CASE REPORT

Biparietal variant of Alzheimer's disease: a rare presentation of a common disease

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SUMMARY

Alzheimer's disease (AD) is a clinically heterogeneous disease that may have atypical presentations with focal cortical syndromes and relatively preserved episodic memory. The posterior variant of AD has two subtypes: occipitotemporal, presenting with visuoperceptive impairment, and biparietal, presenting with visuospatial dysfunction and apraxia. We report a case of a 51-year-old woman with progressive limb apraxia and choreiform movements. Her neuropsychological evaluation was compatible with dementia, and revealed ideomotor and ideational limb apraxia, severe visuoconstructive ability impairment, dyscalculia and posterior aphasia. Workup excluded metabolic, infectious, inflammatory or neoplastic causes, and hereditary conditions as Huntington's disease and familial AD. Cerebrospinal fluid biomarkers revealed β-amyloid reduction and τ protein increase. Brain imaging showed marked biparietal atrophy and hypoperfusion, and widespread cortical β-amyloid deposition. Biparietal variant of AD was diagnosed and acetylcholinesterase inhibitor treatment induced clinical stabilisation. AD may present with atypical features and a high clinical suspicion is necessary for an early diagnosis.

BACKGROUND

According to the original criteria,[1] Alzheimer's disease (AD) was assumed to be a clinically homogeneous disease, with memory impairment being the initial and dominant feature.[2–5] Nonetheless, atypical clinical presentations, mainly with aphasic and frontal-executive profiles, have been frequently described in patients with pathologically confirmed diagnosis of AD.[6–8] In 2011, the new criteria from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD proposed three non-amnestic presentations: language and visuospatial presentations, and frontal dysfunction.[9] Recently, the International Working Group published the IWG-2 criteria[10] and proposed specific diagnostic criteria for the atypical forms of AD, including a posterior, logopenic and frontal variant. These AD variants usually present as focal cortical syndromes with predominant impairment of cognitive functions other than episodic memory, such as visual perception, visuospatial functions, language or frontal functions.[5–8 11–13]

We report the case of a 51-year-old woman presenting with limb apraxia, posterior aphasia, impairment of visuospatial functions and choreiform limb movements associated with marked biparietal atrophy and hypoperfusion on neuroimaging, investigation of which ultimately allowed the diagnosis of a rare atypical presentation of AD, the biparietal variant of AD.

CASE PRESENTATION

A 51-year-old right-handed housewife with 4 years of formal education reported progressive difficulty with object manipulation leading to a compromise of manual tasks. During the next 2 years she also developed involuntary movements of the limbs and gradually lost the ability to write and perform daily household activities.

Her medical history was unremarkable and she had no family history of dementia. There was a history of alcohol abuse in multiple elements of the family, including her father, brother, uncle and cousin, and a history of suicide in her brother and uncle.

The neurological examination revealed severe bilateral ideomotor apraxia and choreiform movements of the limbs, both more pronounced in the distal left upper extremity; hyperactive tendon reflexes and positive glabellar; and snout and palmomental reflexes. The patient's brief cognitive status was compatible with dementia, with a score of 21/30 on the Mini-Mental State Examination (MMSE), a score of 14/30 on the Montreal Cognitive Assessment and a score of 21/60 on the Alzheimer's Disease Assessment Scale-Cognitive.

INVESTIGATIONS

A comprehensive neuropsychological assessment identified ideomotor and ideational apraxia, severe impairment of visuoconstructive ability (figure 1), agraphia, dyscalculia and posterior aphasia (with anomia, semantic paraphasias and impaired comprehension of complex verbal information). Frontal functions such as Luria sequences, verbal initiative, graph-motor flexibility and abstract reasoning were moderately compromised. A mild impairment of visual and verbal episodic memory was also identified, but her orientation to time, space and person was preserved.

Blood workup, including complete blood count, coagulation study, biochemistry, erythrocyte sedimentation rate, C reactive protein, protein electrophoresis, folic acid, cyanocobalamin, thyroid function tests, serological testing (*Treponema pallidum*, *Borrelia burgdorferi* and *Brucella*) and progranulin measurement were unremarkable, as were cerebrospinal fluid (CSF) cytochemical analysis, direct microscopy and cultures. CSF biomarkers study showed a marked reduction of β-amyloid (Aβ) protein levels (122.7 pg/mL; normal values >500 pg/mL), very high titres of τ protein

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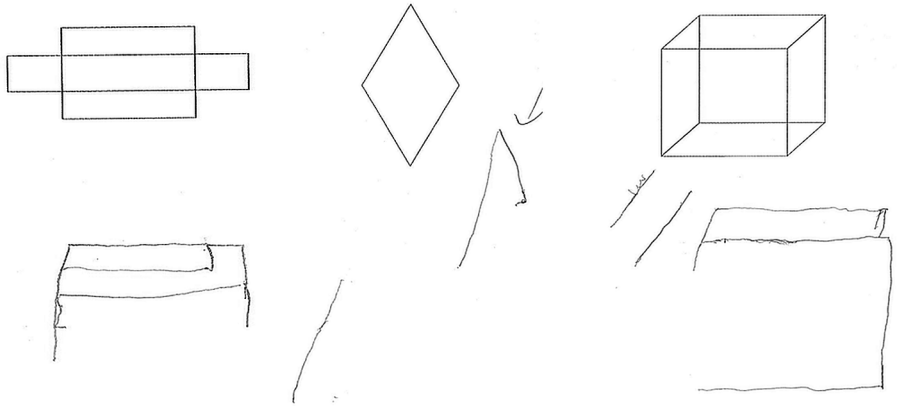

Figure 1 Patient copies of figures revealing constructional apraxia.

(1106.8 pg/mL; normal values 119.4±30.4 pg/mL) and borderline levels of phosphorylated τ protein (61 pg/mL; normal values <61 pg/mL).

Brain MRI revealed marked bilateral parietal atrophy and moderate bilateral frontal, temporal and occipital atrophy, with relative preservation of hippocampal volumes (figure 2). Brain single photon emission CT (SPECT) imaging revealed severe hypoperfusion in the parietal lobes and mild bilateral frontal and temporal hypoperfusion (figure 3). Positron emission tomography with ^{11}C-Pittsburgh compound B positron emission tomography (PiB-PET) revealed marked and diffuse increase in Aβ deposition in cerebral cortex and caudate nuclei (figure 4).

Apolipoprotein E (ApoE) genotyping revealed ε3/ε3 genotype. Genetic testing was negative for mutation analysis for Huntington's disease, Huntington's disease-like (HDL)-1 and HDL-2, dentatorubropallidoluysian atrophy (DPRLA), spinocerebellar ataxia 17 (SCA17), neuroferritinopathy and AD, including presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP) mutations.

TREATMENT, OUTCOME AND FOLLOW-UP

Treatment with an acetylcholinesterase inhibitor (donepezil, 10 mg/day) induced clinical stabilisation and the patient presented a MMSE score of 20/30 after 2 years of treatment.

DISCUSSION

Atypical presentations of AD are estimated to occur in 6–14% of cases and usually start at an earlier age than typical AD, presenting with predominant focal cortical deficits other than episodic memory, which is usually relatively well preserved until late in the course of the disease.[5–8 11–14] In these atypical forms, the neuropsychological profile and neuroimaging findings have been found to reflect the clinical syndrome and to correlate with the distribution of AD pathology, suggesting that the

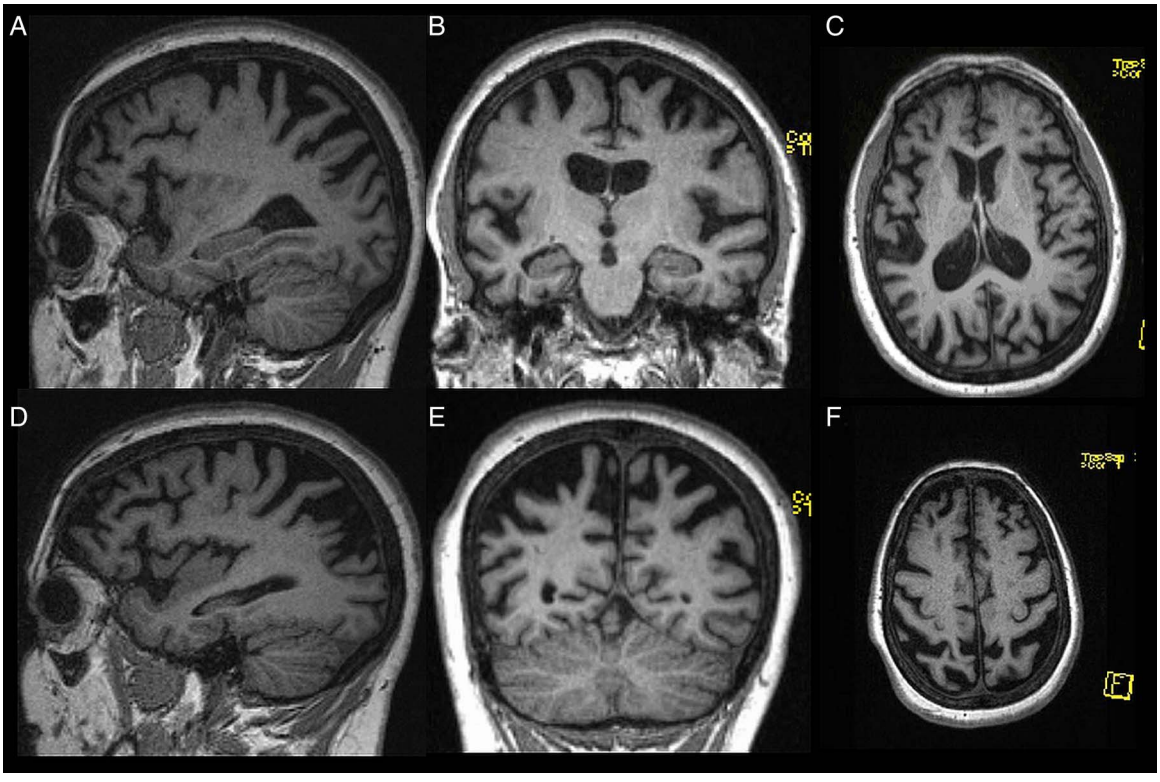

Figure 2 Brain MRI showing marked atrophy of both parietal lobes and moderate atrophy of the frontal, temporal and occipital lobes. Hippocampal volumes are relatively preserved.

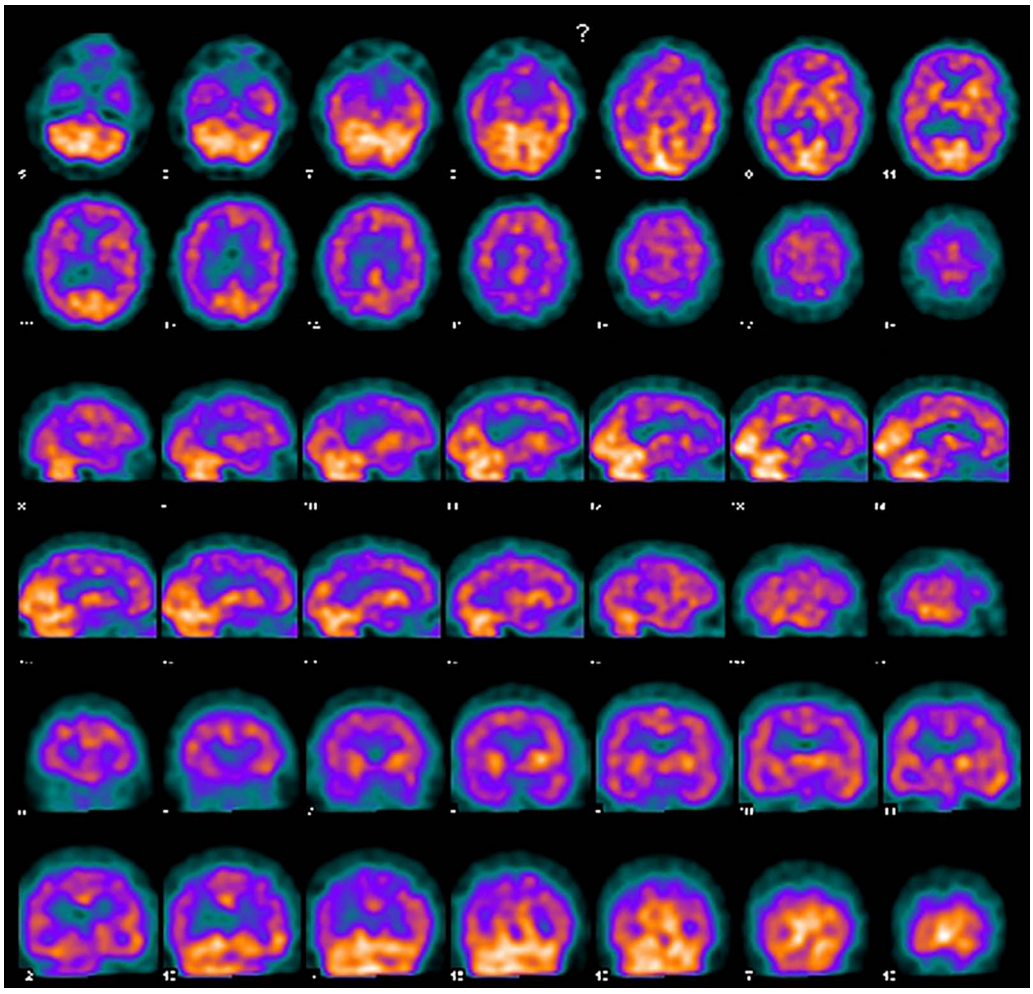

Figure 3 Brain single photon emission CT scan showing severe hypoperfusion of both parietal lobes, more marked on the right, and mild hypoperfusion of frontal and temporal lobes.

distribution of the pathology is more a determinant than the nature of the disease in defining the clinical syndrome.[5 15] The reason for this disparity in regional neuronal vulnerability in AD variants remains unsolved, although biological and pathological footprints related to a genetic propensity are discussed.[16]

The posterior variant of AD presents as posterior cortical atrophy and is proposed to be divided into two subtypes,[6 10] reflecting the predominant site of AD pathology: the occipitotemporal variant, which results from disruption of the ventral visual pathway, responsible for visual recognition (Ventral stream—WHAT), and presents with early, predominant and progressive visuoperceptual impairment or visual agnosia with impairment in identifying objects, symbols, words and faces; and the biparietal variant, which results from disruption of the occipitoparietal stream of the visual pathway responsible for visuospatial and perceptual motor processing (Dorsal stream—WHERE), crucial in object location, visual guidance of movements and motor planning, and presents with early, predominant and progressive visuospatial dysfunction, featured by Balint or Gerstmann syndromes, limb apraxia or neglect, with preserved basic visual abilities.[5 6 17]

The biparietal variant of AD was first denominated as progressive biparietal atrophy and was reported to be associated with marked bilateral parietal lobe atrophy and hypoperfusion in neuroimaging, and with predominant and severe parietal lobe involvement by AD pathology in neuropathological examination.[5 6 15]

Our patient's clinical presentation with limb apraxia, agraphia, posterior aphasia and impairment of visuospatial functions, reflect parietal dysfunction and can be included in the biparietal variant of AD. The observed exuberant choreiform limb movements can be explained as resulting from loss of multimodal sensory inputs to the parietal lobe with subsequent interruption of the normal coordination of motor output.[18 19] In fact, focal motor symptoms, including limb clumsiness, apraxia, ataxia, hemiparesis, dystonic posturing, myoclonus, athetosis, choreoathetosis, pseudoathetosis and pseudocoreoathetosis, or posterior alien hand syndrome, have been documented in several reports of patients with parietal lobe damage.[18 20–27] Besides, the alternative diagnosis of Huntington's disease or HDL, supported by a family history of addiction and suicide, was excluded by genetic study. Other medical conditions that may account for the clinical symptoms such as severe depression, cerebrovascular disease and toxic, inflammatory or metabolic disorders, were also excluded.

The IWG-2 proposed criteria for atypical AD diagnosis[10] include a clinical phenotype consistent with the known atypical presentations (posterior, logopenic and frontal variants) and at least one in vivo evidence of Alzheimer's pathology: CSF biomarkers with decreased levels of Aβ protein together with elevated levels of total τ or phosphorylated τ proteins; increased tracer retention on amyloid PET (PiB-PET); or the presence of an autosomal dominant mutation of AD. Our patient presented a CSF

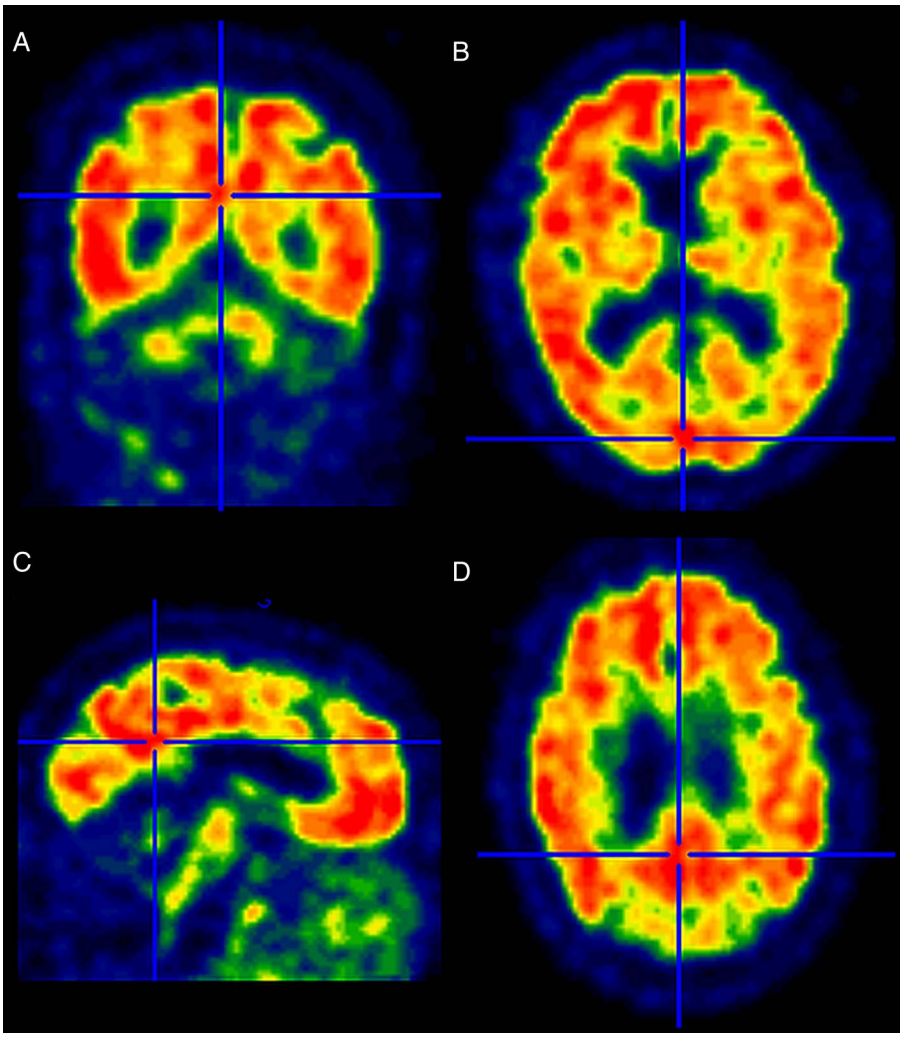

Figure 4 Pittsburgh compound B (PiB) positron emission tomography showing increased β-amyloid deposition in cerebral cortex with high ^{11}C-PiB uptake in the posterior cingulated gyrus, precuneus and in the frontal, parietal, lateral temporal and occipital lobes. Increased ^{11}C-PiB uptake is also seen in caudate nuclei.

profile typical of AD, with marked reduction of Aβ protein levels and very high titres of τ protein, and also a positive biomarker for Aβ cortical deposition. Although some authors report greater ^{11}C-PiB uptake in the posterior cortex of patients with posterior cortical atrophy,[28–31] the majority of reports found no correlation between Aβ deposits and the clinical syndrome or the regional brain dysfunction, and most cases present with widespread ^{11}C-PiB uptake, as in the case of our patient.[32–37]

The presence of atrophy in MRI and hypoperfusion in fluorodeoxyglucose (FDG)-PET are no longer considered useful markers for AD diagnosis, as they lack pathological specificity, and are now considered markers of regional structural and metabolic changes, probably useful to monitor disease progression.[10]

In the case of our patient, the MRI revealed marked bilateral parietal atrophy with relative preservation of hippocampal volumes as well as severe hypoperfusion in the parietal lobes in SPECT. The genetic study was negative for the most common AD mutations (PSEN1, PSEN2 or APP), which is acceptable as the patient had no family history of dementia, and the familial autosomal dominant forms of AD usually have an earlier onset and are very rare, being estimated to account for less than 5% of AD cases.[38] ApoE genotyping revealed a common non-risk ε3/ε3 genotype, a result also comprehensible as APOE4, which is generally considered a risk factor for late-onset forms of AD.[39]

The presence of CSF biomarkers as well as a positive amyloid tracer on PET, surrogate markers of Alzheimer's pathology, allowed the diagnosis of AD in our patient, which is reinforced by the clinical stabilisation induced by an acetylcholinesterase inhibitor. Moreover, the main clinical features and also the imaging changes support the subclassification as biparietal variant, one of the atypical focal forms of AD described in the most recent criteria. According to these criteria, further work is needed in order to better characterise the clinical core of the atypical presentations using the same conceptual paradigms implemented for the amnestic typical AD.[10]

Learning points

- Alzheimer's disease (AD) is a clinically heterogeneous disease that may have atypical presentations.
- Atypical AD usually presents earlier than typical cases and episodic memory is relatively preserved.
- The main atypical AD phenotypes are the posterior variant, logopenic variant and frontal variant.
- The posterior variant of AD has two main subtypes: the occipitotemporal variant, which presents with visuoperceptive impairment, and the biparietal variant, which usually presents with visuospatial dysfunction and apraxia.
- According to the recently proposed criteria, further work is needed in order to better characterise the clinical core of these atypical presentations, using the same conceptual paradigms implemented for the amnestic typical AD.

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