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Korsakoff's syndrome as the initial presentation of multiple sclerosis

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Summary. A 37-year-old man presented with an acute amnestic syndrome of Korsakoff's type and an upper brain-stem oculomotor syndrome. After a moderate improvement with steroid therapy, he developed progressive behavioural changes due to a frontal lobe syndrome, in addition to motor and visual impairment. Memory performance was investigated on several occasions during an 11-year follow-up. Diagnosis of laboratory-supported definite multiple sclerosis was established and magnetic resonance imaging showed disseminated white matter lesions, especially in both medial temporal lobes. No other cause than multiple sclerosis was found for the amnestic syndrome. Among the rare cases of Korsakoff's syndrome in the course of multiple sclerosis, this is to our knowledge the first case in which a memory deficit was the initial manifestation of the disease.

Key words: Korsakoff's syndrome – Multiple sclerosis

Introduction

It is well known from the initial description by Charcot [9] that "weakening of memory" *(affaiblissement de la mémoire)* frequently occurs in the later stages of disabling multiple sclerosis (MS). However, memory loss is usually only one component of a generalized intellectual deficit with personality changes. Some reports have shown that cognitive impairment, disproportionately severe compared with the motor disability, presenting as dementia or frontal lobe syndrome, may occur soon after onset of the disease [4, 12, 16, 18, 34]. We present an apparently unique case of definite MS in which a severe amnestic syndrome of Korsakoff's type was the initial manifestation of the illness.

Case report

A 37-year-old right-handed man, an advertising manager, was referred in November 1978 with a 10-day history of memory loss. Three months previously, he had been hospitalized in the department because of a depressive episode. At that time, neurological examination, including memory, was unremarkable. Initial evaluation showed an attentive and cooperative patient with severe amnestic syndrome. Memory for recent events was poor. He could not recall his first admission to the hospital or his recent visit to the doctor. Details of his daily life as well as current political events were not remembered and he made repeated queries about his state of health. It took him several days to learn the topography of the department. He could repeat seven verbal items, but he was unable to recall a single one of five words after a 5-min delay. By contrast, he was oriented to place, to month and year and he only failed to give the date. Remote memory was fair, as he could give correctly his age, personal address, autobiographical landmarks, as well as the name of the current French president and major historical facts. He had no confabulation. He was aware of his trouble, but mildly unconcerned and dysphoric. Oral language, reading, writing, praxis, visuospatial perception, calculation and visual fields were normal. Otherwise, neurological examination was remarkable for bilateral tendon hyper-reflexia with Babinski's sign, restriction of upward gaze with vertical nystagmus, paralysis of convergence, and bilateral internuclear ophthalmoplegia. The patient was afebrile, continent and fully ambulatory. Initial and subsequent CT and EEG were normal. CSF contained 2 leucocytes/mm^3, 0.44 g/l protein, and the IgG/protein ratio was 9.8%, without oligoclonal bands. Extensive screening for infectious agents, including virus cultures and antibody titres in serum and CSF was negative, in particular for herpes virus. Visual evoked responses with alternating checker-boards showed pathologically delayed responses for both eyes. Despite this unusual presentation, a diagnosis of probable MS was suspected and steroid therapy was started. Neuropsychological testing demonstrated poor learning performances for both verbal and visual materials. Rey's auditory verbal learning test showed a flat curve; he recalled 6, 7, 7 and 6 of the 15 words along the four successive trials, and only 6 words in recognition. Lhermitte and Signoret's spatial location learning test [20] was similarly affected. While normal subjects memorize the spatial location of the 9 pictures in a maximum of four trials, with no more than 6 errors (false localization) during these trials, the patient could learn only 3 pictures at the fourth trial with a total of 26 errors. These tests were performed again 3 weeks later, after steroid treatment. Improvement was noted only for the spatial location test, as he placed 8 pictures after four trials and made only 10 errors. Rey's figure was easily copied, but poorly recalled after 5 min (score: 11; normal range: 28–36). In February 1979, the Rey's verbal learning curve remained flat (5, 6, 5, and 6 of the 15 words), although the performance was better in recognition (9/15). Visual learning was higher, as in Lhermitte and Signoret's test, he could now place the 9 pictures at the first trial. His performance dropped to 5/9 pictures in a recall condition, in which he had to describe the picture corresponding to each location (normal lower limit: 7), but

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Table 1. Modified Signoret and Whiteley's [20] memory scale performance[a]

	Verbal memory			Visual memory	
	October 1984	March 1989	Controls (SD)[b]	October 1984	Controls (SD)[b]
Short-term logical memory	3	4.5	9.9 (1.2)	7	9.4 (1.4)
Serial learning	5	6.5	9.1 (1.2)	3.5	8.9 (1.5)
Paired-associate learning	4	1	11.5 (.8)	8	11.4 (.9)
Logical memory/delayed recall	1	3	10.1 (1.2)	5	9 (1.3)
Serial memory/delayed recall	5	1	9.4 (1.3)	6	8.8 (1.8)
Recognition memory	–	8	11 (.9)	–	–

[a] Both verbal and visual memory were tested in October 1984, but only verbal memory in March 1989
[b] Age and education-adjusted controls ($n = 55$)

remained normal in the recognition test, as he could show the location of the 9 pictures presented individually to him. In March 1979, as memory continued to improve, the patient was able to recall and comment on current political events. This improvement contrasted, however, with passive behaviour. He stayed dysphoric and unconcerned; for the next few years he remained at his parents' home, where he had the assistance of his parents.

The patient was not again examined by us until October 1984. During the time elapsed, new neurological signs and symptoms had progressively appeared. He then presented with gait disturbances and micturition difficulties, and he used a stick to walk. He had a moderately severe static and kinetic cerebellar syndrome, and mild tetraparesis with left Babinski's sign, in addition to upward gaze paralysis, bilateral internuclear ophthalmoplegia and the vertical nystagmus previously noted. He also had left trigeminal neuralgia. Corrected visual acuity was 10/10 for the right eye and 5/10 for the left eye. Furthermore, the patient exhibited severe neurobehavioural abnormalities. He was apathetic, unconcerned and euphoric. He denied any problem but the facial pain. He could not see any reason that prevented him from resuming his work. However, he had remained in his parents' charge for the last 5 years. He used to spend hours lying in bed, reading magazines or watching TV. He obeyed commands but he had no initiative. His affect was puerile and he occasionally made inappropriate jokes. He was cooperative but poorly motivated. His verbal span was 6 forward and 4 backward. He could give quickly six names of flowers. Mental control was altered as he failed to perform serial subtractions. He was oriented to time and place, he could name the current French president, the prime minister, comment on recent political and sporting events, and give an accurate description of his life. However, there was a striking discrepancy between these good factual memory performances and the poor scores he obtained in more formal testing. The modified Signoret and Whiteley's battery [29] confirmed that both verbal and visual memory were altered, the latter to a lesser extent (Table 1). Other cognitive functions were much less affected. IQ determined with Wechler's scale was 110 (verbal IQ = 123, performance IQ = 92). Elaborate language, including proverb interpretation and judgement on nonsense stories was spared, as well as calculation, and constructions. There was no apraxia, no grasp reflex, and the patient could perform fairly well the Luria's sequences. At this time, a second course of high-dose steroid therapy was initiated, without any beneficial effect, and azathioprine treatment (100 mg/day) was started.

The patient was readmitted in March 1989. His neurobehavioural status remained remarkably unchanged, while his motor disability had become worse, causing him to use a wheelchair because of paraplegia and cerebellar ataxia. His IQ stayed in the high normal range (110; verbal IQ = 111, performance IQ = 108). However, the deterioration index was abnormal (26%). Verbal memory was tested with the same battery as in 1984 (Table 1). Learning scores remained low, with very poor performance in delayed recall contrasting with subnormal results in recognition. Magnetic resonance imaging (MRI) showed diffuse hyperintense punctuate signals on T_2-weighted sequences mainly in periventricular areas and in the white matter of both medial temporal lobes (Fig. 1).

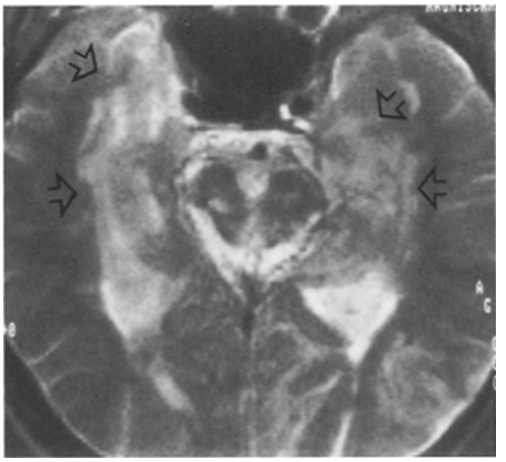

Fig. 1. MRI showing demyelinating lesions in the brain stem and in both medial temporal lobes (spin echo: 60/1800)

Discussion

Several recent psychometric studies have revealed that subclinical or mild cognitive deficits can often be demonstrated in MS [8, 14, 19, 26]. This may occur even in patients with mild physical disability [14, 24, 33], and at the first attack of the disease [7, 23]. Tasks probing memory are most frequently altered in these neuropsychological studies and the nature of the deficit has been extensively analysed. There is ample documentation of short-term memory deficit affecting recall and recognition for both verbal and non-verbal material [2, 14, 26, 30]. Various patterns have emerged, largely depending on the tests used and the population under study. Thus, poor performances have been related to impairment in retrieval strategies [2, 6], reduced learning [33], accelerated forgetting [33], semantic encoding deficit [8], or slowing of information processing [1, 2, 21]. Remote memory could also be altered [2, 3]. In contrast to this wealth of data, the pure amnestic syndrome of Korsakoff's type seems extremely rare in MS. We are aware of only five prior reports [10, 13, 17, 31, 32]. Ule [32] described a young man who developed an acute amnestic syndrome and delusions. As postmortem examination revealed demyelinat-

ing foci in both Ammon's horns and fornices, it was considered that this was a case of acute MS. Kamalian et al. [17] described a case of malignant encephalopathy with hypothalamic cachexia and poorly described anterograde amnesia, initially intermittent then permanent. Neuropathological examination led to a diagnosis of MS. Demyelinating plaques were disseminated, with noticeable involvement of the left lateral hypothalamic area, mamillary body and both fornices. As amnesia had occurred when the patient was cachectic, one cannot rule out an additional role for a nutritional factor. Gherardi et al. [13] presented a case of rapidly progressive memory loss with internuclear ophthalmoplegia occurring a few months after a resolving optic neuritis. Pathological study of the brain showed co-existing lymphoma and demyelinating lesions. The most likely lesion to explain the memory deficit was an inflammatory necrosis of the fornix with secondary atrophy of the mamillary bodies. However, lymphoma extended to the splenium of the corpus callosum, the amygdala, the hypothalamus and the left internal temporal lobe. Regarding the nature of these demyelinating changes, the authors favoured the diagnosis of MS, but could not rule out the possibility of lymphomatous lesions mimicking MS. The case of Trillet et al. [31] is one of definite MS in which an acute amnestic syndrome followed a status epilepticus. The authors discussed on clinical grounds the possible role of anoxic changes in hippocampal regions previously damaged by demyelinating lesions. The case of Feinstein and Ron [10] also had definite MS, but Korsakoff's syndrome occurred in the course of severe and chronic alcohol intoxication. Arguments that MS was a causative or even a contributing factor to the memory disturbances in this context are obviously slim in the absence of pathological correlations. Thus, all the above cases are opened to criticism. Among the three patho-anatomical cases, two had a very atypical course for MS and one had associated cerebral lesions, while in the two clinical cases, another factor was present to contribute to amnesia. In comparison, our case appears to be unique for at least three reasons. First, this is a laboratory-supported definite case of MS according to the criteria of Poser et al. [25]; although no patho-anatomical confirmation is available, an 11-year follow-up in addition to clinical, biological, electrophysiological and imaging data can reasonably exclude any other cause for the memory deficit. Second, a subacute anterograde amnestic syndrome occurred as the initial symptom of the illness, and was only associated with brain-stem oculomotor disturbances. This initial syndrome pointed to a diencephalo-mesencephalic lesion, and was much more suggestive of a thalamo-mesencephalic paramedian infarction, a Korsakoff-Wernicke's encephalopathy or a viral encephalitis than of MS; despite this, the correct diagnosis was suspected quite early after rapid exclusion of other possibilities. Third, neuropsychological investigations were performed longitudinally. They have documented two separate evolutive trends over time. On the one hand, anterograde amnesia was initially severe and persisted chronically over years after a moderate improvement which took place in a few weeks. On the other hand, despite improvement of amnesia, self-generated behaviour worsened because of progressive development of a typical frontal lobe syndrome. The amnesia pattern was complex and changed with time, probably as a consequence of the crossing evolution of the two syndromes. Thus, the initial stage was characterized by poor learning abilities for all types of tests, and later stages by a deficit more marked for recall with relatively preserved recognition, suggesting a prevailing deficit on retrieval strategies. Thus, our case seems to have combined a very unusual subacute Korsakoff's syndrome from a partly remitting first attack with a much more common frontal lobe syndrome, a marker of the severity of the disease in its progressive form [2, 3].

The anatomical basis of cognitive dysfunction in MS remains controversial. Cortical atrophy and ventricular size [27] as well as the degree of white matter involvement detected by MRI [7, 11, 28] have been correlated with the severity of intellectual deficit, but some authors did not find such a correlation [15, 22]. A recent study with MRI showed that anterograde memory deficit could be linked to demyelination of both medial temporal lobes [5]. In our case, precise correlation was not available as MRI was performed 10 years after the onset of Korsakoff's syndrome; however, the most severe changes were present bilaterally in the medial temporal lobes, suggesting that demyelination of both hippocampal regions and surrounding white matter areas might represent a likely basis for the persistent amnestic syndrome.

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