CASE REPORT

Down syndrome with posterior cortical atrophy

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SUMMARY

Down syndrome (DS) is caused by trisomy of chromosome 21. The average age of onset of Alzheimer's disease (AD) ranged from 50 to 55 years in DS, with early symptoms usually characterised by changes in behaviour and executive dysfunction. On the other hand, posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome characterised by progressive impairment of visual functions in the absence of visual deficits and a pattern of atrophy involving posterior cortex. This syndrome is mostly caused by AD pathology. We report the case of patient with DS who developed PCA. While atypical variants of AD are commonly associated with an early age at onset, all focal forms of AD may potentially appear in DS. Specifying the phenotype has an impact on the care of DS patients and could help us to know the evolution. It could also provide a better understanding of the underlying mechanisms of focal forms.

BACKGROUND

Down syndrome (DS) is an intellectual disability caused by partial to complete trisomy 21. Mean age for onset of Alzheimer's disease (AD) is between 50 and 55 years.¹ For patients with DS older than 60 years, it is assumed that the risk of presenting AD is between 30% and 40%.²

In this form of AD, behavioural disorders are usually prominent with dysexecutive syndrome. For example, reduced empathy, emotional lability, apathy, social withdrawal, perseveration, disinhibition, impulsivity and self-care skills, can be observed in the foreground.³

Besides, posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome characterised by progressive impairment of visual functions in the absence of visual acuity deficits and a pattern of atrophy involving parietal, occipital and occipito-temporal cortex. This syndrome is mostly related to AD diagnosis.

We report the case of a patient with DS who developed PCA. It is, to our knowledge, the first time such a form of AD is described in these patients.

CASE PRESENTATION

The patient was a 55-year-old man with a trisomy 21. He had a medical history of dysthyroidism treated by L-thyroxine. He had been living at the same establishment for 10 years, when a change in his cognitive abilities appeared. The later were notified by the educators and led to a memory consultation.

Memory complaint was in the foreground. But during the medical interview, the patient and the

relatives seemed to indicate spatial orientation difficulties. For example, the patient could not find his room or the dining room, whereas it was possible a few months ago. He also presented difficulties to find and choose his clothes in his wardrobe, which seemed to be due to gestural and visual troubles. Interestingly, although the patient had always enjoyed drawing and showed good results (figure 1), his drawings were gradually deconstructed (figure 2). An increase of irritability without aggressiveness was also reported. Moreover, the educational team noticed a reduction of autonomy, especially for washing or dressing with apraxia.

Neuropsychological tests showed good temporal orientation, incorrect spatial orientation, no language dysfunction (oral dDenomination 80 test) with respect of past presumed level.⁴ Anterograde memory, assessed with visual test (TNI-93),⁵ was relatively preserved. Visuoconstructional impairment when copying the Mini-Mental State Examination (MMSE) figure was prominent, on this patient who like drawing. Simultagnosia and apperceptive agnosia were also observed. The patient had a normal neurological examination with no motor symptoms and no extrapyramidal symptoms.

Figure 1 Painting of the patient before clinical symptoms of posterior cortical atrophy.

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Figure 2 Painting of the patient after clinical symptoms of posterior cortical atrophy.

INVESTIGATIONS

Brain MRI showed cortical atrophy more marked on the parietal and occipital lobes. (99m)Tc-HMPAO single-photon emission CT (SPECT) of the brain revealed a hypoperfusion of parietal and occipital lobes, predominantly on the left side. Amyloid positron emission tomography (PET) with 18 F-florbetaben of the brain revealed a diffuse fixation of the amyloid marker, predominantly on occipital lobe (figure 3). Therefore, all these clinical and imaging findings led to the diagnosis of PCA.

DIFFERENTIAL DIAGNOSIS

Principal differential diagnoses of AD with visual presentation are Lewy body dementia and Creutzfeldt-Jakob disease.

The patient had no signs or symptoms of dopaminergic denervation, which allowed elimination of diagnosis of Lewy body disease.

Indeed, the disease history and the very slow evolution of the symptoms permitted us to exclude Creutzfeldt-Jakob disease.

TREATMENT

At first, treatment of cortical atrophy is based on orthoptic care and occupational therapy. Anticholinesterase medications, which are symptomatic treatments of typical AD are not indicated when memory is relatively preserved.

OUTCOME AND FOLLOW-UP

We have therefore informed the patient and his entourage of the diagnosis of PCA, focal form of AD. Thus, he is regularly followed in memory consultation, this especially since the evolution of DS with PCA is currently not well known.

DISCUSSION

Chromosome 21, triplicated in DS, contains several genes that are thought to play a critical role in the development of AD neuropathology. Overexpression of amyloid precursor protein gene in DS leads to early-onset beta-amyloid (A β) plaques. In addition to A β accumulation, middle-aged DS people are likely to develop others neurodegenerative pathologies such as neurofibrillary tangles.⁶

A recent research suggests that early symptoms of AD dementia in DS may be characterised by prominent changes in personality/behaviour and executive dysfunction. Informant-reported

Figure 3 Brain imaging of patient (MRI, SPECT and amyloid PET). (MRI showed preserved temporal lobe with prominent posterior atrophy (first line). Representative axial views of 99mTc-HMPAO brain SPECT (upper row) revealed hypoperfusion in the parieto-occipital and posterior temporo-occipital cortices, more severe in the right (second line). 18F-florbetaben brain PET (lower row) was rated visually positive: tracer activity appeared greatest in all cortical regions (ie, precuneus, occipital cortex, posterior cingulate, parietal cortex, temporal and frontal) (third line). PET, positron emission tomography; SPECT, single-photon emission CT.

personality/behaviour changes are a significant predictor of AD.⁷ Caregivers usually report symptoms as: a reduced interest in relationships, a decreased enthusiasm for usual activities, a decrease of sociability, but also sadness, irritability, uncooperativeness or aggression. No visuoconstructional or visuospatial impairments have been reported.

However, a diagnosis based on prominent behavioural and emotional changes associated with AD in DS may reveal an advanced stage of the disease. There are in fact different ways to explain this delay: (1) given the heterogeneity of premorbid intelligent quotient and functional independence,⁸ it is difficult to determine cognitive decline in this population.⁹ (2) Diagnosis of AD is based on a decrease of cognitive functions compared with premorbid abilities. Standard screening tools such as the MMSE are often not appropriate because of a 'floor effect'.¹⁰ (3) Subtle cognitive decline may be difficult to determine, notably

for people living in residences where environmental stimulations can be rare.

So, for clinicians, the informations reported by caregivers are absolutely crucial. Our case is a good illustration of this, since the diagnostic suspicion was essentially based on the caregivers' interview.

PCA is a neurodegenerative syndrome characterised by progressive impairment of visual functions in the absence of visual acuity deficits associated to a pattern of atrophy involving parietal, occipital and occipitotemporal cortex.^{11 12} Pathological studies have all shown that AD is the most common cause of PCA with seniles plaques and neurofibrillary tangles. Studies assessing cerebrospinal fluid biomarkers and amyloid PET have reported similar findings supporting that PCA is typically associated with underlying AD pathology.¹¹ PCA is now part of the AD diagnostic and research criteria.^{13 14}

Contrary to typical AD, episodic memory is relatively preserved during the initial stages of PCA, while reading, object recognition, navigational orientation and praxis are early affected. Other posterior symptoms, such as symptoms of Balint (simultagnosia, optic ataxia and ocular apraxia) or Gertsman syndrome (agraphia, acalculia, finger agnosia and right-left confusion) are also frequent. These differences between PCA and amnesic AD have an impact on treatment because if anticholinesterasic medications are symptomatic treatments of typical AD, they are not indicated in PCA when memory is relatively preserved.

The intellectual disability in DS make difficult the achievement of neuropsychological tests used to detect posterior symptoms. For our patient, the recent difficulties that he met on drawing and in particular copying drawings contributed to the diagnosis that was confirmed by morphological imaging, functional imaging as well as amyloid marking.

The age at onset (AAO) of AD has increasingly been recognised as a factor that may influence both the pattern of atrophy and the clinical symptoms. PCA is typically considered as a young-onset form of AD. The onset might also be partially associated with genetic risk factors. For example, homozygous $\epsilon 4$ allele carriers develop AD up to 10 years earlier than individuals who do not carry this allele.¹⁵ People with earlier onset PCA may possess genetic risk factors that predispose them to develop both earlier AD and PCA and may potentially lead to the specific clinico-anatomical phenotype of this group. In patients with DS, the overexpression of the *APP* gene, on chromosome 21, leads to early-onset AD. This is to our knowledge the first description of posterior form. Progressive aphasia has never been reported in the literature either. Furthermore, atypical variants of AD are commonly associated with an early AAO¹⁶ and more often present with non-memory symptoms including visuospatial function, apraxia and language deficits. So, all focal forms of AD may potentially appear in these patients with DS and have to be specifically investigated.

Assessing cognitive decline and estimating the onset of AD type dementia is challenging in DS subjects. Heterogeneity of premorbid intellectual abilities in DS complicates interpretation of individual tests' results. Moreover, this presentation differs from typical AD. This diagnostic accuracy has an impact on patient care; occupational therapy has an important role and understanding disorders (ie, visuoperceptual impairment in this case) by the medical team also provides better support for patients.

Learning points

- Posterior cortical atrophy is a rare form of Alzheimer's disease (AD) but must be search because the diagnostic accuracy has a major impact on patient care with indication of orthoptics, occupational therapy, etc.
- Assessing cognitive decline and estimating the onset of AD type dementia is challenging in Down syndrome (DS) subjects because heterogeneity of premorbid intellectual abilities in DS complicates interpretation of individual tests' results.
- Chromosome 21, triplicated in DS, contains one gene that plays a critical role in the development of AD neuropathology.

Contributors CB-B: conception and design, acquisition of data, analysis and interpretation of data; drafting the manuscript. AP: acquisition of data, analysis and interpretation of data; revising the manuscript.

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