J Neurol (2005) 252 : 27–35
DOI 10.1007/s00415-005-0594-5

ORIGINAL COMMUNICATION

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Posterior cortical atrophy: variant of Alzheimer's disease?

A case series with PET findings

Received: 5 March 2004
Received in revised form: 17 June 2004
Accepted: 23 June 2004

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Abstract Nine patients with posterior cortical atrophy (PCA), a rare degenerative brain disease of unclear etiology and nosology, were followed over a mean time of 7.4 years. The mean age at onset was low (56.2 years). At onset, eight patients had visuo-spatial and eight had memory impairment. A minority showed early signs of occipital lobe involvement with visual agnosia or hemianopia. Eight patients developed dementia after a mean course of five years. 18F-FDG-PET data of six patients were analysed with statistical parametric mapping. They showed hypometabolism centred on the lateral and medial parietal associative cortex, with variable involvement of the adjacent temporal and occipital associative cortex. A minority showed involvement of the frontal lobes, possibly related to deafferenting of areas related to the control of eye movements. Atrophy and hypometabolism were markedly asymmetric in a subset of cases. Autopsy was performed in one patient. Presenile onset, location, and asymmetry of atrophy suggest that PCA represents a biologically separable variant of Alzheimer's disease.

Key words posterior cortical atrophy · Alzheimer's disease · dementia · positron emission tomography

Introduction

Posterior cortical atrophy (PCA) is a rare degenerative condition of unknown etiology. The term PCA was first applied by Benson et al. in 1988 [3]. They described a group of patients with progressive dementia and disorders of higher visual function, in whom predominant parieto-occipital atrophy was demonstrated by cerebral imaging. PCA patients display early deficits in visuo-spatial tasks including drawing, writing, calculating, finding their way around unfamiliar places etc. Further possible deficits are visual agnosia for objects, faces and letters, visual field cuts and apraxia. Elements of the PCA symptomatology are sometimes summarised under the notion of Gerstmann syndrome (left-right disorientation, autotopagnosia, dysgraphia) and Balint syndrome (gaze apraxia, optic ataxia, simultanagosia, visual hemineglect). When the disease progresses, transition to global dementia regularly occurs. The number of post-mortem-studies is very limited. Alzheimer-type pathology was present in most cases. Victoroff et al. [31] reported subcortical gliosis, non-specific cortical degeneration and Creutzfeldt-Jakob disease (CJD) in one case each.

It is debatable whether the term PCA should primarily be applied to degenerative brain disease with disproportionate parieto-occipital atrophy, or to presumed AD cases with disproportionate visuo-spatial dysfunction, with or without disproportionate posterior atrophy ("visual variant AD"). Some authors do not differentiate between imaging- and neuropsychology-guided concepts of PCA [8, 20, 24, 31]. There is obviously a large overlap between cases that fit into either definition, but

PCA in the morphological sense can be due to pathologies other than AD, and AD can present like PCA in the absence of conspicuous atrophy.

Previous articles on PCA, as defined by atrophy, include single case reports and a few series of four to six patients [3, 23, 26]. The present series of nine cases was compiled to examine the range of clinical findings and to delineate the regional distribution of cerebral hypometabolism in a series of patients with PCA. Positron emission tomography (PET) data were available in six cases. We applied a morphological concept of PCA, as suggested by the term itself. Therefore, the inclusion criterion was the presence of focal uni- or bilateral atrophy of the parietal and/or occipital cortex, as shown by magnetic resonance imaging (MRI).

Methods

Subjects

Nine patients of the Freiburg University Hospital Memory Clinic were identified retrospectively in 2001. They showed focal atrophy of the parieto-occipital cortex in the absence of, or out of proportion to, generalised cortical atrophy. Patients in whom atrophy extended to the adjacent temporal cortex were included. MRI was performed in the course of routine clinical investigations and were evaluated visually by neuroradiologists and one of us (KS).

Cerebral F18-fluoro-2-deoxy-D-glucose (F18-FDG) PET was performed in six patients (nos. 4 to 9) in the course of routine clinical studies. The recordings were made after a mean period of 3.7 years after onset of disease. The mean Mini Mental State Examinations score (MMSE) at that time was 26.2 (range: 23–28). In one patient, the MMSE was not available. He still carried out his manual job at the time of the PET study and kept on doing so for further 18 months.

The normal data base for the analysis of PET data constituted 12 neurologically healthy subjects with hepatitis C who were examined at the baseline of a pharmacological study (seven men, five women, mean age 48 years).

Patients 3 to 9 were followed up clinically at least once in 2002 and/or 2003. The mean time from onset of disease to last follow-up was 7.4 years. Onset of disease was determined as the time when cognitive deficits were first noted by patients and/or relatives. Neuropsychological test results included visuo-spatial cognition, memory and naming, but testing did not follow a standardised scheme. Two patients (nos. 1, 3) died during the follow-up period. Autopsy was performed in one (no. 3).

PET imaging

A Siemens CTI ECAT EXACT 921/31 tomograph was used (10.8 cm FOV, 6.8 mm FWHM). Subjects were fasted for four hours prior to the PET procedure. They were allowed to rest for at least ten minutes in an acoustically isolated and dimmed room. Then FDG was injected intravenously at a dose of 200 ± 20 MBq. 30 min after FDG injection the patients' heads were positioned in the scanner according to the orbitomeatal line. Six dynamic frames of five minutes duration each were acquired. Axial images were reconstructed using filtered back-projection by Shepp-Logan filter (cutoff 0.35 cycles/pixel). Attenuation correction was performed using the standard mathematical algorithm implemented in ECAT software. The dynamic frames were then checked for motion artefacts and summed up to generate a single dataset of 31 transaxial planes.

Analysis of PET data

Statistical parametrical mapping (SPM) was done using SPM99 (Wellcome Department of Cognitive Neurology). All SPM calculations were performed with Matlab, version 6.5 (The MathWorks, Inc.). The PET images were anatomically standardized using an affine transformation to the stereotactic Montreal Neurological Institute (MNI) template and bilinear interpolation. Before statistical analysis, data were smoothed using an isotropic gaussian kernel of 12.0 mm. The global cerebral metabolic rate for glucose (gCMRGlc) was normalized to a mean of 50 µmol/100 ml/min. The normalized FDG-PET data of the patients were compared with a normal data base by computing a voxel by voxel t-statistic for detection of apriori hypometabolic areas. The resulting statistical parametrical map of the t-statistic (SPM(t)) was transformed to a normal distribution, SPM(Z), with a threshold at 4.02 (or $p = 0.001$ uncorrected). The corrected threshold was $p = 0.05$ for spatial extent. For visualisation of the Z-score statistics, the Z-score voxel clusters were displayed as maximum intensity projections. This standard feature of SPM99 results in a three dimensional glass brain view (sagittal, coronal and transverse). Furthermore, the statistical maps were overlayed on the standard MRI data set provided by SPM99, using the SPM projection routine. Only lesions located at the surface of the brain were displayed on the surface of the rendered MRI using a grey scale. For anatomical localization, the MNI coordinates were transformed into Talairach- and Tournoux-coordinates using the subroutine implemented by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) and matched to the corresponding cortical region by means of the Talairach Daemon software (Research Imaging Center, University of Texas Health Science Center). The same procedure of the SPM analysis was carried out for a group-wise comparison of the patient and control groups.

Results

Demographic and clinical data

All patients suffered progressive cognitive deterioration. No patient had motor impairment, psychosis, major depression, hallucinations or unexplained fluctuations of vigilance during the time of observation. Demographic data are listed in Table 1. The mental status of all patients deteriorated between initial and follow-up-examination. Seven patients became demented within five years, one only after ten years. The mean period to dementia (i. e. cognitive impairment in at least two domains and more than minor impairment of regular personal and occupational activities) was 5.0 years. When conversion to dementia had occurred, the clinical profile was compatible with Alzheimer's Disease.

One patient's mother had become demented at age 74, and her mother at age 80 (no. 6). One patient's father was reportedly confused at a late age (no. 9). There was no further history of dementia in first-degree relatives. A favorable effect of cholinesterase inhibitors was reported by caregivers in three out of five patients for whom information was available.

A post-mortem examination was performed in one patient (no. 3, Fig. 1a). His illness began at age 44, when he noted difficulty in assembling ideas, altered handwriting, unspecified problems of vision, and forgetful-

Table 1 Demographic data, delay to dementia and timing of PET scans

Case no.	Sex	Age at onset (years)	Length of observation (years)	Delay to dementia (years)	Delay to PET registration (years)	MMSE at the time of PET registration
1	m	57	16	10	–	–
2	m	58	7	3	–	–
3	m	44	11	5	–	–
4	m	60	6	6	4	27
5	m	60	4	4	3	–
6	m	54	7	4	3	27
7	f	58	5	3	4	23
8	m	55	7	–	3	28
9	m	60	5	5	5	26
Mean		**56.2**	**7.4**	**5**	**3.7**	**26.2**

ness. He later developed a pronounced deficit of visuo-spatial cognition, but kept working in a responsible executive position. His memory remained relatively good. His mood was sometimes inappropriately elated. He later developed global dementia. In the time preceding his death eleven years after onset, he was bed-ridden and mute. Autopsy showed Alzheimer pathology with widespread amyloid plaques and neurofibrillary tangles in the cerebral cortex and some brainstem nuclei (Braak stage 6, CERAD plaque score C).

Neuropsychological deficits

Key neuropsychological deficits are listed in Table 2. Eight patients presented with a disorder of *visuo-spatial cognition*, including difficulties in reading clocks and instruments, assembling, calculating, drawing, writing, driving, navigating the familiar environment, dressing and tying shoelaces. These deficits were confirmed by tasks of figure-copying, clock-drawing and clock reading [30]. Four patients had consulted an optometrist or ophthalmologist.

Eight patients had a *disorder of memory* at the onset of disease or soon after. Two to four years after onset, the

Table 2 Findings at earliest formal neuropsychological examinations

Case no.	years since onset	MMSE score*	Visuo-spatial cognition	Memory	Object naming*
1	3; 10	n. a.	3 years: inability to copy figures.	10 years: 4–5–6–6–9 of 15 words, 5 at delayed recall.	n. a.
2	3	15	Inability to copy figures.	0 at delayed recall of 3 MMSE words	n. a.
3	3	n. a.	Inability to copy figures, read clocks. Score 0 at WAIS* – Block Design	2–3–4 of 15 words, 1 at delayed recall; 10 picture recognition without error.	24/28 Oldfield
4	4	27	Inability to copy figures. Clock Drawing score (Shulman): 3.	3–4–4 of 10 words, 2 at delayed recall.	13/15 Boston
5	2	n. a.	Inability to copy figures, write, read clocks, calculate.	3–4–3 of 10 words, 0 at delayed recall.	14/15 Boston
6	3	27	Impairment at figure copying, clock reading, calculation, writing, reading.	0/10 at delayed picture recall, 10 at recognition, 1/10 false-positive	20/20 AAT 27/28 Oldfield
7	2	25	Minor impairment at figure copying and clock reading.	3–7–6 of 15 words, 0 at delayed recall.	
8	3	28	Minor impairment at figure copying, clock reading. Score 5 at WAIS* – Block Design.	4–8–9 of 10 words, 8 at delayed recall.	15/15 Boston
9	2	27	Inability to copy figures and read clocks. Mild visual agnosia for object drawings.	3–9–9–10–14 of 15 words, 5 at delayed recall. Fife years post-onset: 4–8–11–9–12, 9 at delayed recall.	20/20 AAT

n. a. not assesed; *MMSE* Mini Mental State Examination; *WAIS* Wechsler Adult Intelligence Score; *AAT* Aachen Aphasia Test, 20 items object naming series; *Boston* – 15 item object naming series; *Oldfield* – 28 object naming series

degree of impairment ranged from mild to marked, as assessed by word- and picture learning tasks. In case no. 7, memory disorder preceded other symptoms and became a major problem within two years. Three years after disease onset she also showed marked visuo-spatial deficits. She had a right > > left asymmetric parietal, occipital and temporal atrophy (Fig. 1c).

Two patients had *visual agnosia* at an early stage. Case 1 presented with agnosia for objects. Seven years after onset he showed a mild left visual hemineglect and was unable to read, to identify famous faces and many real objects. He could recognise eight of 27 object drawings. He became functionally blind when his personality, memory, language and general intelligence were no more than mildly altered. Case 6 developed a *right hemianopia*. Another patient reported unspecified disturbances of vision (no. 2).

In two patients, signs of *apraxia* were reported two to three years after disease onset. One showed difficulty in performing movements during the neurological examination (no. 2). Another was reported to have difficulties using cutlery, but remained able to carry out manual work in a factory (no. 5). The other patients exhibited no early signs of apraxia during neurological and neuropsychological examinations.

Early signs compatible with *frontal lobe dysfunction* were observed in two cases, i. e. inappropriate elation and logorrhoea (case 3) and inertia, intrusions and confabulations (case 7).

Early-onset *dynomia* or other signs of aphasia were not reported or observed. Four to five years after onset, mild dysnomia was present in three cases (nos. 5, 7, 9) and marked dysnomia in one (no. 2).

Five years after onset, follow-up MMSE scores were available in six cases: case 4: 26, case 5: 8, case 6: 19 (mean of two measurements), case 7: 18, case 8: 27 (mean of two measurements), case 9: 26.

Structural imaging

MRI was performed two to four years after disease onset. Two patients underwent initial cerebral computed tomography and later had MRI (no. 1, 2). All patients had atrophy of the parietal cortex. Occipital lobe involvement was present in four cases (no. 1, 4, 6, 7), and unilateral temporal lobe involvement in three (no. 5, 6, 7). Frontal lobe atrophy was minor or absent. Occipital and parietal white matter hyperintensity on T2-weighted images, indicating gliosis, was seen in patient no. 1 (Fig. 1b). He presented with visual agnosia and later became functionally blind. Progression to dementia was unusually slow.

There was a pronounced asymmetry of parietal atrophy in three cases (no. 5 and 6: left > right; no. 7: right > left; Fig. 1c) and minor asymmetry in one (no. 2: left > right). Patient no. 6 with unilateral atrophy of the medial occipital primary visual cortex developed a hemianopia.

Long-term follow-up imaging was available in three patients. It showed extension of atrophy to the temporal lobes in case 1 (ten years after onset), generalized exter-

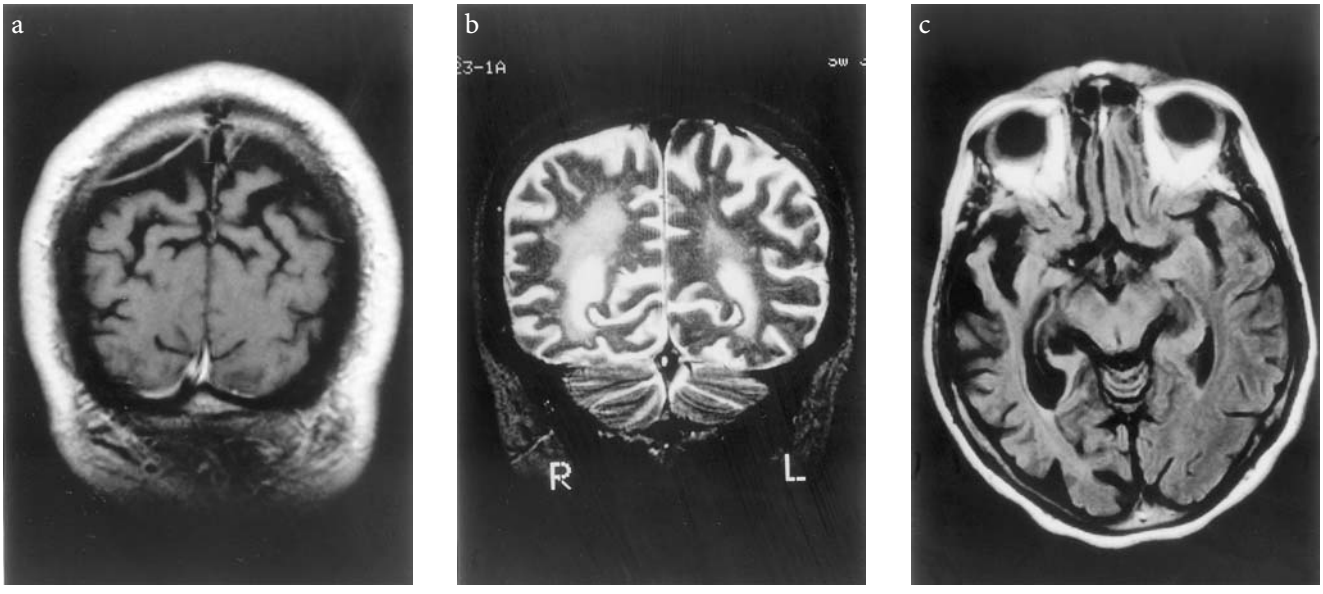

Fig. 1 **a:** Case 3, MRI, T1-weighted image, coronal section through the posterior parietal lobe, showing bilateral cortical atrophy. **b:** Case 1, MRI, T2-weighted image, coronal section through the posterior parietal and inferior occipital lobe, showing cortical atrophy and white matter hyperintensity. **c:** Case 7, MRI, T1-weighted image, axial section at the level of the temporal lobe, showing markedly asymmetric atrophy of the temporal and occipital lobe

nal and internal atrophy in case 2 (seven years after onset) and mild generalized external atrophy in case 6 (seven years after onset).

Positron emission tomography

Table 1 lists the period since onset and the MMSE score at the time of PET registration. Three-dimensional surface reconstructions of the brain from different views were computed, onto which cortical areas with significantly reduced metabolism were marked. Fig. 2 shows selected views of these reconstructions. Additional "glass brain" reconstructions are shown in Fig. 3.

In one case (no. 7), hypometabolism extended to the head of the right caudate nucleus (not shown in figures). Otherwise, subcortical stuctures were not involved.

Discussion

Progressive course, focal cerebral atrophy and absence of focal neurological signs other than disturbances of vision indicated degenerative brain disease in all cases. PCA presented as a presenile illness in the entire group (age at onset: 44–61 years). Age of onset was thus markedly lower than in typical AD, where incidence increases sharply with age and the mean age of onset is approximately 80 years [13]. The mean age of onset was also low, i. e. 58 years, in two recent series [24, 26], and there are many case reports of patients with presenile onset [1, 4, 9, 12, 16, 19, 21, 23, 25, 31, 32]. In a review of 58 cases, the mean age was 60.8 years [29]. The uneven sex distribution in our series is in contrast to findings in AD. It is not paralleled by other PCA series and may represent a chance finding, since we are not aware of a bias favoring the observation or inclusion of men.

There was a clear trend towards the development of dementia. Eight patients became demented after a mean course of five years. However, one patient was not demented seven years after onset (case 8) and in another the delay was ten years (case 1), which shows that the course of PCA can be much less rapid than in "typical" AD.

Presentation with *visuo-spatial deficits* in eight cases corresponds to the presence of parietal atrophy as visu-

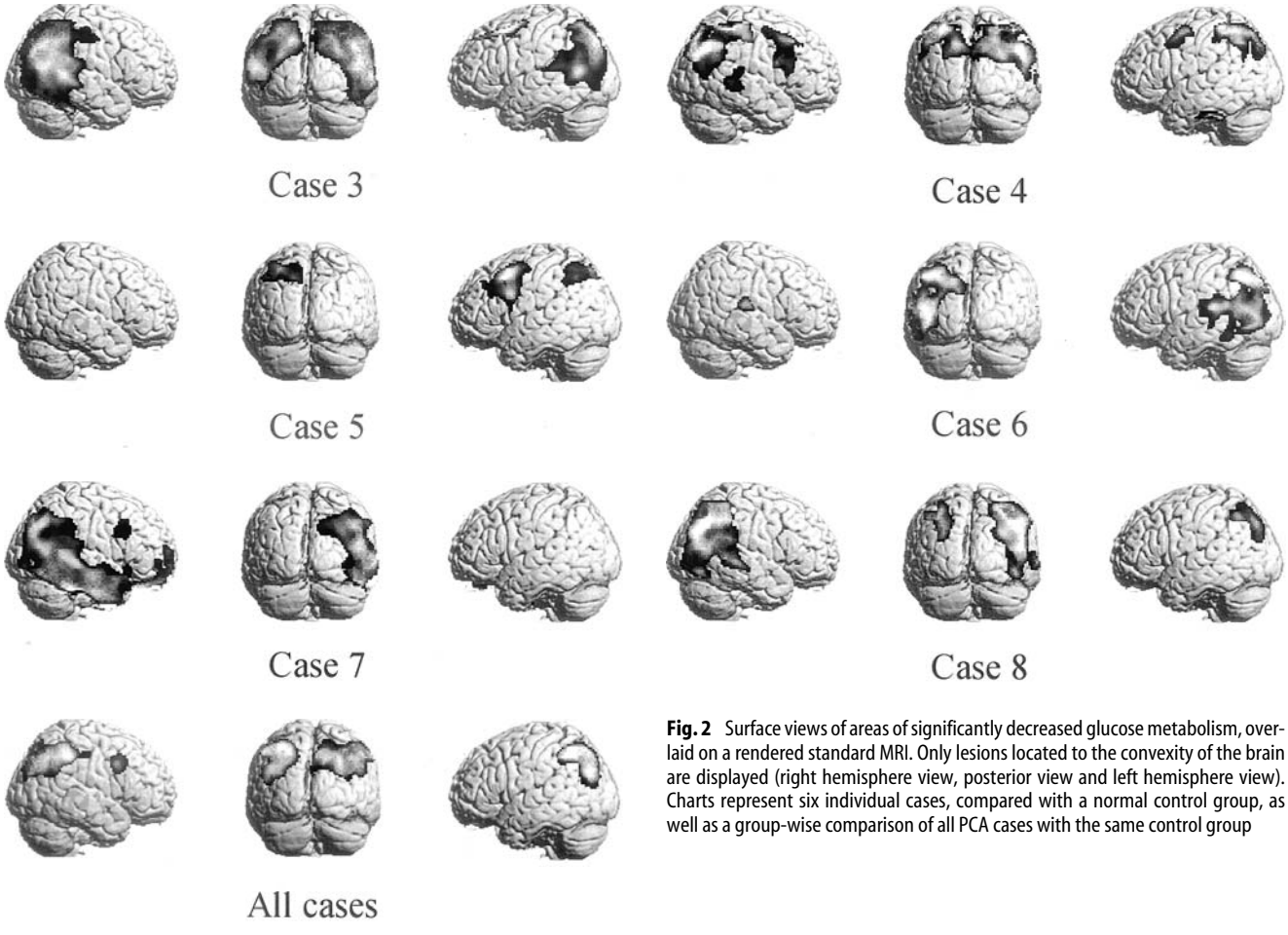

Fig. 2 Surface views of areas of significantly decreased glucose metabolism, overlaid on a rendered standard MRI. Only lesions located to the convexity of the brain are displayed (right hemisphere view, posterior view and left hemisphere view). Charts represent six individual cases, compared with a normal control group, as well as a group-wise comparison of all PCA cases with the same control group

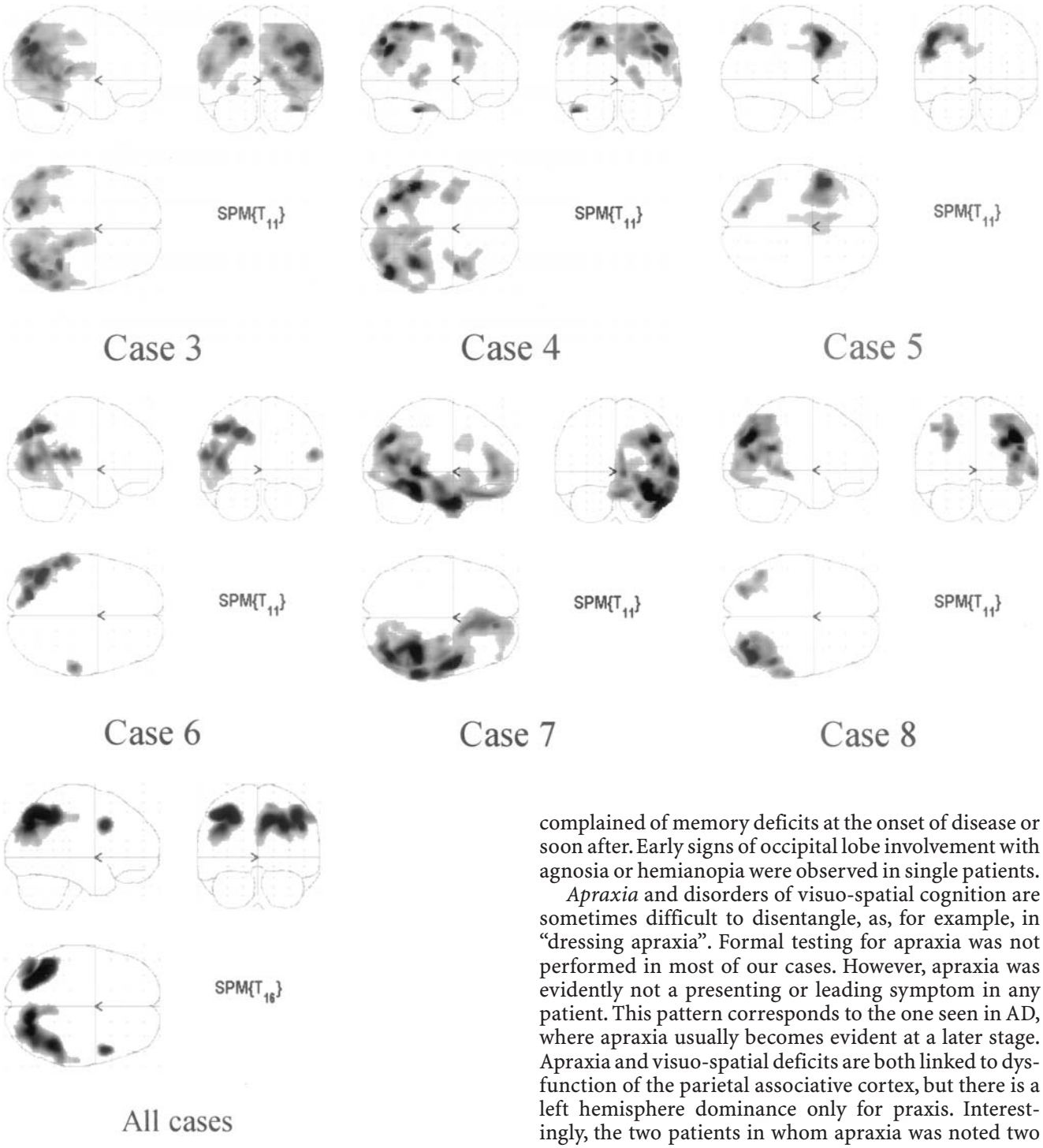

Fig. 3 Spatial distribution of areas with significantly decreased glucose metabolism, compared with a normal control group, displayed in three orthogonal planes of a standard brain ("glass brain")

alized by MRI (all cases). There was one patient in whom memory deficits were noted first, and visuo-spatial deficits became evident later. A further seven patients complained of memory deficits at the onset of disease or soon after. Early signs of occipital lobe involvement with agnosia or hemianopia were observed in single patients.

Apraxia and disorders of visuo-spatial cognition are sometimes difficult to disentangle, as, for example, in "dressing apraxia". Formal testing for apraxia was not performed in most of our cases. However, apraxia was evidently not a presenting or leading symptom in any patient. This pattern corresponds to the one seen in AD, where apraxia usually becomes evident at a later stage. Apraxia and visuo-spatial deficits are both linked to dysfunction of the parietal associative cortex, but there is a left hemisphere dominance only for praxis. Interestingly, the two patients in whom apraxia was noted two to three years after onset had asymmetric, left > right parietal atrophy (nos. 2, 5), whereas the other had right > left or symmetric parietal atrophy. The dissociation of apraxia vs. visuo-spatial dysfunction may be related to the centre of atrophy within the parietal lobes. Apraxia results mostly from lesions to the inferior (left) parietal lobe, while visuo-spatial dysfunction also occurs in lesions to more dorsal areas including the supe-

rior parietal lobule ("where" – stream of visual analysis). The minor role that apraxia played in our series is in line with most other reports of PCA. There is, though, a minority of cases with leading apraxia, as described by Azouvi et al. and Aharon-Peretz et al. [1, 2].

Visual agnosia and a visual field defect, progressing to functional blindness (case 1) and right heminaopia (case 6) suggest predominantly occipital degeneration. MRI showed bilateral occipital atrophy with T2-hyperintensity of the occipital white matter in one, and gross atrophy of the medial face of the left occipital lobe, with milder changes on the right side, in the other. Predominant involvement of the occipital lobe is rare in degenerative disease and even in PCA.

Two patients showed minor early clinical and neuropsychological signs compatible with *frontal lobe involvement*. In one of them in whom PET was available cortical pathology was found to extend to the frontal lobes (see below).

The clinical course of PCA was thus found to be variable with regard to the pattern of neuropsychological deficits and the mode of progression. Previous reports have shown that the leading symptoms of PCA are quite variable. They may include alexia, agraphia, apraxia, visuo-spatial processing disorder, visual agnosia, visual hemineglect, visual field defects and features of Balint's syndrome, i. e. optic ataxia, optic dysmetria and simultanagnosia. Mackenzie Ross et al. [23] and Galton et al. [11] proposed dividing PCA into subtypes, which are distinguishable at onset but tend to merge as the disease progresses: (A) predominantly occipito-temporal with visual agnosia, (B) predominantly parietal with deficits of visuo-spatial cognition and (C) a "primary visual failure" subtype with early visual-perceptual deficits. Seven of our cases can be assigned to subtype B (2 to 6, 8, 9). One of them had additional early disturbances of vision and developed hemianopia (no. 2). He represents a transitional case of subtypes B and C. One case is typical of subtype A (no. 1). Case 7 does not fit into this scheme.

Imaging findings

Atrophy extended to the occipital or temporal cortex in a subset of cases. Marked asymmetry was seen in the three patients who had temporal lobe involvement. Follow-up scans performed in three patients showed atrophy to have progressed towards anterior regions.

PET was performed when dementia was absent or at an early stage. Since correction for atrophy was not done, areas of hypometabolism due to atrophy cannot be differentiated from those that were only metabolically impaired. Since the mean age of the control group was approximately ten years lower, an age-related slight reduction of brain volume may have imposed a minor bias towards enlargement of areas of hypometabolism.

Areas of significantly reduced cerebral metabolism are depicted in Fig. 2 (surface view) and Fig. 3 (glass brain view). The analysis for the whole group shows that pathological hypometabolism centres on the convexity and medial surface of the associative parietal cortex. Single case charts show that it extends, in a variable fashion, to the adjacent occipital and temporal association cortex (all cases except no. 5). This extension to areas that appeared structurally unremarkable corresponds to the clinical trend towards the development of dementia.

The marked asymmetry of structural atrophy in cases 5 to 7 was corroborated by PET. Hypometabolism was almost exclusively limited to one hemisphere in these cases. Asymmetry of hypometabolism was seen in a further case without conspicuous structural asymmetry (no. 8). Among these four cases, two each showed hypometabolism that was more pronounced on the left and the right side, respectively. Similarly, previous single case PET studies showed bilateral as well as asymmetric hypometabolism, without consistent preference for either hemisphere [9, 12, 19, 25, 32]. In AD, asymmetry of hypometabolism is not uncommon [14], but atrophy and hypometabolism that are almost limited to one hemisphere are highly unusual.

There are two earlier case series of PCA with F18-FDG PET investigations. Bokde et al. [5] studied ten patients with clinically defined "visual variant of AD" and 15 patients with "typical AD". Information on the degree and focal features of posterior atrophy in the "visual variant" cases is not provided. SPM analysis showed a relative reduction of metabolism in occipital, parietal and superior temporal areas in "visual variant" patients when compared with "typical AD", and in occipital associative cortex only when compared with a control group. After correction for atrophy, areas of lower metabolism were essentially limited to the occipital associative cortex (Brodman Areas 17, 18 and 19). In a recent study, Nestor et al. examined six PCA cases as well as "typical AD" patients and control subjects [26]. Compared with the control group, PCA patients showed a hypometabolism of the occipito-parieto-temporal cortex (right > left) that was more widespread than in our study. This difference might be because their patients were examined at a later stage of their illness (5.7 years post-onset, mean MMSE score 21.2).

Three of our cases showed involvement of the dorsolateral frontal cortex, i. e. Brodman area 9 and areas 6/8 (cases 4, 5, 7). These frontal areas of hypometabolism were ipsilateral to the side of greater atrophy in the asymmetric cases (5 and 7), and bilateral in the case with bilateral posterior atrophy (no. 4). The group-wise comparison showed a corresponding unilateral hypometabolic area in the nearby junction zone of Brodman areas 6, 8, 9 and 44 (see Fig. 2). Nestor et al. [26] observed similar hypometabolism in frontal areas related to the

control of eye movements (Brodman areas 6, 8). As they pointed out, this finding may represent a remote effect due to deafferentation, caused by the degeneration of projecting fiber from posterior visual association areas. In line with this hypothesis, our cases 4 and 5 were free of early "frontal" behavioral symptoms. In case no. 7, who showed intrusions and confabulations, there was anterior and medio-basal frontal lobe involvement. Thus, in five of our cases, and in all of Nestor et al.'s, hypometabolism did not extend to anterior frontal areas.

We found no significant hypometabolism in the medio-basal temporal lobes. Although memory impairment was present at the time of PET recordings, it was only mild to moderate (Table 2). An exception is again case 7, who showed marked memory impairment and hypometabolism of the entire right temporal lobe including inferior and medial-basal areas (not shown in Fig. 2).

Subcortical structures were not involved, except for the head of the caudate nucleus in case 7. This observation could be explained by a deafferentation due to the involvement of the ipsilateral prefrontal cortex.

In summary, our findings showed that early pathological changes of PCA center on the parietal associative cortex bilaterally. MRI and single case metabolism charts demonstrated a highly variable and asymmetric involvement of temporal, occipital and frontal areas. While a posterior focus of pathology is typical of AD, this is not true for the observed degree of asymmetry (cases 5–7, Figs. 2, 3), for an involvement of the primary visual area (case 6) and for gliosis of the posterior white matter (case 1, Fig. 1b).

Nosology of posterior cortical atrophy

Relationship to Alzheimer's Disease: Early memory disorder was present in eight patients. In seven, it appeared less pronounced than is typically seen in AD, but in one, it was the leading symptom (no. 7). Early memory disorder suggests that pathology involved the transentorhinal cortex and/or hippocampus, which are the earliest to be affected in AD. Most PCA cases that came to biopsy [4] or autopsy [11, 15, 17, 21, 23], including one of the present series, indeed show the histopathological characteristics of AD. Hof et al. describe further six autopsies of AD patients with Balint's syndrome, but did not comment on imaging or macroscopic findings of atrophy [15]. According to a 1996 review of 58 cases, AD was found in 14 of 18 autopsies [29].

Evidence for a nosological relationship comes from the presence of an early deficit of memory, parieto-temporal involvement, the progressive decline towards dementia and the demonstration of AD-type pathology in most PCA cases that came to autopsy. However, the regular presenile onset, occurrence of atrophy of the primary visual cortex and striking asymmetry in a subset of cases suggest that PCA is not a mere localisational subtype of AD, but a biologically separable variant.

AD can also present with other focal symptoms, i. e. aphasia, frontal-type behavioural abnormalities, and even motor deficits, and thus imitate various focal cortical degenerative syndromes. Cognitive deficits tend to generalize quickly in these cases, and, with rare exceptions [11, 20], do not show the pronounced and asymmetric lobar atrophy that is typical of FTD and histologically non-specific focal degenerative syndromes. Hence, PCA appears to be the most frequent "focal" variant of AD.

Differential Diagnosis: Lüers and Spatz [22] quote a series of 30 *Pick's disease* (FTD) cases of whom nine had parietal involvement. Jakob analysed a series of 12 cases with predominant temporal atrophy, and found that cortical degeneration extended to the parietal lobe in nine and to the occipital lobe in five [18]. Delay et al. reported a case of presumed Pick's disease with early-onset, familial dementia, behavioral disturbance, echolalia, aphasia, apraxia, visual and visuo-spatial disturbance and both frontal and parieto-occipital atrophy [7]. There is thus evidence that the parietal lobes can be involved in FTD. However, cases of predominantly posterior atrophy do not seem to occur. Cambier et al. reported "une forme pariétale de maladie de Pick" with asymmetric, exclusively parietal atrophy, putaminal involvement, ballooned neurons and argentophilic neuronal bodies [6]. This patient was not demented for many years after he developed dystonia and spasticity of the right arm, gait disorder and myoclonia. Today, this case would be diagnosed as Cortico-Basal Degeneration (CBD), a condition which regularly affects the parietal lobes. Fukui et al. describe a further patient with progressive apraxia, speech disorder and motor impairment, in whom brain atrophy extended to the superior parietal lobes, although it was centered in more anterior regions [10]. Pathology showed numerous Pick bodies and ballooned neurons. The authors considered this case as intermediate between Pick's disease and CBD. The presence of early motor disturbances clearly distinguishes CBD from PCA.

Our case 1 showed MRI findings indicative of white matter gliosis. Whether this was due to an unusually marked glial reaction is unknown. *Progressive Subcortical Gliosis* [27], a condition of unclear status, was diagnosed in one previous PCA case [31, case 1].

Victoroff et al. and Pantel et al. reported single cases of *Creutzfeldt-Jakob disease* (CJD) with posterior cortical dysfunction [29, 31]. However, one might consider these cases as CJD with leading visual impairment (Heidenhain-variant) rather than PCA, for lack of parietal and/or occipital atrophy. To our knowledge, there are no autopsy-confirmed cases of CJD with focal posterior atrophy.

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