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Basal ganglia mineralization in Alzheimer's disease: a comparative study of clinical, neuroradiological and neuropathological findings

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Fifty patients from a longitudinal study on 178 cases of Alzheimer's disease were examined at postmortem. The clinical features, CT-scans and neuropathological findings of five patients, with verified Alzheimer's disease, who had bilateral basal ganglia mineralization (BGM; 2 male, 3 female; age 78-91 years) were compared with the data of five age- and sex-matched Alzheimer patients without BGM and of five control subjects. Persecutory and other delusions (4 patients), persistent depression (2), parkinsonism (4), myoclonus (1) and epileptic seizures (1) were observed more frequently in the patients with BGM than was expected. The BGM-group had significantly lower counts of large neurons in the pallidum internum than the demented patients without BGM or the control group. We did not find other differences between the dementia groups regarding the CT-scans, or plaque, tangle and neuron counts in neocortex and brainstem. We suggest that the combined effects of Alzheimer pathology and BGM might lead to an increased manifestation of psychotic and motor disturbances.

INTRODUCTION

Pick (1905) and Taft (1916) were among the first to comment on a possible relationship between extensive cerebral mineralization and neuropsychiatric disease, e.g. tetany, epilepsy, depression, schizophrenia and dementia. Later the name of Fahr (1930), who had described only one patient with predominant white matter mineralization, became associated with basal ganglia mineralization (BGM) even though BGM had already been reported in mid 19th century (Virchow, 1854). The view that BGM can cause neurological disorders or disturbances of thought and affect has long been based on anecdotal reports until the introduction of CT-scanning facilitated the investigation of larger series of patients with BGM. An increased rate of BGM has been suspected in patients with seizures, in patients receiving antiepileptic drugs and in patients suffering from movement disorders (Puvanendran *et al.*, 1982; Kazis *et al.*, 1985). The specificity of such associations has been questioned and it has been suggested that various underlying metabolic, familial or infectious diseases, which cause the neurological and psychiatric symptoms, may also be responsible for BGM (Förstl *et al.*, 1991a, 1992; Philpot and Lewis, 1989). Neither the reports of individual anecdotal cases nor of case series allow the evaluation of a statistical relationship between BGM and clinical findings.

Recent work, which compared patients with and without BGM has substantiated the hypothesis that this "incidental" neuroradiological finding of BGM may indeed be associated with delusions, disorders of mood, a variety of neurological disturbances, but that there may not be a direct association with dementia (Burns *et al.*, 1990a; Förstl *et al.*, 1991a, 1992). The statistical association is, however, weak and can only be detected in large case comparative studies. The nature of such relationships is presently unclear.

Our study presents clinical, CT and neuropathological findings from patients with a diagnosis of Alzheimer's disease and with BGM. These results are compared to an age- and sex-matched sample of patients with Alzheimer's disease with and without BGM and also to a control group without neuropsychiatric disease.

METHODS

Patients

The patients described in this paper were part of a prospective long-term study (Burns *et al.*, 1990a) on clinically diagnosed Alzheimer's disease as defined by NINCDS-ADRDA criteria (McKhann *et al.*, 1984). Full neuropathological investigation has been completed on 50 patients to come to autopsy. Of these, five had basal ganglia calcification on CT scan. They were examined with a clinical

interview including the "CAMDEX" (Roth *et al.*, 1986), "Mini-Mental State examination" (Folstein *et al.*, 1975) and further standardized instruments (see Burns *et al.*, 1990a). The clinical diagnoses were verified on postmortem in every case here presented (Burns *et al.*, 1990b). The patients with BGM were compared to age- and sex-matched samples of (1) five Alzheimer patients from the same study without BGM (CT-scans and neuropathology) and (2) with a group of matched controls (neuropathology).

CT-scans

The records of 8-10 mm-slices taken parallel to the orbitomeatal line were stored on tape for post-hoc analysis on an independent viewing console. Computer-assisted measurements of the intracranial and ventricular areas were carried out using predetermined Hounsfield units (Förstl *et al.*, 1990b). The radiodensity of the inner parts of the globus pallidus was measured ("region of interest" with 150-200 pixels; Solomon and Huang, 1980).

Neuropathology

Brains were fixed in 10% formol saline. Blocks were taken from the frontal, temporal, parietal and occipital neocortex, the hippocampus, the midbrain and pons. The basal ganglia were examined on large frontal ("coronal") sections comprising the inner part of the globus pallidus the optic tract and the basal nucleus of Meynert. The sections were stained with Luxol-fast cresyl-violet (LFB/N; 14 μm), haematoxylin-eosin (HE; 7 μm) and according to Glees and Marsland (14 μm). The pallidum internum was outlined on the LFB/N stains. All nucleolated cells with a diameter over 25 μm were twice counted independently within this area (magnification × 400; Alheid and Heimer, 1988). The differences between counts and recounts were smaller than 5%. The averaged results of these "neuron" counts and of the plaque and tangle counts were expressed per unit area. Because of the difficulties in determining the volume of the entire globus pallidus (Pakkenberg, 1963), we made no attempt to estimate a total number of cells. The severity of the vascular mineralization was estimated semi-quantitatively (0 = not present; + = mild; ++ = moderate; +++ = severe, mineralization of capillaries and larger vessels in every visual field). Details of the neuropathological examination of all patients who have undergone postmortem examination will be presented elsewhere.

Statistics

Between-group comparisons were carried out with non-parametric tests (Wilcoxon Whitney–Mann U-test; the *p* values reported were corrected for ties).

RESULTS

Five of the patients with neuropathologically verified Alzheimer's disease showed bilateral BGM on unenhanced CT-scans obtained 3-15 months prior to death. The clinical histories are given below.

Case vignettes

Patient A developed gradually increasing apraxia about age 66. Seven years later she had spatial disorientation, difficulties with writing and speech and a poor memory for names. She became suspicious of her husband whom she suspected of poisoning her. A diagnosis of senile dementia of the Alzheimer type was made one year later, when the patient showed severe cognitive impairment with predominant dysphasia. At the age of 75 the patient constantly accused her husband of stealing money and of consorting with other women. On one occasion she tried to push a (non-existent) woman out of their bed. At this stage she could neither dress herself properly nor could she use a knife and fork. She had predominant persecutory delusions and attacked her husband frequently. Whe she was admitted for inpatient treatment, she appeared confused and agitated. She had a poor short term memory, severe apraxia and aphasia. Two years prior to her death, she developed myoclonic jerking of her arms and trunk. She had a resting tremor and a positive snout reflex. The patient died of bronchopneumonia (see patient A, Table I).

Patient B first showed difficulties with his memory when he was 74. He forgot to post letters, to pay his telephone bills, etc. Two years later he suddenly became disorientated in the course of a urinary tract infection. He was admitted for inpatient treatment. Dysphasia and memory loss persisted after the infection resolved. He experienced several grand mal seizures with tongue biting and incontinence. By the age of 78 he no longer recognized his wife, was severely aphasic but not apractic. At 79 he had a resting tremor, mild cogwheel rigidity and a festinant gait (patient B, Table I).

Patient C developed a slowly progressive deterioration of her short-term memory after the age of 77. She was disorientated to time, exhibited a tendency to blame others for her own mistakes, and did not recognize family members. Four years later she was not able to look after herself and was completely disorientated to time and place. She suffered from severe depressive symptoms, which still prevailed during the following year. Eventually she became aphasic and did not recognize her own mirror image. The patient died of cardiac failure (patient C in Table I; the CT-scan is shown as Fig. 1; the histological findings in the pallidum internum are shown in Fig. 2).

The personality of patient D was described as aggressive and difficult even before the onset of her illness. She lost her interests when aged 66 and stopped washing and

TABLE I. A summary of clinical, neuroradiological and neuropathological findings of the patients with histologically verified Alzheimer's disease and bilateral basal ganglia mineralization (BGM)

	Gender	Age at death	Duration	Symptoms	CT-scan: BGM +	Neuropathology
A	♀	78	13	Apraxia, dysphasia, myoclonus, persecutory delusions	Moderate cortical atrophy and ventricular enlargement, most pronounced at the temporal lobe; mild white matter hypodensities	1010 g; AD
B	♂	79	5	Dysphasia, grand mal seizures, R, T, G	Moderate cortical atrophy and mild ventricular enlargement; mild periventricular white matter hypodensities	1190 g; severe AD and congophilic angiopathy
C	♀	82	4	Depression, "mirror sign", R, G	(see Fig. 1)	1220 g; AD and diffuse Lewy bodies
D	♀	85	19	Persecutory delusions, agitated depression, R, G	Widening of the Sylvian and anterior fissures, severe enlargement of the lateral and third ventricles, moderate periventricular hypodensities	1115 g; AD with predominance of "core-only" plaques
E	♂	91	21	Delusions, R	Moderate cortical atrophy, predominantly over the left hemisphere and both parietal lobes	1300 g; AD

R, rigidity; T, tremor; G, gait disturbance; AD, Alzheimer plaques and tangles sufficient for a diagnosis of Alzheimer's disease.

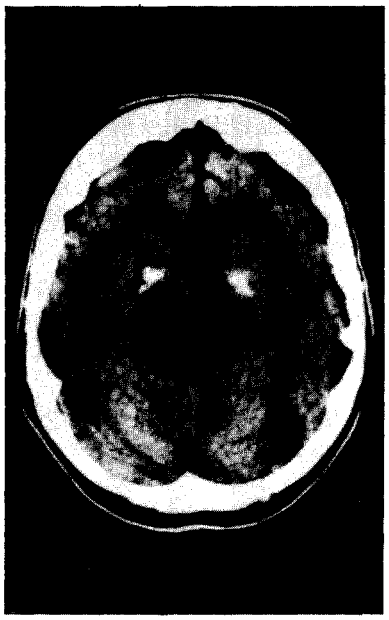

FIG. 1. Bilateral basal ganglia mineralization and cortical atrophy in an 80 year-old patient with dementia and long-lasting depressive symptoms (patient C).

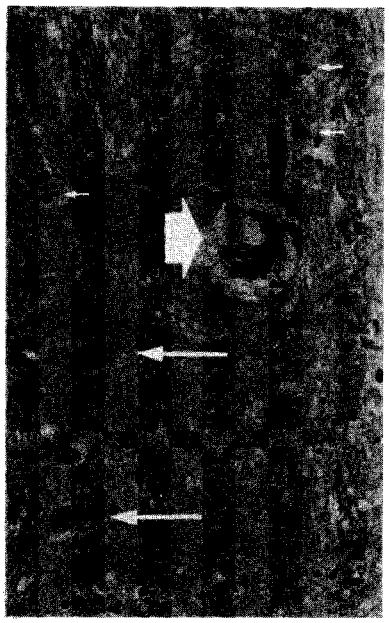

FIG. 2. Large neurons (long arrows), small vessel (broad arrow) and capillary mineralization (small arrows) in the pallidum internum (patient C; H&E stain; magnification × 400).

ironing her clothes. She remained much the same until 12 years later when she went to the police to accuse her neighbours of ringing her door-bell and hammering next door in the middle of the night. She neglected herself and did not eat well. Her memory deteriorated at age 80. She tended to forget appointments and lose her handbag. At night she did

not undress and did not put the light on for fear that somebody might threaten her in her room. At the age of 82 she developed difficulties walking, had repeated falls and fractured her wrist and hip. On admission for inpatient treatment she showed features of agitated depression. She went into frequent rages during which she screamed so loudly that she had to be put into a separate room. At 84 she was wheelchair-bound and had cogwheel rigidity of both arms. The patient died of bronchopneumonia (patient D in Table I).

Patient E showed a gradual memory loss starting at the age of 70. He became suspicious and preoccupied with money. He could not find his way around the house. He became completely deaf but often claimed to hear music playing in the basement. By 80, he seemed to live in the past and asked frequently whether he should go to school. He was admitted for inpatient treatment at the age of 90. He had a poor eyesight and mild cogwheel rigidity. During the last year of his life he was preoccupied with the idea that he had fathered his recently born great-grandchild. The patient died of a myocardial infarction (see patient E, Table I).

Computed tomography

All of the five patients had cortical atrophy and ventricular enlargement (Table I; Fig. 1). The "ventricle-brain ratios" were 7-20 (median 13). Four showed mild to moderate hypodensities around the frontal horns. The radiodensities of the internal segment of the globus pallidus, i.e. in the area of the most severe calcification was between 49 and 116 Hounsfield units (HU; median 79 HU). This was significantly higher than in the group of age- and sex-matched patients with confirmed Alzheimer's disease (34-38 HU; median 37 HU; $p = 0.01$). No other neuroradiological differences were observed.

Neuropathology

The clinical diagnosis of Alzheimer's disease was verified by postmortem in every patient. One patient (C) had coincidental Lewy bodies in the neocortex and brainstem. A moderate to severe mineralization of arteries, capillaries and veins was found in the pallidum internum of every patient with neuroradiologically detectable BGM. Patients without BGM and controls showed no histological evidence of mineralization. The numbers of large neurons in the pallidum internum showed discrepancies between Alzheimer's patients with BGM (range 6.0 to 14.3/mm^2; median 11.9/mm^2), Alzheimer's disease without BGM (range 13.1-44.0/mm^2; median 19.0/mm^2) and controls (range 16.6-39.2/mm^2; median 26.2/mm^2). These differences were statistically significant for the comparison of Alzheimer patients with BGM vs. patients without BGM ($p = 0.021$) and vs. controls ($p = 0.01$). The plaque and tangle counts in the pallidum internum were too low to permit meaningful comparisons. A comparison of neuron, plaque and tangle counts in the cortex, hippocampus, basal nucleus of Meynert, substantia nigra and locus coeruleus did not reveal remarkable differences between the demented patients with and without BGM.

DISCUSSION

The main findings of our study were:

—Four of five patients with Alzheimer's disease and BGM suffered from delusions, two were depressed over a long period of time, four developed signs of parkinsonism, one myoclonus and one cerebral seizures.

—Apart from the BGM itself, the CT-scans did not shown any other differences between the demented patients with and without BGM.

—Patients with BGM showed a significantly lower number of large neurons in the pallidum internum than the patients without BGM and the controls.

In comparison to the present findings, delusions (15.7%), depression (23.5% as observed by rater), severe extrapyramidal signs (11.7%), myoclonus (4.6%) and epileptic seizures (2.8%) were observed in a relatively small percentage of patients from the original sample of 178 patients with a clinical diagnosis of possible or probable Alzheimer's disease (Burns *et al.*, 1990a; Burns *et al.*, 1991). A clear association of BGM with these disorders of thought and of affect cannot be definitely established in view of the small numbers of patients involved in the present study. However, this relationship is in agreement with previous results (Burns *et al.*, 1990a; Förstl *et al.*, 1990a, 1991). The association between extrapyramidal disorders or seizures and BGM in elderly patients is obscured by psychopharmacological side-effects and therefore difficult to determine (Burns *et al.*, 1991; Mölsä *et al.*, 1987). We could not identify any differences in medication between the groups of demented patients, which could explain the higher rate of these symptoms in our patients with BGM.

Apart from mineralization, the decreased number of large neurons in the pallidum internum was the only microscopic difference between the patients with and without BGM. This finding, which will need replication, could relate to the symptoms observed in BGM. The basal ganglia have attracted interest, not only as a possible substrate of extrapyramidal movement disorders, but also as a mediator of cognitive disturbances in psychosis. Their role in perception and behaviour modification had been recognized (Mettler, 1955; Schneider, 1984). Recent studies yielded controversial results regarding a decrease (Bogerts *et al.*, 1985) or an increase of the size of the pallidum internum in schizophrenia (Heckers *et al.*, 1991). Grünthal (1927) reported a decreased size of the pallidum

internum in Alzheimer's disease with "catatonic" symptoms. Histologically the pallidum internum is relatively unaffected by Alzheimer pathology, whereas preferentially immature plaques (β/A4), tangles and a loss of large neurons can occur in the striatum (Braak and Braak, 1990; Oyanagi *et al.*, 1987; Suenaga *et al.*, 1990). The spiny striatal neurons relay cortical afferents to the large pallidal neurons which form the major output from the basal ganglia to the ventral anterior thalamic nucleus, the centromedian nucleus (Luys), the superior colliculus and the midbrain reticular formation (Alheid and Heimer, 1988). We suggest that a combination of Alzheimer lesions in the striatum with BGM-related neuronal loss in the pallidum internum could lead to the decompensation of cognitive and motor function observed in our patients.

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