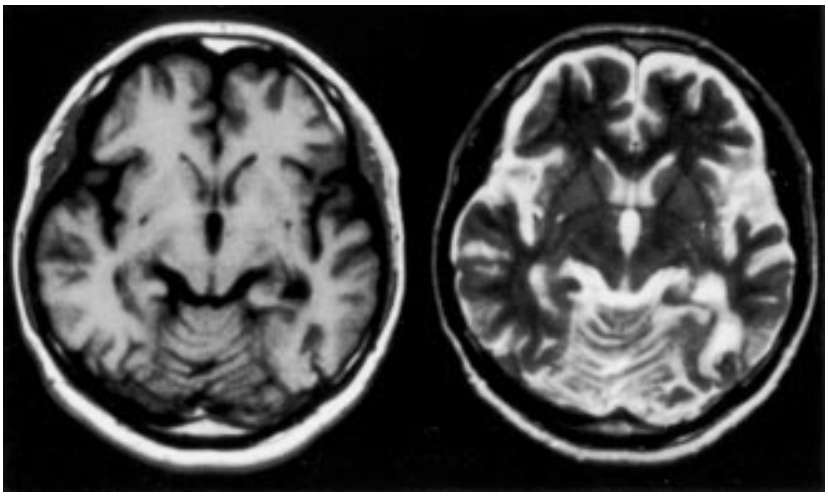

Figure 2 Brain MRI 3 months after admission showed the subcortical lesions in the left temporo-occipital lobe.

exhibited amnestic aphasia, alexia, and agraphia in the acute phase, disturbances other than agraphia of Kanji disappeared in a few months. Yokota *et al*[3] also reported a case with pure agraphia of Kanji, and suggested that the process of writing Kanji involves a different pathway from that which mediates Kanji reading in the left temporal lobe.

Iwata[1] proposed a hypothetical neuronal mechanism in the writing of Kanji and Kana as follows: the Broca's and motor association areas are the final coordination centres, but the angular gyrus plays an important part in sending the graphic information to the motor areas. However, spontaneous writing and responses to dictation are usually initiated by Wernicke's area, which gives rise to two different pathways to the angular gyrus. One is the auditory somaesthetic association pathway leading directly from Wernicke's area to the angular gyrus; Kana writing mainly depends on the intactness of this route. The second pathway is from Wernicke's area to the occipital lobe by way of the posterioinferior temporal area. This is the pathway involved in selecting the correct Kanji graphemes according to the meaning of the word, and thus recalled visual engrams of letters are sent to the angular gyrus.

Our patient demonstrated that initial amnestic aphasia, and agraphia of Kanji were associated with a lesion in the left temporal lobe. Because the posterior temporal region is located in close proximity to the angular gyrus and Wernicke's area, the pathological process in the first area affects the second two regions in its acute phase. We conclude that the persistent symptom of pure agraphia for Kanji in this study was caused by the left posterior temporal lesion which disconnected the pathway for Kanji writing selectively.

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Successful autologous stem cell transplantation in a patient with chronic inflammatory demyelinating polyneuropathy

A patient with chronic inflammatory demyelinating polyneuropathy is reported on who never had spontaneous remissions for 10 years, but who is in remission for 2 years after an autologous stem cell transplantation (ASCT). Before ASCT he needed at least 20 mg prednisone/day and in addition intravenous immunoglobulin (IVIg) treatment at regular intervals. An ASCT was considered in this patient because of serious side effects of immunosuppressive treatment.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterised by weakness with sensory impairments in the arms and legs. The reflexes in the arms and legs disappear. The onset is insidious. There may be progressive deterioration or a course with remissions and exacerbations. Routine blood examination is usually normal. Protein in CSF is increased in most patients. Electrophysiological studies may show slow nerve conduction velocities, conduction blocks, or dispersion.[1] Inflammatory demyelinating polyneuropathy is considered to be an autoimmune disease which is supported by the presence of inflammatory cells in sural nerve biopsies and the beneficial response to immunosuppressive treatment in most patients.[2] We describe a patient with CIDP who has had this disease for 10 years without spontaneous remissions. He responded to immunosuppressive therapy, but needed high doses and had severe side effects. Therefore, we decided to try to induce a long lasting remission by autologous stem cell transplantation (ASCT).

This patient was 38 years old when, in 1988, he began to have tingling and numbness in his fingers. The sensory symptoms progressed to his arms and legs, followed by weakness. Initially his symptoms were attributed to too much stress but at the end of 1990 when weakness had worsened to such an extent that he was no longer independent in his daily activities, it was decided that it was time for a neurological evaluation. At that time he had weakness of his arms and legs, MRC grade 4. There was atrophy of his intrinsic hand muscles and fasciculations were seen in the muscles of his arms. Except for diminished knee reflexes, there was areflexia. He had numbness of his arms and legs in a glove and stocking distribution. Electrophysiological studies showed slowed nerve conduction velocities of the median, ulnar, tibial posterior, and peroneal nerves in the range of 15–25 m/s with prolonged distal latencies and F wave responses. The distal compound muscle action potentials were small. Few muscles had signs of denervation. Blood examination was unremarkable and CSF total protein was 0.67 g/l without cells. Sural nerve biopsy was consistent with CIDP, showing inflammatory cells and demyelination.

In 1990 he was started on 60 mg/day prednisone. After 2 weeks improvement began. This improvement continued to normal strength leaving only slight numbness in his fingers. During tapering off of the prednisone dose he had mood disturbances at every change of dose. Repeatedly he had a relapse at doses lower than 20 mg/day. Subsequently we tried to replace prednisone by 150 mg/day azathioprine but after 2 years of treatment with azathioprine it was still not possible to decrease the dose of prednisone to less than 20 mg/day. Azathioprine was replaced by methotrexate (7.5 mg/week) for 6 months without a beneficial response. Thereafter he was treated with IVIg. After two cycles of 30g/day IVIg for 5 days he needed infusions every other week to maintain his improved condition. We tried to prolong these intervals by adding prednisone. With 20 mg/day prednisone he remained free of relapses for about 4 months. However, these intervals became gradually shorter; he developed arthralgias after administration of IVIg, and had repeated gastric pain. After 8 years of immunosuppressive treatment, without spontaneous remissions, we discussed the possibility of autologous stem cell transplantation (ASCT).

In May 1998 peripheral blood stem cells were harvested by leukopheresis after mobilisation with cyclophosphamide (4 g/m^2) and granulocyte colony stimulating factor (G-CSF; 5 μg/kg). CD 34+ cells were positively selected by immunomagnetic beads (Clinimax®, purity 98.7%) and cryopreserved. Before this procedure the patient had had IVIg every other week together with 20 mg/day prednisone. With this regular IVIg treatment he was in an optimal condition: he had no weakness and only mild sensory impairment of his fingers. After the mobilisation procedure, prednisone could be tapered off to 8 mg/day. Even without IVIg he remained in this improved condition for 5 months before he relapsed. Weakness in the arms and legs returned together with sensory impairment. Electrophysiological studies were repeated. We decided firstly to improve his neurological condition by IVIg treatment before myeloablative treatment was started. This treatment resulted in considerable improvement; only mild sensory impairment of the fingers remained.

In March 1999 he was treated with BEAM myeloablative chemotherapy (300 mg/m^2 BCNU on day –6, 200 mg/m^2/day etoposide on days –5, –4, –3, and –2, 200 mg/m^2/day cytosine arabinoside on days –5, –4, –3, and–2, and 140 mg/m^2/day melphalan on day–1) followed by stem cell re-infusion at day 0 (11.2 x 10^6 CD 34+ cells/kg). After re-infusion recovery of peripheral blood cells occurred within 16 days. Prednisone was tapered off but doses lower than 5 mg were accompanied by complaints of fatigue probably due to adrenal insufficiency. Two years after stem cell re-infusion, he is still free of relapses with 5 mg/day prednisone and without IVI g treatment. He works full time and the only neurological signs consist of mild numbness of his fingertips. Electrophysiological studies were repeated 1 year after re-infusion and compared with the latest study performed when he had relapsed after the mobilisation phase. For the right median nerve, the distal CMAP improved from 2.1 mV to 7.3 mV, the distal latency from 14.6 to 12.3 ms, and the motor nerve conduction velocity from 12 to 24 m/s.

This is the first report of autologous CD 34+ stem cell transplantation in a patient with CIDP. Recently, Marmont reviewed the results of autologous stem cell transplantation (ASCT) in autoimmune diseases.[3] He discussed a group of 143 patients, including patients with multiple sclerosis (n=51), systemic sclerosis, (n=30), rheumatoid arthritis (n=15), juvenile chronic arthritis (n=18), systemic lupus erythematosus (n=12), vasculitis (n=4), other connective tissue disease (n=4), and various autoimmune haematological disorders (n=9). The treatment of these patients was variable: some had transplantation of bone marrow stem cells, others had mobilised peripheral blood haematopoietic stem cell transplantation. The graft was unmanipulated in 36 patients and was T cell depleted in the remaining patients. The highest relapse rate at 1 year was seen in juvenile chronic arthritis (50%) whereas only 10% of patients with multiple sclerosis had relapsed. The transplant related mortality at 2 years post-transplantation was 6%. Multiple sclerosis has become the autoimmune disease which is most often treated by ASCT.

Marmont discussed a group of 24 patients with multiple sclerosis with a progressive course who were treated similarly to the patient with CIDP in this report. The patients with multiple sclerosis were conditioned with the BEAM regimen; the mobilisation phase consisted of cyclophosphamide followed by granulocyte colony stimulating factor and finally CD 34+ cells were cryopreserved. The only difference was that our patient was not treated with antithymocyte globulin. In the group of 24 patients with multiple sclerosis, one patient died of aspergillosis in the post-transplant period. The other 23 patients had no severe transplant related morbidity. Improvement in disability was seen in 10 patients, stabilisation in another 10.

The question is how ASCT is capable of eradicating autoimmunity. Remissions after allogeneic stem cell transplantation are easier to explain, as a "diseased" immunological and stem cell compartment is replaced with one that is normal and likely to develop tolerance. However, allogeneic transplantations are accompanied by high mortality figures and are therefore not considered in non-lethal autoimmune diseases.[3]

Autologous transplantations can better be described as rescue therapy. High doses of cytotoxic therapy as is given in ASCT are also myeloablative and are only possible with stem cell rescue treatment. It might be that the effects of this treatment on autoimmune diseases can be attributed completely to the high levels of cytotoxic treatment.[4] However, development of tolerance by "re-educated" lymphocytes from the purified CD 34+ cells has not been ruled out.

We certainly do not advise the routine use of ASCT in patients with CIDP. Most patients have an excellent response to immunomodulating therapy without serious side effects. Moreover, after several years of treatment many patients reach long lasting remissions. However, if high doses of immunosuppressive therapy are necessary for long periods and are poorly tolerated, ASCT with a well tolerated conditioning regimen may be considered.

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CORRESPONDENCE

Unusual presentation of a primary spinal lymphoma

Wilkening *et al*[1] described the unusual history of a formerly healthy immunocompetent white woman initially presenting with an S1 syndrome with lymphocytic pleocytosis in the CSF, leading to the misdiagnosis of meningoradiculitis. Repeated spinal MRI disclosed an epidural mass lesion, and histological examination of the tumour biopsy confirmed the diagnosis of primary spinal lymphoma of Burkitt's type. The authors emphasise that in every case with suspected meningoradiculitis including neuroborreliosis, meningeal lymphoma should be considered as an important differential diagnosis. In view of the occasionally difficult diagnosis of primary meningeal lymphoma we briefly present the clinicopathological report of a primary malignant lymphoma with almost selective involvement of the spinal roots: A woman aged 65 years without known systemic lymphoma presented with a painful focal right brachial plexus lesion and, 2 weeks later, developed progressive motor neuropathy with flaccic paraparesis of the lower limbs. Laboratory tests were negative except for her CSF showing increased protein content and 85 lymphocytes/mm^3, not expressing the B cell tumour marker CD 20. Nerve conduction studies suggested subchronic demyelinating neuropathy without motor conduction block. Cranial and cervical CT and MRI were negative. Sural nerve biopsy disclosd a demyelinating neuropathy with acute myelin loss, some remyelination with incipient onion bulb formation, and wallerian degeneration, but without inflammatory or neoplastic infiltration. Muscle biospy showed neurogenic muscle atrophy. Despite high dose corticosteroid and intravenous immunoglobulin treatment, her condition deteriorated rapidly with develoment of flaccid paraplegia and paresis of the right arm. Repeated CSF analysis showed increasing protein content and pleocytosis up to 180 cells/mm^3, mainly transformed but with no neoplastic lymphocytes, again none being immunopositive for the B cell markers CD 19 and CD 20. Extensive search for extraneural malignancy including repeated cranial, spinal, and abdominal CT and MRI scans were all negative. The patient died 6 months after the onset of neurological symptoms. Necropsy disclosed diffuse B cell lymphoma[2] restricted to the cauda equina with massive infiltration of the anterior lumbal spinal nerve roots and dorsal ganglia, and very mild neoplastic infiltrates in the schiadic and femoral nerves associated with severe myelin loss. There was no involvement of the spinal cord, brain, meninges, or cranial nerves. The right brachial plexus showed severe demyelination without onion bulb formation and perivascular infiltrates exclusively formed by T lymphocytes. Search for systemic malignant lymphoma was negative except for an isolated small focal area of B cell lymphoma in the thyroid gland.[3] As in the case reported by Wilkening *et al*,[1] this finding widens the range of possibilities and differential diagnostic difficulties of selective involvement of the spinal roots (and peripheral nervous system) by primary malignant non-Hodgkin's lymphomas, often also referred to as "neurolymphomatosis"[3–5] making an extensive diagnostic investigation necessary.

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Authors' reply

We greatly appreciate the interesting comments of Jellinger and Grisold who describe