience, Karolinska Institutet; Department of Neurology, Karolinska University Hospital, Stockholm, Sweden	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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

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