Eur Arch Psychiatry Clin Neurosci (1991) 241:73–76

European Archives of Psychiatry and Clinical Neuroscience

Liquorpheresis (CSF-Filtration): an Effective Treatment in Acute and Chronic Severe Autoimmune Polyradiculoneuritis (Guillain-Barré Syndrome)*

K. H. Wollinsky[1], M. Weindler[1], P.-J. Hülser[2], P. Geiger[1], N. Matzek[1], H.-H. Mehrkens[1], and H. H. Kornhuber[2]

Departments of [1] Anaesthesiology/Intensive Care Medicine and [2] Neurology, Rehabilitation Hospital Ulm, Academic Hospital of the University, Oberer Eselsberg 45, W-7900 Ulm, Federal Republic of Germany

Received June 18, 1990

Summary. In recent years, plasmapheresis has become a well established treatment of acute and chronic polyradiculoneuritis (Guillain-Barré syndrome, GBS). Nevertheless, there are still non-responders and there are particular risks associated with this treatment. Despite all efforts, the duration of severe forms of Guillain-Barré syndrome is still considerable. Inflammation and demyelination start intrathecally. We therefore used liquorpheresis (cerebrospinal fluid filtration) as a new effective therapeutic approach. Our first patient, severely disabled with acute GBS, artificially ventilated, had undergone plasma exchange without effect. Plasma immunoadsorption led only to transient improvement. After several liquorphereses, the patient recovered completely. In three additional patients with acute and two with chronic GBS an improvement of clinical signs in close temporal relation to liquorpheresis was observed. Twice, liquorpheresis was combined with immunoadsorption of cerebrospinal fluid. Liquorpheresis was well tolerated in all cases. This procedure may be effective by eliminating humoral or cell-bound factors responsible for the onset or/and maintenance of inflammation. Further controlled studies are necessary and are in progress.

Key words: Liquorpheresis – CSF-pheresis – CSF-filtration – CSF-immunoadsorption – Acute Guillain-Barré syndrome – Chronic polyradiculoneuritis

Introduction

More than a decade ago, Brettle and coworkers [2] were the first to demonstrate a beneficial effect of plasmapheresis in acute polyneuritis, later confirmed by controlled studies [8, 13]. A similar efficacy was seen in some cases of chronic relapsing polyneuritis [4, 6, 11, 16]. Plasmapheresis may improve some patients dramatically; some are non-responders [7]. Specific risks of plasma exchange are known [5].

Despite plasmapheresis, the course of polyradiculoneuritis (Guillain-Barré syndrome, GBS) in severely disabled patients requires long-term treatment, including intensive care and ventilatory support. Seventy percent of the patients recover within 1 year; the overall mortality is 2–5% [5].

There is good evidence for an autoimmune aetiology of GBS, often preceeded by viral infection. First signs of inflammation usually occur at the nerve root. The demyelination then spreads from proximal to distal parts of the peripheral nerves, implying that at least in the early stage of the disease important pathophysiological events take place in or adjacent to the intrathecal compartment. We therefore submitted parts of the cerebrospinal fluid (CSF) of GBS patients to repeated extracorporeal liquorpheresis, in order to counteract the inflammatory break down of the myelin sheaths [19].

Patients and Methods

Informed consent concerning the planned liquorpheresis was obtained in advance in all patients. Four patients were suffering from acute and two from chronic GBS (AIDP and CIDP, respectively, Table 1). Two patients with AIDP and one with CIDP had not sufficiently responded to preceeding plasma exchange. Two patients had never been subjected to plasma exchange.

The clinical status was assessed daily using an eight-item score first proposed by Besser [1] (Tab. 2) in a slightly modified form.

At the spinal processes L 3/4 or L 4/5 the subarachnoideal space was punctured with a Touhy needle 18 G (Braun Melsungen). Then a sterile catheter was introduced intrathecally, as it is standard for continuous spinal anaesthesia. By means of 0.2 µm filters (Pall Biomedicine Dreieich) and three-way stopcocks a closed system was set up, primed with normal saline solution for suction and reinfusion of 20–40 ml CSF (Fig. 1). This procedure was repeated several times leading to a maximum filtrate of 150 ml CSF/day. Liquorpheresis was performed on up to 5 consecutive days. Then, the spinal catheter was removed; if necessary, we installed a new

* Parts of this paper were presented at the symposium of the German Neurological Society, Bad Nauheim, 29.09.1989

Table 1. Treatment

Patient	Sex	Age (years)	Form	Previous therapy	Therapeutic trials
1.	Female	73	AIDP	3PPH 1 PIAD	5 LPH
2.	Male	21	AIDP	IG	8 LPH
3.	Male	61	AIDP	CST	7 LPH
4.	Male	75	AIDP	CST 2 PPH	6 LPH 2 LPH + LIAD
5.	Male	68	CIDP		3 LPH
6.	Male	34	CIDP	CST IG β-IFN 6 PPH	12 LPH 1 LPH + LIAD

AIDP = Acute inflammatory demyelinating polyneuritis
CIDP = Chronic inflammatory demyelinating polyneuritis
LIAD = Liquorimmunoadsorption
LPH = Liquorpheresis
PIAD = Plasmaimmunoadsorption
PPH = Plasmapheresis
IG = Immunoglobulins
CST = Corticosteroids
β-IFN = β-Interferon

Table 2. Clinical score

1. Needs ventilatory support
2. Tetraplegic, helpless
3. Tetraplegic, hand motor function partially preserved
4. Able to stand with support
5. Standing alone, able to walk with support
6. Able to walk without support, paretic gait
7. Minimal sensory or motor deficits
8. Unremarkable neurological examination

catheter system some days later. CSF protein and glucose were measured before and after liquorpheresis. In two patients (nos 4 and 5) the last liquorphereses were combined with an additional immunoadsorption with a small phenylalanin-packed mini adsorption column (content 1 ml) (made by Asahi-Diamed, Tokyo-Köln).

In the first four liquorphereses, we used two prototyp filters, 0.2 µm (Pall) coupled in series. We found their capacity limited to 50 to 100 ml CSF per filter, depending on the CSF protein content. Thus, filter systems sometimes had to be exchanged during one single liquorpheresis. This problem was overcome by a newly developed filter with larger active surface (Pall). The procedure was simplified by using an infusion pump (Perfusor Braun). Maximum flow rates were 2 ml/min and 5 ml/min for suction and infusion, respectively.

Results

The procedure was well tolerated in each case; the only side effect was a mild headache whenever the amount of CSF filtrated in one portion exceeded 40 ml. Headache always disappeared upon reinfusion. In particular, we never observed signs of infection caused by this treatment.

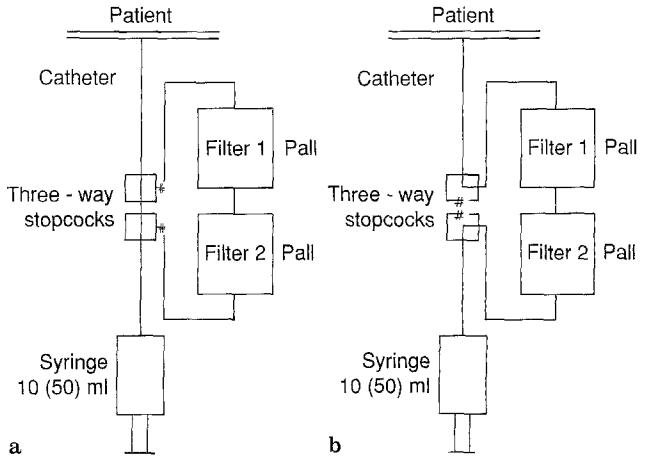

Fig. 1. Set up of the system for liquorpheresis, 2 filters (Pall) in series connection (**a**) suction phase; (**b**) reinfusion and filtration phase

Each liquorpheresis was effective in reducing CSF protein concentration (Fig. 2a–f). Usually the decrease was transient; repeated filtrations finally resulted in reduced protein concentrations in three patients only (nos 1, 4, 6). CSF glucose levels were not significantly affected (Fig. 3).

In all patients treated with liquorpheresis a neurological improvement was observed. In patients with an acute form of the GBS motor function gain was seen in close temporal connection with liquorpheresis (Fig. 4a–f). In some cases minor functional changes not detected by our clinical score due to its global nature occurred within one hour after liquorpheresis. Patient no 2 for example recovered dorsiflexion of his feet against gravity when tested at the end of the third liquorpheresis. Before the therapeutic procedure, only a partial movement was possible with gravity eliminated.

Our first patient (no 1, aged 73 years) developed a rapidly progressing tetraparesis, marked slowing of radicular conduction on electrophysiological testing, and deteriorated despite plasma exchange and plasma-immunoadsorption. Liquorpheresis, however, was followed by a dramatical improvement; the total duration of the hospitalization was 72 days.

In two additional patients (nos 2 and 3) with acute GBS the favourable course of the disease after liquorphereses lead to only minor symptoms remaining on the day of discharge. In both we observed that after liquorpheresis the clinical status improved, but stabilization was achieved after repeated treatment.

One patient (no 4, 75 years) suffered a relapse of giant cell arteriitis. Despite oral corticosteroid treatment (200 mg prednisolone) daily, the erythrocyte sedimentation rate did not fall. One week later he developed rapidly progressive tetraparesis with high CSF total protein and pulmonary infection. Five days later artificial ventilation became necessary. Two plasmaphereses were performed. Still on assisted ventilation, the patient did not improve. We then initiated eight consecutive liquorphereses, two combined with immunoadsorption. Within 24 h, the patient was breathing spontaneously for

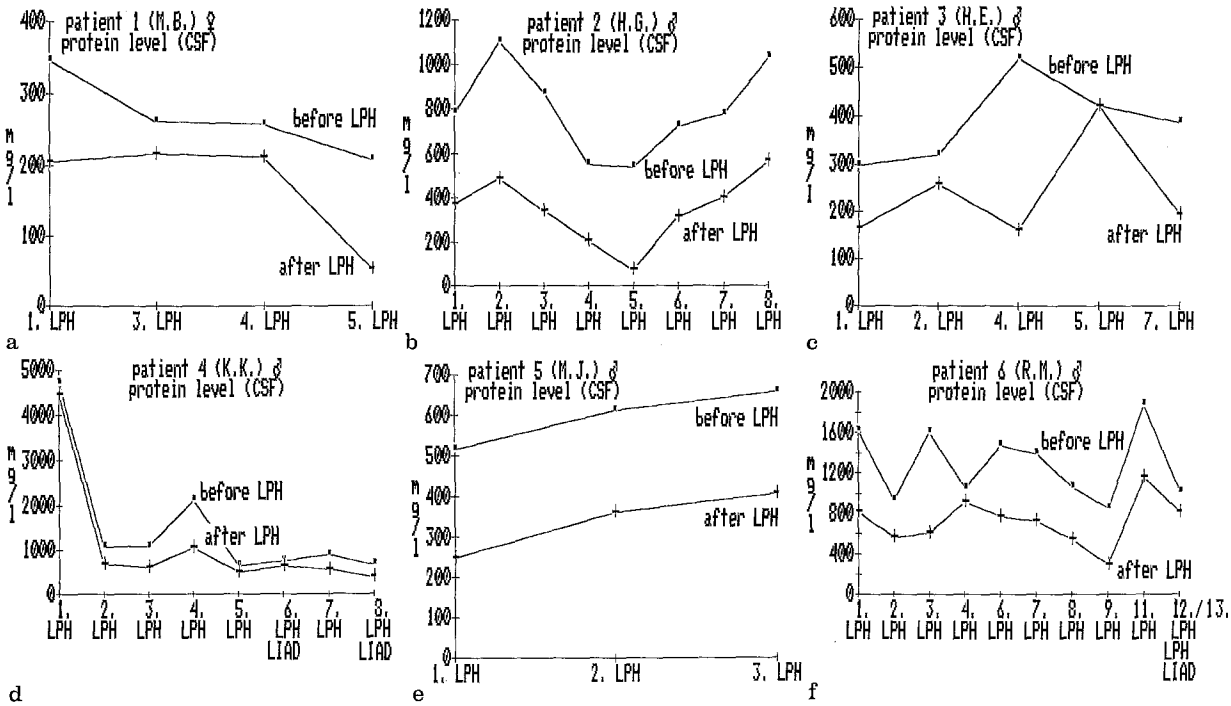

Fig. 2a–f. Protein levels (CSF) before and after liquorpheresis

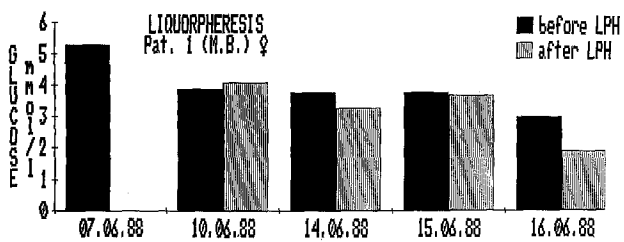

Fig. 3. Alterations of glucose levels (CSF) before and after filtration exemplary from pat. no. 1, M.B.

hours. Despite intensive antibiotic therapy he died four weeks later of further severe bronchopneumonia and septic shock, probably due to prolonged corticosteroid treatment.

Patients nos 5 and 6 suffered from a chronic form of GBS. They exhibited a slowly progressive weakness. High-dose corticosteroid treatment was only transiently effective in case 6, while plasmapheresis, β-interferon and high-dose i.v. immunoglobulins did not alter the course. Following repeated liquorphereses, an insiduous

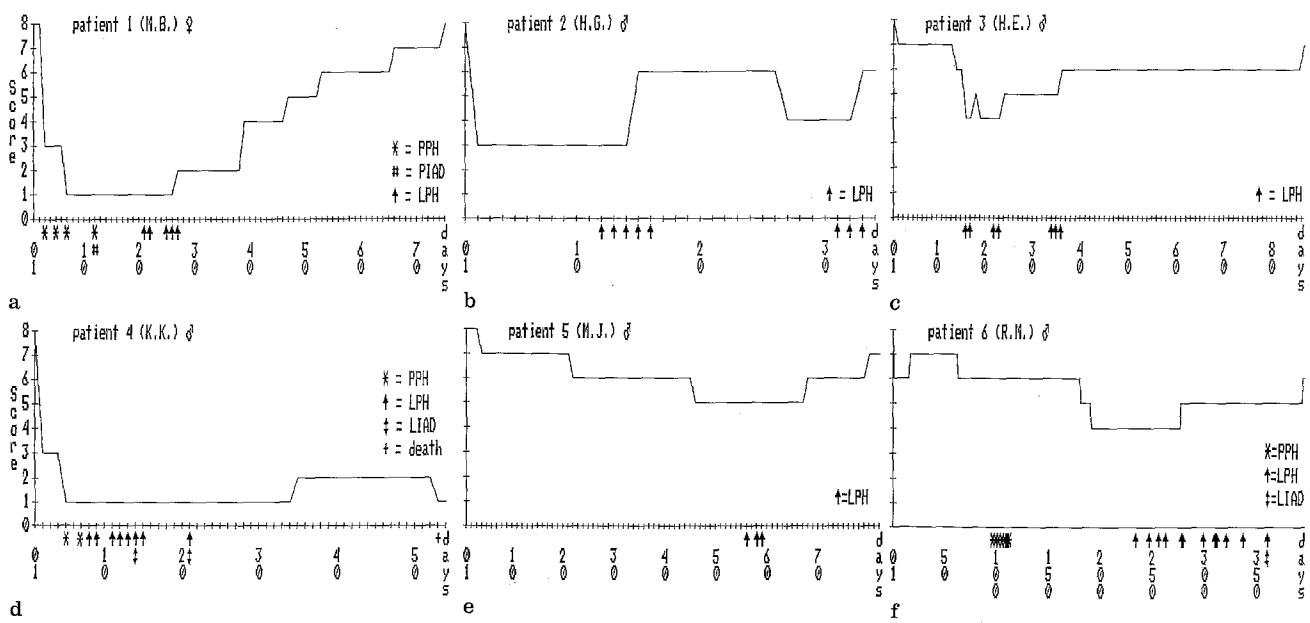

Fig. 4a–f. Duration of the hospitalization in days. Alterations of the clinical score of the patients. Therapeutic trials as PPH = plasmapheresis, PIAD = plasma immunoadsorption, LPH = liquorpheresis, and LIAD = liquor immunoadsorption

and prolonged clinical improvement was seen in patient no 6.

In patient no 5, a neoplasm was suspected, and previous episodes of gastric ulcus were known. Therefore we used no corticosteroids or immunosuppression as malignancy was not excluded. Preexisting pain diminished and muscle strength gradually improved after liquorphereses. Twelve days later walking without support was possible again.

Discussion

It is so far unknown which substances are washed out by plasmapheresis in GBS [4, 14]. Experimental allergic neuritis (EAN) is a well established model for acute GBS [17] in which the cell mediated immune responses predominate [18]. Suppression both of T-cells and of macrophage functions decreases its severity [10]. These cells regulate their activity by secretion of interleukines [12]. In GBS, activated complement fractions are also elevated [9, 15]. Judging from the results of experimental therapy in EAN, filtration of humoral constituents is pathophysiologically important for effective treatment [17].

A reduction of interleukines, immunoglobulins, proteases and complement factors is to be expected by liquorpheresis. Although the protein content of CSF rose again after liquorpheresis treatment, symptoms improved. The interpretation is difficult. Possibly the secondary increase of CSF protein is due exclusively to plasma protein leakage, whereas pathological factors sustaining the inflammatory process are removed from the CSF or diluted beyond effective concentrations. Alternatively, a decrease in the number of intrathecal lymphocytes or macrophages could be important. Close temporal association of liquorpheresis and the clinical improvement strongly suggests a causal relation. In addition, alterations of Na^+ currents in human myoballs, voltage clamped, by CSF of GBS patients (but not in control series) may indicate effects on sodium channels [3].

The time of hospitalization (72 days) of the artificially ventilated patient (no. 1) was relatively short considering the severity of the neurological disturbances. Data of the Guillain-Barré syndrome Study Group show a median of 169 days of clinical treatment time without the use of plasma exchange in patients with respiratory insufficiency. After plasma exchange, the corresponding median was 97 days [8]. Compared with these data we postulate a specific effect of liquorpheresis.

In our small number of patients, liquorpheresis appeared to accelerate the remission of polyradiculoneuritis, and to shorten the time of in-patient care and to reduce residual neurological damage. Controlled studies with larger numbers of patients are necessary to confirm these findings.

References

1. Besser R, Pfeifer B, Weilemann LS, Hopf HC (1986) Plasmapherese beim Guillain-Barré Syndrom. Med Klin 12:409–413
2. Brettle RP, Gross M, Legg NJ, Lockwood M, Pallis C (1978) Treatment of acute polyneuropathy by plasma exchange. Lancet II:1100
3. Brinkmeier H, Wollinsky KH, Rüdel R, Hülser P-J: unpublished data
4. Dyck PJ, Daube J, O'Brien P, Pineda A, Low PA, Windebank AJ, Swanson C (1986) Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med 314:461–465
5. Ferner R, Barnett M, Hughes RAC (1987) Management of Guillain-Barré syndrome. Br J Hosp Med 12:525–530
6. Gross MLP, Thomas PK (1981) The treatment of chronic relapsing and chronic progressive idiopathic inflammatory polyneuropathy by plasma exchange. J Neurol Sci 52:69–78
7. Gruener G, Bosch EP, Strauss RG, Klugmann M, Kimura J (1987) Prediction of early beneficial exchange in Guillain-Barré syndrome. Arch Neurol 44:295–298
8. Guillain-Barré syndrome Study Group (1985) Plasmapheresis and acute Guillain-Barré syndrome. Neurology 35:1096–1104
9. Hartung H-P, Schwenke CH, Bitter-Suermann D, Toyka K (1987) Guillain-Barré syndrome: activated complement components C3a and C5a in CSF. Neurology 37:1006–1009
10. Hughes, RAC (1989) Immunotherapy in neurology. Curr Opin Neurol Neurosurg 2:186–190
11. Levy RL, Newkirk R, Ochoa J (1979) Treatment of chronic relapsing Guillain-Barré syndrome by plasma exchange. Lancet II:259–260
12. Nathan CF (1987) Secretory products of macrophages. J Clin Invest 79:319–326
13. Ostermann PO, Fagius J, Säfwenberg J, Danersund A, Wallin BG, Nordesjö LO (1982) Treatment of the Guillain-Barré syndrome by plasmapheresis. Arch Neurol 39:148–154
14. Pollard JD (1987) A critical review of therapies in acute and chronic inflammatory demyelinating polyneuropathies. Muscle Nerve 10:214–221
15. Sanders ME, Koski CL, Robbins D, Shin ML, Fank MM, Joiner KA (1986) Activated terminal complement in cerebrospinal fluid in Guillain-Barré syndrome and multiple sclerosis. J Immunol 136:4456–4459
15. Server AC, Lefkowith J, Braine H, McKhan GM (1979) Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. Ann Neurol 6:258–261
17. Wiethölter H (1989) Verlaufsformen der experimentell- allergischen Neuritis. Elektrophysiologische Untersuchungen und Behandlung durch Plasmaseparation. In: Bauer HJ, Baumgartner G, Davison AN, Gänshirt H, (Eds) Schriftenreihe Neurologie, part 31, Springer Berlin Heidelberg New York Paris Tokyo
18. Wiethölter H, Hülser P-J, Linington C, Meier CH, Wessel K (1988) Electrophysiological follow-up of experimental allergic neuritis, mediated by permanent T-cell line in rats. J Neurol Sci 83:1–14
19. Wollinsky KH, Mehrkens H-H, Hülser P-J, Weindler M, Geiger P, Matzek N, Kornhuber HH (1989) Liquorpherese, Liquorfiltration als neues Therapieverfahren bei der Behandlung eines schweren Guillain-Barré Syndroms. Anaesthesist 38 Supplement 1:630