A case series of "atypical" atypical Alzheimer's disease: the key role of in vivo markers of neurodegeneration

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Background and Objectives

Alzheimer's disease (AD), the most common cause of age-related dementia, includes typical and atypical forms. The latter can be characterized by more pronounced involvement of frontal functions, visuo-spatial abilities or language, while memory is relatively spared. In some cases, however, clinical presentation may be so peculiar that it would not suggest a diagnosis of AD at all. Here we present four "atypical" atypical patients in whom only the research for in vivo markers of neurodegeneration led to a correct diagnosis.

Methods

Our series comprises three males and one female, all without positive familial history. The onset was presenile in all patients except for case 1. In patients 1 and 2 the disease started with behavioural disorders of apathetic type, followed in the subsequent years by the appearance of asymmetric L-dopa responsive parkinsonism in case 1 and pyramidal/extrapyramidal syndrome, hallucinations and myoclonus in case 2. An expressive language disorder, rapidly progressive until mutism, was the main feature at onset in patients 3 and 4, later complicated by generalized motor slowness in case 3, mixed hypertonia, myoclonus, exaggerated startle reaction and severe limb apraxia in case 4. All patients underwent a complete diagnostic protocol including neurological and neuropsychological evaluation, extensive laboratory assays, structural (MR) and/or functional (^{18}FDG-PET) neuroimaging of the brain and research for AD pathophysiological biomarkers, either CSF $A\beta_{42}$, total tau and phospho-tau dosage or Amyloid Tracer PET.

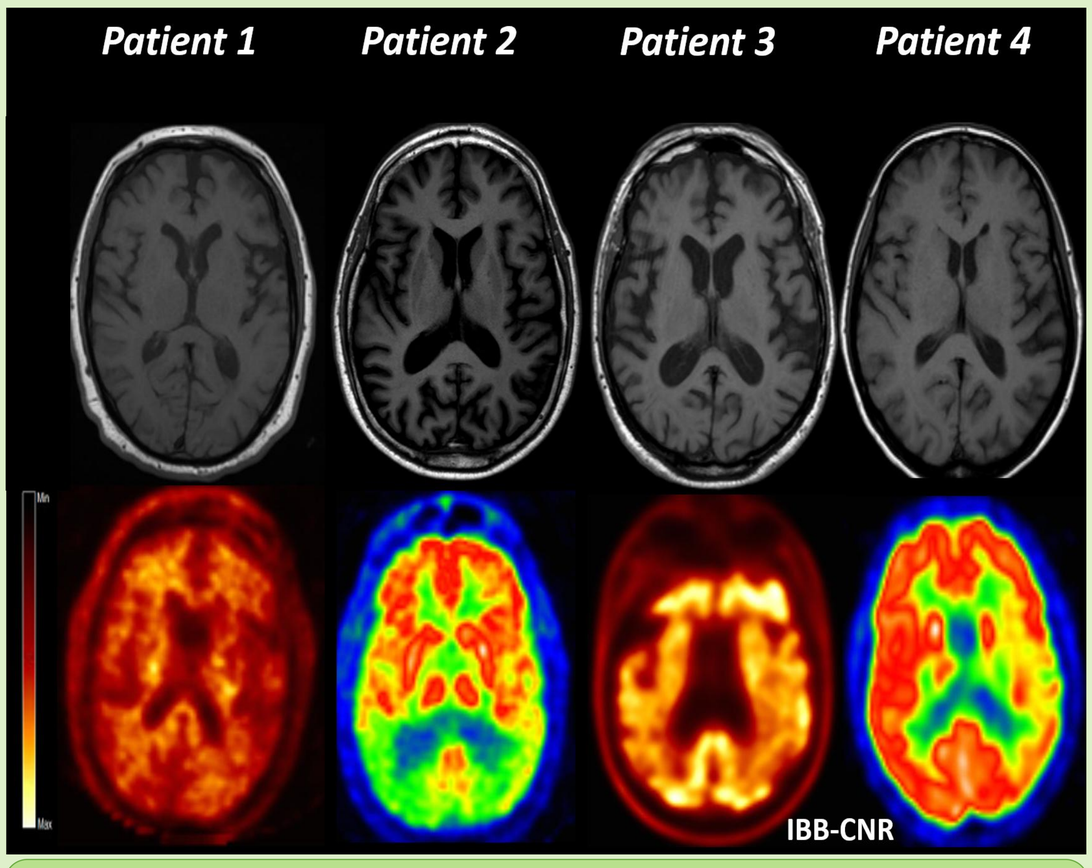

Figure 1. MRI showed, in addition to bilateral medial temporal atrophy present in all patients, involvement of the frontal cortex in cases 1 and 4 and of the parietal cortex in case 2. Significant bilateral posterior hypometabolism in case 2 and markedly asymmetrical hypometabolism (L<R) in case 4 were evident on ^{18}FDG-PET scan. Amyloid tracer PET revealed diffuse cortical uptake in patients 1 and 3.

Results

MRI showed, in addition to bilateral medial temporal atrophy present in all patients, involvement of the frontal cortex in cases 1 and 4 and of the parietal cortex in case 2. ^{18}FDG-PET, not performed in case 1, revealed in all the remaining patients temporo-parietal hypometabolism, with additional evidence of occipital involvement in patient 2 and primary sensori-motor cortex hypometabolism in patient 4. At least one pathophysiological AD biomarker was positive in all cases: amyloid tracer PET in cases 1 and 3 and CSF biomarkers in the others.

Discussion and conclusions

A condition more and more frequently reported is to observe cases of Alzheimer's disease with such a peculiar clinical presentation that the correct diagnosis cannot be reached on clinical grounds alone, as our case series paradigmatically exemplifies. Therefore, in vivo biomarkers of AD pathophysiology (^{18}FDG-PET, amyloid tracer PET, CSF amy/tau, MRI-hipp) and in particular amyloid biomarkers might assume a crucial importance to properly classify the patients and avoid misdiagnoses.

	Age at onset	Main symptoms	MRI/CT atrophy	FDG PET hypometabolism	Amyloid tracer PET	CSF biomarkers	Presumed diagnosis	Final diagnosis
Case 1 M	75	apathy; asymmetric parkinsonism	asymmetric fronto-temporal with left prevalence	n.a.	diffuse uptake	n.a.	bvFTD with parkinsonism	frontal variant LOAD with parkinsonism
Case 2 M	45	apathy; pyramidal and extrapyramidal syndrome, hallucinations, myoclonus	bilateral posterior (mainly parietal)	bilateral temporo-parietal and occipital	n.a.	$A\beta_{42}$: 456 T-tau: 3435 P-tau: 470 IATI: 0.1	DLB (with additional features)	atypical EOAD
Case 3 M	59	expressive aphasia; generalized motor slowness	bilateral temporo-insular	bilateral temporo-parietal	diffuse uptake	n.a.	PNFA	atypical EOAD
Case 4 F	52	expressive aphasia; mixed hypertonia, myoclonus, startle reaction, limb apraxia	asymmetrical fronto-temporal with left prevalence	bilateral temporo-parietal with left prevalence and primary sensori-motor cortex	n.a.	$A\beta_{42}$: 235 T-tau: 293 P-tau: 34 IATI: 0.4	PNFA vs CBD	atypical EOAD

Table 2. For each patient, presumed diagnosis (based on clinical and neuroimaging findings) and final diagnosis (reached after performing either CSF biomarkers or amyloid tracer PET) are showed. IATI: Innotest Amyloid Tau Index. Values below the cut-off of 0.8 are considered strongly suggestive of AD.

References

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