J. Neurol. 221, 59—66 (1979)

Journal of
Neurology

Plasma Exchange in Motor Neuron Disease

A Controlled Study

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Summary. In vitro studies seem to indicate that a serum factor may be involved in the pathogenesis of motor neuron disease. If so, plasmaphoresis might influence the course of amyotrophic lateral sclerosis (ALS) favorably. In the present study, therefore, ALS patients were subjected to weekly 2l plasma exchanges, using a Haemonetics blood separator. Seven other ALS patients, matched as closely as possible with the treatment group regarding age, sex, duration of symptoms as well as degree of involvement, served as a control group. The progression of the disease was followed by an arbitrary grading system, assessment of muscular power by Zadig's dynamometer, and by tests for motor speed, coordination and for pulmonary function. Duration of treatment was from 6 to 15 months. Monthly evaluations indicated that the rate of deterioration was approximately the same in treatment and control groups. Plasmaphoresis carried out in this way does thus not alter the downhill course of ALS.

Key words: Plasma exchange – Plasmapheresis – Amyotrophic lateral sclerosis – Motor neuron disease.

Zusammenfassung. Aus in-vitro-Untersuchungen scheint hervorzugehen, daß ein Serumfaktor bei der Pathogenese der myatrophischen Lateralsklerose mit im Spiele ist. Trifft dies zu, dann wäre es denkbar, daß Plasmapherese den Verlauf der ALS günstig beeinflussen könnte. Aus diesem Grunde wurden Patienten mit ALS wöchentlich einem 2-Liter-Plasmaaustausch unterworfen unter Verwendung eines Haemonetics-Blutseparators. Es wurden einerseits 7 Patienten so behandelt, andererseits 7 weitere, so sehr als möglich gleichgelagerte ALS-Patienten, als Kontrollgruppe verwendet. Das Fortschreiten der Krankheit wurde aufgrund einiger Kriterien quantitativ beurteilt: Beurteilung der Muskelkraft mit Hilfe des Zadig-Dynamometers, Teste für die

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0340-5354/79/0221/0059/$ 01.60

Koordination der Bewegungsabläufe und für die Lungenfunktion. Die Behandlungsdauer betrug 6—15 Monate. Die monatlich durchgeführte Beurteilung des Zustandes ergab, daß der Grad der Verschlechterung bei den behandelten Patienten und der unbehandelten Kontrollgruppe weitgehend gleich war. Die in der oben beschriebenen Weise durchgeführte Plasmapherese hat also keinen Einfluß auf die progrediente Verschlechterung des Zustandes beim ALS-Patienten.

Serum from amyotrophic lateral sclerosis (ALS) patients has been reported to have a toxic effect on cultures of myelinated CNS fibers (Bornstein and Appel, 1965; Field and Hughes, 1965). In vitro studies indicate that ALS serum has a specific toxic effect upon anterior horn cells (Wolfgram and Myers, 1972, 1973; Wolfgram, 1976). A serum factor might thus hypothetically be involved in the pathogenesis of ALS. If so, the removal of this factor, e.g. by plasma exchange, might possibly improve the clinical course of this illness.

Material and Methods

The effect of regular plasma exchange was studied in seven patients with ALS. The diagnosis was confirmed by autopsy in two of the patients in the treatment group. Patients with other concurrent illnesses were excluded. No regular medication was taken during the study period.

Seven other patients with ALS, matched as closely as possible with those in the treatment group with regard to age, disease duration, and distribution and degree of the neurological signs, served as a control group. The degree of involvement was, nevertheless, somewhat higher in the treatment than in the control group. We were also forced to accept a discrepancy with regard to sex: all seven patients in the treatment group were men, whereas in the control group there were 2 women and 5 men.

The mean ages of the patients in the treatment and control groups were 48 and 51 years, respectively (Table 1). The mean duration of disease in the treatment group was 13.4 months, the corresponding figure in the control group being 12.1 months.

Plasma exchange was carried out once per week in the treatment group, with one exception; patient H.M. (Table 1) was treated biweekly most of the time, due to transport difficulties. On each occasion, 2 l of plasma was exchanged, using a Haemonetics blood separator. Flow into the

Table 1. Age, duration of disease, duration of treatment, and reason for discontinuing treatment

Patients	Age	Duration of disease before treatment (months)	Treatment duration (months)	Reason for discontinuation	
				Patient's wish	Death
T.E.	41	5	6	+	
B.B.	53	16	6	+	
H.R.	54	17	7	+	
K.S.	33	8	7		+
A.K.	57	14	9	+	
O.K.	58	12	10		+
H.M.	36	12	15	+	

Table 2. Evaluation of clinical condition using an I-V scale

Clinical stage	Motor function		Bulbar symptoms
	Lower extremities	Upper extremities	
I	Slight atrophy and paresis, but walking without support	Slight atrophy and paresis, but able to do all activities of daily living	Slight atrophy of tongue; no bulbar symptoms
II	Walking with one cane	Slight difficulties (e.g. when using a key)	Slight dysphagia/ dysarthria
III	Walking with two canes	Dependent on some help with dressing and undressing	Moderate dysphagia/ dysarthria
IV	Dependent on a wheel chair	Unable to write, or to dress and undress	Severe dysphagia/ dysarthria
V	Bedridden	Almost paralytic in upper extremities, incapable of personal care. Must be given food	Unintelligible speech + pronounced difficulty swallowing

centrifuge from the patient's circulation was obtained by means of a cannula in an antecubital vein. After some months, the repetitive opening and closing of the fist—a necessary procedure to maintain sufficient blood flow into the machine—was markedly impeded in three patients because of increasing paresis of the upper extremities. These difficulties were overcome by making a permanent AV fistula. The mean duration of treatment was 8.5 months (Table 1).

The clinical course in both groups was followed by a monthly clinical evaluation. Various parameters for pulmonary function (VC, FEV, and PEF) were routinely checked at the monthly controls in the test group and in four patients in the control group.

Muscle strength was measured by means of Zadig's dynamometer (Zadig, 1963; Karterud, 1977) by two independent investigators (treatment group + four patients in the control group).

The following functions were tested bilaterally: hand grip, extension and flexion at the wrist, elbow, knee, and ankle joints and adduction and abduction at the hip. The reproducibility of this method seemed to be good, and since there were no significant differences between the results obtained by the two independent investigators, mean figures were used. The ensuing figures for the upper and lower extremities were added and divided by 2 to give the over all status of the motor system. For these parametric assessments, the pre-test value was defined as 100%, and the per cent deterioration was calculated. Special tests for physical fitness (speed—coordination tests) were performed by the Department of Physical Medicine.

For a simple, rough, and convenient evaluation of the patients' clinical condition, and for following the course of the disease, we made an arbitrary classification by means of an I-V scale both for the motor and the bulbar symptoms (Table 2).

Blood samples for estimation of hepatitis β-virus antibody titers were taken at regular intervals to exclude the possible transmission of hepatitis as a result of the frequent plasma infusions. All these tests, however, were negative.

Results and Comments

Figures 1 and 2 summarize the individual clinical profiles with regard to motor and bulbar symptoms in the study and control groups. It is evident that a gradual deterioration took place in both groups as a function of time, and that the

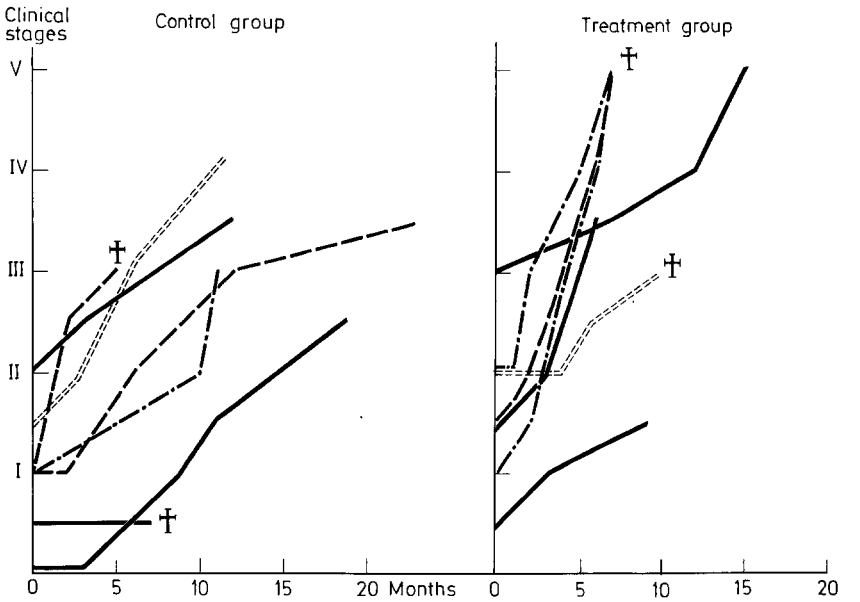

Fig. 1. Progression of motor symptoms in control and treatment groups, according to method adopted for grading symptoms

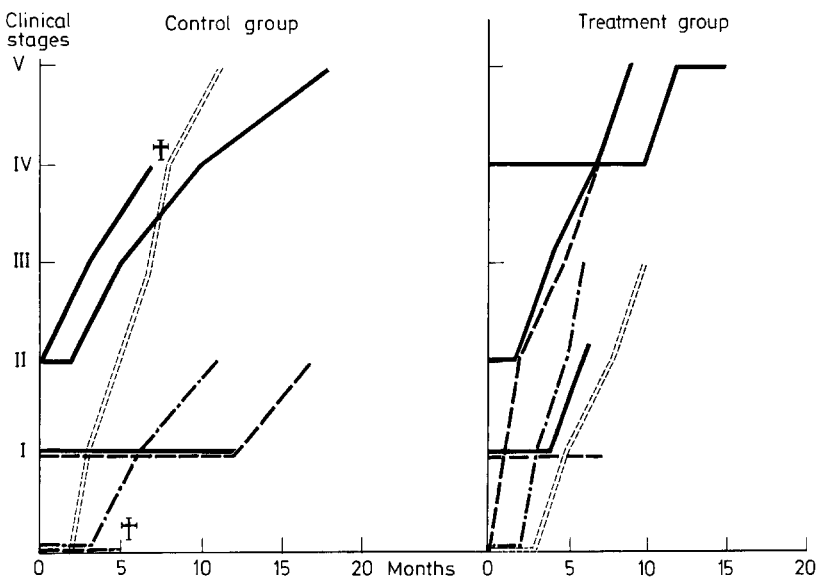

Fig. 2. Progression of bulbar symptoms as a function of time, according to method adopted for grading symptoms

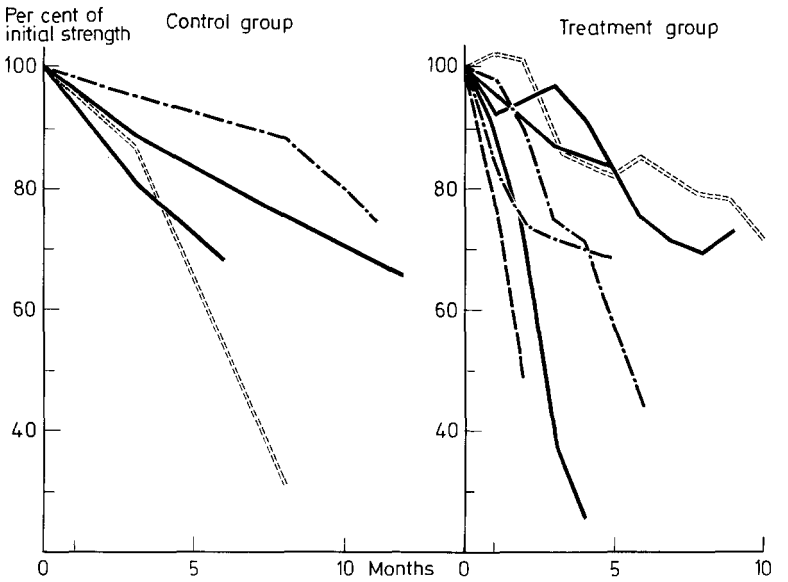

Fig. 3. Assessment of reduction in muscular power by means of Zadig's (1963) dynamometer. Pre-trial strength is set at 100 per cent

Table 3. Pulmonary function tests at beginning and end of treatment (mean values and range)

	VC	(L)	FEV	(L)	PEF	(L/min)
	Beginning	End	Beginning	End	Beginning	End
Control group	4.95 (3.52—6.25)	3.35 (1.02—3.78)	3.1 (2.1—4.2)	1.7 (0.9—2.4)	370 (190—580)	270 (70—470)
Treatment group	3.95 (1.97—6.32)	2.76 (1.07—5.08)	3.0 (1.4—5.4)	2.1 (1.0—4.9)	430 (240—620)	300 (150—500)

progression rate grossly was of the same order of magnitude in both groups. The deterioration in the muscle power values (Zadig's dynamometer) with time is evident from Figure 3. In conformity with the results obtained with the grading system, the rate of reduction of muscular power seems to be nearly the same in the treatment and control groups. The initial irregular shape of the curve in two patients may probably be ascribed to a slight placebo effect of the treatment and/or to the effect of learning; the patients may not have been on an absolutely stable line in regard to performance with this method at the very onset of the study. The slope of the curves based on mean values, seems to be rather similar as far as both bulbar (Fig. 4) and motor symptoms (Figs. 4 and 5) are concerned.

The deterioration both with regard to pulmonary function and the various parameters for speed and coordination also seemed to take place at approximately the same rate in both groups. Thus, the mean performance reduction with the

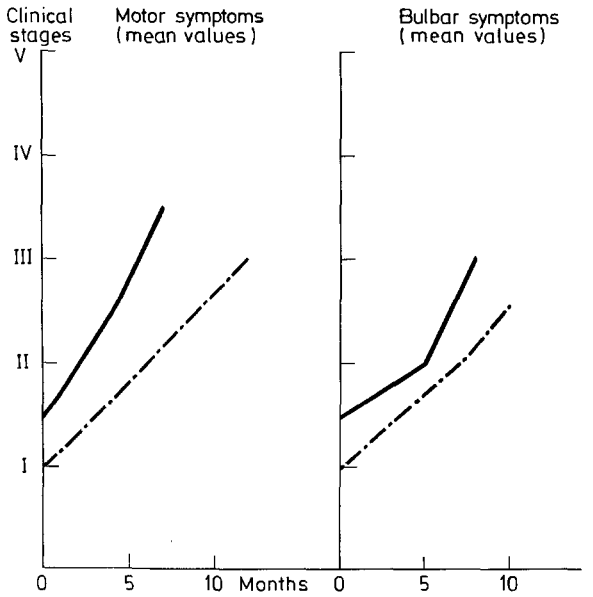

Fig. 4. Progression of motor and bulbar symptom based on mean values for all patients in the respective groups according to grading system adopted. Interrupted line: control group. Continuous line: treatment group

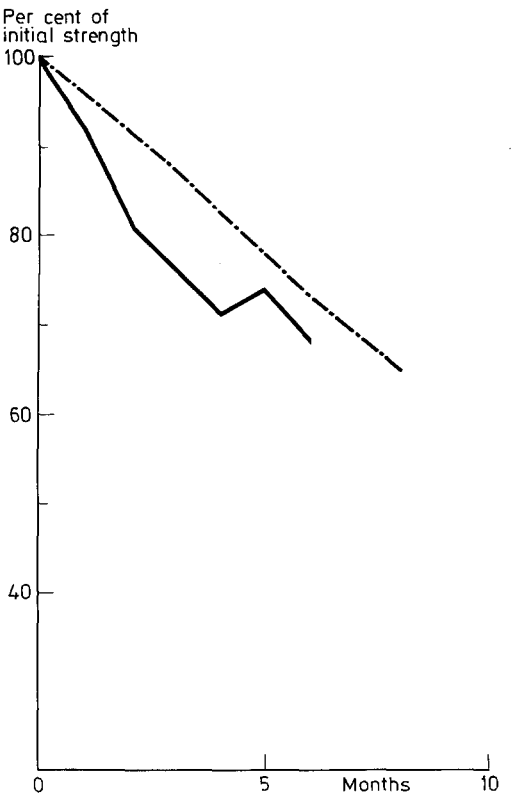

Fig. 5. Mean deterioration in extremity muscular power, based on values obtained by Zadig's dynamometer. Interrupted line: control group. Un-interrupted line: treatment group

"speed-coordination test" was 50% in the treatment group, versus 45% in the control group at 3 months.

Five patients wished to stop treatment after a varying number of months (Table 1). The reasons for this were: final conviction that the treatment was of no avail, or a combination of impeded ambulation and long and tedious transport made the procedure too strenuous for the patient.

Our study conclusively shows that plasma exchange, when carried out in this way, does not improve the longterm clinical course of ALS. There may be several possible explanations for the apparent discrepancy between the results obtained in the in vitro studies and the present results in ALS:

1. There does not exist any toxic serum factor in ALS. It should be emphasized that other workers (Horwich et al., 1974; Liveson et al., 1975) have not been able to reproduce Wolfgram's original results. Some authors (e.g. Field and Hughes, 1969; Tavolato et al., 1975) have discussed other possible explanations for the reported cytotoxicity of ALS sera.

2. The toxic factor may only be active in vitro, and not in vivo, due e.g. to the existence of a blood-brain barrier.

3. The plasma exchange has not been extensive enough. It should be emphasized in this context that in myasthenia gravis, plasma exchange has been carried out daily (Pinching et al., 1976).

4. Irreversible injury to the neuron may already have taken place, so that the later removal of a toxic factor is of no importance.

The suggestion by Ask-Upmark (1950, 1955) that a deficiency factor might be responsible for the development of ALS seems still less likely on the basis of the present information.

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Received January 10, 1979