Figure 1 Regression plot of change in Unified Parkinson's Disease Rating Scale (UPDRS) and mirror movement (MM) scores. The horizontal line represents no change in MM. A negative change in MM indicates more mirroring and a positive change in MM indicates less mirroring.

side,⁶ contralateral to the mirroring limb. In patients with small motor improvement, most of the treatment benefit may be on the more affected side. The reduction in mirror movements may be due to a reduced degree of asymmetry or a reduction in the effort required to perform the tasks used to assess mirror movements.

The potential use of mirror movements in the clinical evaluation of disease progression and the complete characterisation of the effects of dopaminergic dosage will require further studies with longer washout periods. Our mirror movement scale possesses substantial inter-rater reliability for carrying out this objective.

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Cerebrospinal fluid findings in multiple sclerosis patients before, during and after pregnancy

The mechanisms responsible for the lower relapse rate of multiple sclerosis during pregnancy and an increased relapse rate during the postpartum period are still undefined. Putative explanations include pregnancy-related alterations in the function of the immune system, such as a shift towards T helper (Th)2-type immune reactivity and expansion of regulatory T lymphocytes.^{1,2} Analysis of the cerebrospinal fluid (CSF) offers a unique opportunity to characterise immunological pathways in the pathogenesis of multiple sclerosis. The inflammatory activity in the central nervous system (CNS) of patients with multiple sclerosis is reflected in the composition of CSF cells and one hallmark of the disease is the production of intrathecal antibodies. The aim of our study was to investigate the alterations that take place in the CSF of patients with multiple sclerosis during pregnancy. To our knowledge, no previous attempts have been made to analyse the components of the CSF of pregnant patients with multiple sclerosis.

Methods

The study included six patients with relapsing remitting multiple sclerosis, who were enrolled at a time of known pregnancy status.

Follow-up with recording of relapses continued until 6 months after the delivery. Only one of the patients (case 5) was undergoing disease-modifying treatment (subcutaneous interferon (IFN)β-1a) before pregnancy, and the drug was discontinued 3 months before the onset of pregnancy. No immunomodulatory treatment was used during pregnancy or postpartum at the time of drawing the sample. All but one patient (case 4) chose to breast-feed (duration range 6 weeks to 6 months). There were no signs of postpartum depression in any of the patients. One CSF sample was drawn at 26–28 weeks of pregnancy, at a time of putative low disease activity. The second CSF sample was drawn 4–5 weeks after the delivery, at a time of putative high disease activity. Lymphocyte number, IgG-Index and number of oligoclonal bands were analysed from the CSF. At the same time points, venepuncture was performed for peripheral blood lymphocyte isolation and immunofluorescence staining for intracytoplasmic IFN-γ and interleukin (IL)-4 production, which was performed as described earlier.³ The study was approved by the Commission of Ethics of Turku University and the Turku University Central Hospital, and informed consent was obtained from all subjects after a full explanation of the procedure. A lumbar puncture is a standard procedure during diagnostic investigation in Finland and hence is performed often. All patients were fully aware of the scientific nature of the lumbar puncture, and were still willing to give the samples for analysis as accepted by the ethical committee.

Analysis of variance for repeated measurements and Newman–Keuls multiple comparison post-test were used for comparisons of the relapse rate and the differences in the IgG indices. The Expanded Disability Status Scale values were compared by using a paired, two-sided t test.

Results

Six women with definite relapsing remitting multiple sclerosis and a known pregnancy status were studied. The duration of the disease was 1–11 years (range) and the mean (SD) age of the patients was 26 (5) years. During the year before pregnancy, the relapse rate was 1 (0.9) relapses/patient/year (mean (SD)). During pregnancy, only one of the patients experienced a relapse; this was during the first trimester. In the 6-month postpartum period, all but one patient experienced a relapse (relapse rate during pregnancy v postpartum: 0.2 (0.6) v 1.7 (0.9); $p = 0.0336$). The Expanded Disability Status Scale was 1.2

Table 1 CSF findings

Patient	Before pregnancy		During pregnancy			After pregnancy		
	IgG-Ind	Cells	IgG-Ind	Cells	OB	IgG-Ind	Cells	OB
1	0.76	4	0.77	0	0	0.69	8	0
2	0.71	12	0.80	1	1–2	0.67	2	1–2
3	3.18	ND	4.77	0	3–4	4.06	4	3–4
4	2.28	26	3.19	1	1–2	2.08	9	1–2
5	1.22	12	2.19	2	1–2	1.14	2	1–2
6	0.70	0	0.74	0	0	0.72	8	0

Before pregnancy, diagnostic lumbar puncture; during pregnancy, at 26–28 gestational weeks; after pregnancy, 4–5 weeks postpartum; IgG-Ind, IgG-Index; cells, number of lymphocytes $\times 10^6$ /l. Cell number is in bold if sampling was performed during a relapse; OB, number of oligoclonal bands, was determined by using the Paragon Protein (SPE-II) Electrophoresis Kit, Beckman Coulter, Fullerton, California, USA. ND, not detected.

(0.6) during late pregnancy and 1.7 (0.9) at 6 months postpartum (mean (SD), $p = 0.27$). Table 1 shows the CSF parameters in samples taken before (diagnostic lumbar puncture), during and after pregnancy. Notably, the IgG-Index was significantly higher during pregnancy than before pregnancy or after the delivery in all patients ($p = 0.0390$), but no difference was observed in the number of oligoclonal bands (table 1). Enhanced clinical disease activity was associated with a higher number of CSF cells, as expected (table 1), but no alteration was observed in the subtypes of CSF lymphocytes during versus after pregnancy (data not shown).

To study whether the increased intrathecal IgG production was associated with a systemic Th2 shift, we measured intracytoplasmic IFN- γ and IL-4 production in peripheral blood monocyte cells after phorbol myristate acetate and ionomycin stimulation both during and after pregnancy. The percentage of IFN- γ -secreting cells within the peripheral blood lymphocyte pool was significantly lower during pregnancy than in the postpartum period (2.8 (0.7)% (mean (SEM)) IFN- γ -producing cells during pregnancy and 7.6 (0.8)% during postpartum, $p = 0.003$). The difference in IL-4-producing cells during and after pregnancy was less pronounced (1.0 (0.16)% (mean (SEM)) during pregnancy and 1.8 (0.15)% during postpartum, $p = 0.028$). This resulted in a Th2:Th1 ratio of 0.36 during pregnancy and 0.24 after delivery.

Discussion

This study describes, for the first time, that the production of intrathecal antibodies in patients with multiple sclerosis is higher during late pregnancy than in the postpartum period. A shift towards humoral (Th2)-type immune responses was shown during pregnancy, and it is the most accepted theory to explain the amelioration of Th1-type diseases such as multiple sclerosis and rheumatoid arthritis during pregnancy. Most of the data supporting the Th2 shift during pregnancy are derived, however, from mouse experiments, and the corresponding *in vivo* phenomena in pregnant women are poorly documented. Our finding of non-altered oligoclonal bands is in line with previous studies, which have shown that oligoclonal banding in the CSF of patients with multiple sclerosis is persistent, and not affected by treatment, whereas the rate of IgG production is more susceptible to alterations.⁴

The CNS parenchyma is not a physiological site for B-cell responses and antibody production, but, in multiple sclerosis, B cells are demonstrable in inflammatory infiltrates and in the CSF.⁵ Antibodies are indicative of chronic CNS inflammation and probably contribute to demyelination and axonal damage.⁵ Our data imply that factors other than intrathecal antibodies are crucial in the pathology leading to multiple sclerosis relapses in the postpartum period, as a reduction in the IgG-Index was associated with an increase in the relapse rate. Our data suggest that the consequences of alterations in the immune system leading to a Th2 shift in the periphery reach beyond the blood-brain barrier and strengthen the humoral immune responses within the CNS.

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Severe amnesia after a restricted lesion in the left hippocampal body

Severe amnesia is caused by bilateral damage to the medial temporal lobe, specifically cornu ammonis (CA)1 of the hippocampal body.¹ Although some authors have reported that profound amnesia results from a unilateral temporal lobe stroke,^{2,3} the part of the hippocampus that causes severe amnesia remains unknown. Here, we report the case of a patient who developed severe anterograde amnesia and minimal retrograde amnesia after a focal haemorrhage in the hippocampal body.

A 72-year-old right-handed man was admitted to the International Medical Center of Japan, Tokyo, Japan, in May 1999 because of acute memory impairment. A few days before admission, he started forgetting what he had done and said several minutes earlier, and he could no longer name nearby objects. On admission, he was disoriented as to the year, month and day, and could not recall the names of objects that he had been told to remember a few minutes earlier. His symptoms continued and were persistent 1 month later. MRI T1-weighted images

1 month after onset showed a haemorrhage in the left hippocampal body and in part of the hippocampal tail. The lesion included CA1, CA2 and CA3, the dentate gyrus and subiculum (fig 1), and extended subcortically in the parahippocampal gyrus.

A neuropsychological evaluation was carried out from 34 to 40 days after onset. The Wechsler Memory Scale-Revised score showed that verbal and delayed memory indices were markedly low, whereas the visual memory index was relatively preserved (attention and concentration 79, verbal memory 61, visual memory 79, general memory 65 and delayed recall 55). A comparison of the delayed test raw score total (II) with the first test raw score total (I) implied that both encoding and retrieval were impaired for verbal memory (II/I 0/6, full score 58/58), whereas retrieval was mainly impaired for visual memory (II/I 6/33, full score 47/47). The Benton Visual Retention Test score showed that both immediate figure reproduction (7/10) and reproduction after a 15 s delay (3/10) were impaired. Delayed reproduction was also poor in the Rey-Osterreith Complex Figure Test (copying 36/36, 30 min delay 6/36). Conversely, scores for the Wechsler Adult Intelligence Scale-Revised were normal (verbal intelligence quotient (IQ) 105, performance IQ 121 and full-scale IQ 114). Subtest scores for digit span (9/19; forward 4 and backward 4) and arithmetic (6/19), however, were relatively low. Digit span forward was also 4 when presented visually on a personal computer. These findings suggested impaired short-term memory or working memory.

Remote memory was assessed with an autobiographical memory interview and with the specific questions as described below. The patient could recall autobiographical episodes well, but could not remember public events 2 years before onset. For example, he remembered the British royal wedding of Princess Diana and Prince Charles in 1985, but did not remember Diana's death in August 1997. Furthermore, he remembered the Nagano Winter Olympics in February 1998, the Kobe earthquake in January 1995 and the Tokyo subway sarin gas attack in March 1995. To determine whether there was a temporal gradient in his past memory loss, we gave the patient an 80-question multiple-choice questionnaire on public events during the four decades from 1950 to 1989, divided into four sections with 20 questions for every 10 years.⁴ He showed a slight temporal gradient in these sections, but all these scores were above the normal mean (percentage correct (normal mean for ≥ 70 -year-olds, SD)⁴: 1950s, 95 (53.7, 5.45); 1960s, 85 (55.3, 4.83); 1970s, 75 (58.5, 5.05); 1980s, 70 (66.8, 4.94)).

The patient profile was rated as follows: (1) severe anterograde amnesia that affected verbal memory more than visual memory; (2) minimal retrograde amnesia for the occurrence of public events over the 2 years before onset, with temporally graded event memory loss over the preceding 20 years; and (3) impaired short-term memory.

This patient showed severe encoding and retrieval deficits in verbal memory. This can occur because of a unilateral left hippocampal lesion. A comparison of the reported cases shows that bilateral lesions of the hippocampus or medial temporal lobe can cause moderate to severe anterograde amnesia.¹ Examination of our patient suggested that damage to the unilateral (left) hippocampal