Bipolar Disorder and Cerebral Sarcoidosis

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A 40-year-old man suffered both a short-term memory defect and bipolar mood disorder. It is postulated that both conditions are due to progressive cerebral sarcoidosis affecting the limbic system. The need for early detection and treatment is emphasised.
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Sarcoidosis, a systemic granulomatous disorder, affects the nervous system in 5% of cases (Delaney, 1977), and in nearly half of these it is the presenting feature (Stern *et al*, 1985). There may be subclinical involvement of the nervous system as neurosarcoidosis is often only detected at autopsy. Involvement of the peripheral nervous system usually occurs late in the course of the disease, whereas involvement of the central nervous system (CNS) occurs earlier (Delaney, 1977). Similar to systemic sarcoidosis, neurosarcoidosis may follow an acute or chronic course. The former usually has a good outcome while the latter tends to have a relapsing and remitting course (Pentland *et al*, 1985). Involvement of the peripheral nervous system has a better prognosis than that of CNS lesions, where the two-year remission rate is only 25% (Neville *et al*, 1984).

The most common lesions are cranial neuropathies, especially peripheral facial-nerve palsy. These may be due either to granulomatous basal meningitis or to brain-stem involvement. The granulomatous material may spread from these areas or appear elsewhere to affect the spinal cord, cerebellum and cerebral hemispheres and more commonly to infiltrate the hypothalamus, pituitary, third ventricle and surrounding components of the limbic system. Psychiatric phenomena are therefore not uncommon.

We describe a patient suffering from the neurological and endocrinological sequelae of neurosarcoidosis, who subsequently developed a permanent defect of short-term memory and a bipolar mood disorder. As far as we are aware, this is the first case of this type to be described.

Case report

The patient, a 40-year-old, white, Irish, married father of three, with a nine-year history of cerebral sarcoidosis, was admitted for the first time to a psychiatric hospital for the treatment of a rapid-cycling affective disorder. Sarcoidosis was first suspected at the age of 25 years when bilateral hilar lymphadenopathy was seen on a routine chest X-ray. The diagnosis was made by mediastinoscopy and lymph-node biopsy. The lymphadenopathy resolved after a brief course of steroid therapy and there were no further complications until the patient developed sarcoid meningitis six years later. The meningitis subsided over a number of months after a course of steroids. The patient remained on prednisolone (15 mg daily) after that, the dosage being increased temporarily at further relapses.

At the age of 34 years, he developed peripheral sensorimotor neuropathy manifesting as leg muscular weakness and bilateral involvement of the sensory divisions of the fifth cranial nerves with resultant facial numbness and impaired corneal reflexes. Computerised tomography (CT) at this time demonstrated no cerebral abnormalities. Two years later, aged 36, the patient developed diabetes insipidus and shortly afterwards anterior pituitary failure. This required replacement therapy with 1-deamino-8-D-argenine vasopressin (DDAVP), L-thyroxine, continued steroid therapy and depot testosterone. The latter did not produce subjective improvement and was discontinued. After this, the patient, for family reasons, attended an endocrinologist in the United States. The following year, aged 37, he received cranial irradiation (1800 rad) which produced some improvement of the facial numbness. Cerebrospinal fluid (CSF) analysis at this time still indicated active CNS sarcoidosis. Later that year, the patient was noted to have orthostatic hypotension, which was attributed to peripheral neuropathy and diabetes insipidus. The dosage of DDAVP was increased to 0.2 ml nasally b.d. He was also commenced on fludrocortisone (0.2 mg b.d.) and advised to wear support stockings, with good effect. Magnetic resonance imaging (MRI) carried out at this time demonstrated minimal cortical atrophy and, as yet, the patient had no affective symptoms. He had always been able to resume his work satisfactorily after his hospital admissions.

Twenty-one months before his presentation to us, the patient, now aged 38 years, became depressed and developed anorexia, with weight loss (9 kg), loss of interest, indecisiveness and marked guilt feelings about his illness and the burden he was on his family. At the same time he also noticed that his memory for recent events was impaired. Imipramine, prescribed by a psychiatrist, alleviated his depression but had no effect upon the memory disturbance. Twelve months later he began to get mood swings alternating between episodes of depression and hypomania. The latter, characterised by an elevated mood, hyperactivity, pressure of speech and distractability, would last for a few days with normothymic periods in between. Three months later oral lithium carbonate (600 mg daily) was added to his treatment. However, by this time the mood swings had

taken on a circular pattern and had accelerated, changing every 24–28 hours. The imipramine was discontinued one month before admission by a psychiatrist in the United States and instead he was commenced on fluoxetine. His oral lithium dosage was reduced to 400 mg daily, as the higher dose resulted in marked polyuria. CSF analysis at this time indicated that the neurosarcoidosis was still active.

The patient had no past or family history of psychiatric illness. His childhood and upbringing were uneventful. Following secondary school he attended a technical college and qualified as a mechanic. He was employed as a full-time aircraft mechanic when aged 28 years. Three years before presentation to us he was transferred from this manual work to updating technical manuals in order to reduce his exposure to potential neurotoxins in the work place. His wife and family were very supportive. Although an outgoing person, his level of social and leisure activities had been reduced over the years on account of his illness.

On admission, his mood was depressed with an appropriate affect. There was no evidence of any thought or perceptual disorder and he was fully orientated. His short-term memory was impaired, while his long-term memory was intact. He had mildly Cushingoid facies with decreased body hair. There was evidence of bilateral sensory neuropathy of the fifth cranial nerve. His blood pressure was 100/50 mmHg. Otherwise, the remainder of the neurological and physical examination was normal. Routine laboratory tests, including full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests and serum calcium were normal. Apart from low androgen levels, his hormone replacement therapy was correct and his urine concentration was adequate.

A repeat MRI scan demonstrated no change from the previous one. Psychometric assessment confirmed the memory deficit. Index scores on the Weschler Memory Scale-Revised were: verbal memory 58, visual memory 97 (general memory 67) and 76 for delayed recall. His IQ was 96 (Weschler Adult Intelligence Scale - Revised) and his language and calculating abilities were normal.

Following admission, the rapid mood cycling continued, with almost daily mood swings. It became apparent that the patient was relying on mnemonic aids (e.g. note books) to enable himself to recall memories such as recent conversations. From clinical observation, over the three-month in-patient stay, the memory defect proved to be irreversible and unrelated to mood. His short-term memory problem had also caused an increase in his obsessional traits, possibly as a compensatory mechanism.

The antidepressant medication, fluoxetine, was discontinued shortly after admission. Initial attempts to stabilise his mood swings with higher doses of lithium carbonate were unsuccessful in that he developed troublesome polyuria. He was unable to tolerate carbamazepine because of persistent headaches. Consequently he was maintained on only low-dose lithium carbonate (250 mg daily). His mood swings gradually began to stabilise and after six weeks he had no further episodes of hypomania. He continued to be mildly depressed for another three weeks, by which time he achieved a near normothymic level. His memory defect, however, persisted. He was discharged shortly afterwards on his maintenance hormone treatment, prednisolone, fludrocortisone and lithium carbonate (250 mg daily).

He continued to remain mildly depressed for the next three months. He then became seriously depressed again with poor self-esteem and expressed feelings of guilt and worthlessness. While an in-patient for medical treatment of his sarcoidosis, he made a number of suicide attempts. He was subsequently readmitted for psychiatric care but just as his depression was responding to antidepressant medication he unexpectedly took an overdose and died.

At post-mortem a large, burnt-out granulomatous mass (8 mm × 4 mm) was discovered just anterior to the mamillary bodies at the origin of the pituitary stalk. Histological examination demonstrated partial infiltration, by the mass, of sections of the dorsomedial nucleus of the thalamus, mamillary bodies, third ventricle, fornices and pituitary stalk. There was patchy basal meningeal fibrosis with some obliteration of subarachnoid space. Isolated meningeal granulomata were also noted. The cerebral hemispheres, cerebellum and brain-stem were unaffected. Spinal meningeal fibrosis was severe with entrapment of ventral and dorsal roots resulting in appearances of long-standing denervation in leg muscles.

Discussion

This patient had sarcoidosis which progressed gradually, over nine years, through his CNS. It started in his meninges and spread to affect his pituitary and hypothalamus, resulting in hypopituitarism. This was, after its detection, always adequately controlled. It is unlikely that long-term steady-dose steroid therapy contributed to the patient's psychiatric presentation. Such manifestations of steroid therapy usually present within three weeks of commencing treatment (Hall *et al*, 1979). Cranial irradiation of a dose as low as 1800 rad would rarely, if ever, cause disturbance such as an encephalopathy (Marsden, 1987). The major aetiological factor in this patient's presentation was further sarcoid involvement of the limbic system. It is well recognised that lesions of both the mamillary bodies and dorsal medial nuclei of the thalamus (as in Korsakoff's syndrome) and also of the hippocampal area can result in an amnesic syndrome (Lishman, 1987). From the post-mortem findings it is not surprising that the patient had a severe irreversible short-term memory defect. This was temporally associated with a major depressive episode which developed into a bipolar disorder. A causal relationship is therefore postulated between the sarcoid involvement of his limbic system and bipolar disorder.

The neuropathology of secondary affective disorders has been recently reviewed (Jeste *et al*, 1988). Of note, they found one case report of a 45-year-old man with cerebral palsy who developed

a rapid-cycling bipolar disorder with stereotyped mood swings. This man had a right hemispherectomy at the age of 18 years which cured previously intractable epilepsy. He had recurrent unipolar depressive episodes from the age of 18 to 45 years. In our patient the rapid cycling of such an extreme nature was probably precipitated by the tricyclic antidepressant, as it resolved shortly after stopping this medication.

While there has been no research to date specifically devoted to the psychiatric manifestations of cerebral sarcoidosis, there have been a few detailed case reports on the neuropsychiatric aspects (e.g. Thompson & Checkley, 1981). Hook (1954) detailed nine cases of neurosarcoidosis, five of whom had psychiatric symptoms including one patient with fatigue, sleep disturbance and irritability with impaired memory for recent events. Only two out of Silverstein's (1965) 18 cases had psychiatric disturbance consisting of stupor and confusion with memory loss. Eleven cases out of Delaney's (1977) 23 developed encephalopathies with mainly confusion and some psychotic features. Six of these progressed to dementia. By contrast, none of Stern's *et al* (1985) 23 patients had any psychiatric problems. Three of Pentland's *et al* (1985) 19 patients had psychiatric symptoms – personality change with memory loss, persistent intellectual impairment and episodic confusion.

Although metabolic dysfunction due to pulmonary, hepatic and renal involvement is common in sarcoidosis, it is a rare cause of psychiatric disturbance (Delaney, 1977). Secondary hypercalcaemia and the therapeutic use of steroids are more likely to determine a psychiatric presentation. However, the main pathological basis for neuropsychiatric disturbance in sarcoidosis is the structural damage of granulomatous infiltration. There may be diffuse or localised involvement of CNS structures by either granulomatous masses or by contiguous spread of granulomas. Raised intracranial pressure and hydrocephalus may be caused by chronic basal meningitis or by CSF outflow obstruction. Sarcoidosis has a predilection for the pituitary and hypothalamus, which results mainly in endocrinological dysfunction. Focal involvement of the hypothalamus and the rest of the limbic system may result in a defect of short-term memory (as in our patient and in the case reported by Thompson & Checkley, 1981), personality change, somnolence and affective disorder. Organic mental syndromes such as delirium, dementia, hallucinosis and mood and personality syndromes tend to be caused by diffuse parenchymal infiltration or raised intracranial pressure with hydrocephalus (Ho *et al*, 1979). Cerebral sarcoid deposits may also result in epileptic seizures.

Psychiatric symptoms in patients known to have sarcoidosis should alert the clinician to the possibility of cerebral involvement even in the absence of neurological signs and symptoms. The diagnosis of cerebral sarcoidosis can be difficult to make. Useful investigations include CSF analysis, which may demonstrate pleocytosis, raised protein and occasionally lowered glucose levels where there is sarcoid meningitis. In the case of dementia, consistently normal CSF analysis for white cells, protein and glucose probably excludes it being due to cerebral sarcoidosis. Early hypothalamic involvement may cause elevated prolactin levels (Malarkey & Karatis, 1974) and abnormalities in serum osmolality (Stuart *et al*, 1980). CT and MRI may demonstrate mass lesions, evidence of basal meningitis or ventricular dilatation. Diagnosis by biopsy is rarely feasible or warranted. Visual and brain-stem evoked potentials have been advocated in the early detection of cerebral sarcoidosis, even in the subclinical stages (Oksanen & Salmi, 1986). Hopefully, the potential for earlier diagnosis of cerebral sarcoidosis will be realised and lead to earlier intervention with corticosteroid therapy, with an improved prognosis and reduced long-term morbidity.

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Psychiatric Diagnoses in Ulcerative Colitis

A Controlled Study

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Fifty patients with UC and 50 matched controls with urolithiasis were interviewed with the SADS (lifetime version) and completed the SCL-90. According to information given during the SADS, there was a history of psychiatric disturbance in 11 UC patients (22%) and 8 controls (16%). At the time of the interview a psychiatric disturbance was present in 31 UC patients (62%) and four controls (8%), the most frequent diagnoses in the former being minor depression and generalised anxiety disorder. Patients with UC scored significantly higher than the controls on all the different SCL-90 subscales.

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The possible association between psychiatric disturbances and ulcerative colitis (UC) is a topic still open to debate. Pioneering research done by Daniels (1948) and Alexander (1950) clearly suggested the presence of emotional disorders in patients with UC. Helzer *et al* (1982) reviewed the more recent studies and concluded that these were methodologically poor: no explicit psychiatric diagnostic criteria were used except in one study; in this, however, the sample size was very small and the reliability of the psychiatric interview used was not stated. Helzer *et al* (1982), using a structured interview, found no greater frequency of psychiatric disturbances in 50 patients with UC compared with 50 controls suffering from chronic medical illnesses; 26% of the former compared with 30% of the latter reported one psychiatric diagnosis, with depression being the most frequent disorder in both groups.

As far as we know, two other studies which used operational diagnostic criteria and a standardised interview have been published since that of Helzer *et al*. One of these, however, used no controls (Andrews *et al*, 1987), and in the other the size of the experimental group was relatively small ($n = 27$) (Tarter *et al*, 1987).

In the present study we assess the prevalence of psychiatric disturbances in 50 consecutive UC patients and in 50 matched controls. For the psychiatric evaluation, operational diagnostic criteria and a widely utilised standardised interview were used.

Method

The subjects included 50 consecutive patients with UC admitted to the Department of Gastroenterology, University of Padua. There were 27 males and 23 females, with a mean age of 36 years (range 15–62, s.d. 14.1). Mean duration of the disease was 5.2 years (s.d. 4.7). The severity of the physical symptoms was assessed using a slightly modified version of Edwards & Turnlove's (1963) classification. In this there are four degrees of severity ranging from 1 (remission) to 4 (severe activity). Twenty-four patients were in a remission phase of the disease (stage 1), 25 in a phase of mild activity (stage 2) and one in a phase of moderate activity (stage 3). For the treatment of UC, 37 patients were taking sulfasalazine and 8 mesalazine; 12 patients were also taking oral corticosteroids. Nobody refused to participate in the study.

Controls were patients suffering from urolithiasis and undergoing an extracorporeal shock-wave lithotripsy at the Department of Urology of the same university hospital. Each control was matched with an experimental patient for sex, age (± 5 years) and marital status. For a few young male patients with UC it was not possible to find a suitable control and therefore in these cases male patients suffering from symptomatic varicocele were chosen. The mean duration of the disease was 4.8 years (s.d. 6.8). None of the controls refused to participate in the study.