

FRONTOTEMPORAL DEMENTIA WITH SEVERE THALAMIC INVOLVEMENT

A clinical and neuropathological study

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ABSTRACT - Frontotemporal dementia (FTD) is the third-leading cause of cortical dementia after Alzheimer's disease and Lewy body dementia, and is characterized by a dementia where behavioral disturbances are prominent and appear early in the course of the disease. We report the case of a 58 year-old man affected by dementia with behavioral disturbances, in addition to rigid-hypokinetic and a lower motor neuron syndrome that were present at later stages of the illness. Neuroimaging studies showed frontotemporal atrophy. Neuropathological studies revealed intense thalamic neuronal loss and astrocytic gliosis, as well as moderate frontotemporal neuronal loss, astrocytosis and spongiform degeneration. Thalamic degeneration has previously been described among the wide group of neuropathological features of FTD. The aim of the present study is to show the clinical and neuropathological aspects of thalamic degeneration in FTD, along with its role in behavioral disturbances, a common finding in this condition.

KEY WORDS: frontotemporal dementia, thalamic degeneration, neuropathological findings.

Demência frontotemporal com intenso envolvimento talâmico: estudo clínico e neuropatológico

RESUMO - Demência frontotemporal (DFT) é a terceira causa de demência cortical, após doença de Alzheimer e demência dos corpos de Lewy, caracterizando-se por ser uma síndrome demencial em que as alterações de comportamento são proeminentes e aparecem precocemente. Descrevemos o caso de um homem de 58 anos apresentando demência com expressiva alteração de comportamento, somadas a síndrome rígido-hipocinética e de neurônio motor inferior. Os exames de neuroimagem mostraram atrofia frontotemporal. O exame neuropatológico revelou intensa perda neuronal e astrocitose talâmica, bem como moderada depleção neuronal frontotemporal, com astrocitose e degeneração espongiiforme. Degeneração talâmica já foi descrita entre os possíveis achados neuropatológicos na DFT. O objetivo deste estudo é contribuir com uma descrição dos aspectos clínicos e neuropatológicos da degeneração talâmica na DFT, bem como seu envolvimento nos transtornos de comportamento, tão frequentes nesta condição clínica.

PALAVRAS-CHAVE: demência frontotemporal, degeneração talâmica, achados neuropatológicos.

Frontotemporal dementia (FTD) represents 10-20% of all dementias (being the third-leading cause of cortical dementia after Alzheimer's disease and Lewy body dementia)^{1,2}. Loss of personal awareness, impulsiveness, apathy, lack of initiative, perseverative behavior, hyperorality, progressive reduction of speech and preserved spatial abilities, together with frontotemporal atrophy on CT or MRI scans and hypoperfusion / hypometabolism in frontal, temporal and frontotemporal regions in SPECT and PET stu-

dies, are findings that make for a very probable diagnosis of FTD. Family history is described in 20-40 % of such cases. A rigid-hypokinetic and lower motor syndromes have also been described in later stages of FTD^{3,4}.

The Lund and Manchester Groups⁵ defined three neuropathological expressions of FTD: the frontal degeneration type, the Pick type (with Pick cells and Pick bodies) and the motor neuron disease (MND) type with spinal motor degeneration. The most com-

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mon pathological findings in FTD are bilateral and symmetrical atrophy in the frontotemporal regions, with striatal degeneration. There may be a correlation between the clinical presentation and the predominant site of atrophy: the orbitomedial frontal cortex is more affected in those patients with overactivity and disinhibition, while the dorsolateral frontal cortex is more affected in those presenting apathy. In some cases, the striatal degeneration is severe and accompanied by important limbic and nigral alterations, and this subgroup of patients is prone to develop stereotypic and ritualistic behavior, together with rigid - hypokinetic syndrome^{6,7}. Histological studies may show two distinct patterns: one with a severe loss of neurons in layers III and V, spongiform degeneration / microvacuolation of layer II and minimal gliosis (frontal lobe degeneration), and other, being less common, in which there is a severe loss of cells and gliosis, but no spongiform or microvacuolation changes, with swollen neurons or cell inclusions in some cases (Pick-type). The striatum and limbic system seem to be more affected in the second presentation^{5,8}. When the dementia is associated with motor neuron disease, there is a large loss of cells, microvacuolation and mild gliosis involving predominantly the orbitomedial frontal regions; the

striatum and limbic system are less affected, but severe nigral and hypoglossal damage can also be found. There is a massive loss of cells at all levels of the anterior horn^{2,9}.

We report the case of a 58 year-old man affected by dementia, which had evolved over a five-year period, where behavioral disturbances were prominent. There was a positive family history for dementia. In addition, rigid-hypokinetic and lower motor neuron syndromes were present at later stages of the illness while neuroimaging studies showed frontotemporal atrophy. Neuropathological studies revealed intense thalamic neuronal loss and astrocytic gliosis, as well as moderate frontotemporal neuronal loss, astrogliosis and spongiform degeneration. Thalamic degeneration has previously been described among the wide group of neuropathological features of FTD. The aim of the present study is to show the clinical and neuropathological aspects of thalamic degeneration in FTD, along with its role in behavioral disturbances, a common finding in this condition.

CASE

Our patient is a 58 year-old, right-handed, Caucasian businessman, with eight years of schooling. At the age of 54 he presented apathy and lack of interest in his daily activities, which initially had been attributed to financial problems. A global behavioral change was observed in the subsequent months. Paranoid delusions occurred: he always felt threatened, trying to protect himself from imaginary attacks by police or robbers. At the same time, he demonstrated uninhibited behavior, out of character with his previous personality profile, such as talking to strangers in the street, undressing himself in public places, begging for money, for instance. His behavior became progressively less inhibited and he was attended by several psychiatric services, receiving anti-psychotic drugs with partial response. One year prior to admission, he developed a progressive memory impairment that disabled him from continuing his professional activities. Furthermore, he had difficulty in recognizing friends and relatives and hyperorality symptoms were noted. Six months later, he began depending on relatives to perform basic domestic tasks, such as feeding, dressing and bathing himself, with global incontinence occurring three months before admission. No previous systemic or neurological illness, history of trauma, alcohol consumption or drug abuse were present. The patient had an older brother, who died at the age of 53 with a similar dementia lasting for four years.

The general physical examination was normal, while the neurological examination showed a vigilant, time/space oriented patient, with reduced verbal fluency, and preserved oral comprehension and expression. Also, frontal release signs and global rigidity were present and demential syndrome with behavioral abnormalities predominated.

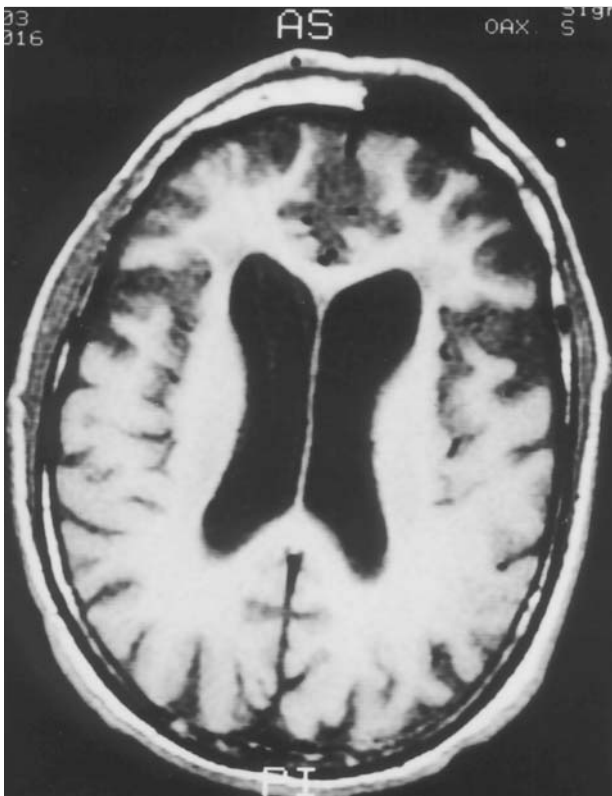


Fig 1. MRI scan (axial plane) demonstrating frontal atrophy with ventricular enlargement.

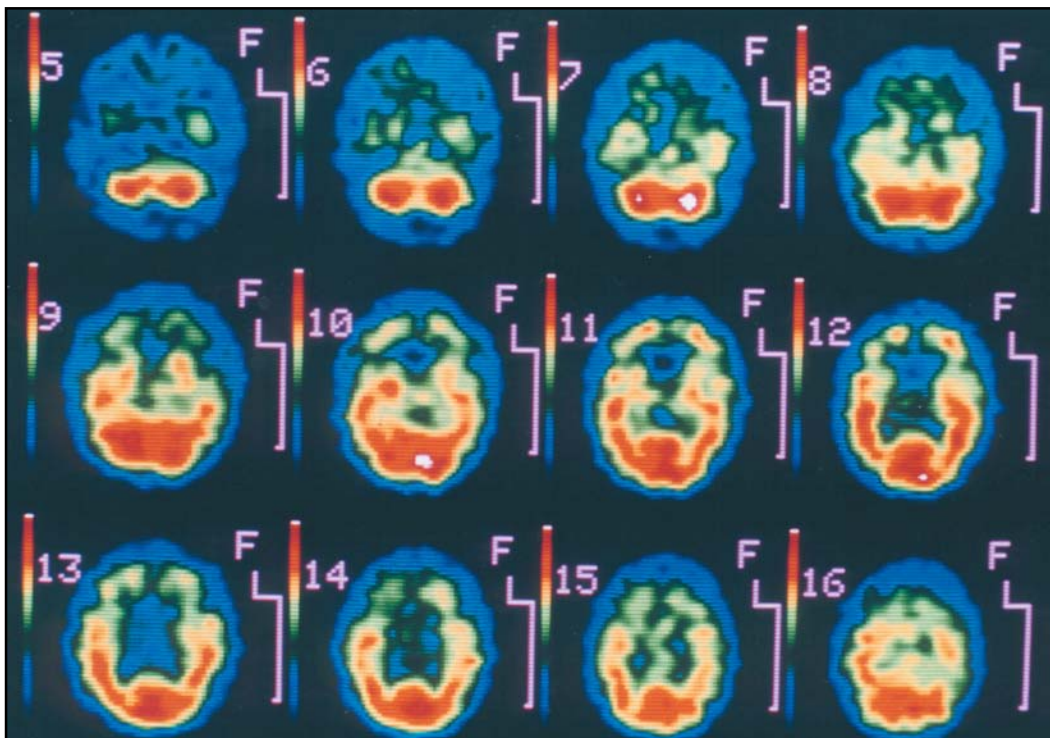


Fig 2. Brain SPECT showing hypoperfusion in the frontal cortex, caudate and thalamus.

The score in the Mini-Mental State Examination (MMSE) was 26/30, revealing impairment in Attention/Calculation (3/5), Recall (2/3) and Copying (0/1). The neuropsychological examination included the Mattis Dementia Rating Scale (score: 101 / 144), and the Hooper Visual Organization, Wisconsin Card Sorting, Trail Making and Benton Visual Retention tests. The scores obtained in the Mattis Dementia Rating Scale showed a greater impairment in Initiation/Perseveration (28/37), Conceptualization (20/39) and Memory (17/25). The overall results disclosed a deep impairment of thinking flexibility, executive functions, memory, visuospatial and constructional skills. A brain MRI scan (Fig 1) revealed predominant frontal cortical and subcortical atrophy and ventricular enlargement without signs of intracranial hypertension. Brain SPECT showed hypoperfusion in the frontal cortex and subcortical structures such as the caudate and thalamus (Fig 2). Blood tests were normal and serologic tests for HIV and for syphilis were negative. Cerebrospinal fluid analysis showed no abnormalities, whilst electroneuromyography revealed signs of chronic degeneration in the anterior horn cells. Analysis of the prion protein gene (by single chain polymerase reaction) did not show any mutation.

Clinical course and neuropathologic examination - Months after admission, the patient developed a progressive loss of contact with the environment and a rigid hypokinetic syndrome. He was bedridden and in a vegetative state in the final stages of the illness. Distal amyotrophy and fasciculations could be seen. The subject died five years after presenting symptoms, of respiratory complications.

General autopsy disclosed bilateral bronchopneumonia. The brain weighed 1,000 g. Gross evaluation of the brain showed widening of cerebral sulci, more evident at the frontotemporal regions, along with ventricular dilatation and relative sparing of subcortical structures (Fig 3). Histopathological study of the frontal cortex showed moderate to severe neuronal loss, with astrocytic gliosis more prominent in the granular layer and spongiform changes in the outer cortical layers (II and III) (Fig 4). Marked neuronal depletion and astrocytosis were observed at the thalamus, especially in the dorsomedial nuclei (Fig 5), substantia nigra and the caudate. The immunohistochemistry study for the detection of prion protein was negative.

DISCUSSION

The initial clinical manifestations of this patient (marked personality and behavioral changes), together with the relative preservation of memory and learning functions, correspond to the progressive compartment /executive dysfunction profile of cognitive impairment as described by Mesulam¹⁰. His initial performance in the MMSE was normal, but already disclosed slight disturbances in attention, memory and praxis. The subsequent neuropsychological examination, however, showed a more widespread impairment, which predominated in the executive functions and memory. Available data from history and from clinical examination, laboratory investigation, neuroimaging studies and the neuropatholo-

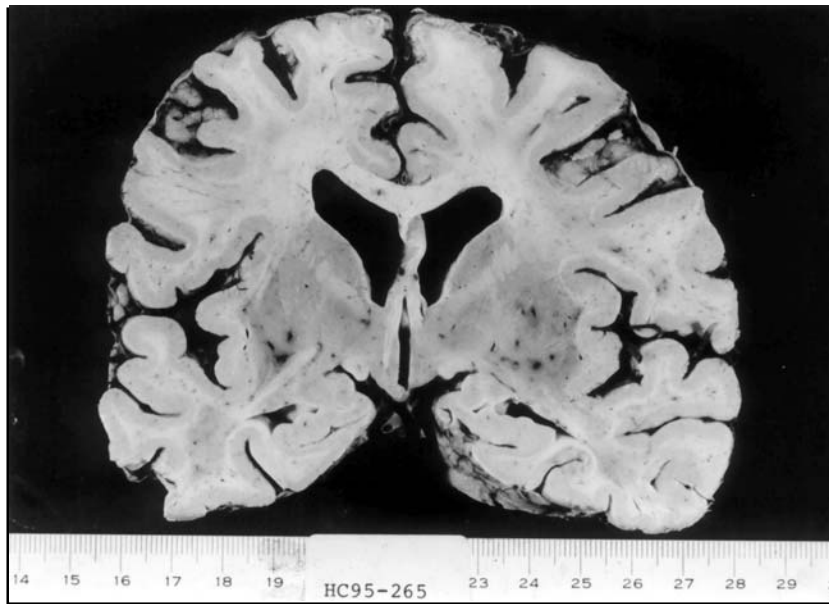


Fig 3. Coronal section of the brain showing widening of sulci (especially frontotemporal) and ventricular dilatation.

gical findings point to a FTD. The cortical histological features included neuronal loss, diffuse astrocytosis, more evident in the granular layer, and spongiosis of the outer layer (II and III). A remarkable astrocytosis and severe neuronal loss were found in the thalamus, especially in the dorsomedial nucleus. A similar pattern of degeneration was found in other subcortical structures such as the caudate and substantia nigra. All these lesions followed a multifocal distribution and are compatible with the diagnosis of FTD. Although the descriptions of the neuropathological features of FTD usually focus on the frontal, temporal and striatal abnormalities, thalamic degeneration was also described in 1990 by Knopman¹¹ in what he termed "dementia lacking distinctive histology" (DLDH), as well as in other studies^{8,12}. However, the prominence of the thalamic atrophy as was found in our case is distinctly unusual.

Primary thalamic degeneration (PTD) causing dementia was first described in 1939 by Stern¹³ in a subject who presented severe atrophy of ventral anterior and dorsomedial thalamic nuclei, and a variable degree of gliosis in the cerebral cortex. Martin, in 1975¹⁴, classified the thalamic degenerations into: preferential thalamic degeneration, thalamic degeneration associated with multi-system atrophies and the thalamic form of Creutzfeldt-Jakob disease. Cognitive alterations in thalamic lesions (thalamic dementia) have been well documented in vascular and degenerative lesions¹⁵⁻¹⁸. In the latter, they may appear in association with motor neuron disease¹⁹ or a

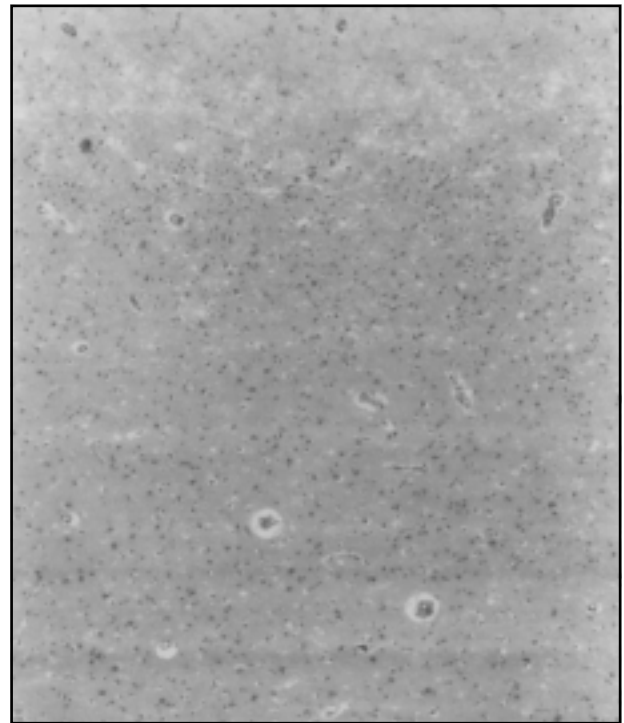


Fig 4. Frontal cortex showing neuronal loss and spongiform changes in superficial layers. H.E. X 25.

more diffuse subcortical atrophy, frequently being familial in character. Since the degenerative alterations frequently spread to other subcortical structures, the term "subcortical gliosis" is also applied to such cases of progressive dementia associated with variable cortical neuronal loss and subcortical / deep white matter gliosis²⁰⁻²².

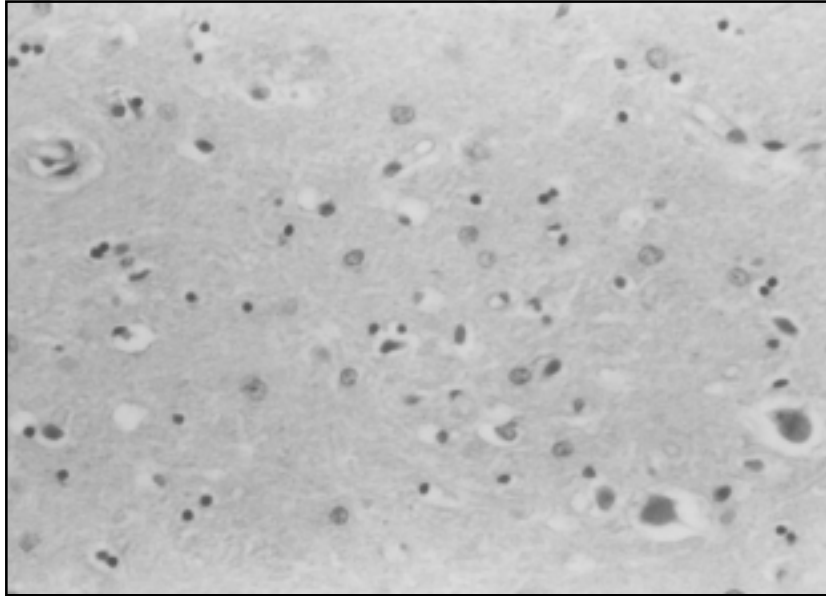


Fig 5. Thalamus. Almost complete depletion of neurons and astrocytosis. H.E. X 200.

The thalamus has massive connections with the frontal lobes, the limbic system and the activating reticular formation of the brainstem, and these connections are directly related to the mechanisms of behavioral control, emotions and memory. Thalamic nuclei are part of the three frontal-subcortical circuits that originate in the prefrontal cortex and which are related to behavioral and cognitive functions. The dorsomedial (parvocellular and multiform divisions) and anteroventral nuclei are inserted in the dorsolateral prefrontal circuit, which is related to executive functions and motor programming. The magnocellular division of the dorsomedial and the anteroventral nuclei are also part of the lateral orbitofrontal circuit, the injury of which leads to personality changes and mood alterations, especially irritability (for this reason, the anteroventral and dorsomedial nuclei are usually referred to as the "limbic thalamus"). Some specific regions of the dorsomedial nucleus belong to the anterior cingulate circuit where lesions of this circuit are associated with apathy and akinetic mutism^{23,24}. The thalamofrontal tracts originate in the anterior and medial nuclei of the thalamus, and some studies have described a picture that very much resembles a "frontal syndrome" in patients with small infarcts involving these tracts. The anterior nucleus is also connected with the mammillary bodies (via the mammillothalamic tract), playing an important role in the production of emotions and memory functions^{16,25}. These neuroanatomical peculiarities may reflect in the clinical picture of FTD: those patients in whom a relative sparing of the thalamus occurs,

may initially have a "disinhibited" frontal syndrome, but as the disease evolves to a more severe pathological stage, the involvement of the basal ganglia and the thalamic nuclei (as presented in this case) can usually be correlated with an "apathetic" frontal syndrome due to the important role of these structures in attention and awareness²⁶.

In conclusion, thalamic degeneration, especially when involving the dorsomedial nucleus, may be included in the spectrum of neuropathological findings for FTD and may contribute to intensifying the behavioral disturbances already found in these cases.

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