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Brain White-Matter Lesions and Psychosis

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In a prospective study of late-life onset psychosis, five of the first 27 patients studied had extensive white-matter lesions demonstrated by MRI and/or CT. None of 60 age-matched psychiatrically healthy controls demonstrated such lesions. All five patients had a mild dementia and a frontal behavioural syndrome. In addition, every patient performed poorly on neuropsychological tests of frontal function. Dysfunction of the frontal cortex associated with white-matter lesions appears to contribute to the clinical picture of some cases of late-life psychosis.

Late in life, elderly patients can develop a psychiatric picture that resembles schizophrenia. Some accept this as part of the spectrum of schizophrenia (Roth, 1955; Kay & Roth, 1961; Bridge & Wyatt, 1980; Gold, 1984), although others suggest that many patients with late-onset psychosis have organic disease (Leuchter & Spar, 1985). With DSM–III (American Psychiatric Association, 1980), this confusion was partially addressed by classifying any patient with the onset of psychosis after the age of 45 who otherwise would meet criteria for schizophrenia as having 'atypical psychosis'.

In recent years there has been increasing evidence that silent vascular disease may be an important factor in the pathogenesis of some late-life psychoses (LLP). Miller *et al* (1986) described four patients with LLP with no clinical evidence for structural brain disease, who had extensive brain lesions demonstrated by newer neuroimaging techniques. The relationship between these lesions and the psychosis was not certain, and it is possible that they were not causal. For this reason a prospective study comparing patients with LLP with normal age-matched controls was started in an attempt to define better the relationship between structural brain disease and this psychiatric syndrome.

Preliminary results from this study have been reported and the authors (Miller & Lesser, 1988) described a variety of abnormalities in these patients. Approximately half had serious structural brain abnormalities, including tumour, and vascular and post-traumatic lesions involving cortical and/or subcortical structures; the control group of age-matched subjects without a history of major psychiatric problems had no serious abnormalities on magnetic resonance imaging (MRI). Although a variety of brain areas were damaged in the patient group, in the majority the injury involved frontal or subfrontal structures.

The largest subgroup of patients with LLP were those with extensive and confluent lesions in the deep white matter underlying the cortex, demonstrated with MRI and computerised tomography (CT). Five of 27 patients studied had this pathology, which has not previously been reported in LLP. These five patients are described in detail, and the significance of the white-matter lesions in the pathogenesis of the psychosis, a topic which has received little acknowledgement in the literature, is discussed.

Method

Patients with the first onset of psychosis after the age of 45 were evaluated with the following protocol: a psychiatric interview (the Structured Clinical Interview for DSM–III–R (SCID; Spitzer *et al*, 1986)); a medical history; a neurological examination; an EEG; an MRI scan (1.5 Tesla magnet with T_1- and T_2-weighted images); and a CT scan. The Mini-Mental State Examination (MMSE; Folstein *et al*, 1975), Hachinski ischaemia scale (Hachinski *et al*, 1974), Hamilton Rating Scale for Depression (Hamilton, 1967) and Brief Psychiatric Rating Scale (Overall & Gorham, 1962) were administered to help evaluate dementia, risks for cerebrovascular disease, and psychiatric symptoms. Patients were excluded from the study if the MMSE rating was less than 24. A battery of neuropsychological tests was administered, including the Wechsler Adult Intelligence Scale (Satz–Mogel format) (Wechsler, 1981; Adams *et al*, 1984), Wechsler Memory Scale (Wechsler & Stone, 1945), Rey–Osterrieth Complex Figure Test (Osterrieth, 1944), the Wisconsin Card Sort (Berg, 1948), Stroop Test (Stroop, 1935), Consonant Trigrams (Stuss *et al*, 1982), and Verbal Fluency Tests (Benton & Hamsher, 1976). The patients had CT, MRI, and EEG read by experienced neuroradiologists or electroencephalographers, who were blind to subject status.

The patients were compared with 60 age- and sex-matched controls, recruited through an advertisement requesting that normal elderly individuals were wanted for a study on normal ageing. All control subjects had an MRI scan.

Case descriptions

Case 1

An 86-year-old right-handed woman was brought to hospital by her daughter because of increasing paranoia

associated with belligerence. Four years earlier, she started to complain that visitors were entering her house at night, and were attempting to steal from her. Also, she developed brief episodes during which she believed her daughter was an imposter, when she would throw objects at the daughter, and would hit her.

There was no history of serious medical problems, and she was not taking medication. She had a history of progressive visual and hearing loss, and was registered as blind.

She was alert but irritable, and was co-operative for only 5–15 minutes at a time. Blood pressure was 190/90 mmHg. She described night-time visitors, but denied that her daughter had been replaced by an imposter. She was orientated to time (month and year), and remembered two of three words over five minutes. Speech and language were normal. Her basic neurological examination was normal, except for absent ankle jerks and severe impairments of vision and hearing. The MMSE score was 26, and the DSM–III–R diagnosis (American Psychiatric Association, 1987) was delusional disorder.

The EEG was normal, but CT showed diffuse cerebral atrophy, with scattered lacunar infarcts, and diffuse diminished attenuation in the deep white matter underlying the frontal and parietal cortex (Fig. 1). She refused MRI and neuropsychological testing, and was unresponsive to neuroleptics.

Case 2

A 73-year-old man was admitted to hospital after complaining that men who were hired by the CIA wanted to assassinate him and President Reagan. In addition, he no longer cleaned his flat properly. There was no history of significant medical illness.

He was alert and co-operative, with a blood pressure of 155/100 mmHg. He described his delusions in vivid detail, but seemed unconcerned. His affect varied widely from flat to euphoric. He had trouble remembering the exact date, but recalled three of three words after five minutes. Speech, language comprehension, and naming were normal, as was his copying of a three-dimensional drawing. Basic neurological examination was normal, except for significant hearing and visual acuity deficits. His MMSE score was 25, and the DSM–III–R diagnosis was of schizophrenic disorder.

Neuropsychological tests revealed impaired recall of new verbal and non-verbal information. Verbal IQ was 95 and performance IQ was 105. Perseveration errors were noted on tests requiring categorisation or shifting of mental set.

Laboratory investigations, including EEG, were normal. Both CT and MRI (Fig. 2) showed diffuse confluent white-matter lesions, in addition to multiple small lacunae and generalised atrophy. The delusions persisted after treatment with haloperidol.

Case 3

A 72-year-old man was admitted to hospital because he was being increasingly aggressive at his board-and-care home, where he had hit some of his fellow boarders. His personal hygiene had deteriorated, and he had been incontinent

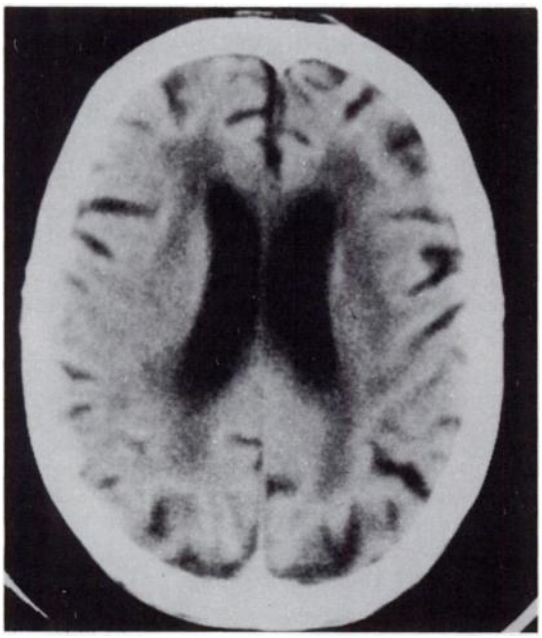

FIG. 1 CT scan from case 1 shows confluent subfrontal and parietal lucencies and atrophy.

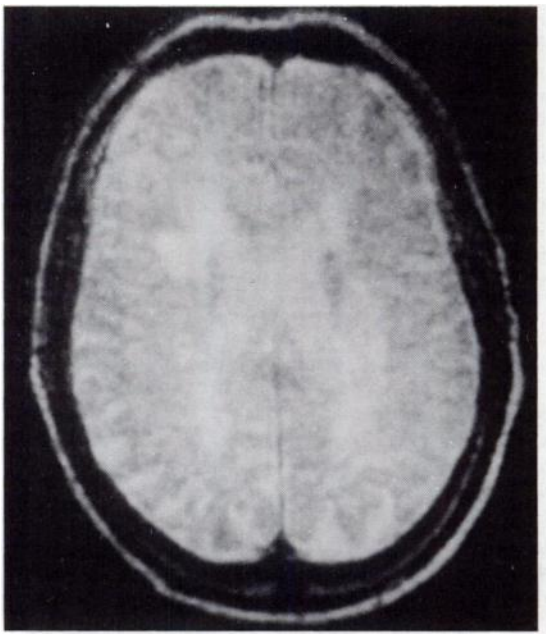

FIG. 2 T_2-weighted MRI scan from case 2 shows increased signal in subfrontal, subparietal, and suboccipital white matter.

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on several occasions. He had a long history of hypertension, and was taking several medications, including prazosin (1 mg/t.i.d), temazepam (30 mg q.h.s), L-thyroxine (0.1 mg q.d.), and carbidopa with L-dopa (25/250 tablets q.i.d.). Four years earlier, he had a coronary artery bypass and had a pacemaker inserted.

He was pleasant and co-operative. He repeatedly complained that someone had inserted a doorknob under his skin at the site of the cardiac pacemaker, but seemed unconcerned about this. He knew the month and year but not the day, and could not remember three words for five minutes. He could not name low-frequency objects (e.g. 'door hinge'), and followed two-step but not three-step commands. Motor tone was increased, and a coarse rapid tremor was noted. Gait was wide based and slow, and toes were downgoing. His MMSE score was 24, and his psychiatric diagnosis was of delusional disorder.

Neuropsychological testing revealed impairment in learning and some responses were confabulatory. Mild impairment of constructional and mathematical abilities were present. Verbal and performance IQ were 74.

The CT scan showed multiple subcortical white-matter lucencies, and several lacunar infarcts in the basal ganglia. The patient's delusional syndrome did not respond after the L-dopa was decreased, and he was discharged to a nursing home.

Case 4

A 62-year-old right-handed man was admitted to hospital to assess a memory disturbance associated with paranoia and delusions. In the months before admission, he began to accuse others of trying to steal his money. There was a past history of diabetes, hypertension, hearing loss, and a vague history of stroke in the year before admission.

The patient had a blood pressure of 160/92 mmHg. He repeatedly stated that people had stolen from him at work. Although irritable and easily angered, at times he was euphoric. The basic neurological examination was normal, except for mild dysmetria and a wide-based ataxic gait, and a moderate sensorineural-type hearing loss was demonstrated. His psychiatric diagnosis was of delusional disorder.

His full-scale IQ was 88, with a significant discrepancy between verbal (95) and performance IQ (78). Verbal and non-verbal memory skills, visual perceptual and constructional abilities, frontal systems, and attentional abilities all were impaired. In contrast, language skills, mathematical ability, and general information were within the low to high average range.

The EEG was normal, but the CT scan showed multiple lacunae in the deep white matter and basal ganglia. He did not respond to drug therapy.

Case 5

A 68-year-old right-handed man was referred to hospital after an attempt to have sexual relations with a 13-year-old niece, a behaviour that seemed 'out of character'. Before admission he had become increasingly disinhibited, and had stated that he had heard God speaking to him. Also, he insisted that he was a captain in the merchant marines, although this was not true. There was a complicated medical history, with chronic obstructive pulmonary disease, diabetes, hypertension, and heart disease. His medications included ibuprofen (400 mg t.i.d.), chlorpropamide (250 mg t.i.d.), clonidine (2 mg t.i.d.), aminophylline (200 mg b.i.d.), digoxin (25 mg q.d.), and furosemide (40 mg q.d.).

He was disinhibited, with pressured speech and flight of ideas. He fluctuated between irritability, anger, and euphoria. The delusions were described with detachment and lack of emotion. He had trouble with memory tasks, but language was fluent and comprehension was good. Basic neurological examination was normal, with the exception of severe sensorineural hearing loss, and moderate visual disturbance secondary to bilateral cataracts. The psychiatric diagnosis was of bipolar disorder, manic phase with psychotic features.

The CT scan showed well circumscribed lucencies, which seemed to undercut both frontal and parietal lobes. His behaviour did not improve with neuroleptics, and he was discharged to a nursing home.

Discussion

The five elderly patients described here were all seen because of a behavioural disorder associated with prominent delusions. Although two of the patients showed minor neurological deficits (cases 3 and 4), only one of these had a history of stroke. Hypertension was present in four of the five patients, and serious deafness and/or visual deficits in three. Intellectual impairment was not recognised as a major problem by the patients' families or primary health care personnel, yet neurobehavioural and neuropsychological batteries did demonstrate evidence for dementia in every patient. However, language function was normal, and the dementia syndrome was not apparent unless special tests assessing frontal lobe and memory function were performed.

The clinical features of these patients differed from those seen in classic schizophrenia: none had a prior history of psychiatric illness, nor was there evidence of a formal thought disorder, yet each had complex delusions with or without hallucinations. Unshakable delusions were a prominent feature of the psychiatric presentation, and although difficult to quantify, all had relative sparing of personality. Three had a DSM-III-R diagnosis of delusional (paranoid) disorder, one met criteria for schizophrenia, and one had a manic syndrome. Although there was some variability in the specific psychiatric presentations, all patients had strikingly similar large subfrontal white-matter lesions on CT and MRI.

Considering all the clinical and radiographic data, these conditions could be rediagnosed as organic delusional or organic affective disorders, but this diagnostic information was not apparent upon entry to the study, when the clinician initially evaluated the patient. In several cases, the additional testing was pursued only because the patient was a study participant.

Lesions in the frontal regions and behavioural abnormalities

It is well recognised that frontal-lobe lesions may produce changes in behaviour, but may be otherwise neurologically silent (Stuss & Benson, 1984). Although none of the patients had lesions evident in the frontal lobes, all had extensive subfrontal white-matter infarction. In two patients (cases 1 and 5), the white matter underlying the frontal lobe was the predominant site of abnormality, and this region was involved in all five cases. Subcortical white-matter lesions can disconnect the frontal areas from the remaining brain, and white-matter diseases such as metachromatic leucodystrophy often start with behavioural changes that include frontal-lobe symptoms and sometimes mimic schizophrenia (Skomer *et al*, 1983).

Irritability, apathy, behavioural disinhibition, and poor judgement, symptoms commonly associated with frontal-lobe injury, were present in all the patients, and euphoria was present in four. All were brought to hospital because of behavioural disinhibition associated with impairment of judgement. It can be argued that in every patient this aspect of their psychiatric syndrome and not the delusions was the major source of concern to family and friends. Irritability and apathy were also present, and in all but case 1, this was seen to fluctuate with periods of euphoria. The group did poorly on tests of frontal function and on the battery of frontal tests, suggesting that the frontal lobes and/or their connections were injured. These findings support a role for the frontal cortex in the pathogenesis of some of the abnormal behaviour seen in LLP.

Delusions as part of a frontal syndrome

Although delusions and hallucinations are not typically indicators of frontal damage, specific delusions have been reported in association with such lesions. Reduplicative paramnaesia syndrome was first described by Pick (1903) in a patient with Alzheimer's disease "who insisted that the hospital she was in was located in her own community rather than in the city of its actual location". It has since been noted that many patients with reduplicative paramnesia have periventricular and right hemisphere dysfunction (Weinstein & Kahn, 1955), and Benson *et al* (1976) described three patients recovering from head traumas with a combination of right hemisphere and bifrontal abnormality who had classic reduplicative paramnesia. Another dramatic delusion which has been described following frontal injury is the Capgras syndrome (Alexander *et al*, 1979), which features the belief that a person close to the patient has been replaced by one or more identical appearing imposters (a feature of case 1). A third syndrome which may approach delusional proportions and which may be seen in patients with frontal damage is confabulation, particularly the 'fantastic' or 'spontaneous' confabulation syndrome (Stuss *et al*, 1978). Even where the degree of confabulation is less pronounced, Mercer *et al* (1977) demonstrated that a consistent clinical feature was a lack of self-criticism, and they postulated a frontal dysfunction.

In each of these three syndromes, the patient presents an incorrect response and maintains the response in the face of contrary evidence. Inability to monitor and self-correct appears to be the primary dysfunction underlying these delusions. In all five of the cases described above, there was a striking inability to monitor and self-correct, and the delusions were part of a more generalised frontal syndrome.

Sensory deprivation has been described as a risk factor for LLP, with 38% of subjects suffering from significant hearing loss compared with 18% of patients with late-life affective disease (Cooper & Curry, 1975). Two of our patients had serious visual and hearing loss, a third patient had mild sensorineural deafness, whereas two had no sensory deficits. The role of the sensory deficits in the pathogenesis of the psychosis is uncertain, and it is possible that the sensory disturbance in conjunction with the mental impairment contributed to the hallucinations and delusions which were present in four of the five patients. Sensory deprivation is common in the elderly and can lead to modality-specific hallucinations, but delusional affirmation of the hallucination is unusual (Cummings & Miller, 1987), and the frontal and subfrontal brain injury appeared to be an important contributor to the psychosis in our cases.

Aetiology of the white-matter lesions

With third-generation CT and, more recently, MRI, it has become increasingly clear that many elderly people have subtle abnormalities in the white matter underlying cortex. In one study, 88% of demented

elderly subjects compared with 61% of non-demented patients with ischaemic vascular disease had at least one lesion in the white matter (Hershey *et al*, 1987). Bradley *et al* (1984) noted small lesions in 30% of all patients over the age of 65; these lesions were not common in younger patients. Some have suggested that these lesions are small white-matter infarctions (Brant-Zawadzki *et al*, 1985). It has been demonstrated that hypertension is present in a higher proportion of patients with these defects than in age-matched controls, suggesting a possible vascular aetiology (Brant-Zawadzki *et al*, 1985). Their clinical significance is debated (Hackinski *et al*, 1987), with suggestions that they correlate with dementia (Brant-Zawadzki *et al*, 1985) or even are asymptomatic (Hershey *et al*, 1987).

Although small lesions may be asymptomatic, larger ones often are associated with dementia (Goto *et al*, 1981; Steingart *et al*, 1987). Some of the original papers on this topic noted that delusions were present in some of the patients (Goto *et al*, 1981; Tomonaga *et al*, 1982), although the psychiatric features of white-matter lesions have not been extensively characterised, and in most cases have been ignored. We have not seen large subfrontal lesions in the 60 control patients that we have so far studied, and doubt that lesions as extensive as those seen in our five patients are asymptomatic or unrelated to their neuropsychiatric presentation.

These five cases demonstrate that the first and primary clinical manifestations of white-matter lesions may be psychiatric. The relationship of these lesions in the subfrontal area to frontal dysfunction needs further study, but in these five cases frontal dysfunction was profound. Neurophysiological studies such as computerised EEG and single-photon emission computerised tomography (SPECT) may clarify the relationship between white-matter lesions and frontal function. Because these lesions are common in the elderly, further study of their clinical significance will be important.

When psychosis appears for the first time in late life, a careful search for organic illness, incorporating CT or MRI, should be undertaken. In particular, a subset of patients with white-matter lesions may present with both delusions and a frontal syndrome.

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