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SHORT REPORT

Autosomal Dominant Gene Negative Frontotemporal Dementia-Think of SCA17

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Abstract

SCA 17 is a rare, autosomal dominant disorder caused by *TBP* gene CAG/CAA repeat expansion. Ataxia and dementia are common. The presence of frontal dysfunction at outset of the disease may mimic frontotemporal dementia (FTD). Parkinsonism, chorea, dystonia, and pyramidal signs may occur. We report an Irish family with autosomal dominant partially penetrant frontal dementia with cerebellar atrophy due to SCA17 and present detailed neuropsychological assessment for the first time. A 44-year-old doctor presented with 18-month history of behavioral problems. She slowed down, became apathetic, and unable to multitask. She became more irritable and short tempered, and her work performance deteriorated. Brain MRI showed cerebellar atrophy and cerebellar hypometabolism was noted on FDG-PET. A sister developed personality changes at age 45 with apathy, and had problems with memory and social skills; another sister at age 39 became dysarthric and unsteady. A brother at age 52 demonstrated emotional lability, and became dysarthric, unsteady, and slowed down. Their mother aged 73 had an abnormal antalgic gait due to arthritis; their father was jocular and disinhibited. *MAPT* testing detected an exon 9 c.726C>T variant in the proband. Subsequent testing in nine siblings and both parents failed to show co-segregation with disease. SCA17 testing revealed a *TBP* gene 43 repeat expansion that co-segregated in all affected siblings and in the mother whose gait problems were initially attributed to arthritis. In over 80% of cases of FTD with clear autosomal dominant inheritance, causative gene defects involve *MAPT*, *GRN*, or *C9orf72* mutations. A minority involves *VCP*, *FUS*, and *CHMP2B*. As evident from our case, SCA17 testing should also be considered, especially if cerebellar atrophy if found on imaging. Segregation analysis is crucial. *MAPT* variant (c.726C>T exon 9) detected in the family was deemed a polymorphism.

Keywords SCA 17 · Frontal symptoms · FTD · Ataxia

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Introduction

Spinocerebellar ataxia type 17 (SCA 17) is a rare, autosomal dominant ataxia caused by CAG/CAA expansion in the TATA-box-binding gene (*TBP*) coding transcription initiation factor. Dementia, parkinsonism, chorea, dystonia, and pyramidal signs may occur [1] Frontotemporal lobar degeneration is the second most common cause of dementia below age 65, and frontotemporal dementia (FTD) with behavioral change is the most common subtype [2]. Behavioral change is the most common FTD presentation, irrespective of the causative gene defect [1]. Here, we report a family with FTD-like presentation due to SCA17.

Case Presentation

A 44-year-old female physician (Fig. 1, II-7) presented with an 18-month history of difficulties in initiating complex tasks (e.g., clinical audit, dealing with multiple-problem patients). Her clinical judgment, record keeping, and time management skills deteriorated rapidly. In an effort to cope, she worked longer hours. She started to use expletives and became "louder," but no frank disinhibition or dietary alterations were reported. She lost empathy and demonstrated stereotyped behaviors, preference for routine, concrete thinking, and impulsive buying.

During neuropsychological evaluation, she was casually dressed, well-groomed, and general comportment was appropriate. She was intermittently tearful and emotionally distressed when reflecting on her recent occupational dismissal, but did not appear pervasively depressed. She demonstrated poor insight into her cognitive disturbances: she had not noticed any changes in her work quality, although she acknowledged difficulties retrieving words and people's names. Speech articulation appeared normal. While grammatically correct, language expression was "adynamic," with a stutter quality, occasional inter-syllabic segmentation, and interjections between words "ah...ah...ah." She rarely initiated conversation, and her responses to questions were unelaborated, particularly on broad queries requiring mental organization of responses, suggestive of economy of mental effort.

While compliant with testing, she showed poor perseverance on tasks. Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III) yielded a Full Scale IQ of 72 (3rd percentile), a Verbal IQ of 77 (6th percentile), and a Performance IQ of 71 (2nd percentile), representing a profound decline from her estimated high average premorbid ability. The cognitive profile was dominated by profound and disproportionate attention and executive control deficits with very defective mental abstraction skills, poor self-monitoring, impaired cognitive flexibility, reduced inhibition control, and very impaired problem-solving skills. While fully spatio-temporally oriented, mental control was defective with labored reversal of overlearned sequences (e.g., months of the year) and defective serial subtraction by 7 s (3/5). Working memory was very impaired (arithmetic at 2nd percentile) and psychomotor speed was also substantially decreased (Digit Symbol-Coding at 9th percentile; Trail Making A at 16th percentile). On Trail Making Test Part B (1st percentile), she made two set-loss errors. On the modified Wisconsin Card Sorting Test [2], she only achieved two categories, showing marked difficulties maintaining and shifting cognitive set, with moderate levels of perseverative errors, becoming irritable on performance feedback. Proverb interpretation was concrete and she failed to abstract commonalities between two objects (similarities at 2nd percentile). On the inhibition condition of the Stroop Test [3], her performance was defective (< 1st percentile).

Generative naming was equally defective for both semantic categories (Combined Animals and Boys' Names = 13 at 1st percentile) and phonetic fluency (FAS = 17 at 2nd percentile). Anterograde episodic memory was clearly affected but she did not impress as clinically amnesic, demonstrating detailed recall of recent personal and news events. On the Wechsler Memory Scale Third Edition (WMS-III), she manifested poor registration and free delayed recall but no pervasive rapid rate of forgetting. Immediate recall of two prose stories was poor (Logical Memory Immediate Recall at 16th percentile) showing a very disjointed recall of the material, but delayed recall was better maintained (Logical Memory Delayed Recall at 37th percentile), retaining 80% of the material previously encoded (50th percentile). On Verbal Paired Associates I (VPA I), she demonstrated a shallow learning curve (0, 2, 2, 3 at 16th percentile) appearing overwhelmed by the task. While delayed recall was defective (VPA II at 9th percentile), she retained 2/3 paired-associates (66% savings score). On the Word List I, she demonstrated a positive but modest learning curve (0, 6, 5, 8 at 2nd percentile) but again delayed recall was better maintained (Word List II at 50th percentile), retaining 87% of the material registered. Her immediate and delayed recall of a complex geometrical figure (Rey Osterrieth Complex Figure) was very defective but clearly confounded by her piecemeal rendition with marked size distortion and misplacement of specific elements. In contrast, lower level visuoperceptual skills appeared intact (Cambridge Cognitive Examination Object Perception = 6/6). Semantic memory appeared largely intact. On the Category Comprehension subtest from the Semantic Memory Battery [4], requiring Word-to-Picture Matching, her performance was unremarkable (48/48). Visual confrontation naming was impaired (Boston Naming Test = 42/60 at 5th percentile) but she derived significant benefit from phonological cueing, suggestive of primary lexical retrieval deficits. Reading

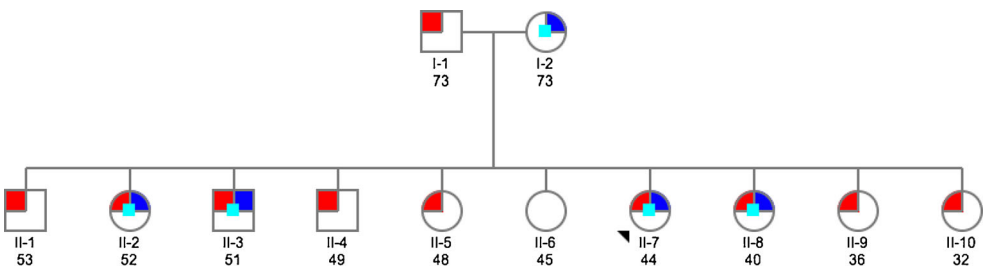

Fig. 1 Family pedigree: red, MAPT+; dark blue, expanded TBP repeat; light blue, symptomatic

aloud was carried out fluently with no evidence of surface dyslexia, and reading comprehension was intact. Single-word repetition was preserved and sentence repetition was only mildly defective. Performance of communicative gestures, both emblems (i.e., intransitive gestures) and pantomime of tool use (i.e., transitive gestures), was intact.

The neuropsychological profile was strongly suggestive of a behavioral variant (bv) FTD, albeit with some uncharacteristic features (frontal-executive cognitive deficits outweighed the behavioral alterations and there was a substantial IQ decline). The proband was characterized by pure frontotemporal dementia clinically and the scale for the assessment and rating of ataxia (SARA) was zero [5]. The proband met the diagnostic criteria for probable FTD [6–8].

Her MRI brain showed cerebellar atrophy involving both hemispheres and the vermis and hypometabolism was observed on and FDG-PET/CT (Figs. 2a, b and 3a).

Family History

She had nine siblings (Fig. 1). A 52-year-old sister (Fig. 1, II-2) presented at age 44 with personality change, unsteadiness, and dysarthria. She was inappropriate, forgetful, and withdrawn. Her neuropsychological testing showed fronto-striatal abnormalities and neuroimaging demonstrated cerebellar atrophy/hypometabolism. FTD was diagnosed. At present, she is fully dependent due to dementia.

Independently, another sister aged 40 (Fig. 1, II-8) presented to a different neurologist with mild personality change (highly strung) since age 32. She was dysarthric, unsteady, spastic, and forgetful. On examination, she had spastic ataxic gait and impaired tandem gait. There was finger-nose more than heel-shin ataxia. Her MRI brain showed cerebellar atrophy.

Neuropsychological testing revealed difficulty with nonverbal material including psychomotor speed, poor spatial construction, and visual reasoning. There was some difficulty coordinating and organizing the material with poor planning and poor organization. She performed poorly on semantic fluency, and short-term working memory was impaired. She scored in the moderate range on a measure of anxiety. The findings were consistent with fronto-striatal abnormalities.

A 51-year-old brother (Fig. 1, II-3) had personality change, dysarthria, unsteadiness, and forgetfulness from age 50. FDG-PET/CT showed anterior temporal hypometabolism and MRI brain demonstrated vermian atrophy (Fig. 3b). A 49-year-old brother (Fig. 1, II-4) laughed throughout assessment; however, neurological examination and MRI brain were normal. Other siblings were clinically unaffected. The 73-year-old father (Fig. 1, I-1) had a reputation for being a "funny man," playing constant jokes but clinical assessment was unremarkable. The 73-year-old mother (Fig. 1, I-2) was ataxic but attributed her difficulties to knee pain. The SARA score for the proband's mother was 6 (marked staggering, intermittent support of the wall required (4), able to stand with feet together for > 10 s, but only with sway (2)). Proband's mother declined any further investigations including MRI.

Negative genetic tests in affected individuals included *C9orf72* gene expansion, SCA 1,2,3,6, Huntington disease, dentato-rubral pallidoluysian atrophy (DRPLA).

MAPT testing demonstrated a novel NM_005910.5:c.726C>T (p.Arg242Arg) variant (Ensembl transcript ID ENST00000351559, NCBI Accession Number AH005895) [9, 10] in II-2. *MAPT* c.726C>T (p.Arg242Arg) variant was not found in ExaC [11], GnomAD [11], or 1000G [12] databases. Similar variant NM_005910.5:c.726 C>G (p.Arg242Arg), rs749827621 was found in 1/244,550 alleles (allele frequency 0.000004089) (GnomAD database) [11].

Mutation taster [13] predicted this synonymous variant to be pathogenic possibly affecting splicing. However, as per the

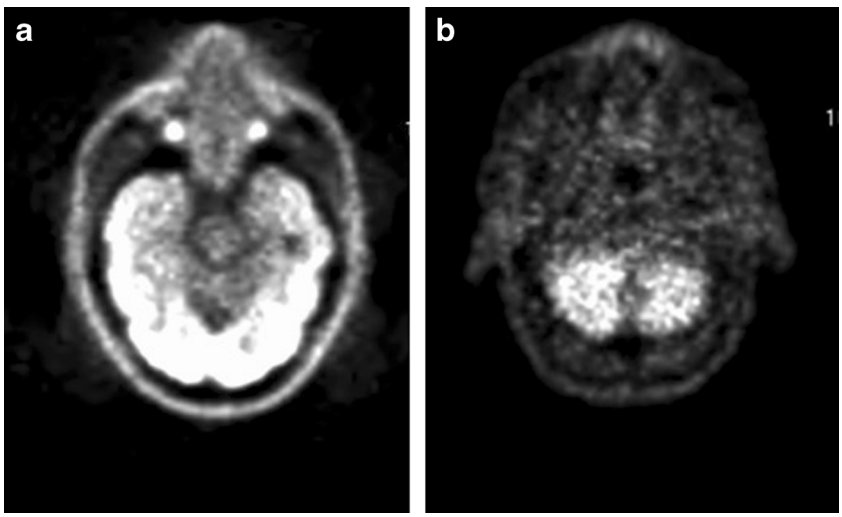

Fig. 2 PET/CT brain imaging of the proband (II-7), **a** anterior temporal hypometabolism, **b** cerebellar hypometabolism

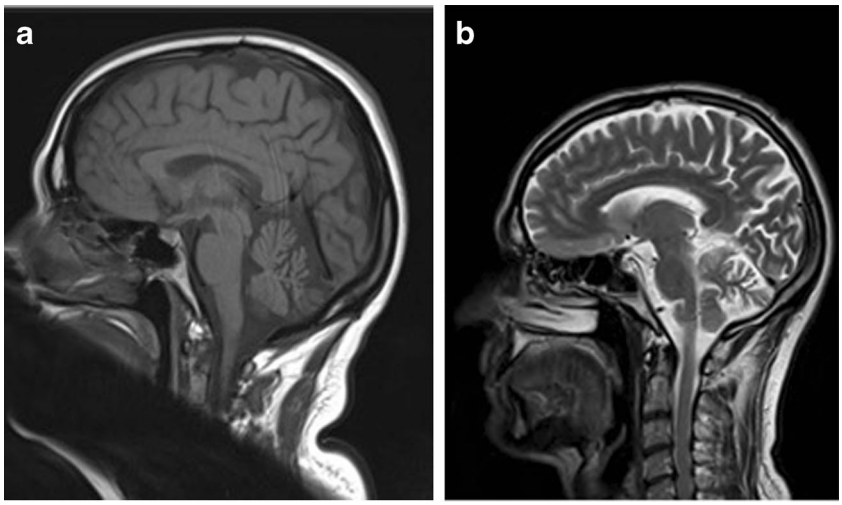

Fig. 3 MRI brain imaging sagittal cut. **a** FLAIR brain imaging of the proband (II-7) showing cerebellar atrophy, **b** T2 brain imaging of the proband's brother (II-3) showing vermian atrophy

American College of Medical Genetics and Genomics (ACMG) guidelines [14], there is insufficient data to support its pathogenicity. Two criteria support this variant as being benign: BS4 lack of the segregation within the family (Fig. 1), and BS2, observed in the healthy individuals.

II-8 had genetic testing for cerebellar ataxias including SCA 1, 2, 3, 6. Subsequent SCA17 testing demonstrated 43 repeats in *TBP*; in all affected siblings and in the mother whose problems were initially attributed to arthritis.

Discussion

SCA17 is one of a few known genetic causes of psychiatric symptoms. The presence of frontal symptoms is a recognized feature; however, exclusive manifestation with psychiatric symptoms is unusual at symptom onset [15–18]. We report the first family with SCA17 with 43 CAG/CAA repeats in *TBP* and frontal symptoms at onset and present the full neuropsychological assessment [15–18]. Thirty-one individuals (13 individuals with 52 repeats [16], 7 individuals from four families with 47–55 repeats, 14 individuals with 46–50 repeats [17], and 7 individuals from three families with 45–54 repeats [18]) had been reported in the literature to have behavioral symptoms or dementia at the outset of the disease; however, the number of repeats in TBP varied between 45 and 55. The number of repeats in patients presenting with psychiatric symptoms reported in the literature to date has been greater than the 43 repeats detected in our family.

The age-at-onset of SCA17 is variable (from 3 to 75 years) and not associated with CAG/CAA repeat length. Anticipation is not clearly defined [15, 16]. Normal repeat length is 25–42, with reduced penetrance reported for 43–48 repeats [16, 19, 20].

The vermis of the cerebellum has the appearance of a "limbic cerebellum," and in patients with particular disturbance in this region, the personality changes (cerebellar cognitive affective syndrome) can be almost indistinguishable from those of frontal variant-Frontotemporal dementia (fvFTD) [21]. Marked cerebellum and brain stem atrophy is seen in SCA17 [15]. Psychiatric symptoms occur frequently in the context of FTD due to *C9orf72* hexanucleotide expansions, and cerebellar atrophy may also be seen, reported up to 10 years preceding clinical onset [22].

Genetic testing in II-7 was initially performed looking for FTD variants, given the clinical presentation, and the *MAPT* variant was suspected as potentially relevant. However, the variant found was a synonymous change and did not segregate with the clinical status. Due to clinical cerebellar features in II-8 (who presented at a later date, to a different neurologist with a special interest in ataxias), genetic testing for the cerebellar ataxias was performed initially.

Cognitive symptoms are reported in SCA 1, 2, 3, 6, 7, 8, 10, 12, 13, 19, 21, but usually later in the disease course [7, 23]. In familial dementia mimicking FTD, cerebellar signs and/or atrophy on MRI should trigger SCA17 testing [7, 24].

Conclusion

We report a complex familial FTD with cerebellar features and co-inheritance of an MAPT variant and SCA17 CAG/CAA expanded repeat. As the *MAPT* variant is synonymous and did not co-segregate with the disease, it is likely a benign polymorphism. SCA17 can present as FTD, and carriers of 43 repeats may be symptomatic. The number of symptomatic repeats in SCA17 should be re-examined.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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