CASE REPORT

Case of posterior cortical atrophy (PCA) evolved to PCA-CBS

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Accepted 18 May 2018

SUMMARY

A 68-year-old lawyer developed insidious disturbances in topographic orientation and apraxia. He underwent a geriatric evaluation, only documenting slight cognitive disturbances, and a 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), showing mild right-lateralised frontoparietal hypometabolism. After 1 year, because of worsening in spatial orientation and the onset of dressing apraxia, he was referred to our memory clinic. The neuropsychological evaluation documented prominent visuospatial, praxis deficits and dysgraphia. Cerebrospinal fluid biomarker analysis showed mild increase of total- τ , with normal A β 1–42, ruling out Alzheimer's disease. Progression of the right parietal hypometabolism at FDG-PET and right superior longitudinal fasciculus damage at high-field MRI revealed a probable neurodegenerative aetiology. The neurological examination disclosed then Gerstmann's and Balint's syndromes, and extrapyramidal signs later appeared, suggesting the diagnosis of posterior cortical atrophy associated with corticobasal syndrome. Genetic analysis for mutations in microtubule-associated protein tau (*MAPT*), *C9orf72* and *GRN* genes was negative. A 1-year follow-up documented significant worsening of the cognitive and functional impairment, revealing a frank dementia.

BACKGROUND

Posterior cortical atrophy (PCA) represents a rare neurodegenerative disease. In PCA, the most common underlying cause is represented by Alzheimer's disease (AD), which accounts for about 80% of cases; other non-AD causes (dementia with Lewy bodies, corticobasal degeneration (CBD), prion-associated diseases, etc.) have been reported in previous studies.^{1–3} Cerebrospinal fluid (CSF) biomarkers have been proven to be useful in discriminating AD from non-AD processes associated to PCA according to the clinical phenotype, where CSF AD-like profile is found in PCA with isolated cognitive deficits, while CSF non-AD profile is found in PCA associated with asymmetric motor signs.^{4–6}

CASE PRESENTATION

In 2013, a 68-year-old right-handed brilliant lawyer developed insidious disturbances in topographic orientation and praxis, for which he underwent a geriatric evaluation. The Mini Mental State Examination (MMSE) score was

27/30, and the brain MRI scan only documented unspecific white matter changes. A brain 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), performed in 2014, showed mild hypometabolism in the right parietal and frontal lobes. Due to these inconclusive data, no diagnostic judgement was reached. In October 2015, because of worsening in spatial orientation and the occurrence of dressing dyspraxia he was referred to our memory clinic. The neuropsychological evaluation documented an impaired global cognitive functioning (MMSE=22), with visuospatial deficits, ideomotor apraxia, agraphia, dyscalculia, as opposed to well-preserved verbal logical abilities. We administered the following tests: MMSE and Montreal Cognitive Assessment (global cognitive functioning); Frontal Assessment Battery (executive functions); Attentional Matrices and digit symbol substitution test (visual attention and speed processing); Rey Auditory Verbal Learning Test, Story recall, Corsi span, Digit span forward and backward (short/long-term memory); Standard Progressive Matrices and Similarities from the Wechsler Adult Intelligence Scale (WAIS) (logical reasoning); Clock Drawing Test, Copy of drawing and Copy with landmarks (constructional praxis); phonemic and category fluency (language); imitation of gestures (ideomotor apraxia).

INVESTIGATIONS

In order to exclude an underlying Alzheimer's pathology, CSF biomarker analysis was carried out, showing a profile not compatible with AD (A β 1–42 1081 pg/mL, normal values: >500; A β 1–42/1–40 ratio: 0.150, normal values: >0.076; total- τ 435 pg/mL, normal values: <400; phosphorylated- τ 55 pg/mL, normal values: <60). In March 2016, brain FDG-PET disclosed significant progression of the right parietal hypometabolism. At 3.0 Tesla diffusion tensor MRI (DT-MRI) sequences (tractography), the superior longitudinal fasciculus was not detectable in the right hemisphere, as a consequence of disruption of the right frontoparietal network. The genetic analysis was negative for mutations in *MAPT*, *C9orf72* and *GRN* genes. The neurological examination showed marked apraxia with alien limb syndrome (left hand), haemineglect, right-left confusion, acalculia and finger agnosia (Gerstmann's syndrome, GS). Later on, optic ataxia, simultanagnosia, oculomotor apraxia and slight extrapyramidal signs (left>right limb rigidity,

To cite: Salvadori N, Russo M, Biscetti L, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224312

Figure 1 (A) Brain 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showing mild hypometabolism in the right parietal and frontal lobes (2014); (B) brain FDG-PET showing significant progression of the right parietal hypometabolism (2016); (C) diffusion tensor MRI (DT-MRI) showing thinning of the left frontoparietal longitudinal fasciculus (2016); (D) DT-MRI showing no detectability of the right frontoparietal longitudinal fasciculus, as a consequence of disruption of the frontoparietal network (2016); (E) dopamine transporter single-photon emission computed tomography showing asymmetric, severe presynaptic dopaminergic dysfunction (2017).

bradykinesia) appeared. ^{123}I -Ioflupane dopamine transporter single-photon emission computed tomography (DAT-scan-SPECT) showed asymmetric, severe presynaptic dopaminergic dysfunction, involving the right putamen and caudate nuclei, possibly related to CBD (see figure 1).

DIFFERENTIAL DIAGNOSIS

PCA is a rare, clinicoradiological syndrome, typically characterised by MRI parieto-occipital atrophy and posterior FDG-PET hypometabolism.¹ Visual complaints, especially spatial attention deficits and visual agnosia, in the absence of primary sensory and motor impairment, often represent the earliest features.² As a consequence of higher-order visual processing disruption, reading, parking/driving concerns and difficulties in spatial navigation may primarily lead to an inconclusive ophthalmological consult.^{3,4} The clinical picture may also show optic ataxia, oculomotor apraxia and simultanagnosia (Balint's syndrome, BS), and/or agraphia, acalculia, finger agnosia and left-right disorientation (GS).¹ The most common underlying cause of PCA is represented by AD, which accounts for about 80% of cases²; other non-AD causes (Dementia with Lewy bodies, CBD, etc.) have been reported.¹

Due to the complexity of the clinical picture and the heterogeneity of the neurodegenerative causes, a biomarker-based approach is mandatory in order to reach a satisfactory diagnostic accuracy. Here, we describe a PCA case with evidence of GS, later developing corticobasal syndrome (CBS) features. The patient underwent a thorough clinical, neuropsychological and multiple biomarker

assessment, that is, CSF analysis, FDG-PET, DT-MRI, DAT scan and genetic testing and a 2-year follow-up.

TREATMENT

As symptomatic treatment, amantadine 100 twice daily and levodopa/carbidopa 50 mg tid were prescribed.

OUTCOME AND FOLLOW-UP

Both cognitive and functional performances documented a marked worsening at 1-year follow-up. A weak response to the symptomatic pharmacological treatment was observed.

DISCUSSION

PCA is often associated with AD pathology⁷; therefore, the first diagnostic step should be to rule out an underlying AD. Considering the high accuracy of CSF biomarkers for AD diagnosis, their determination is suitable as the first step in PCA diagnostic work-up. Recently, CSF profiles have been investigated in PCA patients.^{5,7} These non-AD-like CSF profiles have been found to be associated with motor extrapyramidal signs. These pictures have been defined as 'PCA-CBS'.⁶

Recently, a consensus classification has been proposed in order to establish a conceptual framework for the multilevel assessment of the PCA.⁸ Besides the classical presentation of PCA, defined on the basis of core clinical features as 'pure PCA', the authors introduced as novel diagnostic category 'PCA-plus'. In this entity, symptoms characterising CBS (asymmetric extrapyramidal signs, cortical sensory loss, haemineglect) may occur (PCA-CBS). Cognitive impairment is also found in CBS, with ideomotor apraxia, speech disturbances, dysexecutive symptoms and dysgraphia.⁹ Acalculia, usually found in PCA, is rarely observed in CBS.¹⁰ Our case met the criteria for possible PCA-CBS.

Different neuropathological entities can underlie CBS and PCA clinical pictures. CBS is mainly associated with CBD—which can also be present in PCA—even if progressive supranuclear palsy, AD and frontotemporal lobar degeneration may also occur.¹¹ Notably, the positive predictive value of CBS diagnosis for CBD only ranges from 25% to 56%.¹²

A case of PCA associated with both GS and BS including post-mortem examination has been described.¹³ It was negative for *MAPT* mutations, showing CBD pathology with severe 4R-tau pathology in cortical and subcortical neurons, allowing the diagnosis of 4R primary tauopathy.

Although the case we are discussing lacked the neuropathological examination, that remains the gold standard for a definite diagnosis,^{8,14} all the clinical and biomarker data assessed in our patient suggest as possible origin a primary tauopathy.

In conclusion, in the diagnostic work-up of neurodegenerative disorders with atypical presentations, the accurate clinical examination should be coupled to multiple biomarkers. Specifically, the measurement of CSF AD biomarkers is recommended as first step in order to rule out an AD pathophysiology, followed by advanced neuroimaging techniques.

Learning points

- ▶ A comprehensive clinical, neuropsychological and biomarker assessment is mandatory in order to increase diagnostic accuracy in neurodegenerative disorders with atypical presentation.
- ▶ Cerebrospinal fluid analysis is the first step in order to rule out Alzheimer's pathology.
- ▶ The use of advanced structural and functional neuroimaging may be supportive for a biomarker-based diagnosis.

Acknowledgements The authors would like to acknowledge Dr V Lisetti (Centre for Memory Disturbances, University of Perugia) for the contribution in the critical revision of the manuscript, Dr P Chiarini (Neuroradiology, S Maria della Misericordia Hospital, Perugia) and Dr A Chiappiniello (Medical Physics Unit, S Maria della Misericordia Hospital, Perugia) for the analysis of 3T MRI examination and the quantitative analysis of the DTI sequences; and Dr P Prontera (Medical Genetics Unit, S Maria della Misericordia Hospital, Perugia) for genetic consult and the genetic analysis.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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