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CASE REPORT

MAPT mutation associated with frontotemporal dementia and parkinsonism (FTDP-17)

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ABSTRACT

We present a 56-year-old patient suffering from frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The history included a three-generation pedigree and the patient was found to be a mutation carrier. The diagnosis was hindered by late appearance of the hypokinetic movement disorder. For clinicians, it is important to consider rare neurodegenerative disease variants in early-onset familial dementia syndromes with behavioral, cognitive, and motor symptoms.

Key words: frontotemporal dementia, dementia, genetics, Parkinson's disease

Introduction

Although the general causes and classification of early-onset (<65 years) dementia do not differ from old life dementia (Lambert *et al.*, 2014), familial dementia syndromes, such as monogenetic Alzheimer's disease due to amyloid precursor protein (APP) and presenelin (PSEN1, PSEN2) gene mutations, often present as early onset disease (Kasuga *et al.*, 2015). Regarding familial tauopathies, the clinician should consider MAPT (microtubule-associated protein tau) mutations (Im *et al.*, 2015; Irwin, 2015). These mutations are associated with frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (Sperfeld *et al.*, 1999), but for specific MAPT mutations Alzheimer's disease-like phenotypes have been described (Rademakers *et al.*, 2003; Wszolek *et al.*, 2006; Kasuga *et al.*, 2015). A genetic overlap between Alzheimer's disease and Parkinson's disease in the MAPT locus has been reported recently (Desikan *et al.*, 2015). Patients with MAPT mutations may show highly variable clinical syndromes including frontotemporal lobar degeneration with parkinsonism, behavioral variant of frontotemporal dementia, as well as progressive supranuclear palsy- and corticobasal degeneration-like syndromes (Im *et al.*, 2015; Irwin, 2015). FTDP-17 is a rare autosomal dominant neurodegenerative disease with three core features: (a) behavioral and personality changes, (b) cognitive dysfunction, and (c) parkinsonism-like motor symptoms (Wszolek *et al.*, 2006). Approximately, 40 MAPT mutations have been described (Wszolek *et al.*, 2006). The parkinsonism often presents as a parkinson-plus syndrome with poor Dopa-responsiveness, frequent falls, supranuclear gaze palsy, and sometimes apraxia or dystonia (Wszolek *et al.*, 2006). FTDP-17 patients may suffer from a parkinson-plus predominant disease, but a dementia predominant phenotype is more common (Reed *et al.*, 2001).

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Case report

In 2013, a 56-year-old Caucasian woman presented to our memory clinic with an approximately three-year history of progressive memory impairment, orientation deficits, and subtle behavioral changes. Her husband told us about a new preference for chintzy things, which he considered inconsistent with her rational character before symptom onset. He also remembered an episode of compulsive behavior when his wife repeatedly checked their locked apartment entrance door. Finally, he reported a tendency to fall when riding her bicycle.

Our patient had a positive family history of early onset dementia. Her mother with severe dementia died at the age of 56. Due to a detailed psychiatric evaluation her mother had to undergo because of her incapacity to work, we learned about her cognitive, dysexecutive, and behavioral symptoms that were similar to our patient's. Her maternal grandfather committed suicide at the age of 54 being affected by severe cognitive deficits despite his young age.

In the clinical and neurological examination, we initially observed increased right-lateralized tone and vivid reflexes, accompanied by a general psychomotor slowing, depressed mood, and a tendency to dissimulate cognitive deficits. Brain magnetic resonance imaging (MRI) showed no abnormalities. Cerebrospinal fluid (CSF) analysis did not reveal amyloid or tau pathology and fluodesoxyglucose positron emission tomography (FDG-PET) showed a normal glucose metabolism except for subtle hypometabolic changes in the posterior cingulate cortex. Detailed neuropsychological testing revealed deficits in verbal and visual memory, concentration performance, and verbal fluency.

We first discussed a frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) spectrum disorder. However, candidate gene analyses for the chromosome 9 open reading frame 72 (C9ORF72) gene, fused in sarcoma (FUS) gene, and granulin encoding (GRN) gene yielded negative results. In the course of the disease, the patient's husband reported new behavioral abnormalities. His wife started to watch children's programs on TV, and could not select adequate clothes for herself. However, in the neurological examination there were neither relevant signs of frontal disinhibition nor an obvious progression of motor symptoms, such as paralysis or dysphagia. In addition to FTD-ALS, we therefore considered a behavioral variant of early-onset familial Alzheimer disease, but we did not find mutations in the APP, PSEN1, and PSEN2 genes. In early 2016, the cognitive impairment showed moderate progression, however, the motor signs changed significantly to a poorly Dopa-responsive, right-lateralized hypokinetic-rigid Parkinson syndrome. We obtained follow-up MRI- and FDG-PET brain imaging, now showing global atrophy and widespread hypometabolism with pronounced changes in the posterior cingulate cortex and in both hippocampi. Follow-up CSF analysis again showed negative results for amyloid-, tau, and hyperphosphorlated tau protein. The patient's family history still pointed to a fully penetrant monogenetic neurodegenerative disease. Because of the changes in motor symptoms over time, we considered MAPT genotyping, and we finally detected a heterozygous exon 10 splice side mutation in the MAPT gene (c.915+16C>T; Ex10 splice + 16) which has been previously described in families in the USA, UK, and in Australia (Hutton *et al.*, 1998).

Discussion

This case illustrates various clinical symptoms of a FTDP-17 patient even during the course of the disease. For clinicians, it is important to recognize the value of longitudinal changes in cognitive, behavioral, and motor symptoms, and to evaluate rare neurodegenerative diseases in patients with unusual dementia presentations. Even though MAPT mutations are named FTDP-17, it is of note that clinical symptoms vary even in between family members (Reed *et al.*, 2001; Wszolek *et al.*, 2006). Although treatment options may be limited, as in our case, pedigree data and genetic assessments can be crucial for how to educate patients and their families.

Conflict of interest

None.

Description of authors' roles

R. Haußmann and M. Donix formulated the concept and design, collected and/or assembled the data, and drafted the manuscript. M. Wysocki, M. Brandt, and A. Hermann were involved in the collection and/or assembly of data and critical revision of manuscript.

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