The Diagnostic Challenge of Frontal Alzheimer's Disease: Case Report and Literature Review

Soreya Belarbi
Department of Neurology, Ali Ait Idir Hospital, Algiers, Algeria
Mokrane Samira Makri
Department of Neurology, Ali Ait Idir Hospital, Algiers, Algeria

Abstract

Atypical forms of Alzheimer's disease (AD) have long been described, but it's only recently that the aphasic, frontal, and visuospatial variants have been included in the clinical diagnostic and research criteria for AD. The frontal form, also known as the behavioral and/or dysexecutive form of AD, is still a poorly understood and poorly defined entity. Patients present with either behavioral or executive disorders, or both. It is now possible to establish, in vivo, a diagnosis of frontal variant AD (fv-AD) with a high degree of probability by comparing the neuropsychological profile and biomarkers. However, the neuropsychological and behavioral profile of patients with fv-AD is still poorly understood, often leading to diagnostic difficulties and confusion with the behavioral variant of frontotemporal lobar degeneration (bv-FTLD), which is the main differential diagnosis. We will illustrate the difficulties sometimes encountered in practice in the differential diagnosis between these pathologies through a clinical observation.

Introduction

Alzheimer’s disease (AD) is a very common degenerative pathology whose prevalence increases with age (from 5% over the age of 65 to 30% over the age of 80) [1]. In its classic form, AD is characterized by an initial prominent episodic memory deficit, combined with difficulties in other cognitive domains [1]. In the early stages of the disease, however, some patients may show isolated impairment in a particular non-memory cognitive domain. Neurocognitive studies have long made it possible to distinguish subgroups of AD patients who present verbal (mainly logopenic aphasia) or visuo-spatial (posterior cortical atrophy) disorders that are isolated or largely predominant in relation to other cognitive deficits [2-5]. Language or visuospatial deficits are present at all stages [5], regardless of the severity of the disease.

The scientific literature has long focused on validating the existence of a frontal variant of the disease rather than studying it per se. Although these variants have long been described, their validation as AD variants is recent and seems to coincide with the more systematic use of biomarkers in the diagnosis of this condition. Recently, the three AD variants (aphasic, visual-spatial and frontal) have been included in the revised diagnostic criteria for the disease established by the National Institute on Aging and Alzheimer’s Association (NIA-AA) think-tank [1], as well as in the research criteria established by the International Working Group [6]. These variables represent one extreme on a continuum of variations in the presentation of AD, from the most usual and canonical forms to the rarest forms, without being strictly spoken atypical [7]. Patients with these particular forms of AD show the same biomarker changes in vivo as patients with classic AD, including cerebrospinal fluid markers and the demonstration of amyloid deposits on positron emission tomography [8].

The frontal form, which is also called behavioral and/or dysexecutive AD, is an entity that is still poorly understood and defined. The concept of frontal AD was cited by Johnson et al. in 1999 in an Archives of Neurology article entitled "Clinical and pathological..."
evidence for a frontal variant of Alzheimer disease". This involved the study of 3 patients with a predominantly dysexecutive syndrome, in whom it was shown that, for the same amyloid load, the neurofibrillary degeneration component was more marked in the frontal lobe [9]. Patients with a frontal form of AD present either behavioral or executive disorders, or both. However, the few descriptive studies also point to the presence of more significant memory disorders than in the frontal form of frontotemporal degeneration, which is the main differential diagnosis. This form affects younger people than AD, and progresses more rapidly. There are many discrepancies between the frontal clinical presentation and imaging or neuropathological studies, which do not always reveal specific frontal lobe involvement. We report a case of frontal AD that posed a problem of differential diagnosis with a frontal variant of frontotemporal degeneration (fv-DFT).

Observation
Mr F., aged 70, with a cultural level (CL7) (according to the Barbizet scale), with a family history of AD in his mother”, came to our memory consultation, accompanied by his daughter, a doctor. Over the past two years, her daughter has observed that her father has undergone changes. While he used to be elegant, he’s now not paying attention to his clothes. His behavior is uninhibited (verbal and sexual disinhibition). He’s lost all social propriety and good manners, even though he’s reputed to be a distinguished and courteous person. She also noted a loss of empathy, gestural stereotypies and apathy. The patient is anosognosic. The psycho-behavioural problems progressively worsened, and were followed by language problems, such as a lack of words, as well as planning and reasoning problems. Her father’s memory, however, is relatively good according to her. This patient underwent:

- A neurological examination, which came back normal.
- A neuropsychological and neuropsychiatric evaluation, including:
  - A Mini Mental State Exam (MMSE), for global cognitive assessment.
  - Dubois 5-word test, to assess verbal episodic memory.
  - Grober and Buschke test (16 words), to assess verbal episodic memory.
  - The DMS 48 "Delayed matching to sample 48 items", to assess visual recognition memory. Digit span test "Forward and Backward", to assess short-term and working memory.
  - The Frontal Assessment Battery "FAB", for assessing executive functions.
  - The Mattis Dementia Rating Scale (MDRS), to assess executive functions.
  - Trail Making Test A and B. "TMT-A, TMT-B, to assess attention and mental flexibility.
  - The “Animals” categorical verbal fluency test.
  - A Clock Test, to assess visuospatial functions.
  - Assessment of reflexive praxis.
  - Assessment of functional autonomy using the IADL (Instrumental Activities of Daily Living) scale.
  - Assessment of behavioral disorders using the "FDS" frontal dysfunction scale.

The neuropsychological evaluation revealed (Table 1):
- Dysexecutive syndrome with mental flexibility disorders and loss of inhibitory control.
- Attention disorders.
- Decreased verbal fluency.
- Constructive apraxia (Figure 1).
- Visuospatial disorders (Figure 2).
- No impairment of episodic memory.
- No impairment of short-term or working memory.
- Absence of reflexive apraxia.
- Brain MRI showing hippocampal atrophy (figure 3).
- Biological work-up (standard work-up, thyroid work-up with anti-thyroperoxidase antibodies "AC anti TPO", vitamin B12, folic acid and homocysteine), which came back without any abnormalities.

Figure 1: Constructive Apraxia

Figure 2: Visual-Spatial Disorder
Figure 3: Bilateral Hippocampal Atrophy

Table 1: Neuropsychological, Biological and Radiological Data

<table>
<thead>
<tr>
<th>Neurological examination</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychological assessment MMSE</td>
<td>27/30</td>
</tr>
<tr>
<td>Dubois 5-word test</td>
<td>10/10</td>
</tr>
<tr>
<td>Grober and Buschke Immediate recall</td>
<td>14/16</td>
</tr>
<tr>
<td>Recognition</td>
<td>16/16</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>16/16</td>
</tr>
<tr>
<td>DMS 48 Set 1</td>
<td>95%</td>
</tr>
<tr>
<td>Set 2</td>
<td>93%</td>
</tr>
<tr>
<td>Digit Span test Forward</td>
<td>5</td>
</tr>
<tr>
<td>Backward</td>
<td>4</td>
</tr>
<tr>
<td>FAB [GO-NO-GO ]</td>
<td>14/18 [1/3]</td>
</tr>
<tr>
<td>The Mattis Dementia Rating Scale (MDRS)</td>
<td>122/144 ↓</td>
</tr>
<tr>
<td>Trail Making Test TMT A</td>
<td>193 secondes ↑↑↑</td>
</tr>
<tr>
<td>TMT B</td>
<td>653 secondes ↑↑↑</td>
</tr>
<tr>
<td>Verbal fluency “Animals”</td>
<td>10 in 2 minutes ↓</td>
</tr>
<tr>
<td>A Clock Test</td>
<td>0/7</td>
</tr>
<tr>
<td>Reflexive Praxis</td>
<td>50/50</td>
</tr>
<tr>
<td>IADL</td>
<td>1/4</td>
</tr>
<tr>
<td>FDS</td>
<td>4/4</td>
</tr>
<tr>
<td>Biological tests</td>
<td>Normal</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Hippocampal atrophy</td>
</tr>
</tbody>
</table>

According to the 2011 Rascovsky criteria [10], the patient meets the diagnosis of a possible frontal variant of frontotemporal lobar degeneration “fv-DLFT” with inaugural behavioural disorders, a marked dysexecutive syndrome on the MATTIS and TMT-B, and mild impairment of episodic memory on the DMS48 (Table 1). This patient was suspected of having frontal-onset Alzheimer’s disease due to:

- The presence of hippocampal atrophy on brain MRI
- The presence of visuospatial disorders on the Clock Test.
- The presence of constructive apraxia.

There were 2 competing diagnostic hypotheses: fv-AD and fv-FTLD, and it was impossible to make a decision based on neuropsychological and radiological data alone, even though there were several arguments in favor of fv-AD.

As a result, a lumbar puncture (LP) with cerebrospinal fluid (CSF) assay for AD markers "Amyloid B1-42 protein (AB1-42), total tau protein (T-Tau), phospho tau (P-Tau) and calculation of the INNOTEST amyloid tau index (IATI) and the AB42/P-Tau ratio" was recommended. Assays for the three biomarkers were performed using ELISA kits and enzyme-linked immunosorbent assays: Innotest TAU Ag®, Innotest PHOSPHO-TAU(181P)* and Innotest β-AMYLOID(1-42)*. The biological profile, with the presence of the pathophysiological markers of AD “AB1-42 ↓, T-Tau ↑ and P-Tau ↑, IATI< 0.8 and AB1-42/P-Tau >9”(cf. Table n°2), led to the diagnosis of frontal form AD, based on the criteria of the IWG2 (International Working Group) [11].

Table 2: Results of AD Biomarkers in CSF

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Limit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB1-42 (pg/ml)</td>
<td>550 pg/ml</td>
<td>412 ↓</td>
</tr>
<tr>
<td>T-tau (pg/ml)</td>
<td>450 pg/ml</td>
<td>573 ↑</td>
</tr>
<tr>
<td>P-tau (pg/ml)</td>
<td>60 pg/ml</td>
<td>99 ↑</td>
</tr>
<tr>
<td>IATI</td>
<td>0.8</td>
<td>0.45 ↓</td>
</tr>
<tr>
<td>AB1-42/ P-tau</td>
<td>9</td>
<td>4,16 ↓</td>
</tr>
</tbody>
</table>

The patient was treated with Donepezil 5mg and 10mg anti-cholinesterase drugs, followed by Mémantine, an anti-glutamate drug. After 3 years of evolution from the onset of the disorders, the patient had clearly worsened. Psychotic disorders set in, with visual hallucinations, prosopagnosia and praxis disorders “apraxia of dressing and ideational apraxia”.

Discussion

Here, we describe the clinical, neuropsychological, neuroimaging and biofluidic biomarker features of a patient with fv-AD. The patient presented with progressive cognitive impairment associated with behavioral symptoms, mainly apathy and disinhbition. Neuropsychological examination showed impairment in several cognitive domains, with prominent features of the dysexecutive syndrome, mimicking fv-FTLD. However, brain MRI showed hippocampal atrophy and some elements of the neuropsychological assessment.
"visuospatial disorders and praxis disorders", suggested the diagnosis of AD vf in the patient. The study of CSF biomarkers, which showed low levels of Aβ1-42, high levels of total tau and phospho tau, was consistent with the diagnosis of AD [12]. Our patient with a predominantly behavioral presentation fits the diagnosis of fv-AD with evidence of biomarkers of AD pathology.

According to Ossenkoppele et al [13], the term "fv-AD" refers to patients with biologically proven AD and a clinical profile in which behavioral and dysexecutive disorders are prominent. These reasons why some patients develop this clinical variant are unknown and debated. It could be the consequence of more advanced disease, a different clinical expression of AD illustrating its heterogeneity, or the co-occurrence of AD and fv-DLFT [14-16].

A study of a small series of patients showed that the clinical criteria for fv-DLFT can correspond to histologically confirmed AD [17]. On the other hand, in an autopsy series of 60 patients with a clinical diagnosis of vf-DLFT, 7% had histologically confirmed AD, and 10% a combination of both diseases [14]. The existence of these different profiles has subsequently been suggested by several studies [18-20]. The presence of a similar case in our patient could be linked to a mutation in the PSN1 gene. Raux et al. 2000 [21] reported a family case of frontal AD, linked to a mutation in the PSN1 gene, whose autopsy confirmed the lesions characteristic of AD.

The clinical distinction between AD and the frontal variant of FTLD (fv-FTLD) is sometimes difficult, as some symptoms may be common to both conditions, leading in some cases to similar clinical profiles [22].

In a study investigating the sensitivity of criteria established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association [23] to distinguish patients with AD from those with fv-FTLD, Varma et al [21] showed that 29 of 30 AD patients met the criteria for AD, but that 20 of 26 fv-FTLD patients met both AD and fv-FTLD criteria. These results suggest a high sensitivity but low specificity of these former AD criteria. For example, the fv-FTLD criteria do not exclude the presence of deficits in tests assessing episodic memory, without specifying that strategic retrieval is the most impaired process (unlike encoding in AD) [10].

Patients with fv-FTLD may present memory disorders from the earliest stages of the disease, making the distinction between the two pathologies tricky [24]. Moreover, early executive disorders have long been specifically attributed to patients with fv-FTLD, whereas studies show that early executive function deficits may exist in AD [25]. Concerning the distinction between classic AD and fv-AD, while patients with a typical AD presentation are often aware of their memory difficulties, at least in the early stages of the disease, patients with fv-AD are less aware of their disorders [26, 27]. Some authors suggest that anosognosia is linked to frontal abnormalities and may develop in the early stages of the disease [26].

Few studies have looked specifically at behavioral problems in patients with fv-AD. Studies comparing fv-AD patients with fv-FTLD patients report conflicting results. A study comparing 18 patients with fv-AD with 26 patients with fv-FTLD showed that both groups of patients had similar levels of behavioural disturbance, as measured by the Frontal Behavioral Inventory (FBI) [28]. Item-by-item analysis of responses revealed more hyperorality in fv-FTLD patients and more aspontaneity in fv-AD patients. However, no information on biomarkers to confirm patients’ fv-AD diagnosis is reported in this study. Patients with fv-AD are reported to have behavioral disorders of lesser magnitude than patients with fv-FTLD [29-32], but to have more personality changes [29]. There may even be purely dysexecutive variants of fv-AD in which behavioral disorders are not present [31]. One retrospective study showed that patients with fv-AD tend to show more frequent apathy, disinhibition, and loss of empathy and less perseverative compulsive behavior or hyperorality compared to patients with fv-FTLD [30,33].

The same study also used "behavioral/dysexecutive" variant instead of “frontal” variant to address the relatively symmetric and insignificant atrophy in frontal lobes and some distinct clinical patterns between behavioral and dysexecutive forms. Motor presentations may also differ between fv-AD and FTLD because myoclonus tends to favor fv-AD and early parkinsonism suggests FTD [33].

Cases of vf-MA are frequent, and it is important to identify them correctly in order to avoid misdiagnosis and improve intake. In this context, the assessment of social cognition appears to be able to make an important contribution. The fv-AD showed a similar though slightly milder pattern of social cognition deficits as observed in bvFTD, characterized by deficits in emotion recognition, empathy, and knowledge of social norms, with a similar eyetracking signature to bvFTD. Compared to typical AD, fv-AD showed social cognition impairments in emotion recognition and knowledge of social norms and divergent eye movement patterns.

At present, the differential diagnosis between AD and fv-FTLD remains difficult in some cases. In such cases, biomarker analysis is currently essential to distinguish between the two, with a specificity of 85% [34]. The CSF Aβ1-42, Aβ1-42/Aβ1-40 ratio, and tau (especially phosphorlated tau) serve as biomarkers for AD [35], whereas in FTD, only a nonspecific increase in tau is involved because of neurodegeneration.
Conclusion
Although the differential diagnosis between different neurodegenerative diseases has improved considerably in recent years, diagnostic difficulties may still arise. Patients with fv-AD have a clinical profile almost similar to that of patients with fv-FLDT, with cognitive and behavioural dysexecutive syndrome in the foreground and memory disorders, often in the background. Cerebral imaging and cerebrospinal fluid biomarkers, combined with the atrophy profile, enable us to pinpoint the underlying neuropathology in most cases.

Conflict of Interests
Authors declare no conflict of interest.

References


