Benign hereditary chorea (BHC) was originally described in 1967, but it was not until 2002 that linkage analysis and positional cloning identified the causative gene, NKX2-1 (also known as TTF-1). The range of manifestations spans from isolated chorea, pulmonary disease, or thyroid dysfunction, with one-third of patients having the full brain-lung-thyroid syndrome. Recent reports have expanded the NKX2-1 phenotype, as patients may present with additional movement disorders such as dystonia and myoclonus. We present a case with early-onset chorea, ataxia, and dystonia.

Case report. A 2.75-year-old girl with a predicted pathogenic variant of NKX2-1 was evaluated. She was born after an uneventful pregnancy, complicated only by well-compensated maternal hypothyroidism and transient hyperbilirubinemia. She was found to have congenital hypothyroidism on newborn screening and began early hormone replacement therapy.

Her parents noted hypotonia and delayed motor development. She sat unsupported at 12 months and walked at 24 months, both complicated by irregular trunk and limb movements later recognized as chorea. Language and social development were normal. Basic metabolic profile and venous pH were normal. Whole-exome sequencing was performed using the Nextera Exome Capture kit (Illumina, San Diego, CA) in a HiSeq2500 platform (Illumina) at Mendelics Genomic Analysis (Sao Paulo, Brazil). Alignment and variant call was conducted using bioinformatics protocols, using human reference genome version GRCh37. Overall, 98.3% of the target bases were covered by >10 reads; on average, each base was read 139 times. A nonsense heterozygous variant (c.524C>A, p.Ser175*) was identified in NKX2-1, which if translated would lead to a truncated protein, lacking the latter two-thirds of the DNA-binding domain and C-terminal transactivation domain. This variant is predicted to be pathogenic; it was previously reported in a family with hypothyroidism and benign familial chorea. No other reportable variant associated with the patient’s phenotype was detected. Sanger sequencing confirmed this variant but did not detect it in the parents. Treatment with tetrabenazine for 3 months (maximum 1.5 mg/kg/day) was ineffective, with no improvement and asthenia at higher dosages. Levodopa/carbidopa for 2 months (maximum 3 mg/kg/day) was ineffective.

Examination revealed a sociable, cognitively appropriate girl with axial and appendicular hypotonia. In repose she had frequent choreic intrusions of the trunk, limbs, and face. These worsened with movement and made fine motor tasks difficult. Her gait was wide-based with an irregular stride length and frequent falls, requiring parental support (video, segment 1 at Neurology.org/ng). Navigating stairs induced lower extremity dystonia, with plantar flexion and inversion of the feet and extension at the knee, not evident during the remainder of the examination (video, segment 2).

Discussion. This case illustrates the rich phenomenology of NKX2-1-related disorders. The core features of early hypothyroidism, female predominance, hypotonia, delayed motor milestones, and chorea were present. The patient’s early-onset chorea (median onset in NKX2-1-related disorders: 3 years) and the addition of dystonia and ataxia may reflect her relatively severe nonsense mutation. The case also illustrates movement abnormalities beyond the historical expectation in these patients (dystonia and ataxia, although previously described, are not common). Although chorea in NKX2-1-related disorders may improve or subside by the third to fourth decade, other movement abnormalities may persist. Our patient’s lack of improvement with tetrabenazine may reflect this greater persistence of dystonia relative to chorea. The absence of pulmonary involvement is not unexpected: brain-thyroid-lung involvement occurs in 36% of cases, brain-lung involvement occurs in 10% of cases; and isolated brain involvement occurs in 21% of cases. The maternal history of hypothyroidism with normal sequencing of NKX2-1 is intriguing. Epidemiologically, it is substantially more likely that this represents sporadic hypothyroidism than a partial phenotype attributed to maternal mosaicism for NKX2-1. However, mosaicism cannot be excluded. The complexity of mixed movement disorders described in this case may prompt clinicians to consider BHC in early-onset
dystonia and chorea, in addition to disorders such as myoclonus-dystonia and ADCY5-related dyskinesias. With ataxia, the differential diagnosis expands to ataxia telangiectasia and some spinocerebellar ataxias.⁷⁻⁹ New cases are likely to be diagnosed as awareness of the phenotypic expression of NKKX2-1 continues to evolve.

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