

Mental change as an early feature of multiple sclerosis

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SYNOPSIS Five patients with mental change as a prominent and early feature of an illness which appeared to be multiple sclerosis are reported. All the patients had in addition clinical signs of predominant brain stem involvement and the cerebrospinal fluid findings were similar. It is emphasised that mental change may be an early feature of multiple sclerosis even in those patients in whom the onset of the disease is insidious.

It is well recognised that mental and emotional changes occur in patients with multiple sclerosis but the rarity of mental changes in the early stages of the disease is always emphasised. If this feature is a presenting symptom the diagnosis of multiple sclerosis is made reluctantly. We describe here five patients with mental change as an early and prominent symptom of an illness which appeared to be multiple sclerosis.

CASE 1

A.P. is a 30 year old housewife. Four years before admission to Churchill Hospital in July 1974 she began to neglect her housework and to sit around doing nothing. Her mother described a change from a sparkling active girl to a nervous inactive person. About a year later she developed diplopia. She was seen elsewhere in January 1972 with these complaints when examination revealed bilateral ptosis, disorganised eye movements, vertical nystagmus, and hyperreflexia. Investigations were normal except for the CSF which contained 16 lymphocytes mm^{-3} , protein 0.25 g/l, and IgG 0.12 g/l (48% of total protein).

Psychological assessment in May 1972 showed the following: on the Wechsler Adult Intelligence Scale (WAIS) she obtained a verbal IQ of 102, performance IQ of 97, and full scale IQ of 97. The psychologist commented that 'intellectual assessment showed evidence of fall-off in both verbal and performance areas and thus her present overall IQ score of 97

would seem to be an underestimate of her pre-morbid level which would probably have been in the above average range'.

She had a course of steroids with apparent improvement. In June 1973 her mental state deteriorated and she became ataxic and dysarthric. She was readmitted for lumbar pneumoencephalography (LAEG), which showed ventricular dilatation and widening of the subarachnoid channels. Again she improved but she remained ataxic and there was pallor of the right optic disc. Psychological testing was repeated (June 1973) and she obtained on the WAIS a verbal IQ of 77, performance IQ of 78, and full scale IQ of 76, indicating further generalised deterioration.

Her clinical state continued to fluctuate and on admission to Oxford her main disability was the unsteady gait but she also had dysphagia, occasional urinary incontinence, and intermittent diplopia. On examination she was disorientated in place. She performed bedside tests of intellectual function poorly and she lacked insight. The optic discs were pale, particularly the right. Visual acuity was J2 bilaterally. On upward gaze the eyes diverged and there was nystagmus on right lateral gaze. She had developed a left lower motor neurone facial palsy since attending the outpatient department two months previously. She was dysarthric and there was a curious dystonic posture of the neck. There was ataxia of all the limbs, the gait was ataxic but sensation was normal. All the reflexes were brisk with extensor plantar responses.

An EEG showed a moderately severe abnormality without localising features. The CSF contained 1 lymphocyte mm^{-3} , protein 0.30 g/l, IgG 0.1 g/l (44%

of total protein), Lange curve 4433221, and W.R. negative.

CASE 2

G.H., a 35 year old investment manager, was admitted to the Churchill Hospital in October 1973. He complained of anxiety and difficulty with interviews for six months, his speech drying up and becoming slurred. Both hands had become clumsy and his gait had become unsteady. His wife felt that the clumsiness subsequently improved but his memory had become exceedingly poor. He would forget day-to-day arrangements and where he had left objects about the house. On direct questioning he also admitted transient paraesthesiae of both hands for a similar period.

On examination he was euphoric. Although normally orientated, bedside testing showed evidence of intellectual impairment. There was scanning dysarthria. The temporal portion of both optic discs was pale, but the visual acuity was J2 bilaterally. Fine vertical nystagmus was present on upward gaze and the jaw jerk was exaggerated. The tendon reflexes were increased on the right with absent right abdominal reflexes and a right extensor plantar response. There was moderate finger-nose and heel-shin ataxia.

Psychological testing showed that he had on the WAIS a verbal IQ of 114 with subtest scores (age scaled) as follows: information 13, arithmetic 13, similarities 11, digit span 11, vocabulary 14. The psychologist felt that this might reflect a mild degree of generalised intellectual deterioration in a man who had held fairly senior executive jobs in advertising. There was no clear evidence of dysphasia and he named 35 out of 36 object drawings. Evidence of considerable memory impairment was found in his scores on subtests of the Wechsler memory scale I (logical memory 11, delayed recall 1; visual reproduction 3, delayed recall 2; paired associate learning 10.5, delayed recall 6) and in his very poor performance in learning tasks (word lists and mazes).

Investigation produced the following results: chest and skull radiographs, blood count, ESR, serum urea, electrolytes, liver function tests, serum proteins and electrophoretic pattern and serum B12 were all normal. Blood WR was negative. A LAEG showed cortical atrophy with particular enlargement of the right lateral ventricle. The CSF contained 7 lymphocytes mm^{-3} , protein 0.30 g/l, IgG 0.10 g/l (33% of total protein), Lange curve 432110. No virus was isolated.

A diagnosis of multiple sclerosis was made. Four months later the cerebellar signs had remitted and the right optic disc appeared paler but there was no other

change on examination. His wife thought that his memory, if anything had deteriorated further.

CASE 3

P.R. is a 54 year old housewife who initially presented in December 1960 when 40 years of age, first to a general physician and then to a psychiatrist. She complained of anxiety, depression, and an inability to perform ordinary household duties. Additional complaints of writing difficulty and dragging of the right leg were noted but as neurological examination was normal these complaints were considered hysterical. She was treated with chlorpromazine and imipramine and by June 1961 she had 'improved enormously'. In 1966 she deteriorated with mood instability, euphoria, and garrulousness. Psychological assessment was performed in September 1966. Her behaviour in the test situation was typical of the demented patient in that she was over-talkative and what she said was frequently circumstantial, irrelevant, or off the point. She was perseverative, had difficulty in understanding test instructions, and tended to forget what she was supposed to be doing. WAIS scores were verbal IQ 66, performance IQ 69, full scale IQ 65 (subtest scores: information 7, comprehension 6, arithmetic 2, similarities 0, digit span 1, vocabulary 8, digit symbol 0, picture completion 6, block design 6, picture arrangement 0, object assembly 5). These results clearly indicated organic intellectual impairment. She was subsequently admitted to Churchill Hospital in 1967 for neurological assessment.

On examination the only other findings were hyper-reflexia and equivocal plantar responses. Brain scan and skull radiographs were normal. An EEG showed a mild excess of slow activity without localising features. The CSF contained 4 lymphocytes mm^{-3} , protein 0.45 g/l, WR negative and the Lange curve was 2211000. A provisional diagnosis of Alzheimer's disease was made, although a LAEG had not been performed. She remained unchanged for six and a half years but in 1973 she developed unsteady gait, slurred speech, and right-sided facial weakness. Her husband thought her memory had deteriorated once again. Over a few weeks she recovered from this episode. In 1974 she was readmitted to Churchill Hospital with complaints of dizziness, disorientation, poor balance, and clumsiness.

On examination she was orientated in time and place but exhibited evidence of a patchy dementia on bedside testing; she had a superficial grasp of current affairs but she was totally unable to perform the simplest arithmetic. Psychological testing showed no evidence of further deterioration since 1966. There was nystagmus on left lateral gaze, a brisk jaw jerk,

and a mild right facial palsy. She had a spastic quadriplegia with vibration sense loss in all limbs and proprioceptive loss in the arms. She was unable to stand.

Normal results were obtained for blood count, ESR, serum urea, electrolytes, liver function tests, chest and skull radiographs, brain isotope-scan, and myelogram. The EEG was unchanged since 1967. LAEG showed cerebral atrophy. The CSF contained 6 lymphocytes mm^{-3} , protein 0.25 g/l, IgG 0.11 g/l (44% of total protein), Lange curve 4321100, and WR negative.

A spontaneous improvement occurred, power and joint position sense returning to normal but ataxia of the limbs and gait remained.

CASE 4

M.H. is a 35 year old furniture polisher. Six months before admission to Churchill Hospital in June 1974 his wife noticed that he was tiring easily, sleeping more, and becoming forgetful. His employer had noticed a similar change. Three months later, after a febrile illness, his gait became unsteady and his memory progressively worse. One month before admission he complained of poor vision in the right eye and he became very hungry, often appearing to forget that he had just eaten. Aggressive behaviour precipitated his admission.

On examination he was disorientated in time and place, dyscalculic and dysphasic but able to obey commands. He lacked insight. There was right optic atrophy with a right visual acuity of J20. On lateral gaze there was unsustained nystagmus and he had a mild right lower motor neurone facial palsy. All the limbs and the gait were ataxic. Sensation was normal and there were no pyramidal tract signs.

On psychological testing he tended to become upset and aggressive as he had sufficient insight to realise he was performing badly. On the WAIS he obtained a verbal IQ of 62 (age scaled subtest scores: information 2, comprehension 2, arithmetic 5, digit span 2, vocabulary 5) and zero scores on performance subtests (digit symbol, picture completion, block design). He was unable to produce any items from two paragraphs immediately after they had been read to him (from Wechsler Memory Scale I) and 75 minutes later could not recall having heard them at all. Paired associate learning was extremely impaired. The nominal dysphasia was confirmed and his drawing, reading, and writing were grossly impaired. It was concluded that there was severe intellectual deterioration and the dysphasia was part of this general breakdown in function.

Investigations produced the following normal

results: blood count, ESR, serum urea, electrolytes, liver function tests, blood WR, and radiographs of chest and skull. An EEG showed a moderately severe abnormality without lateralising features. A LAEG showed severe cerebral atrophy with ventricular dilatation. The CSF contained 26 lymphocytes mm^{-3} , protein 1.05 g/l, IgG 0.26 g/l (24.7% of total protein) and the WR and Lange curve were negative.

He was treated with steroids and chlorpromazine was given for his aggressive behaviour. Although he became less irritable and no longer liable to aggressive outbursts, physical examination was unchanged. There was no improvement in verbal functioning and memory. Repeat examination of the CSF one month after admission showed 13 lymphocytes mm^{-3} , protein 0.30 g/l, IgG 0.06 g/l (20% of total protein) and Lange curve negative. Measles and herpes simplex antibody levels in the CSF and serum were not significantly raised.

CASE 5

C.L., a 39 year old business executive, was admitted to Churchill Hospital in August 1974. After a university education and a highly responsible managerial job his work record had deteriorated over eight years. In 1967 after the loss of his first job he had been seen by a neurologist elsewhere because of attacks of trembling in the right arm and leg and subsequently the left arm. Examination was normal and after a period of follow-up he was thought to be hysterical. He had group therapy for depression in 1970 and 1972. In January 1974 he complained of difficulty in reading small print but an ophthalmologist found no abnormality. Depression, retardation, and feelings of guilt and unworthiness led to his admission to a psychiatric unit in July 1974. He was thought to be preoccupied with delusional ideas but not organically confused. After three sessions of electroconvulsive therapy he became inappropriately confused and was transferred for neurological investigation.

On examination he was orientated but rambling. Bedside testing showed evidence of intellectual impairment. The left optic disc was pale with a corrected visual acuity of J4. There was ataxia of all limbs with hyperreflexia in the left arm and both legs. The abdominal reflexes were absent but the plantar responses were flexor. Sensation was normal.

On psychological testing his responses were very slow in both verbal and non-verbal tests and test questions had to be repeated. Test results were: WAIS verbal IQ 120, performance IQ 78 (age scaled subtest scores: information 15, comprehension 15, arithmetic 13, similarities 16, digit span 4, vocabulary 16, digit symbol 5, picture completion 8, block

design 6, picture arrangement 7, object assembly 5); Wechsler memory scale I, logical memory 10 (delayed recall 2), paired associate learning 16 (delayed recall 10), Benton visual retention test, number correct = 2, errors = 14 (expected scores correct = 8, errors = 3). The results indicated considerable deterioration of non-verbal cognitive skills and there was evidence from memory test scores, particularly delayed recall, of generalised impairment.

Blood count, serum urea, electrolytes, liver function tests, calcium, phosphate and radiographs of chest and skull were all normal. LAEG showed gross cerebral atrophy. The CSF contained 3 lymphocytes mm⁻³, protein 0.20 g/l, IgG 0.05 g/l (25% of total protein); WR and Lange curve were negative. Measles and herpes simplex antibody titres in the CSF were less than 1 in 4.

DISCUSSION

Brain (1930) in a comprehensive review of multiple sclerosis noted that the mental symptomatology of the disease had received inadequate attention. Early reports were marred by the difficulty of distinguishing multiple sclerosis from general paresis until the introduction of lumbar puncture and serological tests for syphilis (Guillain, 1924). The nature and frequency of mental changes in multiple sclerosis remained uncertain, for until 1950 objective evidence of intellectual impairment was rarely sought (Bergin, 1957). However, with the wider application of psychometric tests there were more reports of mental changes in patients with multiple sclerosis of varying duration and severity (Canter, 1951; Baldwin, 1952; Pratt, 1951; Ross and Reitan, 1955; Parsons *et al.*, 1957; Jambor, 1969; Surridge, 1969). To avoid diagnostic doubts, the patients studied in most instances have had the disease for several years. Thus, in one study (Jambor, 1969; Surridge, 1969), patients who had been ill for less than two years were excluded and there was no indication of the time of onset of the intellectual deterioration eventually noted in two-thirds of the cases. However, there are some reports of patients who developed mental symptoms early in the course of multiple sclerosis or even as the first symptom and in some there was pathological confirmation of the diagnosis (Dercum, 1912; Parker, 1956; Bergin, 1957; Crémieux *et al.*, 1959; Bignami *et al.*, 1961; McLardy and Sinclair, 1964; Mür *et al.*, 1966; O'Malley, 1966; Salguero *et al.*, 1969). Unfortunately, results of psychometric testing have not always been included and the distinction between affective and intellectual disturbance has not always been made.

All the patients reported here had evidence of intellectual impairment on simple bedside testing

and it was confirmed by more detailed psychological testing. In addition cerebral atrophy was demonstrated in each case by LAEG. Moreover, the patients and/or their relatives had noted a change in affect or a deterioration in intellect at or soon after the onset of their illnesses and in patients 1, 3, 4, and 5 behavioural or intellectual change had been the presenting symptom. Patients 1, 2, and 4 had neurological symptoms with or without signs coinciding with the mental change but patients 3 and 5 are of particular interest in that mental symptoms were present several years before neurological symptoms and signs developed. A justifiable assumption from a study of these cases is that mental change may occur early in the course of multiple sclerosis, not as a psychological response to progressive physical disability but as a result of brain damage.

The clinical picture in each case ultimately suggested multiple sclerosis. Patients 4 and 5 each had unilateral optic atrophy and cerebellar signs; patients 1, 2, and 3 each had at least one remission of the disease of the brain or spinal cord.

Cerebrospinal fluid abnormalities were present in all the patients to support the diagnosis of multiple sclerosis, but in cases 1, 2, and 3 the IgG levels were very high and the Lange curves were parietic. Similar CSF findings are found in subacute sclerosing panencephalitis but the age of onset, clinical presentation, and course in the patients described here were not in keeping with that disorder. A search for viral antibodies, including measles, was made in two of these patients with negative results. In none of these patients was the onset of the illness sufficiently acute to suggest acute encephalitis or acute disseminated encephalomyelitis. None of them had systemic signs of sarcoidosis and none had orogenital ulceration.

Intellectual deterioration is said to be 'rare in the early stages of multiple sclerosis except in acute cases with evidence of widespread cerebral involvement' (McAlpine *et al.*, 1955). None of the patients described here had a particularly acute illness, yet all had evidence of intellectual deterioration. Absence of physical signs of widespread cerebral involvement does not exclude such involvement for plaques of demyelination may be clinically silent (Russell, 1964). It is not unreasonable to suppose that diffuse cerebral involvement may occur insidiously and present only as dementia. The presence of cerebral atrophy demonstrated by LAEG in our patients would be in keeping with widespread cerebral involvement. Zimmerman and Netsky (1950), in a pathological study including acute and chronic cases, found severe hydrocephalus secondary to cerebral atrophy in only three out of 50 cases. However, as the series was not restricted to patients with behavioural or intellectual change, such a low incidence of hydro-

cephalus is probably not surprising. Although CSF studies have not always been included, many of the previously reported patients with mental changes have had positive Lange curves. The raised CSF immunoglobulins and paretic Lange curves in our patients might be taken as further evidence of widespread disease for it has been suggested that such findings occur more frequently with multiple lesions (Yahr *et al.*, 1954; Castaigne *et al.*, 1967).

Attempts have been made to relate mental changes to the site of the lesions. McAlpine *et al.* (1955) noted that 'change of affect is quite unusual at or soon after the onset of the disease except in cases with widespread involvement of the brain stem'. Bergin (1957) attributed mental change and alteration of consciousness to widespread lesions of the hemispheres and to involvement of the brain stem. In the case reported by Crémieux *et al.* (1959), lesions in the centrum ovale, paraventricular zones, temporal white matter, and thalamus were suggested as possibly significant in the genesis of the mental change. Bilateral hypothalamic lesions were proposed as the basis of the mental changes in the patient described by Bignami *et al.* (1961). More recently intellectual deterioration in multiple sclerosis has been related to demyelination in the corpus callosum (Barnard and Triggs, 1974). The five patients reported here with behavioural and intellectual change all had signs of predominant brain stem involvement. Nevertheless, it is clear from the necropsy studies in previous reports that mental changes occurring early in the course of the disease are invariably associated with widespread plaques of demyelination not just confined to the brain stem. The probability is that such diffuse damage in the cerebral hemispheres accounts for the mental changes even in those patients in whom clinically the brain stem is predominantly affected. In a disease characterised by dissemination of lesions, attempts to correlate mental change with specific anatomical damage must be made with caution. Regardless of the anatomical basis, it is clear that mental changes, including dementia, may occur as an early feature of multiple sclerosis. How frequently they occur is uncertain but the rarity of such change may have been underestimated. Such cases may not be reported because of the difficulty of the diagnosis in the early stages and once the disease behaves in a more conventional manner the earlier, apparently unusual features may be forgotten. Multiple sclerosis deserves to be considered more frequently in the differential diagnosis of behavioural and mental change in the young patient even in the absence of neurological signs.

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