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Review Article

Atypical Presentations of Alzheimer's Disease: Beyond Amnestic Dementia

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ABSTRACT

Neuropathological and biomarker-based studies indicate that Alzheimer's disease may sometimes present not with the typical amnestic dementia syndrome of the hippocampal type but with atypical clinical pictures. Atypical presentations include frontal dementia sometimes with additional behavioural component mimicking frontotemporal dementia, logopenic primary progressive aphasia and posterior cortical atrophy, while mixed presentations include patients with additional vascular or Lewy body pathology. More atypical presentations include non-logopenic (semantic, non-fluent agrammatic and unclassifiable) primary progressive aphasia, corticobasal syndrome and cases mixed with normal pressure hydrocephalus. Atypical clinical presentations of Alzheimer's disease may be more common than previously thought. Cerebrospinal fluid levels of biomarkers such as amyloid beta peptide, hyperphosphorylated tau protein and total tau protein, may offer a useful tool for correct ante mortem identification of such patients, which is likely to affect therapeutic decisions.

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Introduction

Traditionally, Alzheimer's disease (AD) was considered synonymous to amnestic dementia, according to diagnostic criteria suggested 30 years ago [1]. However, pathological studies suggested that AD patients may present at pre-dementia stages or with atypical clinical pictures, including primary progressive aphasia (PPA), corticobasal syndrome (CBS), posterior cortical atrophy (PCA) and frontotemporal dementia (FTD)-like frontal or frontal-behavioural syndrome or may be mixed with other conditions, such as cerebrovascular and Lewy body pathology [2-8]. Besides neuroimaging, cerebrospinal fluid (CSF) biomarkers offered a major contribution for the *in vivo* recognition of these unusual presentations of AD, since they may identify the biochemical 'fingerprint' of AD during life [9-11]. This expanded concept of AD has been incorporated in diagnostic criteria and AD is now viewed *in vivo* as a biological process, regardless of the presence or absence of symptoms and their type or severity [12-16]. Early, accurate diagnosis of unusual AD presentations, as well as exclusion of other primary or secondary

causes of dementia, reduces diagnostic uncertainty and may have significant implications in therapeutic decisions and prediction of prognosis [17-19].

Atypical Presentations of Alzheimer's Disease

Community oriented studies suggest that the percentage of atypical AD presentations may be 16% but it may reach 37-46% according to studies conducted in research centers [20-22]. Additionally, atypical presentations are known to be overrepresented in early-onset AD [23]. Besides the atypical presentations described in research criteria (mixed, frontal, posterior, logopenic) other, more atypical presentations, not clearly recognized in diagnostic or research criteria for AD do exist [13-15].

Non-logopenic PPA presentations of AD have been described in neuropathological and CSF biomarker studies, with AD being the underlying cause, not only in more than half (~75-86%) of the patients

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with logopenic, but also in ~20% of the non-fluent agrammatic and ~16-35% of the semantic subtypes of PPA [3, 24-28]. AD may be the underlying pathology in 30-38% of the patients fulfilling even the criteria for probable CBD [4, 29, 30]. A CSF biomarker profile compatible with AD has been reported in up to 10% of PSP patients, but it is not sure if they represent an atypical presentation of AD or mixed pathology [29]. Mixed cases with NPH are known to exist for a long time now. AD and/or cerebrovascular pathology may be present in ~¾ of NPH patients [31]. CSF biomarkers may offer a useful tool for identification of AD coexistence which, in turn, may affect therapeutic decisions since it may predict a worse neurosurgical outcome, although there might be some sort of improvement in the quality of life [32-34].

Concluding Remarks

Atypical clinical presentations of AD are not uncommon and CSF biomarkers seem to offer a useful index for ante mortem identification of most such patients in routine practice, especially in cases mixed with vascular or Lewy-body pathology, and in some atypical presentations such as PPA, CBS, frontal dysexecutive and/or behavioural syndrome or PCA [28, 35-48]. It is unknown whether currently available treatments for AD have the same effectiveness in atypical as in typical amnesic presentations. However, accurate diagnosis is possible to have an impact on therapeutic decisions both nowadays and especially in the future where new treatments targeting specific AD biochemical mechanisms are anticipated [49]. Non-logopenic language presentations, corticobasal syndrome presentations, and presentations mixed with NPH should be incorporated in newer versions of clinical or research criteria for AD. Rarely, mixed neurodegenerative pathologies may increase clinical diagnostic vagueness, requiring postmortem pathological verification.

Table 1: Clinical presentations of Alzheimer's disease.

Typical amnesic presentation (of the hippocampal type)
Atypical presentations
Frontal dysexecutive and/or behavioral presentation
Language presentation
Logopenic
Non-fluent agrammatic
Semantic
Other
Posterior cortical atrophy
Corticobasal syndrome
Mixed types
With cerebrovascular disease
With Lewy-body pathology
With normal pressure hydrocephalus
Rapidly progressive dementia

Conflicts of Interest

None.

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