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Clinical Study

Right temporal lobe variant of frontotemporal dementia

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ABSTRACT

We present two women with the right temporal lobe variant (RTLV) of frontotemporal dementia (FTD) and analyse the clinical features that are determined by the anatomical distribution of atrophy. Each of our patients displayed different clinical and radiological profiles which were in line with findings reported by other authors. One of two patients carries a novel mutation in the granulin gene. FTD is heterogeneous with regard to clinical manifestation, genetics, distribution of cortical atrophy and underlying disease. Its clinical manifestations are related to the distribution of the cortical atrophy. The RTLV of FTD is an uncommon entity. There is no consensus about its name despite the fact that its clinical and radiological features are well-defined and distinguish it from other types of FTD including semantic dementia.

1. Introduction

Frontotemporal dementia (FTD) is a clinical syndrome characterized by the presence of behavioral disorders, altered executive functions and/or progressive language disturbance [1]. While this term is reserved for the clinical syndrome, frontotemporal lobar degeneration (FTLD) is a macro-anatomical descriptive term referring to the atrophy of the grey matter that selectively affects frontal and temporal lobes. These processes are typical in most patients with FTD [2].

There are two major clinical subtypes: behavioral-variant FTD and primary progressive aphasia (PPA). Semantic variant of PPA, also known as semantic dementia (SD), is characterized by a profound impairment in understanding concepts and word meanings leading to progressive fluent aphasia with marked anomia and vocabulary loss [3]. Even in the early stages of the disease, structural neuroimaging studies reveal signs of atrophy in the anteromedial region of the temporal lobes; atrophy is asymmetrically distributed and predominant on the left side in most patients [3,4]. Although atrophy may also be predominant in the right temporal lobe (RTL), this finding is far less common with a prevalence of three to four times lower [4,5]. The clinical manifestation differs depending on which side is most affected by atrophy [5–7].

The language disorder associated with left-sided temporal lobe atrophy has been described extensively but this is not the case when aphasia is not the dominant clinical symptom and signs of atrophy predominantly affect the RTL. Experts do not yet agree on a name for this entity. Some authors use the term 'right temporal lobe variant (RTLV) of SD' [4,5], others use 'RTLV of FTD' [8,9] and a third group clinically diagnoses patients with predominantly right-sided temporal lobe atrophy as having either SD or behavioral variant FTD [10]. Nevertheless, the clinical profile of this condition is distinctive and characterized by familiar people recognition disorder, episodic memory impairment, topographical disorientation and severe behavioral disorder [6,10,11]. Some authors have proposed that in FTD patients in whom signs of atrophy predominantly affect the RTL, certain clinical and radiological features are useful for predicting the underlying pathology [8].

In this manuscript we present two women with a diagnosis of FTD and more pronounced atrophy of the RTL as shown by structural neuroimaging studies using MRI. We analyze clinical and radiological features of both women, particularly those caused by impairment of the RTL. One woman carries a novel mutation in the granulin (*GRN*) gene.

2. Patients and methods

The study was performed in the Unit for Behavioral Neurology and Dementia at Hospital San Vicente. Ninety-one patients diagnosed with FTD in our hospital were retrospectively examined by three neurologists. Of these patients, two showed clinical and neuroimaging features on MRI suggestive of RTLV. We reviewed both patients' medical histories, neuropsychological studies (the short version of the Barcelona test and the frontal assessment battery) and their structural and functional neuroimaging studies. The

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MRI and functional neuroimaging studies were also reviewed by a radiologist and a nuclear medicine specialist, respectively. We performed mutation analysis for *MAPT* and *GRN* genes in one of the two patients. Coding and intron-exon junction regions of the *MAPT* and *GRN* genes were amplified using polymerase chain reaction (PCR) and direct sequencing.

3. Results

Two women were identified as presenting with FTD with predominantly right-sided atrophy. Each displayed different clinical and radiological features, as described below. One carries a novel *GRN* pathogenic mutation not previously described in databases (Human Gene Mutation Database, Alzheimer's Disease & Frontotemporal Dementia Mutation Database).

3.1. Patient 1

The patient was a 57-year-old woman whose family history included a mother and maternal aunt with dementia, possibly with presenile onset, and maternal grandmother with probable dementia. She experienced multiple symptoms that had developed over approximately 3 years including a behavioral disorder with profound apathy, compulsive eating, visual, auditory, and olfactory hallucinations, disinhibition and changes in social conduct with inappropriate behavior at the table. The family reported that the woman was unable to distinguish between tones people used when speaking to her. The main cognitive concerns were short-term memory loss, attention deficit and language disturbance (limited content and difficulties with comprehension). She did not manifest any symptoms that would suggest rapid eye movement sleep behavior disorder or impaired recognition of familiar people.

The neurological examination showed no signs of parkinsonism or of motor neuron disease. The palmar grasp reflex was positive on the right side. Some disorders were noted in the neuropsychological examination including deficit of selective and sustained attention, impaired temporal and spatial orientation, fluent language with limited content, echolalia, poor sentence repetition and altered comprehension of complex commands with two or more parts. Working memory showed severe impairment and episodic memory and immediate semantic recall were also mildly impaired. Her results were better for cued recall tasks. Severe impairment was also found for the executive functions (organization, planning, initiation, mental flexibility, motor sequencing). The examination also demonstrated incorrect recognition of people, impulsive and perseverant responses and difficulty curbing behavior and recognizing emotions. MRI identified signs of atrophy located mainly in the right frontotemporal area (Fig. 1). Cerebral single-photon emission CT scan showed moderate hypoperfusion of the RTL and mild hypoperfusion of the right frontal lobe (Supp. Fig. 1). Genetic analyses of *MAPT* were normal but the *GRN* sequence showed a new, previously unreported pathogenic mutation (c.147G>A; p.Trp49*).

3.2. Patient 2

Patient 2 was a 70-year-old woman with no family history of dementia who had developed cognitive impairment over a 4 year period. Her main concerns were short-term memory loss, topographical disorientation with difficulty navigating familiar places and inability to remember familiar routes and impaired recognition of familiar people. The woman reported having been unable to recognize her daughters who lived abroad when she went to meet them at the airport. Her behavior was rigid and inflexible.

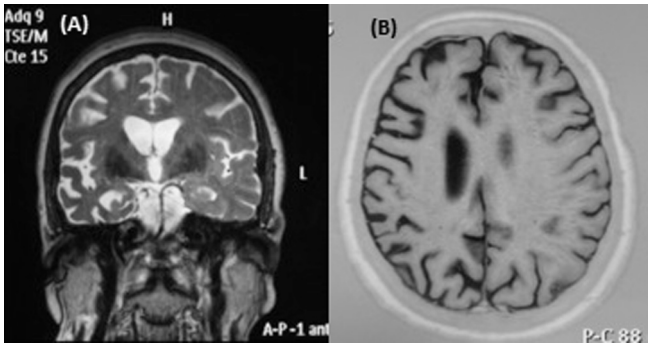

Fig. 1. Cranial MRI showing predominantly right-sided frontotemporal lobar atrophy. (A) coronal, T2-weighted, (B) axial, T1-weighted.

She showed no tolerance for changes in her daily schedules and routines, no ability to improvise, emotional blunting, indifference to her husband's illness and loss of empathy.

The neurological examination showed no signs of parkinsonism or of motor neuron disease. The neuropsychological examination revealed mild deficits in attention, episodic and immediate memory and executive functions. There was also moderate impairment of delayed verbal and visual episodic memory. Language was fluent with no semantic deficits. The MRI revealed signs of atrophy with selective and profound asymmetrical impairment of the RTL (Fig. 2). The functional imaging study also showed selective hypoperfusion of the right anterior temporal lobe (Supp. Fig. 2).

4. Discussion

FTD is a clinical syndrome that includes two major subtypes: behavioral-variant and PPA. Clinical manifestations are related to the distribution of the cortical atrophy. FTD patients in whom signs of atrophy predominantly affect the RTL are characterized by behavioral disorders accompanied by face recognition disorders, topographical disorientation and episodic memory deficits.

Positive family history is observed in 40–50% of all FTLD patients. Molecular genetic studies have identified five genes that when mutated cause FTLD. The most frequently appearing mutations are in the *MAPT* gene (encoding the tau protein), the growth factor precursor gene *GRN* and *C9orf72* [12].

Almost all cases of FTLD can be assigned to one of three categories according to the abnormal protein being deposited: tau,

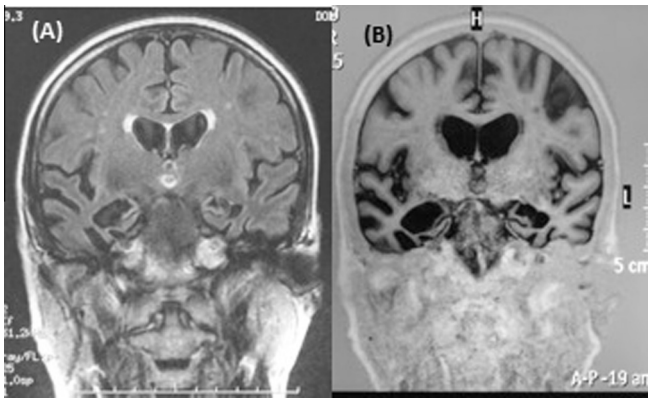

Fig. 2. Patient 2 cranial MRI revealing clear signs of predominantly right-sided temporal atrophy. The images correspond to different stages of the disease. The image on the right (B), taken more recently, shows signs of temporal atrophy that are bilateral but noticeably asymmetrical. We observe that the MRI for Patient 1 shows more severe frontal atrophy with less pronounced hemispheric asymmetry. (A) coronal, fluid-attenuated inversion recovery (B) coronal, T1-weighted.