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Two cases with postural axial tremor: *Consider a genetic origin*R. Zutt^a, J.W. Elting^{b,c}, P. Santens^d, G.J.R. Luijckx^b, M.A.J. Tijssen^{b,c,*}^a Department of Neurology, Haga Teaching Hospital, the Hague, the Netherlands^b Univ Groningen, Univ Med Ctr Groningen, Dept Neurol, 9713, Groningen, NL, the Netherlands^c Expertise Center Movement Disorders Groningen, University Medical Center Groningen (UMCG), Groningen, the Netherlands^d Department of Neurology, Ghent University Hospital, Ghent, Belgium

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ABSTRACT

We present two cases with postural axial tremor predominantly involving the head, trunk, and shoulders. In the first patient, the postural tremor occurred in multiple attacks a day lasting approximately 10 min. The second patient developed a progressive tremor of his head and arms, worsened during sitting and standing. Electrophysiological supported the postural axial tremor in both patients with a varying 3–10 Hz tremor frequency between different muscles and within the same muscles at different times.

Postural axial tremor is a rare and complex movement disorder. The majority of cases are caused by acquired cerebellar pathology. However, isolated cases with underlying genetic disorders are described in literature.

Here, we illustrate how to differentiate paroxysmal axial tremor from other axial hyperkinetic movement disorders and extend the genetic heterogeneity of this intriguing movement disorder phenotype.

Postural axial tremor is characterized by predominant tremor of the head, trunk and shoulders, sometimes expanding to the upper and lower limbs. Tremor is usually more pronounced during sitting, standing, and decreases in a supine position. Clinical phenotyping of postural axial tremor and distinction from other axial hyperkinetic movement disorders can be challenging, but important as underlying pathology and treatment options differ.

In these cases, electrophysiological testing might be a helpful diagnostic tool showing a 3–10 Hz tremor frequency. In addition, a characterizing feature of postural axial tremor is that the tremor-frequency can vary between different muscles and within the same muscles at different times. The vast majority of postural axial tremor is caused by acquired cerebellar pathology. However, if acquired causes are excluded, one should consider a genetic cause.

The first patient, a 28-year-old male, presented with a four weeks history of paroxysmal trunk movements. Episodes occurred five to twenty times a day and lasted about 10 min. Movements were provoked by sitting, standing, and walking.

Medical history revealed hemiplegic migraine diagnosed at the age of nine. Treatment with Verapamil (80 mg daily) the attacks of migraine and hemiplegia disappeared. There was no family history of movement disorders or neurological diseases.

Clinical assessment showed episodes with irregular alternating movements of his trunk, head, shoulders, and proximal legs during

sitting and standing, disappearing when lying (Video 1). The clinical phenotype was classified as paroxysmal axial postural tremor. In addition, mild posturing of the head (lateroflexion to the left/rotation to the right) was diagnosed as cervical dystonia. Patient had no sensory trick. Eye movements were normal, there were no signs of parkinsonism. Tandem gait was impaired.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.parkreldis.2020.04.013>

The second 22-year-old patient developed a progressive tremor of his head and arms at the age of 19. The tremor worsened during sitting and standing. In addition, he experienced unsteady gait with widening of gait base. His family history was unremarkable. Neurological examination showed irregular postural tremor of the head and trunk, accompanied by a postural tremor of the arms and legs during standing. The eye movements were saccadic with a mild oculomotor apraxia. The patient had a distal sensorimotor polyneuropathy, absent tendon reflexes, and a widened base gait with irregular steps. Other neurological examination was unremarkable.

The major movement disorder in both patients is a postural axial tremor.

The differential diagnosis of axial hyperkinetic movement disorders includes (1) orthostatic tremor (OT), (2) cerebellar/midbrain tremor (C/MT), (3) propriospinal myoclonus (PSM), and a (4) functional movement disorder (FMD). Clinical signs can be used to differentiate

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between these movement disorders. OT is characterized by a postural tremor of the lower limbs during standing. In our patients, the absence of relief by walking and leaning, the clear visibility of the tremor and distribution including the head, trunk, and shoulders argue against OT. A proximal distribution and slow frequency tremor is seen in C/MTs, however, C/MT classically appear with a unilateral intention tremor with frequencies lower than 4 Hz. PSM is characterized by large amplitude and long lasting irregular jerks (> 300 ms) involving the trunk and proximal limbs often triggered by a supine position. FMD is diagnosed based on positive signs (e.g. inconsistency, entrainment), not observed in our patients.

Video-polymyography showed in **case 1** rhythmic alternating activity of agonist and antagonist trunk and proximal limb muscles with a frequency jumping from 6.2 to 7.5 Hz within the same muscles over time (Video 2). Electrophysiological testing in **case 2** showed tremor in the proximal muscles during sitting and standing, with a dominant frequency of 5.4 Hz. On outstretching a 5.9–6.1 Hz tremor occurred in the arm muscles. The combined effect resulted in jerky tremorous movements of the head, shoulders and arms (Video 3&4). A variable alternating and synchronous activation was measured in the rectus abdominis and lumbar paraspinal muscles at 6.2–7.5 Hz. There was no distractibility or entrainment. The varying tremor-frequency within and between muscles has only been described with postural axial tremor.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.parkreldis.2020.04.013>

Postural axial tremor is a rare movement disorder. In the literature a few cases with mainly cerebellar pathology have been described e.g. hemorrhage, infarction, neoplasm, late onset cerebellar degeneration, and paraneoplastic cerebellar syndrome [1–4]. Occasionally genetic causes were found, such as mutations in the DYT 11, SCA 3, or SCA 14 genes (Supplementary table 1) [5,6].

Brain MRI in both patients showed pronounced cerebellar atrophy (Fig. 1) without other structural lesions. In patient 1, the history of hemiplegic migraine combined with a paroxysmal movement disorder led to the detection of a heterozygous missense pathogenic variant in exon 5 (653C > T; Ser218Leu) in the *CACNA1A* gene, which is strongly associated with familial hemiplegic migraine. Paroxysmal tremor has only been described in two patients with a missense mutation in *CACNA1A* [7,8]. After treatment with Valproic acid (1500 mg daily) complete remission of the tremor was obtained. In **patient 2**, routine blood tests revealed an elevated alpha-fetoprotein (AFP) (74 µg/L). The cerebellar ataxia, sensimotor polyneuropathy, oculomotor apraxia, and increased AFP suggested ataxia-oculomotor apraxia-2 (AOA2), genetic analysis confirmed the diagnosis with a homozygous variant (p. His2261Pro) in the *SETX* gene. The computational predictive programs predicted this variant to be pathogenic due to a loss of function. Head and postural arm tremor, but not postural axial tremor have been reported in patients with *SETX* mutations [9]. The tremor slightly improved with clonazepam (1 mg) and propranolol (80 mg daily).

Our two cases are classic postural axial tremor phenotypes with tremor during sitting and standing, disappearing in a supine position with the pathognomonic feature of changing tremor frequency within or between muscles. In addition, these cases support that although postural axial tremor is generally associated with acquired cerebellar pathology, a genetic cause should be considered, especially in the ataxia or dystonia genes.

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Fig. 1. MRI Brain (patient 1) shows pronounced atrophy of the cerebellar hemispheres and vermis.

CRediT authorship contribution statement

R. Zutt: Data curation, Writing - original draft. **J.W. Elting:** Data curation. **P. Santens:** Data curation. **G.J.R. Luijckx:** Data curation. **M.A.J. Tijssen:** Data curation.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2020.04.013>.

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