Cerebrovascular Lesions in Patients with Frontotemporal Lobar Degeneration: A Neuropathological Study

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Abstract

Background: Cerebrovascular lesions are frequently observed in Alzheimer brains. Not all of them are due to cerebral amyloid angiopathy. Some of them are related to the severity of the degenerative process itself, implying additional vascular factors in the pathogenesis of Alzheimer’s dementia. The aim of the study was to investigate the impact of cerebrovascular pathology on brains with frontotemporal lobar degeneration (FTLD).

Patients and Methods: Twenty-two brains with autopsy-proven FTLD were compared to 15 brains of age-matched patients without evident cognitive decline, who died from an illness not related to a brain disease. The prevalence and the severity of small ischaemic and haemorrhagic lesions were determined. Vascular risk factors and the use of antithrombotic agents were also recorded.

Results: The patients with FTLD were heterogeneous concerning age of onset, disease duration, clinical presentation, genetic background and neuropathological typing. Cerebrovascular risk factors and lesions were overall rare in FTLD brains without differences in their prevalence and severity compared to the controls. Only white matter changes were more prevalent in the FTLD group (p = 0.04) and showed a trend to greater severity (p = 0.08).

Conclusions: Cerebrovascular pathology is not contributing to the evolution of the disease process of patients with FTLD. The isolated prevalence of white matter changes should not be considered as a vascular indicator.

Introduction

With the use of T2*-weighted magnetic resonance imaging, microbleeds are increasingly observed in patients with dementia [1]. They are seen in 17% of patients with various degrees of cognitive impairment [2] and also found in 5% of healthy adults [3]. These small bleeds are more frequent in brains of patients with Alzheimer’s dementia (AD) and with associated cerebral amyloid angiopathy [4–6]. However, not all cerebrovascular lesions in...
AD brains have to be attributed to cerebral amyloid angiopathy. Some of them are also related to the severity of the degenerative process itself, implying additional vascular factors in the pathogenesis of AD [7].

Also on comparing AD brains to small series of brains with other neurodegenerative dementias of age-matched elderly patients showed that small cerebral bleeds are frequently observed in Lewy body disease but not in frontotemporal lobar degeneration (FTLD) [5].

FTLD is a heterogeneous disorder with various clinical and histological subtypes [8–10]. FTLD is the second most common cause of presenile dementia with different genetic subtypes [11]. Despite the fact that most cases have a presenile onset, FTLD is not rare amongst elderly patients [12]. In a recent neuropathological study associated AD features were present in more than one third of the FTLD patients with late disease onset. Also 10% had moderate to severe atherosclerosis and micro-infarcts [13].

As most neurodegenerative diseases have frequently overlapping signs [14], the question arises whether cerebrovascular lesions can have an influence on the progression of the neurodegenerative process and on the cognitive decline of FTLD patients.

The present post-mortem study investigates the prevalence of cerebrovascular lesions and their responsible factors in a series of post-mortem brains from patients with FTLD, compared to normal controls.

Material and Methods

Dementia and Control Population

From 2000 to 2010, 155 consecutive patients with a clinical history of a neurodegenerative dementia came to autopsy: in 22 (14%) of them the neuropathological diagnosis of FTLD was made.

Twenty-one (95%) patients had been followed up in the Memory Clinic of the Lille University Hospital. One (5%) patient came from a general hospital, and detailed clinical data were not available.

During the same period of time, 15 post-mortem brains from controls were obtained. The controls consisted of brains of elderly patients without evident signs of cognitive decline and who died from an illness not related to a brain disease.

Neuropathological Analyses

The brain tissue samples were first used for diagnosis and afterward integrated in the Lille Neuro-Bank, dependent from the Lille University and cofederated by the Centre des Resources Biologiques, acting as institutional review board. The neuropathological evaluation was performed blinded to history and clinical data.

Neurodegenerative Lesions

The post-mortem diagnosis of FTLD was made according to the neuropathological diagnosis and the nosological criteria of the Consortium for Frontotemporal Lobar Degeneration [15]. Additional AD features were staged according to the classification of Braak and Braak [16].

Several small samples of cerebral cortex and hippocampus of one fresh cerebral hemisphere were taken for histochemical examination. The remaining brain was fixed in formalin, and, after 3 weeks, samples were taken from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulate gyrus, the basal nucleus of Meynert, the amygdaloid body, the hippocampus, basal ganglia, mesencephalon, pons, medulla and cerebellum. Slides from paraffin-embedded sections were immunostained for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin.

Cerebrovascular Lesions

The gross visible cerebrovascular lesions and the ones detected on microscopic examination of the small samples were carefully noted.

In addition, a whole coronal section of a cerebral hemisphere, at the level of the mammillary bodies, and a horizontal section through the mid pons and the cerebellar hemispheres were taken for the semi-quantitative evaluation of small microscopic lesions, after staining with haematoxylin-eosin, Luxol fast blue and Prussian Perl.

The considered cerebrovascular lesions were bleedings, infarcts and lacunes. White matter changes were also taken into account.

Microbleeds were defined as small macroscopically visible lesions of 1–3 mm diameter on gross examination. They consisted of red blood cells, when recent, and of macro- and siderophages, when older. Minibleeds were not visible macroscopically. They were found mainly located around small vessels on microscopic examination. Isolated Perl-positive deposits were not retained as minibleeds [5]. The term ‘minibleed’ was used to avoid confusion with the term ‘microbleed’, used in the magnetic resonance imaging literature [1–3].

The degree of white matter changes was mainly evaluated on the Luxol fast blue staining [17].

A semi-quantitative scale, ranking (R) 0–3, was used on the large coronal cerebral and on the horizontal brainstem and cerebellum section to evaluate the severity of the white matter changes and the frequency of micro-infarcts and of micro- and minibleeds. The latter were also evaluated according to their location in the cerebral cortex and cortical-subcortical junction, the deep white matter, the striatum, the thalamus, the pons and the cerebellar hemispheres.

The white matter changes were restricted to the periventricular regions (R1), scattered in the centrum semi-ovale (R2) or forming confluent lesions (R3). For the micro-infarcts and micro- and minibleeds, R1 corresponded to 1–2, R2 up to 5 and R3 to more than 5 lesions. Also the regional distribution of the minibleeds was determined.

The prevalence and the severity of cerebrovascular lesions in the brains with FTLD were compared to those of the controls.
Statistical Analyses
The statistical analysis compared the items of the FTLD group with the control group. Univariate comparisons of unpaired groups were done with Fisher’s exact test for categorical data. The non-parametric Mann-Whitney U test was used to compare continuous variables. The significance level was set at $\alpha = 0.05$, two-tailed.

Results
The most important demographic features, the clinical onset and phenotype of the disease, the genetic data, the neuropathological subtypes and the eventual associated histopathological features of the patients with FTLD are labelled in table 1. The median age at the clinical onset of the disease was 60 years (interquartile range IQR 47–66). The average disease duration was 7.9 years (SD 4.1). None of the brains showed cerebral amyloid angiopathy. Two brains of patients with FTLD had associated amyotrophic lateral sclerosis as cause of death. Two of them had also mild AD features.

The median age of the 22 deceased patients with FTLD was 69 years (IQR 57–78) versus 60 years (IQR 51–74) in the controls ($p = 0.36$). Male gender was 50% in the former and 60% in the latter group ($p = 0.74$).

The vascular risk factors and the use of antithrombotic treatment were similar in both groups (table 2).

Brains with white matter changes were more prevalent in the FTLD group than in the control ($p = 0.04$). The mean age of the deceased FTLD patients with white matter changes was 68 years (IQR 54–70) and 69 years (IQR 56–74) for those without ($p = 0.872$). There was no significant prevalence of other cerebrovascular lesions in the FTLD brains (table 3).

Quantification of the histological lesions did not show statistically significant differences, except for a moderate trend of severer white matter changes in the FTLD group.
compared to the control (p = 0.08). Also, according to their location, minibleeds were not severer in the FTLD brains than in the controls (table 4).

**Discussion**

In the present neuropathological study, the prevalence of cerebrovascular lesions was low in brains of patients with FTLD compared to controls. These findings are comparable to the results of previous studies [13, 18]. Only white matter changes were prevalent in the FTLD brains. They were not found to be related to age.

The distribution of the neuropathological subtypes of FTLD was more or less similar to that in previous large series [19]. A rapid progression of the disease with death within 5 years was observed in 8 cases (36%) [19]. Fused in sarcoma pathology was also observed in 3 young patients with disease onset before the age of 41 years and 1 above 50 years [20]. FTLD-TDP with progranulin mutation was found in 2 cases (fig. 1) [21, 22].

The low prevalence of cerebrovascular lesions, observed in post-mortem brains of patients with FTLD, is in contrast to the high prevalence in patients with AD [5, 6], stressing the importance of vascular risk factors in the pathogenesis of AD.

White matter changes are generally considered to be due to chronic ischaemia [23, 24]. However, in particular in AD, a correlation was observed between the severity of

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**Table 2.** Comparison of the number (percentages in parentheses) of patients with vascular risk factors and the use of antithrombotic medication among the group with FTLD and among controls

<table>
<thead>
<tr>
<th>Items</th>
<th>FTLD (n = 19)</th>
<th>Controls (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>3 (16)</td>
<td>1 (8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (6)</td>
<td>1 (8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>3 (16)</td>
<td>2 (15)</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
<td>1 (8)</td>
<td>0.42</td>
</tr>
<tr>
<td>Antithrombotic treatment</td>
<td>0</td>
<td>2 (15)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Table 3.** Comparison of the number (percentage in parentheses) of brains with cerebrovascular lesions among patients with FTLD and among controls

<table>
<thead>
<tr>
<th>Items</th>
<th>FTLD (n = 22)</th>
<th>Controls (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter changes</td>
<td>10 (45)</td>
<td>2 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>1 (5)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cortical territorial infarcts</td>
<td>1 (5)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cortical micro-infarcts</td>
<td>3 (14)</td>
<td>2 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>Haematomas</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>2 (9)</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Minibleeds</td>
<td>14 (64)</td>
<td>8 (53)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**Table 4.** Comparison of mean ranking scores with standard deviations of the severity of the cerebrovascular lesions in post-mortem brains among patients with FTLD and among controls

<table>
<thead>
<tr>
<th>Items</th>
<th>FTLD (n = 22)</th>
<th>Controls (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter changes</td>
<td>0.64 ± 0.80</td>
<td>0.13 ± 0.35</td>
<td>0.08</td>
</tr>
<tr>
<td>Lacunes</td>
<td>0.05 ± 0.21</td>
<td>0.0 ± 0.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Cortical micro-infarcts</td>
<td>0.15 ± 0.37</td>
<td>0.13 ± 0.35</td>
<td>0.99</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>0.09 ± 0.29</td>
<td>0.0 ± 0.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Minibleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.95 ± 0.95</td>
<td>0.53 ± 0.52</td>
<td>0.26</td>
</tr>
<tr>
<td>Corticosubcortical</td>
<td>0.82 ± 0.91</td>
<td>0.33 ± 0.49</td>
<td>0.14</td>
</tr>
<tr>
<td>Centrum semi-oval</td>
<td>0.50 ± 0.74</td>
<td>0.47 ± 0.64</td>
<td>0.99</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.14 ± 0.35</td>
<td>0.13 ± 0.35</td>
<td>0.99</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.09 ± 0.43</td>
<td>0.07 ± 0.26</td>
<td>0.94</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.14 ± 0.64</td>
<td>0.0 ± 0.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.18 ± 0.50</td>
<td>0.20 ± 0.41</td>
<td>0.80</td>
</tr>
</tbody>
</table>

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Fig. 1. Widespread neuronal degeneration in the frontal cortex with one TDP-43-positive neuron (arrow) in the post-mortem brain of an 86-year-old woman with FTLD-TDP type 3.
the neurofibrillary pathology and the extension of the white matter changes [25, 26]. Also white matter changes in the prefrontal regions were found to be the most vulnerable to ageing in healthy subjects [27]. As typical cerebrovascular lesions are absent in the FTLD brains, one should not consider the isolated prevalence of white matter changes as the expression of chronic ischaemia but rather as the result of secondary axonal degeneration due to the cortical neuronal loss. On review of the literature, we found only one case report describing severe bifrontal white matter changes in a 76-year-old patient with amyotrophic lateral sclerosis and FTLD [28].

In conclusion, although FTLD is a heterogeneous disorder with sometimes overlapping features, vascular pathology is not contributing to the disease process.

In the future 7.0-tesla magnetic resonance imaging should be a technique of choice in conjunction with the neuropathological data to detect small cerebrovascular lesions in post-mortem brains with neurodegenerative diseases [29, 30].

References


