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SHORT REPORTS

Cerebellar Involvement in DYT-THAP1 Dystonia

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Abstract

DYT-THAP1 dystonia is known to present a variety of clinical symptoms. To the best of our knowledge, this is the first case with DYT-THAP 1 dystonia and clinical signs of cerebellar involvement studied with transcranial magnetic stimulation in vivo. We report a case of a 51-year-old male DYT-THAP1 mutation carrier with dystonia, who additionally developed ataxia 1.5 years ago. To study cerebellar involvement in our patient, we used a TMS protocol called cerebellar inhibition (CBI). The lack of CBI in our patient strongly suggests cerebellar involvement. According to our findings, cerebellar syndrome may be part of the phenotypical spectrum of DYT-THAP1 mutations.

Keywords Ataxia · DYT-THAP-1 · Dystonia · TMS

Abbreviations

CBI	Cerebellar inhibition
THAP1	Thanatos-associated protein 1
TMS	Transcranial magnetic stimulation
MEP	Motor evoked potential
ISI	Inter-stimulus interval

Background

THAP1 gene mutations are associated with highly variable phenotypical spectrum of dystonic symptoms, consisting of focal and generalized dystonia forms [1, 2]. The large number of mutations in THAP1 gene, described in the literature, matches the topographical variety of dystonic symptoms and age of onset. Nevertheless, information regarding further clinical symptoms, associated with THAP1-gene mutations, besides dystonia, is scarce. To the best of our knowledge, this is the first case with DYT-THAP 1 dystonia and clinical signs of cerebellar involvement studied with transcranial magnetic stimulation in vivo.

Case Presentation

We report the case of a 51-year-old male THAP1 mutation carrier with dystonia since childhood who developed additionally cerebellar ataxia 1.5 years ago. The study was conducted in accordance with the Declaration of Helsinki and written informed consent for publication was obtained from the patient.

The dystonic symptoms comprised a dystonic action tremor of both hands since childhood, worsening over the last 6 years, writer's cramp, and cervical dystonia. Gait uncertainty, dysarthria, and occasional dysphagia developed 1.5 years ago. Fine motor skills, such as writing and cutting, became more difficult to accomplish. DYT-THAP1 mutation (heterozygous compound as variant of unknown significance in THAP1-gene, intron 1 (c.71+9C>A)) was revealed by dystonia gene panel analysis at age 50 during diagnostic work-up after manifestation of cerebellar symptoms. Father, uncle, grandfather,

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and sister also reported hand tremor and the sister carried the identical DYT-THAP1 mutation. His two daughters (20 and 23 years old) were without any symptoms and a genetic test was yet not obtained. The patient reported no excessive alcohol consumption. Given the phenotype, combining dystonia and cerebellar symptoms, SCA14-mutation was genetically excluded earlier. Further genetic investigation was not performed due to lack of therapeutic consequences.

Neurological examination showed generalized dystonia including cervical dystonia and upper limb dystonia with writer's cramp, mirror movements of both hands during writing, saccadic ocular pursuit, dysmetria of the upper and lower limbs, and gait ataxia. Postural and action tremors with marked intention tremor were present on both hands. The patient scored 21 out of 120 points on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDS) [3], 20 out of 76 points on the modified International Cooperative Ataxia Rating Scale (mICARS) [4], and 10 out of 40 points on the Scale for Assessment and Rating of Ataxia (SARA) [5]. SARA subscores were as follows: gait (1), stance (0), sitting (0), speech disturbance (1), finger chase test (2), finger-nose test (3), fast alternating hand movements (2), heel-shin slide (1). Hereby, we interpreted the upper limb tremor as rather intentional, than a dystonic one, because of the obvious overshoot on ballistic tracking.

Brain MRI and PET-CT were unremarkable with no evidence of cerebellar abnormalities or atrophy. The dopamine transporter scintigraphy showed no signs for degeneration of dopaminergic neurons. Screenings for other symptomatic causes of cerebellar ataxia (systemic autoimmune diseases, paraneoplastic antibodies, and Wilson's disease) were negative. CSF was normal. Biomarker screening tests in blood for other ataxia forms, including alpha-feto protein and vitamin E, were negative. Motor, somatosensory, and visually and auditory evoked potentials were unremarkable. Action tremor and gait ataxia responded slightly to dopaminergic medication (300 mg L-dopa/D). Medications with metoprolol, trihexyphenidyl, primidone, gabapentine, clozapine, and budipine showed no benefit or had led to intolerable adverse effects in the past.

To study cerebellar involvement in our patient, we used a transcranial magnetic stimulation (TMS) protocol called cerebellar inhibition (CBI) [6, 7]. Hereby, a conditioning cerebellar TMS pulse precedes the test TMS pulse to the primary motor cortex with an interstimulus interval (ISI) varying between 4 and 8 ms. For this purpose, a double cone coil was used for cerebellar stimulation and a round coil for motor cortex stimulation. Motor evoked potentials (MEPs) were recorded from the first dorsal interosseus muscle with the electrodes placed in belly-tendon montage. The primary motor cortex was stimulated with an intensity to evoke single pulse MEP with amplitude of 1 mV, the cerebellum with intensity of 95% of the brain stem active motor threshold. In the current case, CBI was completely abolished suggesting cerebellar involvement. Figure 1 shows absent CBI in our patient and normal CBI in 10 healthy controls (mean age 53.4 ± 5.4 years).

Discussion and Conclusions

To the best of our knowledge, this is the first case with DYT-THAP 1 dystonia and clinical signs of cerebellar involvement studied with TMS in vivo. Despite extensive work-up, no other cause for cerebellar ataxia was found. Cerebellar inhibition is known to occur at ISI between 5 and 7 ms in healthy subjects. The lack of CBI in our patient strongly suggests cerebellar involvement, most likely due to disturbed cerebello-thalamo-cortical pathways. Imaging studies reported in non-manifested DYT6 carriers reduced metabolism of the cerebellum and upper brainstem extending into the thalamus, and reduced integrity of cerebello-thalamo-cortical fiber tracts in both, clinically manifesting and non-manifesting DYT1 and DYT6 mutation carriers [8]. Neuropathological examination in patients with cervical dystonia carrying in part the identical mutation, as in our patient, revealed a lower

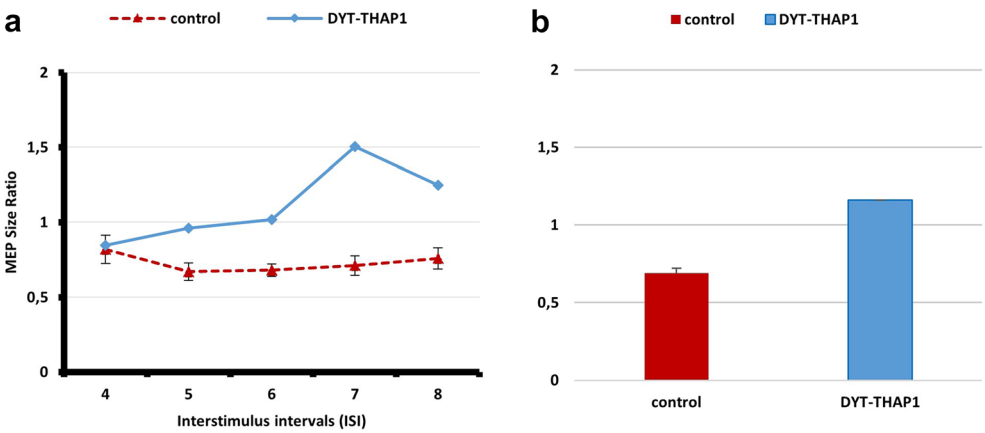

Fig. 1 **a** MEP size ratio of paired stimulation/stimulation alone at 4–8 ms ISI. Cerebellar inhibition is known to occur at ISI between 5 and 7 ms in healthy subjects. In contrast to the healthy controls, the cerebellar inhibition was absent in the DYT-THAP1 patient. **b** Average values of the MEP size ratio of 5–7 ms ISI on controls vs. DYT-THAP1. No inhibition was found in the DYT-THAP1 patient. Error bars refer to SEM

density of cerebellar Purkinje cells [9]. Furthermore, animal studies already proved a link between DYT-THAP1 mutation and cerebellar involvement in mice [10]. Based on this literature, the combination of dystonic and ataxic symptoms in the current case could possibly be explained through his genetic defect. However, although the likelihood seems rather low, we cannot rule out for sure that the patient harbors an additional genetic mutation responsible for the cerebellar phenotype.

Taken together, deficient CBI suggests cerebellar involvement in our patient and supports the notion that cerebellar affection may be part of the phenotypical spectrum of DYT-THAP1 mutations. In this relation, further research is needed to determine whether abnormal CBI can also be found in THAP-1 mutation carriers without ataxic features. Should this be the case, then cerebellar involvement in DYT-THAP1 mutations might be independent from clinical phenotype.

Availability of Data and Materials The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Ethical Approval and Consent to Participate All of the diagnostic procedures, performed on the patient, were carried out as a part of the clinical routine. No additional procedures on the patient were performed in relation to this study. Therefore, the need for ethical approval in this particular case is considered as waived. Moreover, written consent to participate was obtained from the patient.

Consent for Publication A written informed consent for publication was obtained from the patient.

Conflict of Interest SJG received honoraria and/or travel support in the past from Abbott Medical, Actelion, Boston Scientific, Medtronic, UCB, Rogue Research not related to the current study.

AS received consulting fees and/or speaker honoraria and travel support in the past from Abbott/SJM, Boston Scientific, Teva Neuroscience, UCB, MEDA Pharma, Novartis, and Abbvie. He has received research grants from the German Research Council, BMBF, the German Ministry of Education and Health, and the Helmholtz Association.

PA received compensation in the past for serving on Scientific Advisory Boards for Ipsen, Novartis, and Biogen; he received speaker honoraria and travel support in the past from Novartis, Teva, Biogen, Merz Pharmaceuticals, Ipsen, Allergan, Bayer HealthCare, Esai, UCB, and Glaxo Smith Kline; he received research support from Novartis, Biogen, Teva, Merz Pharmaceuticals, Ipsen, and Roche.

CJH received honoraria and/or travel support in the past from Abbott Medical und UCB, not related to the current study.

PN, SSH, AA, JK, and MM have no competing interests to report.

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