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Frontotemporal dementia : a clinical-pathological study

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Abstract

We report a 44-year-old female patient without any familial history of dementia presenting with increasing disturbances in behaviour and language followed by a progressive cognitive deterioration. Neuropsychological evaluation revealed a significant impairment on frontal lobe tests. A brain PET scan disclosed a severe frontal hypometabolism. The tentative diagnosis of frontotemporal dementia was made. Her condition rapidly worsened and she died 2 years after the beginning of her disease. Gross examination of the brain showed a selective symmetrical atrophy of both frontal and anterior part of the temporal lobes. Microscopical examination revealed severe neuronal loss in the frontal and anterior temporal cortex associated with gliosis and microvacuolar spongiosis in the superficial cortical layers in the absence of any specific neuronal or glial inclusions. These neuropathological findings were consistent with the diagnosis of dementia lacking distinctive histology. We discuss the nosology of the frontotemporal dementias, the diagnostic value of PET scan, the recent genetic developments which strongly support the pathogenic role of tau and we emphasise the importance of immunohistochemical examination for a definite neuropathological diagnosis.

Key words : Frontotemporal dementia ; dementia lacking distinctive histology ; tauopathy ; neuropathology ; immunohistochemistry ; PET scan.

Introduction

The frontotemporal dementias (FTD) belong together with Lewy body dementia, corticobasal degeneration, progressive supranuclear palsy, and some recently described disorders such as grain dementia and tangle-only dementia to a large group of neurodegenerative disorders, the so-called non Alzheimer degenerative dementias (Lowe and Spillantini, 1998). Pick's disease described more than a century ago with its characteristic Pick bodies and ballooned neurones (Pick cells) is the best known form of FTD (Rosen *et al.*, 2000). However, new developments in neuropathological techniques allow better identification of inclusion bodies such as Lewy bodies or Pick bodies and

demonstrate that the brain of most patients presenting with FTD lacks such specific inclusion bodies. Pathologically characterised by a neuronal loss in the frontotemporal cortex associated with moderate gliosis and microvacuolar spongiosis, this type of FTD was called dementia lacking distinctive histology (Knopman *et al.*, 1990) and has also been reported using other names like progressive subcortical gliosis and non-Pick form of FTD. We report a patient with the typical clinical features of FTD and pathologically confirmed dementia lacking distinctive histology.

Case report

A 44-year-old lady worked as computer clerk in a bank. She had a hysterectomy in October 1998 and on returning to work she found it difficult to do her usual work. She was abnormally slow, her speech was slow, she had some difficulty to find the correct words and she appeared distractable. According to her ex-husband, her behaviour was unusual and she appeared somewhat disinhibited on occasions. A neurologist saw her early April 1999. She appeared rather tense, her speech was described as slow, she did not know the day, the date, the month and the year. She knew the name of the hospital, did not know the name of the present king of Belgium, could perform simple subtractions but not a series of subtractions. By this time, she had stopped her work. Clinical and neurological examination was otherwise normal, there were no metabolic abnormalities, VDRL and tests for HIV virus were negative, brain MRI scan and an EEG were normal.

On admission at the end of April 1999, neurological examination was unremarkable. She appeared anxious and depressed and scored 26/30 on the MMS score. She had a slow speech without dysarthria and answered questions with some hesitation. Speech was characterised by circumlocutions with semantic and phonemic paraphasias. Reading and writing were noted to be abnormal. Performances on the Wisconsin card sorting test, the Stroop test and the Tower of London test were

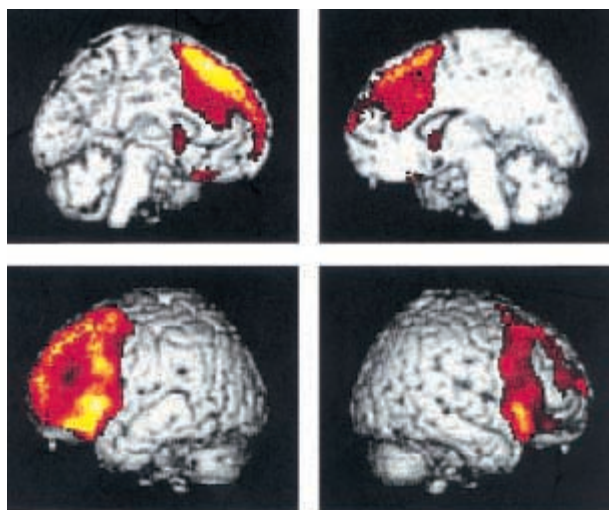


FIG. 1. — Display of cerebral areas with significant hypometabolism ($p < 0.001$ uncorrected) projected on a MRI template of the normal brain. Upper and lower images illustrated the mesial and lateral aspects of the brain, respectively. Right hemisphere is on the right. On first PET examination, hypometabolic areas are essentially prefrontal with left hemisphere predominance.

very poor. Positron emission tomography (PET) was performed using ^{18}F -2-fluoro-2-deoxy-D-glucose as a tracer of cerebral glucose metabolism (Fig. 1). Her cognitive and behavioural problems continued to deteriorate. By the end of the year 1999, she was unable to prepare a simple meal and to live alone. She neglected personal care, had to be prompted to wash and change clothes. She was reported to be aggressive occasionally and to have some paranoid thoughts. Speech fluency had deteriorated. When asked to name items she would buy when shopping, she only could name one. She could correctly name most objects of her surroundings, repetition of simple short sentences was often abnormal with marked perseveration. Comprehension was preserved for simple orders but reduced for more complex sentences. Writing sentences was abnormal (ex. “*Je veux me aller cinéma*” instead of “*Je veux aller au cinéma*”). She performed well, however, on memory testing (digit span, block tapping test, Grober and Busschke test). By February 2000, oral expression was reduced to grunting and occasional murmur of “*oui*”. She was able to follow simple commands with perseverations. When asked to follow simple written commands, she would copy the written order but not do what was written. She was able to write down her name and address with marked perseverations. Her behaviour became grossly abnormal over the following month with excessive eating, excessive and constant smoking. If she noticed some food dropping on the floor during a meal, she would throw herself to the floor and voraciously gulp the food down. She was totally mute by October 2000 and developed marked pout and

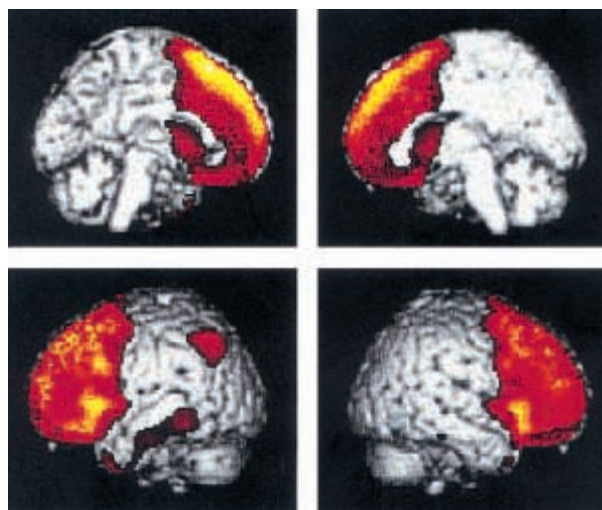


FIG. 2. — On the second PET examination, hypometabolism extends to symmetrically involve all lateral and mesial parts of the prefrontal regions. On this second PET, two complementary hypometabolic areas appear in the left parietal cortex and the inferior part of the left temporal lobe.

snout reflexes, no grasping was elicited. A second brain FDG-PET scan was performed (Fig. 2). Her family noticed that she would choke during meals but declined investigation and treatment. She died suddenly in February 2001, presumably after inhaling food. The family granted permission for autopsy of the brain.

PET RESULTS

Brain FDG-PET was obtained on 23/4/1999 (PET 1) and on 6/10/2000 (PET 2). The PET tomograph was a CTI-Siemens HR+ operated in 3D mode. Each scan was compared to a set of FDG-PET images from 27 controls (mean age 32 years) using the SPM99 software developed at the FIL (www.fil.ion.ucl.ac.uk/spm/spm99). We applied a statistical procedure designed to evaluate individual PET scans as in our previous study on temporal lobe epilepsy (Signorini *et al.*, 1999; Van Bogaert *et al.*, 2000). On PET 1, SPM analysis revealed a large hypometabolic cluster of voxels covering the whole prefrontal cortex and partially extending in the right prefrontal areas (Fig. 1). Mesial aspect of the frontal cortex was included in this hypometabolic area. The hypometabolism was significant at a “corrected” (i.e., when the correction for multiple comparisons is applied) p value < 0.0005 . Evaluation of cluster extend was significant (cluster-level $p < 0.0005$ corrected). On PET 2, the frontal hypometabolic area was more symmetrical than on PET 1 at a similar level of statistical significance (Fig. 2). It more extensively involved the right frontal lobe and the mesio-frontal regions including their most ventral portions. A parietal area of hypo-

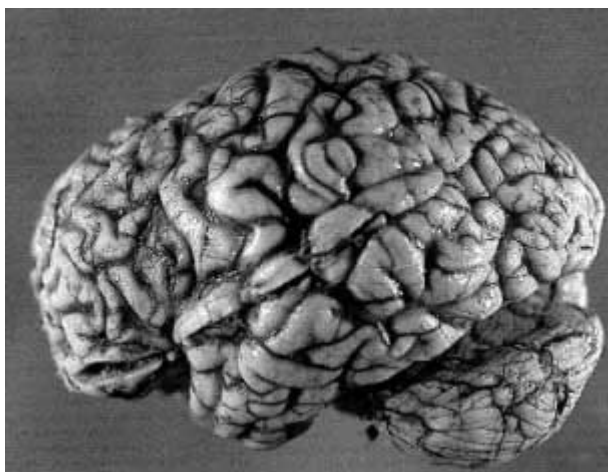


FIG. 3. — Left lateral view of the brain showing moderate atrophy of the frontal lobe.

metabolism, undetected on PET 1, was present on PET 2 (p value < 0.01 corrected, cluster-level $p < 0.0005$ corrected). A second area of hypometabolism which appeared on PET 2 concerned the inferior part of the temporal lobe (p value < 0.05 corrected, cluster-level $p < 0.0005$ corrected).

NEUROPATHOLOGICAL FINDINGS

The brain weighed 954 g. Gross examination revealed moderate, symmetrical cortical atrophy involving both frontal and anterior part of the temporal lobes (Fig. 3). The brain was cut in a coronal plane in successive 1 cm thick slices. There was a focal frontotemporal cortical thinning and sulcal widening with some moderate dilatation of the lateral ventricles and mild atrophy of the basal ganglia (Fig. 4). No focal lesions were observed. Locus niger and coeruleus appeared well-pigmented. Blocks of frontal, temporal, parietal and occipital cortex, hippocampus, basal ganglia, midbrain, pons and cerebellum were embedded in paraffin. Six μm slices were stained with Masson's trichrome, Klüver-Barrera and hematoxylin-eosin. Immunohistochemical examination was performed according to standard techniques using antibodies against following proteins: GFAP (Biogenex, 1:10), Tau (Zymed), Alpha-synuclein (Novocastra, 1:50), Beta-amyloid protein (Dako, 1:100), Ubiquitin (Dako, 1:100) and PrionProtein (Dako, 1:25, micro-wave antigen retrieval). Microscopical examination revealed neuronal loss in the frontal and anterior parts of the temporal cortex associated with subpial gliosis and microvacuolar spongiosis in the superficial cortical layers (Fig. 5). Some gliosis was also observed at the border of the cortex and underlying white matter (Fig. 6). With the exception of a few ubiquitinated inclusions in the granular neurons of the Ammon's horn, no specific inclusion bodies were observed with standard

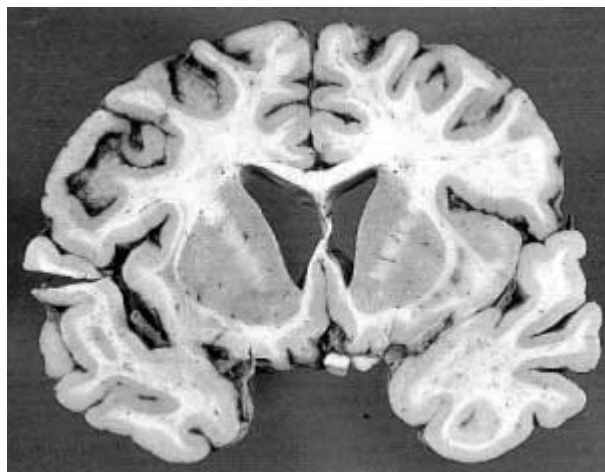


FIG. 4. — Coronal section of the brain through the anterior part of the basal ganglia illustrating the frontotemporal cortical atrophy.

staining and immunohistochemical techniques. There were no histological features of Alzheimer's disease, Pick's disease or Lewy body pathology. Negative results of immunohistochemical examination for Prion Protein and histological findings excluded the diagnosis of CJD. Brainstem, basal ganglia and cerebellum were unremarkable. The neuropathological findings lead to the diagnosis of dementia lacking distinctive histology.

Discussion

Frontotemporal dementia (FTD) is an important cause of dementia, especially before the age of 70 years. FTD represents the third most common cause of dementia following Alzheimer's disease and Lewy body dementia (Lowe and Spillantini, 1998; Neary *et al.*, 1998). Recently, clinical criteria for the diagnosis of FTD were proposed (Neary *et al.*, 1998). Three clinical subtypes are identified: frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia. Their onset is insidious and their progression slow. Early personality change and behavioural abnormalities are typical for FTD. Our patient developed progressively worsening behavioural disturbances including disinhibition, loss of insight, neglect of personal care, aggressiveness, perseverations and eating behaviour with hyperorality. Neuropsychological evaluation showed a strong impairment of the traditional frontal lobe measurements with initial relative preservation of memory and progressive loss of verbal fluency ending in mutism. Two successive PET scans showed bifrontal hypometabolism consistent with the diagnosis of FTD and different from what is observed in Alzheimer's disease and Lewy body dementia (Jagust, 2000). PET scans were performed in the early and late stage of her disorder. They revealed an extension of hypometabolism from prefrontal regions to other parts of

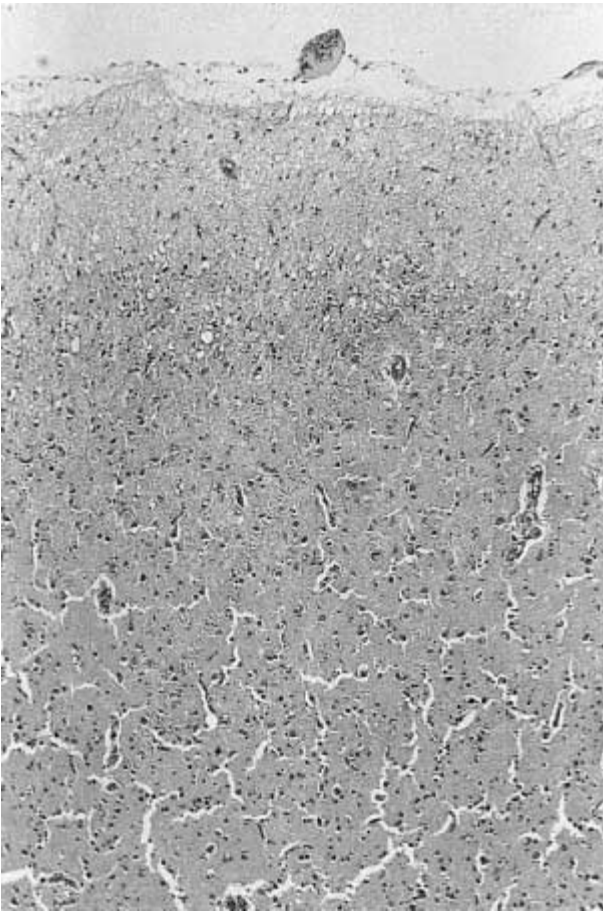


FIG. 5. — Photomicrograph of the left frontal cortex showing the microvacuolar spongiosis in the upper layers associated with neuronal loss and gliosis. Hematoxylin-Eosin, original magnification $\times 50$.

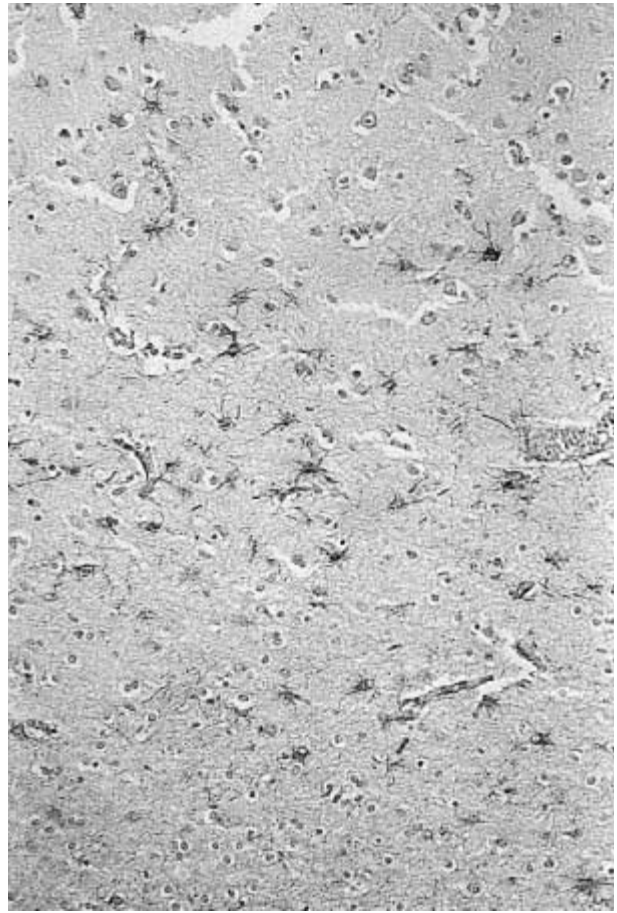


FIG. 6. — Photomicrograph of the left frontal cortex showing the moderate gliosis at the junction of the cortex and the white matter. GFAP, original magnification $\times 144$.

both frontal lobes in parallel with further cognitive decline. She died only 2 years after her first symptoms appeared. This short survival time is unusual but not exceptional since a variable duration of the disease has been reported ranging from 2 to 17 years (Dickson, 1998).

It has been shown that not all patients with dementia and frontal lobe dysfunction have FTD pathology (Rosen *et al.*, 2000) and that clinical presentation cannot predict the underlying pathology. Cognitive decline, behavioural changes and aphasia not rarely occur in the early stages of corticobasal degeneration (Bergeron *et al.*, 1998), as opposed to progressive supranuclear palsy where early severe dementia is rare. The term "Pick complex" has been suggested to stress the substantive overlap both clinically and pathologically between frontotemporal dementia, primary progressive aphasia and corticobasal degeneration (Kertesz *et al.*, 1999). Other possible diagnoses must sometimes be considered, like Creutzfeldt-Jacob disease or status lacunar (Rosen *et al.*, 2000). Neuropathological examination is therefore mandatory to establish a definite diagnosis. At the microscopical level, two main variants of histological changes are encountered in FTD. The first described and best

known entity is Pick's disease with its typical Pick bodies and ballooned achromatic neurones, the so-called Pick cells. Pick bodies are round, intracytoplasmic, argyrophilic inclusions that are composed of filamentous proteins containing an abnormal form of Tau protein structurally different from that found in Alzheimer's disease and progressive supranuclear palsy (Dickson, 1998). They are most often found in the cingulate, insular, temporal cortex and in the hippocampus especially in the granular neurones. Immunohistochemistry plays an essential role in the detection of the Pick bodies that are strongly positive for Tau with somewhat weaker staining for ubiquitin. They are negative for alpha-synuclein, which differentiates them from cortical Lewy bodies. Severe loss of large pyramidal neurones in the affected cortex associated with florid transcortical gliosis and fine spongiosis completes the neuropathological findings in Pick's disease. The second variant of FTD is characterised by microvacuolar spongiosis and severe neuronal loss mainly in the outer cortical layers, associated with moderate gliosis in the absence of any specific inclusion bodies (Mann, 1998). In some cases, cell loss in the pigmented neurones can be observed as well as some atrophy and gliosis in the basal gan-

glia. Some cases like our patient display a few ubiquitinated inclusions within the granular cells of the hippocampus. This second variant more frequently occurs than Pick's disease and has been reported under different names, including dementia lacking distinctive histology, frontotemporal lobar degeneration, diffuse subcortical gliosis and Pick's disease without Pick bodies (Knopman *et al.*, 1990 ; Neary *et al.*, 1998 ; Foster *et al.*, 1997). Patients with FTD have also been reported in association with motor neurone disease. Such patients present with dementia and usually die after 2-3 years due to respiratory failure consequent to bulbar involvement. The duration of this disease is shorter than that of FTD alone. In many cases the clinical signs of motor neurone involvement are not seen although confirmed at autopsy. Histologically, in addition to the microvacuolar spongiosis and gliosis, intraneuronal inclusions are found in the affected frontal and temporal cortex (Mann, 1998). These inclusions are immunoreactive for ubiquitin but not for tau and alpha-synuclein, what differentiates them from the Pick and Lewy bodies. Munoz (2000) proposed to call them ITSNU (Inclusions Tau and Synuclein Negative, Ubiquitinated). These ubiquitinated inclusions are found in the brain, brainstem and spinal cord and are entirely similar to those seen in classic motor neurone disease (Mann, 1998).

In almost half of the FTD cases, a strong familial occurrence is recorded with an autosomal dominant pattern of inheritance in 80% (Chow *et al.*, 1999). In the last decade, several families presenting with frontotemporal dementia and a parkinsonian syndrome have been identified linked to chromosome 17q21-22 (Spillantini *et al.*, 1998). The disease usually starts with behavioural disturbances and frontal lobe type impairment, followed in the later stage by a parkinsonian syndrome, often without resting tremor and generally little or no response to dopaminergic agents. The disease is known as "Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17)" (Foster *et al.*, 1997). Neuropathologically, atrophy of the frontal and temporal cortex is observed as well as of basal ganglia and substantia nigra. At the microscopical level, neuronal loss, gliosis, and tau deposits are seen both in neurones and glial cells (Spillantini *et al.*, 1998). Tau deposits found in this disorder as well as in other degenerative diseases lead to the introduction of a new category of disorders known as tauopathies. The group of tauopathies is not only composed of FTDP-17 and FTD, but also of Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, and tangle-only dementia. The distribution of tau deposits, the type of cells in which they are found, their structural and biochemical characteristics allow to make a pathological distinction between the different tauopathies. It was shown by Western

blot analysis that in several cases of dementia lacking distinctive histology, all six tau isoforms were dramatically reduced (Zhukareva *et al.*, 2001). This means that, although no specific tau deposits are found at autopsy, this type of FTD also belongs to the group of tauopathies. There is strong evidence that mutations in the gene for microtubule-associated protein (MAP) tau located at 17q21-22 cause the disease in at least some families with FTDP-17 (Poorkaj *et al.*, 1998). In one family, the disease has been linked to chromosome 3 (Brown *et al.*, 1995). It is still unclear if there exists a relationship between FTDP-17 and the more common FTD, which frequently occur either sporadically or with other familial cases but no clear mode of inheritance (Poorkaj *et al.*, 1998). There were no other known cases of dementia in our patient's family and DNA analysis of the tau gene was not performed. The relationship between genetic alterations and the clinical and pathological phenotype is not clear. Recently, the case of a man with FTD and his son with corticobasal degeneration was reported both with an identical mutation in the tau gene (Bugiani *et al.*, 1999). It seems likely that identification of new mutations in the tau gene and the discovery of new genes on other chromosomes linked with FTD and other tauopathies will lead to a genetic classification of these disorders (Lowe and Spillantini, 1998). In the mean time, detailed neuropathological examination with immunohistochemical evaluation remains essential for the definite diagnosis of the non-Alzheimer dementias.

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