

Motor Neuron Disease-Frontotemporal Dementia Spectrum Disorder: A Different Phenotype Related With a Novel *TBK1* Gene Variant

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Abstract

The association of frontotemporal dementia (FTD) and motor neuron disease (MND) is a clinical continuum with genetic and neuropathological overlap. Cohort analysis has been broadening our phenotypic and genotypic knowledge on amyotrophic lateral sclerosis-frontotemporal dementia spectrum disorders. A 57-year-old woman presented with a progressive speech disturbance followed by the development of progressive upper MND in the next 2 years. Rapid progression of disease included anarthria, severe dysphagia requiring a gastrostomy tube and a tetrapyramidal syndrome without lower motor neuron signs. Death occurred within 4 years. Complementary investigation showed a left mesial temporal and frontal lobe atrophy, as well as a corticospinal tract hyperintensity on magnetic resonance imaging (MRI). Hypometabolism in the left parietal-temporal and frontal lobes was also evident in FDG-PET. The association of progressive apraxia of speech with upper motor neuron signs in our patient prompted genetic testing and the finding of a novel *TBK1* gene variant. Genetic testing should be considered in patients presenting with FTD, particularly with a positive family history or secondarily associated with an MND. Population-based studies are needed to clarify the prevalence and clinical phenotypes of *TBK1* variant carriers.

Keywords: Motor neuron disease; Frontotemporal dementia; *TBK1* gene

Introduction

The recognition of frontotemporal dysfunction in patients with motor neuron diseases (MNDs) leads to the publication of

amyotrophic lateral sclerosis-frontotemporal spectrum disorder (ALS-FTSD) diagnostic criteria in 2009 and its revised version in 2015 [1]. Since then, a growing number of reports have expanded our understanding on the clinical phenotypes, genetic variability and neuropathologic correlations of this disorder.

Frontotemporal dementia (FTD) can present with behavior, personality and/or language abnormalities. The main clinical subtypes include behavioral-variant FTD, semantic dementia and non-fluent primary progressive aphasia (PPA). ALS is characterized by upper and lower motor neuron degeneration resulting in motor weakness, spasticity, hyperreflexia, muscle atrophy and/or fasciculations.

The neuropathological substrate of FTD is most often selective frontal and temporal lobe atrophy, termed frontotemporal lobar degeneration (FTLD). Depending on the specific protein that abnormally aggregates in neurons and glial cells, four major subtypes of FTLD can be recognized. TAR-DNA-binding protein-43 (FTLD-TDP-43) accounts for one of those and is responsible for most cases of ALS-FTSD [2]. Within the same family, a genetic variant may result in FTD, MND or ALS-FTSD phenotypes, strengthening the concept of an FTLD/MND-TDP-43 disease spectrum.

More than half of ALS-FTSD with a known genetic variant are caused by hexanucleotide repeat expansions in the *C9orf72* gene [1, 2]. Variants in *VCP*, *FUS*, *TARDBP*, *SQSTM1*, *OPTN*, *UBQLN2* and *TBK1* are included in the remaining genetic spectrum [1, 2]. The *TBK1* (tumor necrosis factor-associated factor NF- κ B activator (TANK)-binding kinase 1) gene is located on chromosome 12 and encodes a 729-amino acid multifunctional protein kinase that acts as a regulator of various cellular pathways, including inflammation, immune response, insulin signaling, cell proliferation and autophagy [3]. Previous reported carriers of *TBK1* variants are clinically heterogeneous, presenting with variable language, behavior, movement and MNDs [4, 5]. Here, we describe a case of ALS-FTSD caused by a novel *TBK1* variant with an atypical phenotype.

Case Report

A 57-year-old right-handed woman presented with an 8-month history of progressive speech and memory impairments. She reported slowness of speech, wordfinding and naming dif-

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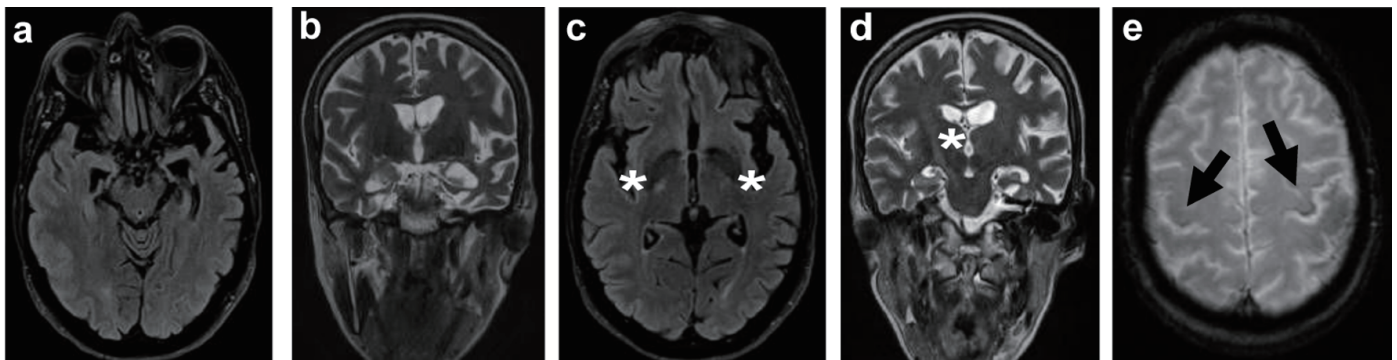


Figure 1. Brain MRI: axial FLAIR (a) and T2-weighted imaging (b) showing asymmetrical temporal lobe atrophy more pronounced on the left. Axial FLAIR (c) and coronal T2-weighted imaging (d) revealing hyperintensity in the posterior limb of the internal capsule and corticospinal tracts (white *). Axial T2 GRE (e) showing iron deposition (loss of signal) in the premotor cortex, most notably in the left precentral gyrus, known as the "motor band sign" (black arrows). MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery.

facilities, whereas comprehension, reading and writing were preserved. Other cognitive, behavioral or motor complaints were denied. She was a previously healthy operating room nurse, without usual medication or known family history of neurological disease. Neurological examination revealed a slow, telegraphic and hesitant speech, with short sentences, anomia, syllable suppression or extension, a mini-mental state examination of 27/30 (loss of 2 points on recall task and 1 point on write sentence task). Apart from hyperreflexia on the right upper limb, the remaining motor exam was normal. There were no signs of extrapyramidal, cerebellar, sensory or cranial nerves involvement. Neuropsychological assessment disclosed apraxia of speech dominant over a non-fluent language disorder, with severe alterations in verbal fluency and trail making tests, naming defect with normal performance in repetition and reading tasks, despite the increased effort to achieve them; she also had mild to moderate changes in memory tests but the pattern of performance on these tests was not suggestive of a significant defect in consolidation. Brain magnetic resonance imaging (MRI) (Fig. 1) demonstrated a left predominant mesial temporal and frontal lobe atrophy, as well as a corticospinal tract hyperintensity in T2/fluid-attenuated inversion recovery (FLAIR) and hypointensity in T2* in precentral gyri (motor band sign), most remarkable on the left (Fig. 1). Hypometabolism in the left parietal-temporal and frontal lobes was also evident in fluorodeoxyglucose-positron emission tomography (FDG-PET) (Fig. 2). Cervical MRI excluded spinal cord compression and electromyography, obtained at presentation and repeated in a late stage of disease, excluded a denervation process. Blood tests were normal and cerebrospinal fluid (CSF) biomarkers pointed to an unspecific pattern with slight elevated tau protein (446 pg/mL, normal range ≤ 335 pg/mL). Hexanucleotide repeat expansions in *C9orf72* were excluded. Multigene panel sequencing (including 19 genes: *CHCHD10*, *CHMP2B*, *CSF1R*, *FUS*, *GRN*, *HNRNPA1*, *HBRNPA2B1*, *MAPT*, *OPTN*, *PRKAR1B*, *SIGMAR1*, *SQSTM1*, *TARDBP*, *TBK1*, *TREM2*, *TUBA4A*, *UBQLN2* and *VCP*) revealed a heterozygous variant (c.1372_1373del (p.(Val458Serfs*18)) in *TBK1*, not previously reported in the medical literature. DNA from other

family members was not available to test segregation. This variant results in a premature STOP codon leading to a truncated protein and, for that reason, it was classified as likely pathogenic.

Over the next 2 years, her clinical condition rapidly progressed to include pseudobulbar affect, anarthria, dysphagia, inability to protrude the tongue, dysphagia and a right predominant tetrapyramidal syndrome. Nevertheless, while it was possible to test, comprehension and writing remained unaffected. At 3 years of follow-up, she was unable to leave the bed, totally dependent on nursing care for personal care needs and a gastrostomy feeding tube was inserted to ensure nutrition. She died at the age of 61, 4 years after clinical presentation.

Discussion

Here, we have described a case of ALS-FSTD in association with a previously unreported variant in *TBK1*. The novelty of this report lies on the rarity of the clinical phenotype, initially presenting with apraxia of speech followed by and exclusively upper MND. Over half of patients with an ALS-FSTD present with a progressive upper and lower MND, most frequently fulfilling criteria for ALS, which is accompanied later in disease progression with behavioral disturbances in up to 75% of patients, and cognitive dysfunction (executive, memory or language deficits) in one quarter [2]. Nevertheless, our patient firstly presented with a progressive speech disorder without behavioral dysfunction or motor impairment. Apraxia of speech is thought to result from the impaired planning and programming of the sensorimotor commands necessary for directing movements that result in phonetically and prosodically normal speech. In this speech disorder, the phonetic and prosodic impairment is dominant over the language disturbance that can coexist, which is demonstrated by the patients' retained capacity to write and understand. Apraxia of speech occurs early in various neurodegenerative disorders; therefore, long-term follow-ups watching for additional signs and symptoms are crucial to define the clinical syndrome [2]. In fact, previous reports have shown that up to a quarter of patients with FTD

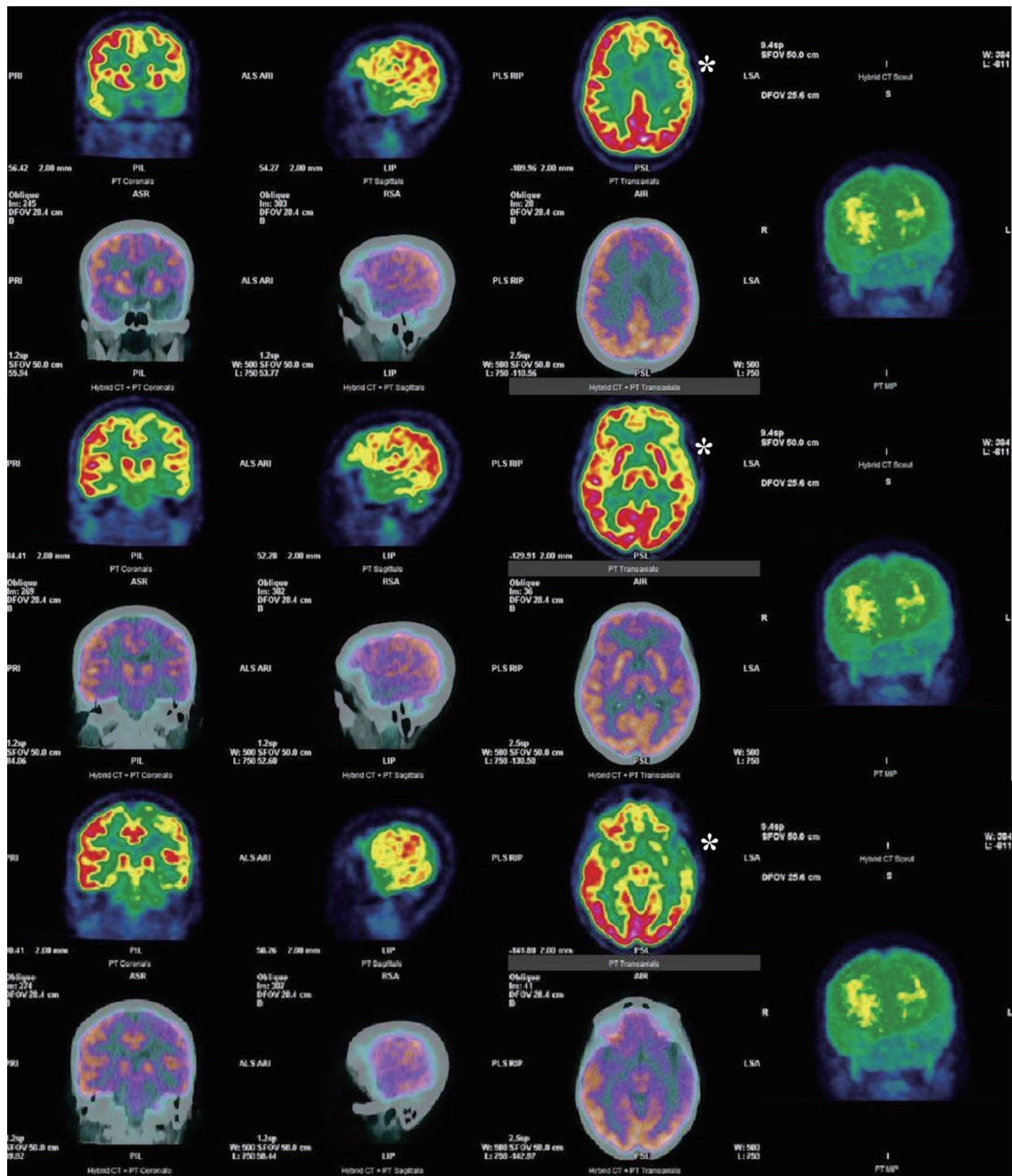


Figure 2. FDG-PET showing reduced [¹⁸F]FDG uptake in the left parietal-temporal and frontal lobes (white *). FDG-PET: fluoro-deoxyglucose-positron emission tomography.

may develop an MND years after disease onset [6].

The absence of evidence for lower motor neuron degeneration was also noteworthy in this patient. Throughout the course of disease, she developed a tetrapyramidal and pseudobulbar syndrome compatible with primary lateral sclerosis (PLS). PLS is a rare form of MND, which only affects upper motor neurons. Both ALS and PLS have some clinical overlap with FTD but PLS is typically uncommon in FTD patients [7]. Neuroimaging studies were consistent with the diagnosis of ALS-FTSD by excluding other causes for upper motor

dysfunction and showing a left predominant frontal and temporal lobe atrophy associated with indirect signs of pyramidal pathway degeneration. While these neuroimaging findings support the clinical suspicion of MND-FTSD, it can equally be observed in sporadic disease. Similar patterns have previously been reported and further explored by other researchers [8, 9]. Genetic testing should be offered for all patients with ALS-FTSD [1]. After exclusion of hexanucleotide expansion repeats in the *C9orf72* gene, a new variant in *TBK1* gene was found in this patient. *TBK1* loss-of-function variants cause

either a frameshift or a premature stop codon, leading to an absent or truncated protein product and suggesting that these variants are likely to be pathogenic through haploinsufficiency [10]. Even though we had no family history and we could not perform a segregation test of the variant, the bioinformatic analysis suggested that it has a deleterious impact and so is highly likely to be pathogenic, as it resulted in the premature inclusion of a STOP codon. Ongoing research on neurodegenerative disorders have shown that variants in *TBK1* are the fourth most common cause of familial FTD and may be the second most common cause of an ALS-FTSD [11, 12]. Notwithstanding, the full clinical spectrum of *TBK1* variant carriers is not completely elucidated, with nearly 100 patients reported [4]. The behavioral variant of FTD (in two-thirds of patients) and PPA (in one-quarter) are the most common clinical presentations, with (in one-quarter) or without MND [1, 2]. Literature available cases included two brothers presenting with PPA and asymmetric-onset primary lateral sclerosis [13]. On the other hand, a growing number of *TBK1* variants have also been found in patients with corticobasal syndrome, progressive supranuclear palsy and progressive cerebellar ataxia, expanding the phenotypic spectrum of *TBK1*-associated disease [5, 14]. Blood samples from other family members, as well as a postmortem examination of brain tissue would add value to the report of this novel variant.

Conclusion

In summary, we describe a novel *TBK1* variant in a patient with a rapidly progressive neurodegenerative disorder, presenting with apraxia of speech and upper MND. Following exclusion of *C9orf72* gene variants, sequencing of the *TBK1* gene should be considered in patients presenting with FTD, particularly with a positive family history or secondarily associated with an MND. Population-based studies are needed to clarify the prevalence and clinical phenotypes of *TBK1* variant carriers.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent for publication of this report was obtained from a patient's relative.

Authors Contributions

All the authors had substantial contributions to conception and design, acquisition of data or analysis and interpretation of data. In the same way, all the authors participated in the drafting the article or reviewing it critically for important intellectual content. All the authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

The authors declare that data supporting the findings of this article are available within the article.

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