Movement Disorders
CLINICAL PRACTICE
CLINICAL VIGNETTES

A Case of Chorea with Slow Saccades Caused by *NKX2-1* Mutation

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Co-occurrence of chorea and slow saccades is highly suggestive of Huntington's disease and has only very rarely been reported in patients with other conditions, such as spinocerebellar ataxia type 2 (SCA2)[1] and neuroacanthocytosis.[2] Heterozygous loss-of-function mutations in *NKX2-1* (formerly called *TITF-1*), a gene encoding a homeodomain-containing transcription factor that plays a critical role during embryogenesis of brain, thyroid, and lungs, cause childhood-onset, non-progressive or slightly progressive chorea in isolation or in variable association with other neurological problems such as dystonia, myoclonus, tremor, ataxia, hypotonia, and motor developmental delay.[3] In addition, patients with *NKX2-1* mutations can have hypothyroidism and pulmonary disorders, such as neonatal respiratory distress, asthma, and interstitial lung disease. Involvement of all three systems ("brain-lung-thyroid syndrome") has been reported in 30% to 50% of *NKX2-1* mutation carriers. Recent literature has not described slow saccades as a typical feature of the neurological phenotype of *NKX2-1*-related disorder. Here, we describe a case of *NKX2-1*-related disorder showing a combination of chorea and slow saccades.

Our patient, a 24-year-old female, had bothersome involuntary movements for as long as she could remember. Her early motor and speech milestones had been slightly delayed. In the past, her thyroid stimulating hormone level had been mildly elevated with subsequent spontaneous normalization. She had mild asthma for which she used a formoterol/budesonide inhaler. Pulmonary function testing at the age of 24 years showed a pattern of obstructive airway disease, consistent with asthma. She also took trazodone 50 mg at night for insomnia. Family history was negative for neurological, thyroid, or pulmonary disorders. Clinical exam showed generalized chorea and occasional myoclonic jerks (Videos 1 and 2). There was mild slowing of horizontal saccades (Video 3). Vertical saccades seemed slightly slow (Video 3). Initiation and accuracy of horizontal and vertical saccades looked normal. Horizontal pursuit was normal (Video 3) and vertical pursuit was slightly impaired (Video 3). There was no gaze restriction. There was no nystagmus during sustained eccentric gaze (Video 3). There were no square wave jerks during fixation. The visually enhanced vestibulo-ocular reflex was normal. Tandem gait was mildly impaired, but there were no other neurological abnormalities. Brain magnetic resonance imaging was unremarkable. Analysis of the *HTT* gene showed no repeat expansions. Sanger sequencing of the coding and flanking intronic regions of *NKX2-1* revealed a heterozygous mutation (GRCh38:chr14-36517850-G-A; NM_001079668.2: c.634C>T) leading to a truncation inside the homeodomain (p.Gln212*). The same mutation has previously been reported in a patient with chorea.[4] Multiplex ligation-dependent probe amplification showed no deletions or duplications in *NKX2-1*. Segregation analysis in the parents of our patient indicated that the mutation was de novo. The patient's chorea responded poorly to treatment with tetrabenazine, tiapride, levodopa, and methylphenidate.

We used a video-oculography (VOG) system with a sampling rate of 200 Hz (Metrovision, Perenchies, France) to determine mean peak velocity, latency (time interval between target displacement and saccade initiation) and gain (saccade amplitude divided by target displacement amplitude) of the patient's visually guided reflexive horizontal and vertical saccades. We performed the same VOG measurements in 10 healthy young controls (mean age ± standard deviation, 27 ± 1.6 years; range, 25–30 years; 5 females) to establish normal limits. This confirmed that the patient's horizontal saccades were abnormally slow (Table 1). The mean peak velocities of vertical saccades, despite our clinical impression of slight slowing, were still within normal limits (Table 1). Latency of the patient's horizontal (197.8 ± 12.4 ms; normal

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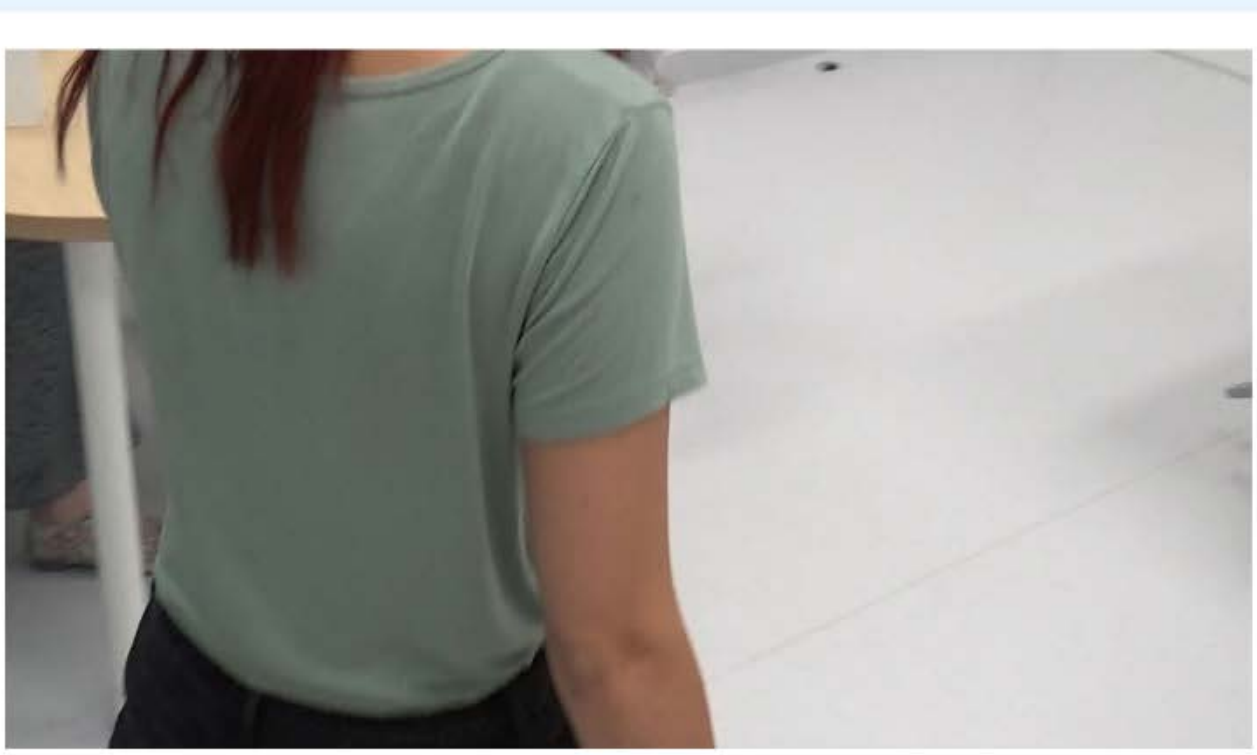
Video 1. The patient has generalized chorea and occasional myoclonic jerks.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14013



Video 2. Gait is choreatic, but otherwise normal.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14013

range, 187.6–293.6 ms) and vertical (253.3 ± 55.3 ms; normal range, 179.6–279.2 ms) saccades and gain of horizontal (0.89 ± 0.17; normal range, 0.74–1.1) and vertical (0.88 ± 0.32; normal range, 0.75–1.27) saccades were normal.

The true prevalence of slow saccades in *NKX2-1*-related disorder is currently unclear. Intriguingly, slow saccades were reported in no less than 20 of 36 neurologically affected members of one of the four families (family "US1") in which *NKX2-1* mutations were first identified in 2002.[3,5] By contrast, in the more than 100 subsequent neurological case descriptions of *NKX2-1*-related disorder, only one patient, to our knowledge, was mentioned to have slow saccades,[6] suggesting that saccadic slowing may in fact be only an exceptional finding in patients with *NKX2-1* mutations. Alternatively, slow saccades in this disorder might be under-recognized or under-reported in the recent literature. Our case report highlights that

Video 3. Eye movements. Segment 1: Horizontal saccades are slow. Segment 2: Vertical saccades seem slightly slow. Segment 3: Horizontal pursuit is normal. Segment 4: Vertical pursuit is slightly impaired. Segment 5: There is no nystagmus during sustained gaze to the right. Segment 6: There is no nystagmus during sustained gaze to the left.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14013

TABLE 1 *Video-oculographic measurement of mean peak velocities of horizontal and vertical saccades of the patient with* NKX2-1*-related disorder compared with healthy young controls*

Saccadic movement	Patient (°/s)	Normal limits (°/s)
Horizontal (10°), center to right	195.6 ± 39.7	235.9–358.7
Horizontal (10°), right to center	199.7 ± 46.8	237.2–346.8
Horizontal (10°), center to left	213.0 ± 39.6	247.8–345.0
Horizontal (10°), left to center	201.2 ± 34.2	249.5–348.3
Vertical (10°), up from center	194.6 ± 32.4	151.8–269.4
Vertical (10°), up to center	185.6 ± 40.2	166.2–274.2
Vertical (10°), down from center	216.8 ± 32.4	174.5–296.9
Vertical (10°), down to center	230.8 ± 34.8	166.2–274.2

Note: Saccades were elicited by 10° displacement of the fixation target from center to periphery, and back from periphery to center. Patient values denote mean peak velocity ± standard deviation (SD). Patient age at the time of video-oculography (VOG) was 25 years. Normal limits were defined as mean ± 2 SD of the values obtained in 10 healthy young controls.

NKX2-1-related disorder should be included in the limited list of conditions that can cause a combination of chorea and slow saccades.

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.

J.V.: 1C, 3A
J.T.: 1C, 2A, 2B, 2C, 3B
S.V.D.: 1C, 3B
S. V.: 1C, 3B
W.V.: 1A, 1B, 1C, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the institutional ethics committee (Ethische Commissie Onderzoek UZ/KU Leuven). The authors obtained written informed consent from the patient. 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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