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Medical rehabilitation of chronic progressive disseminated encephalomyelitis (MS)

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Eight years after diagnosis, 40% of MS patients develop a chronically progressive form. Annually we treat approximately 200 patients with progressive MS. Treatment consists of medication, i.e. agents that help to prevent future impairment, or interferon-beta injections, and intervals of mitoxantrone infusions (Novantrone®), and in some cases cyclic cyclophosphamide (Endoxan®) or nucleoside analogue cladribin (Leustatin®). Without clear scientific evidence, we recommend unsaturated fatty acids (thistle or sunflower oil), sufficient protein, and freshly prepared fruits and vegetables as a sound basis for remyelination. Remyelination profits from general prophylaxis in the use of ascorbic acid to help prevent urinary infections via acidification, autogenic training to reduce fatigue, improve ventilation of deeper airways, and stimulate vagotonic regeneration, and prevention of unnecessary immune stimulation caused by insects and some food. We recommend the use of sun hats and disencourage blood donation (Allain 1998). Physiotherapy can improve strength, reduce spasticity, and train the patient to compensate for dysbalance and ataxia; supported by beta blockers and good antispastics, tremor and gait disturbances can be positively influenced. Music and motion, speech therapy, realistic training of daily activities, and prudent psychotherapy complete the range of measurements to reconstitute as much as possible of the patient's individual freedom. In the individual, we eventually provide prudent technical aids and careful prognostic estimations. Cooperating with local and regional patient networks, we reinforce long-term disease management and spread up-to-date medical research results, and finally gather valuable contextual information and clinical data on an increasingly frequent idiopathic disease of the human central nervous system. *Journal of NeuroVirology* (2000) **6,** S176–S178.

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Introduction

Eight years after diagnosis, 40% of MS patients develop a chronically progressive form. Progression is another word for inflammation that exceeds remyelination. Therapeutic intervention in chronic progressive disease, by definition, is more challenging than in remitting-relapsing MS. We summarize our approaches as in-patient center, and describe the underlying clinical assumptions and beliefs.

Multiple sclerosis, or encephalomyelitis disseminata, is an increasingly frequent disease that has yet no accepted etiology. There is a regional accumulation associated with latitude, scandinavian ancestry, and/or dairy farming, and large differences in incidence on the same geographic line (Malta; Sicily; gipsies in Hungary; magjar descendents in Hungary). Children of affected patients have a risk of only 2–5% of developing MS, whereas homozygotic twins carry three times the concordance of dizygotic twins. Clinically, no characteristic feature is present in more than 95% of patients. The density of oligodendrocytes seems to decrease with duration of disease independent from lesion load. Obviously, there is no single medication that helps more than three quarters of patients, and even after exclusion of differential diagnoses such as sarcoidosis, lymphoma, and Behcet's disease, Leber's hereditary optical neuropathy (LHON), neuroborreliosis, HIV/HTLV infection and neurosyphilis, the entity MS may well be several etiologic entities.

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Results

Medication for treatment, i.e. agents that save future impairment are in our opinion: interferon-beta injections (case and weight-adjusted doses still to be determined); intervals of mitoxantrone infusions (Novantrone®) 10 mg/m², probably cyclic cyclophosphamide, i.v. immunoglobulin-G; potentially the nucleoside analogue cladribin (Leustatin®) or copolymer (Copaxone®). As antispastics: baclofen, tizanidine, tolperison, memantine; for tremor: broad-acting beta blockers (propranolol), budipine. Symptomatically useful or plausible yet impossible to prove is: a high intake of unsaturated fatty acids (thistle/sunflower oil), or fresh fruit and vegetables.

Prophylaxis, i.e. behaviour that potentially improves outcome, should include: additional ascorbic acid (against urinary infections); autogenic training and yoga (counters fatigue, stimulates ventilation, regeneration); avoidance of biting insects (use repellants, avoid mosquito seasons). For the prevention of gastrointestinal infection (do not eat raw fish or shellfish); keep ethanol consumption low and non-daily (Brosseau *et al*, 1993); use sun hats and avoid blood donation (Allain, 1998).

Balneophysiotherapy, psychotherapy (as necessary) and physiotherapy can improve strength, reduce spasticity, and train the patient to compensate for dysbalance and ataxia. In this way tremor and gait disturbances can be positively influenced. Music and motion therapy, speech therapy, realistic training of daily activities, and prudent psychotherapy complete the range.

Counselling usually starts with confirmation of the phenomenologic diagnosis 'MS'. The diagnosis of MS is clinically defined, since individuals without clinical deficits do not visit their doctor. Both Poser criteria in relapsing cases, as well as electrophysiology plus neuroradiology and cerebrospinal fluid analysis in progressive cases provide a very high degree of certainty of multiple sclerosis (Filippini *et al*, 1994) (Table 1).

There are rare cases in childhood and with clinical onset after the age of 50 years, both perhaps the result of a general increase of MS prevalence and diagnostic sensitivity. Social counselling, technical aids, and thorough assessment of locomotion, working, driving and self-supporting abilities help both patient and care-givers to adjust to an almost always progressive handicap. A competent prognostic evaluation is the basis. Therefore, we constantly update our list of prognostic factors. Negative predictors are:

- 1° progression; 2° progression
- initially 'complete' dysfunction (CSF, VEP, SEP, AEP, cortical magnetic stimulation)
- frequent deterioration/incomplete recovery
- cerebellar and/or sphincter signs
- high MRI and/or MT lesion load
- familial occurrence/age at onset
- severe concomitant diseases

and possibly of negative relevance are:

- little medical treatment/rehabilitation/psychosocial support
- pattern of ethanol consumption/drugs
- infectious history (EBV, HHV-6, JCV, blood products?)
- (endogenous) retroviral expression (RGH-2, HERV-W)
- epitope spreading (OCB-CSF, ANA, ASMA, αMBP/MAG ...)
- genetic polymorphisms (MHC-DR2.15, MBP, HRES-1, TNFa.9)

Progressive deterioration in three quarters of MS patients after 20 years, and 'epitope spreading' in the inflammatory response, on one side, and increasing intervals of MRI and clinical deterioration as well as a levelling off in disease activity after the age of 55 cannot be explained by current concepts of infection, inheritance, intoxication or intrinsic autoimmunity.

Table 1

	Negative predictive value (%)	*Positive predictive value (%)*
MRI normal/'MS-typical'	96	53
CSF OCB absent/present	77	44
VEP normal/abnormal	62	26
SEP median nerve normal/abnormal	68	50
SEP tibial nerve normal/abnormal	67	42
AEP normal/abnormal	68	50

Discussion

The progressive form of MS differs immunologically from the relapsing remitting form, yet need not be pathoetiologically different. In retrovirus-associated myelopathy (endemic HTLV-associated myelopathy, HAM), patients who had received blood transfusions had significantly higher CSF levels of sL-selectin than HAM patients without a past history of transfusions, suggesting that HAM patients with higher virus load have a more active immunological state in the central nervous system (Tsujino *et al*, 1998). Mood disorder and inflammatory activity seem to correlate, while successful improvement of mood is difficult to correlate with beneficial reduction of inflammatory CSF markers (Fassbender *et al*, 1998).

The postulation of an unidentified 'MS agent' has not been able to improve our clinical treatment up to now. Opinion goes from 'viruses trigger and perpetuate MS, although MS is not related to a persistent viral infection' (Weiner, 1998), to 'MS is a place-related exogenous acquired disease with preference

for whites . . . .' This infection, the cause of MS, we call the primary MS affection (PMSA). PMSA is a persistent infection transmitted person to person' (Kurtzke, 1999). Certainly, British troops were housed where the first Faroe Island MS patients lived. And in more than one study, cases had more frequently experienced bronchitis and/or pneumonia in the age group 11–15 years, a finding consistent with the idea of MS as an age-dependent, host-immune response to infection during childhood or adolescence (Grönning *et al*, 1993). Some authors postulate a particular ability to acquire MS between the ages of 11 and 26 years, and there is a higher MS risk with higher social status in black men, white men, white women, that is not explained by the consumption of raw or smoked meat, pet/dog ownership and/or illness (Landtblom *et al*, 1993), or consumption or dairy products. MS is potentially more than one or two diseases, and genomic activation/usage may alter during disease progress. We therefore suggest a -85°C long-term storage of serum and cerebrospinal fluid to prepare for future diagnostic progress.

Since MS often appears to 'burn out' after the age of 55, it is worth while including specialized in-patient treatment to reach this age in as good a functional state as possible. In-patient treatment and rehabilitation is cost-effective since it:

- keeps a patient at work (disease of the working age group)
- restores readiness to go on in patients and caregivers
- keeps medical care to standards in patients who often 'have enough' of going to the doctors
- enhances compliance with medical and social support
- brings in additional compensating strategies
- (learning by reiteration in new environment)
- objectively improves counselling based on function and prognosis.

Today, an early prophylactic therapy is in conflict with diagnostic certainty provided by waiting for clinically definite disease. The question, whether early IFN-β therapy could prevent progression to MS of, e.g. optic neuritis in young adults, is under examination.

Conclusion

The answer to several questions concerning multiple sclerosis risk and treatment concern a set of beliefs. Genetic impact, possibility of a transmissible cofactor, and role of psyche and individual immune activation influence the course of what we today call clinically definite multiple sclerosis. From a clinician's point of view, this actual set of assumptions is presented.

The author's perception of MS treatment and counselling is documented on the foil of chronic progressive disseminated encephalomyelitis (MS), as a 'worst case' variant of a disease that in a majority of patients starts with recurring relapses.

We document ten aspects of treatment in the wider sense of chronic progressive MS, i.e. medication, dietary recommendations, immune prophylaxis, practical suggestions, physiotherapy, other training therapies including psychologic support, technical aids, prognostic evaluation, long-term disease management and the collection of contextual data.

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