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TSFM mutations cause a complex hyperkinetic movement disorder with strong relief by cannabinoids

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1. Introduction

Biallelic mutations in *TSFM*, which encodes for the mitochondrial Ts translation elongation factor, cause a complex basal ganglia disease, mostly presenting with infantile-onset disease and death at infancy [1]. Only few descriptions are available on the phenotypic spectrum, in particular of adult presentations, and possible therapeutic strategies are lacking. Here, we report a novel *TSFM* patient presenting with an adult-onset complex generalized hyperkinetic movement disorder and an emblematic MRI of symmetric T2-hyperintensities restricted to the subthalamic nuclei ("subthalamic eyes"). The severely incapacitating hyperkinetic movement disorder showed a dramatic response to cannabis (CB).

2. Case report

A 20-year old man born from consanguineous Turkish parents presented with a severely incapacitating, progressive complex hyperkinetic movement disorder, comprising of generalized chorea and myoclonic and phasic dystonic movements of the neck, trunk and arms (see Supplement 1: video), starting at age 18 years. At this age, he was still capable of training for a driver's license and playing basketball in a local team, despite a history of mild stationary cognitive and motor deficits since developmental delay in childhood (walking at age 3, no regular school). Further neurological examination at age 20 years revealed subclinical bilateral optic atrophy (bilateral acuity 0.5), combined dystonic and cerebellar dysarthria, brisk lower limb reflexes, ankle clonus, impaired vibration sense, mild cognitive impairment (Mini Mental Status Examination: 26/30) and a wide-based gait due to combined hyperkinetic movements and mild gait ataxia. Cerebral MRI revealed a striking, previously unidentified pattern of nodular T2-hyperintensities restricted to both subthalamic nuclei (Fig. 1), without further basal ganglia, brainstem or cerebellar involvement. Lactate was mildly elevated in serum at one examination (2.5 mmol/l, range 0–2.2), but normal in serum and cerebrospinal fluid at next examination. Targeted massively parallel sequencing by a high-coverage high-throughput Agilent (Santa Clara, CA) SureSelect panel of 547 neurodegenerative disease genes (Supplement 2) revealed the established homozygous missense mutation c.944G > A; p.Cys315Tyr in *TSFM* [2].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.031.

Given the incapacitating nature of the movement disorder, symptomatic drug treatments with clonazepam, tetrabenazine and tiapride were attempted, each without effect. However, the patient subsequently initiated a treatment attempt with CB, leading to a dramatic motor improvement without cognitive or other side effects. Application of 60 mg *amnesia haze* (70–80% *sativa*, 20–30% *indica*; 20–22% tetrahydrocannabinol, 1% cannabidiol) by means of an inhaler led to a marked reduction in all components of the complex hyperkinetic movement disorder, with a peak effect lasting for 2 to 3 h (see Supplement 1: video). This treatment effect was confirmed at neurological examination by a reduction of 7.5 points (from 27 to 19.5) on the Scale for the Assessment and Rating of Ataxia (SARA), and of 7 points (from 12 to 5) of the Abnormal Involuntary Movements Scale (AIMS). Based on this dramatic treatment response, the patient now inhales this drug three to four times daily for two years, still with a sustained treatment response. Written informed consent has been obtained from the patient for the publication of the case-report, including the videotape, in both printed and online modalities.

3. Discussion

Our findings extend the phenotypic spectrum of *TSFM* mutations, demonstrating that it includes severely incapacitating complex hyperkinetic movement disorders comprising of chorea, dystonia and myoclonus. At the same time, they confirm that *TSFM* mutations not only cause a fatal infantile-onset symptom cluster, but also a young adult-onset cluster with maintained activities of daily living above 20 years of age (see Supplement 3 for a systematic overview of all 12 previously reported patients) [1,2].

TSFM disease can variably include symmetric bilateral basal ganglia lesions, which can, however, also be missing in 50% of the juvenile-onset TSFM cases (see Supplement 3). Our case demonstrates that basal ganglia lesions in *TSFM* disease can be restricted to the subthalamic nucleus, giving the striking MRI appearance of "subthalamic eyes".

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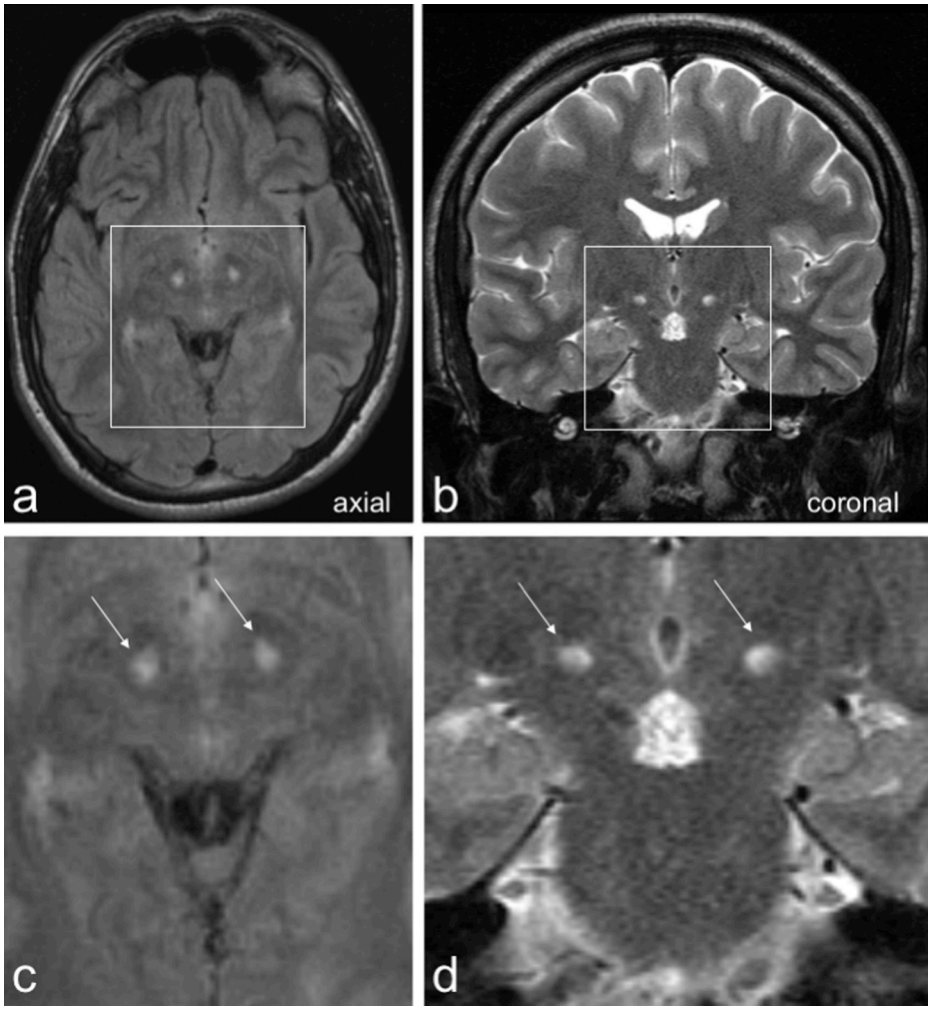

Fig. 1. Symmetric nodular hyperintensities in the subthalamic nuclei on axial FLAIR- (a; enlarged in c) and coronal T2-weighted (b; enlarged in d) cerebral MR images, displaying "subthalamic eyes" (arrows in c and d) in a patient with *TFSM* disease.

Speculatively, this subthalamic gliosis might be the substrate of the complex hyperkinetic movement phenotype in the present subject.

The dramatic response to CB is consistent with the reduction of dyskinesia by cannabinoid receptor agonists in preclinical studies [3]. Two major effects of cannabinoids – increase of GABAergic and decrease of glutamatergic signalling – target dysfunctional basal ganglia transmission in dyskinesia [3]. Given that clonazepam was ineffective, however, a simple GABAergic action is unlikely in the present case. Mechanistically, cannabinoids also modulate the activity of striatal medium spiny neurons, which have recently been identified as key mediators of dyskinesia [4,5]. Despite preclinical data, clinical trials of cannabinoids in movement disorders have been limited and inconsistent, especially for dyskinesia [3]. Different pharmacological agents may be one reason for this inconsistency, and the inhalation of cannabis in the present case probably includes multiple active cannabinoid agents. Nevertheless, the drastic treatment effect supports further investigation of medical cannabinoids as a treatment strategy in TSFM-associated and non-TSFM associated hyperkinetic movement disorders.

Disclosures

Dr. Traschütz reports no disclosures.

Dr. Hayer reports no disclosures.

Dr. Bender reports no disclosures.

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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.2018.09.031.

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