Decline of cognition in multiple sclerosis: dissociable deficits

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SUMMARY Three female patients (ages 32, 37 and 27 years) developed progressive deficits of cognition in stages of multiple sclerosis in which physical disability ratings were low. Neuropsychological examination revealed severe cognitive impairments in the first two patients. Cognitive functioning was essentially intact in the third patient, although her work pace was significantly slowed. CT scanning of the brain showed cortical atrophy as well as white matter lesions in patients 1 and 2, and multiple lesions and oedema of predominantly white matter in patient 3. The differences of cognitive dysfunction between the third and the first two patients may be related to involvement of different anatomical structures.

Mental symptoms of multiple sclerosis have been described repeatedly since the earliest clinical reports,1 without having led to generally accepted views about the kind and the extent of the cognitive impairment2–10 and the pathophysiological mechanism.3 4 9 11 In addition, the relationship to other functional disturbances is as yet unclear; some authors have assumed that the severity of mental changes is related to the extent of motor impairment,2 4 which is denied by others.6–9 Dementia is said to occur predominantly in relatively late stages of the disease.9 12 However, neuropsychological testing may reveal cognitive impairment in patients who are thought to have intact mentation on routine clinical examination.8 13–15 The neuropathological substrate of neuropsychologically documented cognitive deterioration in multiple sclerosis has as yet been investigated by only a few authors.14 16

Two cases with marked dementia concurrent with, and in one patient even preceding, the neurological signs and symptoms of cerebral multiple sclerosis are presented. Both cases suffered from chronically progressive multiple sclerosis. A third patient is described whose CT scan indicated fulminant cerebral multiple sclerosis but who, surprisingly, had near-normal mentation on bedside clinical testing. All three patients were neuropsychologically assessed in order to quantify and, if possible, define the patterns of cognitive deterioration.

The combination of neuropsychological and CT scan findings suggests that in the latter patient slowing of cognitive processing was related to white matter dysfunction, whereas in the first two patients disturbed cognition was related to both cortical atrophy and white matter involvement. This suggests that multiple sclerosis may affect cognition in at least two ways.

Case reports

Case 1
An unmarried, right handed woman, aged 20 years, was in good health until the first half of 1972. She engaged actively in several sports and frequently won prizes in championship matches. In 1972, her fiancé (later her husband) noticed that she occasionally reacted strangely and became almost dull during social events. Surprisingly, she failed an examination as a sports' teacher in 1974, and her achievements in active sports diminished. She married in 1974. In August of that year she complained of sudden visual loss in the right eye, diagnosed by an ophthalmologist as acute optic neuritis. Visual acuity recovered within two weeks. She complained of double vision during a three week period in 1977. Her work record (automatisation of a dairy factory administration) deteriorated; with increasing frequency she forgot tasks or performed them inefficiently so that, by 1980, she had to stop working. During the following 4 years the cognitive deterioration was rapidly progressive and she became unable to run her household. From 1982 it was hazardous to leave her unattended at home and in 1983 she (at age 31 years) was admitted to a nursing home for severely demented people. Lumbar CSF in 1977 revealed oligoclonal IgG bands,
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Wechsler Memory Quotient (MQ) on the Wechsler Memory Scale was 54 (estimated premorbid MQ 110). Arithmetic skills had disintegrated, only addition and subtraction of digits below 10 were correct. On dictated numbers she iterated elements, showing a remote intuition of number structure. Language comprehension and oral language production were childish, without signs of specific language disorders. Picture naming was, however, defective because of erroneous interpretation and a slight anomia. In word fluency tasks the patient produced few and mainly scabrous words. Reading of letters and simple words was intact but in sentence reading she made many mistakes and lost hold of the task. Writing to dictation and copying were defective. Speech melody was scanning. The copies of two and three-dimensional designs showed remarkably good connections of line segments and quite skillful stroke, reflecting only minor motor involvement of the arms. Loss of structure and iteration of segments (fig 1c) were features of constructional disability per se. Recognition of objects, images, sounds and body-parts was intact. Left-right discrimination errors and difficulty in finger naming occurred only when commands were complex. On verbal request she succeeded only in demonstrating object use if concrete objects were at hand. Reaction times were long and choice reactions were erroneous. In summary, she was a woman in whom a range of cognitive abilities had deteriorated severely and whose personality had regressed.

Laboratory testing was repeated in 1984. Blood count, serum urea, electrolytes, liver functions, calcium and phos-
Fig 2  Case 2 (age 37 yr) (a) schematic representation of (b); (b) CT scan showing age-inappropriate enlargement of ventricles and signs of cortical atrophy; (c) copy of three-dimensional design showing severe loss of structure.

phate were normal. The measles antibody titre in the serum was negative. The CSF of the patient contained 11 cells/mm³, with lymphocytes and atypical plasma cells. The IgG index was elevated ¹² and isoelectric focusing revealed a number of oligoclonal bands, indicating intrathecal IgG synthesis. A CT scan showed severe cortical atrophy and ventricular enlargement with white matter atrophy, as well as a number of periventricular hypodense lesions (fig la, b).

Case 2
A 26 year old, right handed housewife presented with feelings of pins and needles in both hands, in February 1971, lasting 6 months. In December 1971 she noticed a dead and heavy feeling in her left foot, lasting 2 months. From April 1972 she noticed a black spot in her right eye for 2 months, and during several weeks in the second half of 1972 she once more had transient paraesthesiae in the hands. Early in 1979 her husband noticed loss of memory for telephone numbers and frequent mistakes in the names of familiar persons. In September 1979, she developed a chronic progressive instability of gait and difficulties with fine motor tasks, such as fine embroidery. Signs of cognitive dysfunction increased during the following years. By 1982, the patient had slurred speech and severe instability of gait. Tendon reflexes were increased. Both the finger-nose and knee-ankle test were bilaterally ataxic. Sense of touch and vibration sense were decreased in the legs.

On neuropsychological assessment the patient was cooperative and persistent. On the WAIS ¹⁷ the FSIQ was 69 (estimated premorbid FSIQ 110). The VIQ of 83 was significantly below her premorbid abilities. The very poor results in the performance subtests (PIQ = 58) could not be explained by the motor impairment of the arms nor by the slow pace of work. Memory functions were impaired. On the WMS ¹⁸ her MQ (memory quotient) was 59 (estimated premorbid MQ 110). There was dyscalculia. Speech was slow and halting with dysarthria. Oral language was simple with some problems of sentence structure and a slight naming impairment. Word fluency (production of words beginning with a given letter) was poor and perseverative. Language comprehension was intact. A written sentence contained several letter perseverations. The constructions (copying three- and two-dimensional designs) were, apart from traces of difficult pencil manipulation, severely disturbed (fig 2c).

In summary, she was a woman aged 37, who was severely deteriorated in all assessed components of cognition.

Normal results were obtained from blood count, ESR, serum urea, electrolytes and liver functions. The CSF contained 5 lymphocytes/mm³ with a cytological picture of chronic infection. Isoelectric focusing of the CSF revealed a number of oligoclonal bands not found in the serum, indicating intrathecal IgG synthesis. The CT scan showed an enlarged ventricular system, periventricular lesions and enlarged cortical sulci, indicating loss of white matter and global cortical atrophy (fig 2a, b).

Case 3
A 27 year old, right handed female lawyer developed a constant frontal headache in January 1984, rapidly progressive and associated with vomiting by March 1984. The patient lost interest in her work and often slept more than 12 hours per day. According to her husband she developed slight difficulties of speech. On admission she was somnolent, disoriented in space and had a slightly slurred speech. Thor-
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Though physical examination revealed no other neurological signs or symptoms. Her headache and spatial disorientation disappeared over a period of 3 weeks. In April 1984 she was discharged in a reasonably good condition. Four months later she had temporary visual loss of both eyes. She was readmitted from February till May 1985 because of another relapse in 1985 during which she developed axial ataxia and signs of pyramidal involvement.

At the time of neuropsychological assessment (April 1985) she was cooperative but somewhat childish in contact. Her work pace was very low. On intelligence testing her WAIS FSIQ was 108 (VIQ was 119, PIQ was 92). The PIQ was definitely below her estimated premorbid level (estimated IQ 120) and the response variability within and between the verbal subtests indicated that the VIQ had suffered as well, but to a smaller extent than the PIQ. Registration of aurally presented digits was normal (7 units) but of visually presented nonverbal material decreased. Reproduction of simple narrations was patchy but improved with multiple choice questioning. Line drawings were poorly reproduced, which had to be attributed to insufficient recall of the stimuli because copying was intact. Learning of word pairs was inadequate. The Memory Quotient was 89 (estimated premorbid MQ 120). In mental arithmetic the patient knew the basic processes but lost the elements of the sums. She made perseverative errors in written arithmetic. She wrote dictated numbers correctly and without hesitation. Language comprehension was intact but slow. Language production was characterised by word finding difficulty and slowness. In confrontation naming, searching for the correct word form

Fig 3  Case 3 (age 27 yr) (a) schematic representation of (b); (b) CT scans showing oedema and ring-forming lesions of demyelination; (c) copy of three-dimensional design which is, apart from slightly uncertain stroke, structurally intact.
and benefit from first letter cueing were observed. A word fluency task was qualitatively well performed. Written language (reading and writing) were intact. Drawings of three- and two-dimensional figures were correctly copied (fig 3c), apart from an unsteady stroke which was a feature of all graphic productions. Simple reaction times were long (476 ms for visual and 374 ms for auditory stimuli) and choice reaction times were extremely long (565 ms). In summary, she was a woman in whom cognitive instrumentalties were intact but in whom slowness of processing was incapacitating.

Extensive laboratory examination was unremarkable, as is reported elsewhere. All virological tests were normal. The CSF contained 9 cells/mm³ (6 lymphocytes). The IgG index was elevated (1·0) and isoelectric focusing revealed a pattern of oligoclonal bands. On the CT scan were oedema and multiple hypodense hemispherical lesions visible, with well-defined ring formation after contrast enhancement (fig 3a, b).

Discussion

Comparison with previous reports

We have described three female, right handed patients (ages 27, 32 and 37 years) with multiple sclerosis. The relapsing and remitting course of the clinical signs and symptoms and the laboratory data confirmed the diagnosis.

Two patients were demented at age 32 and 37 years respectively. In the first patient the cognitive impairment was of longer duration and far more incapacitating than the motor symptoms (Kurtzke disability score: 1). In patient 2 the mental changes started early in the disease, in a stage of moderate physical invalidation, and the progression of mental deficits almost equalled the progression of physical symptoms (Kurtzke disability score: 4). Although the ravaging cerebral process with multiple lesions in the third patient (Kurtzke disability score: 3) seemed incompatible with normal mentation, cognition was slow but otherwise undisturbed.

In early stages of multiple sclerosis progressive decline of cognition is stated to be rare, except in acute cases. We know only two reports of severe mental deterioration early in the disease. Both concerned patients (n = 7) comparable to our cases 1 and 2. We are not aware of a previous report of a patient comparable to our case 3. The patients of Bergin underwent formal testing, but no neuropsychological data are mentioned. The patients of Young et al were tested with the WAIS. FSIQ of these patients varied from 62 to 114. No further systematic neuropsychological assessment was performed in these patients, although WMS scores were mentioned to be poor for some patients.

In group studies intellectual deterioration has been reported, but denied by Marsh. He surveyed differences in patient and test selection that might account for the conflicting evidence on intelligence in multiple sclerosis. Memory disturbances were documented, but again in extremely variable frequencies. There is no unanimity concerning the possible relation of associated motor defects to psychiatric measures of cognition in these studies.

In our patients 1 and 2, in whom motor defects were negligible or slight, a severe memory loss was shown to be embedded in severe intellectual deterioration. In patient 3, deteriorated cognitive performance is more likely explained by slowness than by motor handicap.

Cognitive decline in multiple sclerosis: dissociable deficits?

The differences in cognitive functioning between our first two patients and our third patient suggested different psychopathological mechanisms. In a recent review Cummings and Benson elaborated the distinguishing features of cortical and subcortical dementia. In cortical dementia the point of impact is in the instruments of cognition, the stored knowledge such as language, numeracy, and praxis. A cardinal feature of subcortical dementia is said to be mental slowing. We studied reaction times in simple and choice tasks in 40 multiple sclerosis patients and found motor and not mental slowing. Lehmann, however, found in multiple sclerosis patients evidence for inordinately prolonged reaction times if the task load was increased, and attributed this to disturbances in the central association systems. Apart from mental slowing, forgetfulness, impaired ability to manipulate acquired knowledge, changes of personality and affect including apathy and depression, are characteristics of subcortical dementia that are strikingly similar to Ombredane's careful description of psychic alterations in patients with multiple sclerosis, based on findings in 72% of his patients.

Subcortical dementia is a controversial concept, requiring neuro-anatomical and neuropsychological construct validation. Neuro-anatomic explanations of the decreased cognitive function in multiple sclerosis are abundant but up till now few combined studies of cognition and of the neuro-anatomic substratum have been performed. On CT investigation cortical atrophy and/or ventricular enlargement have been detected in about 50% of multiple sclerosis patients. The relation between CT scans and clinical findings is, however, known to be far from perfect, and many more multiple sclerosis lesions are found by advanced techniques of brain imaging such as magnetic resonance imaging than by CT scanning. Recently positron emission tomography (PET) revealed low levels of oxygen utilisation in
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both grey and white matter of the cortex, particularly in multiple sclerosis cases with cortical atrophy as seen by CT examination. Global intellectual decline was related to widespread cerebral atrophy and it was suggested that cortical atrophy can be a feature of multiple sclerosis in the absence of obvious white matter lesions.14

Our three patients suffered from acquired intellectual impairment. In the first, two specific deficits were difficult to disentangle within the picture of general and severe dementia. However, slowness of cognition as well as cognitive impairment strictu sensu, such as disturbed numeracy and constructional apraxia were present. The behaviour of case 1 showed signs of personality changes in the sense of puerile euphoria. Tentatively following Albert’s23 classification of dementia, these impairments might be interpreted as indicative of cortical and subcortical dementia. Both patients had hypodense periventricular lesions in addition to severe cortical atrophy and severe ventricular enlargement on the CT scans. Patient 3, on the contrary, had devastating white matter lesions without signs of cortical atrophy. Although achieving below her prior abilities on psychometric tests of intelligence and memory cognition was essentially intact, her work pace was significantly slowed. She had difficulty retrieving learned material of whatever kind but no disorder of cognitive instrumentalities, and she rather seemed to show subcortical dementia.

The question may be raised whether disease duration explains the different cognitive patterns, patients 1 and 2 having much longer histories than patient 3. We cannot answer this question on the basis of the present findings. However, in a group of 40 multiple sclerosis patients with disease durations varying from 1 to 48 years, we found no evidence of mental deterioration in relation to duration of illness. Finding duration of illness related only to physical disability, Marsh4 also concluded that chronic multiple sclerosis need not be associated with intellectual deficit. The presence of considerable oedema in patient 3 may have affected cognitive performance. The important point is that patient 3 does not show so-called cortical signs of cognitive decline, notwithstanding considerable oedema.

Disputes about the nature, and even the very existence, of cognitive disorders in multiple sclerosis may be attributed not only to differences in disease variables but also to reliance on tests designed to discover individual differences in performance, and neglect of the search for alterations in component mental processes. Our three case histories demonstrate that cognitive decline in multiple sclerosis may have distinct neuropsychological patterns which appear to be related to CT findings. They strongly suggest that research on the relation between structural and clinical alterations should be a combined effort in which advanced techniques of brain imaging are applied in close combination with psychometric assessment and analysis of deficits in cognitive processing.

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