Case Report

# Frontotemporal dementia parkinsonism: Clinical findings in a large Iranian family

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## Abstract

Frontotemporal dementia (FTD) is a group of neurodegenerative disorders characterized by atrophy of the frontal and temporal lobes. Clinical features suggestive of FTD include pre-senile onset before the age of 65, behavioral changes, social and interpersonal disinhibition, fluent and nonfluent aphasia, and loss of insight. FTD and parkinsonism linked to chromosome 17 (FTDP-17) was defined during the International Consensus Conference in Ann Arbor, Michigan in 1996. FTDP-17 is an autosomally dominant inherited condition. Most genotypic alterations do not correlate with clinical phenotypes. However, mutations affecting exon 10 splicing are associated with parkinsonism. In the present study, a male case with FTDP who presented with insidious onset of speech difficulty at a young age that was associated with signs of parkinsonism and a positive family history of FTD with *MAPT* gene mutation at exon 13 has been reported.

**Key Words:** Dementia, frontotemporal dementia parkinsonism, *MAPT* gene

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## INTRODUCTION

Frontotemporal dementia (FTD) is a group of neurodegenerative disorders characterized by atrophy of the frontal and temporal lobes. It is the second most common cause of dementia in patients under 65 years of age, after Alzheimer's disease (AD), and has become recognized as the third cause of dementia after AD and Lewy body diseases in people of all ages.[1] The age of onset of FTD is usually between 45 and 65 years, although 10% of patients have an onset beyond 70 years of age, particularly in semantic dementia (SD) form.[2] Familial forms of FTD occur in 30–50% of cases. Several clinical phenotypes have been described: (1) Behavioral variant FTD (bvFTD), (2) SD, and (3) progressive nonfluent aphasia (PNFA) and one variant with motor neuron disease.[3-5] The clinical characteristics of these illnesses are diverse, including loss of social skills, apathy, disinhibition, repetitive and compulsive behaviors, progressive inability to represent the self and others, loss of word meaning, and prosopagnosia and empty speech. Parkinsonian signs are common, but typically emerge at a later stage of the disease. Primitive reflexes, akinesia, rigidity, and tremor are the supportive diagnostic features in behavioral and primary progressive aphasia forms.[6] The behavioral variant form of FTD manifests itself typically by disinhibition, compulsive or perseverative behavior, and apathy with emotional bluntness. Executive functions are impaired in patients with FTD;

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however, unlike Alzheimer's disease, memory is preserved.[7] Focal atrophy in frontotemporal lobes on brain imaging and absence of neurological signs at the early period support the clinical diagnosis.[8] Three different diagnostic criteria were developed for clinical diagnosis of FTD by Lund and Manchester group,[9] Neary *et al*.,[6] and McKhann *et al*.[10]

Brain MRI generally reveals gray matter loss, particularly in the anterior and medial temporal lobes, with lesser involvement of the parietal lobes. Nonfluent primary progressive aphasia PPA presents with left perisylvian atrophy and in fluent PPA, temporal atrophy is predominant.[11]

Of the 30–50% of FTD patients with a positive familial history, approximately 10% exhibit an autosomal dominant mode of inheritance.[12] Mutations in seven genes were reported in dominantly inherited FTD: *MAPT*, *GRN*, *TARDBP*, *FUS*, *VCP*, *CHMP2B,* and *C9ORF72*.[13] The most common mutations occur in *MAPT*, *PGRN*, and *C9ORF72*.

Two types of mutations in the gene encoding the microtubule associated protein tau (MAPT) have been detected in FTD.[14-16] The first type is missense mutations that alter the amino acid sequence of the encoded tau protein. In contrast, the second type of *MAPT* mutations alters the pattern of tau.

Here, a male case with FTD with parkinsonism (FTDP) has been reported. Onset was insidious at a young age with speech difficulty characterized by anomia, impaired word finding, and finally aphasia, associated with prominent parkinsonian signs and a positive family history of FTD with *MAPT* gene mutations.

## CASE REPORT

A 44-year-old man, who was a hairdresser, was referred to our tertiary referral neurological department with a 5-year history of gradually increasing difficulty in finding names. He was able to describe events in general terms, but was unable to specifically name individuals or objects. He had been experiencing speech difficulty from about 2 years ago. Compulsive repetition of words was prominent in his history. Speech output required manifest effort and he was nonfluent and hesitant with phonemic and semantic errors. Word finding and repetition were impaired and spelling was poor.

Speech output became progressively constrained, impairing communication. Two years ago, as the disease progressed, comprehension eventually deteriorated and mild behavior disturbances appeared.

In addition, parkinsonian signs such as rest tremor and rigidity appeared. On neurological examination, the patient was apathic and did not have the ability to speak or communicate. Quadriparesia and generalized atrophy with elbow contracture was detected [Figure 1].

Family history was remarkable as his two brothers and one sister died several years ago (when they were 36, 43, and 40 years of age, respectively), with primary progressive aphasia and parkinsonian sign.

Two brothers (52 and 60 years old, respectively) had been having memory loss for several years.

Another brother, 35 years of age, was characterized by early prominent language impairment. Anomia and phonemic paraphasic errors were pronounced. On examination, his brother scored 29/30 on the Mini-Mental State Exam (MMSE).

On testing higher cortical functions, his speech was somewhat rambling and he was hesitant with word finding difficulty. He scored in the impaired range on tests of recall memory. In Luria alternating series, perseveration deficit was found [Figure 2].

Blood samples of the patient and all the family members were analyzed by sequencing.

The patient and his brother (35 years) were homozygotes for R406W mutation (*MAPT* gene mutations), his mother and two brothers (38 and 52 years of age, respectively) were heterzygotes, one sister was normal, and both daughters and cousins were heterozygotes for this mutation.

The first CT of the brain showed mild frontal atrophy. After 2 years, MRI of the brain showed enlarged lateral ventricles and bilateral anterior frontotemporal atrophy [Figure 3].

## DISCUSSION

Clinical features suggestive of FTD include pre-senile onset before the age of 65, behavioral changes, social and interpersonal disinhibition, fluent and nonfluent aphasia, and loss of insight.

Focal frontotemporal atrophy on functional imaging usually supports the diagnosis. In contrast to Alzheimer's disease, where the atrophy is mild and diffuse, the pathologic change in FTD is a severe atrophy of the frontal and temporal lobes.

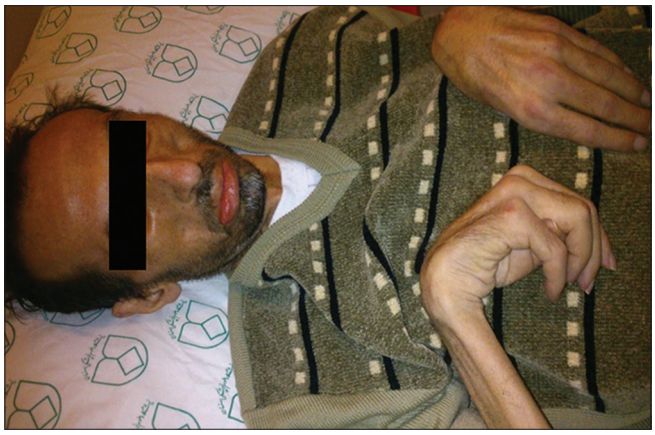

**Figure 1:** Generalized atrophy and elbow contracture was detected in our case

**Figure 2:** Perseveration in Luria alternating series test (drawing of the patient's 35-year-old brother)

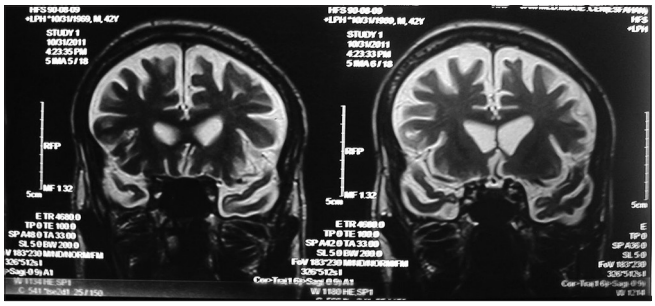

**Figure 3:** T2-weighted MRI of the patient demonstrating prominent frontotemporal atrophy

FTD and parkinsonism linked to chromosome 17 (FTDP-17) was defined during the International Consensus Conference in Ann Arbor, Michigan in 1996.[17] In this, data from 13 families with linkage locus on chromosome 17 were reviewed. This syndrome is a familial disorder with autosomal dominant inheritance. The three major clinical features detected in FTDP are: Behavioral disturbances, cognitive impairment, and parkinsonism.

FTDP-17 is an extremely rare condition. Its prevalence and incidence remain unknown. Over 100 families with FTDP-17 have been reported to date in numerous countries (USA, Great Britain, Japan, The Netherlands, France, Canada, Australia, Italy, Germany, Israel, Ireland, Spain, and Sweden).[18]

Mutations in the gene encoding tau protein account for the vast majority of FTDP-17 cases. Most known mutations in non-coding regions affect the splicing of exon 10.[19] Genotypic alteration often does not correlate with clinical phenotypes. However, overproduction of 4R isoforms (with mutations that affect the splicing of exon 10) are associated with parkinsonian symptoms and mutations which do not affect exon 10 splicing are associated with dementia forms. Parkinsonism could be the first manifestation of the disease, and it is important to note that some FTDP-17 patients were initially misdiagnosed as having Parkinson's disease. In some families, however, the parkinsonism occurs late in the course of the illness or does not occur at all. Parkinsonism in FTDP-17 is characterized by rather symmetrical bradykinesia, postural instability, and rigidity affecting equally axial and appendicular musculature, (usually) absence of resting tremor, and poor or no responsiveness to levodopa therapy. Other motor disturbances seen in FTDP-17 include dystonia, supranuclear gaze palsy, upper and lower motor neuron dysfunction, myoclonus, postural and action tremors, eyelid opening and closing apraxia, dysphagia, and dysarthria. Primitive reflexes, akinesia, rigidity, and tremor are the supportive diagnostic features in behavioral and primary progressive aphasia forms.[6]

Affected individuals should be counseled regarding the estimated probability of passing the genetic bases for their illness onto their offspring. As FTDP-17 is an autosomally dominant inherited condition, each offspring of an affected individual will carry a 50% risk of inheriting the abnormal gene. The individual who inherits a mutation will not necessarily develop the same clinical syndrome as the parent, because penetrance may be incomplete, neurologic manifestations vary greatly even within families, or the individual might die from unrelated causes. Different phenotypes were detected within families, such as our family cases.

The families with FTDP-17 fall into two major groups:[20]

- Dementia predominant phenotype
- Parkinsonism-plus predominant phenotype.

The dementia predominant phenotype is more common and is usually seen in families with mutations in exons 1, 9, 11, 12, 13, and 10. The parkinsonism-plus predominant phenotype is usually seen in families with intronic and exonic mutations affecting exon 10, especially overproduction of 4R tau isoforms.

In conclusion, our patient represents a case of FTDP with language disturbance and parkinsonian sign and positive family history. In this patient, pathogenic mutation was found at exon 13 of *MAPT*.

This particular mutation, heterozygously, is reported to cause the phenotype of Alzheimer's disease, unlike the other mutations of *MAPT*. In a later stage, the same mutation may show symptoms of frontal degeneration, and one report describes a case of familial tauopathy with onset at early 40s. To our best knowledge, this is the first homozygous case of *MAPT* mutation and it is highly likely that it is responsible for the phenotype of FTDP.

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