

Appendix D.—Apheresis in Guillain-Barre Syndrome

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Introduction

Guillain-Barré syndrome (GBS) (65,119,148) is an acute polyneuropathy. It begins in a restricted area of the body, most often distally, and then spreads or ascends to involve many muscle groups. The rate and extent of progression vary widely. Many patients recover spontaneously without life-threatening progression. Some become severely paralyzed within a few days while in others the disease worsens slowly and insidiously over a period of several days or even weeks. The extent of paralysis varies widely. Sensory and autonomic nervous system involvement can also occur. In the most severely involved individuals, control of blood pressure and breathing maybe affected requiring a respirator and intensive care management. Progression of weakness usually ceases less than 4 weeks after onset. Spontaneous recovery usually begins within 2 to 4 weeks after progression stops. Recovery is usually gradual, but abrupt spontaneous recovery has been documented.

With current intensive care management under the most ideal conditions the mortality can be reduced to 5 percent or less. Prognosis for complete recovery is good, with about 85 percent of patients restored to normal function. The remaining usually have only mild residual deficits.

The etiology of GBS remains unknown. Cases have been associated with injection of foreign protein, cat scratches, dog bites, transfusions, and immunizations, including rabies vaccine and the widely publicized association with the 1976 influenza vaccine program.

Rumpl, et al. (119), have summarized the evidence as of 1981 for an immunologic mechanism as follows:

Experimental allergic neuritis has shown striking similarity with the disease in humans. The immune pathogenesis of GBS was further supported by the finding of complement fixing antibodies, of precipitating antibodies against trypsinized white matter extracts and of myelinotoxin serum antibodies of the IgM class in patients with GBS. Cellular hypersensitization to peripheral nervous antigen presented by circulating immunoblasts and lymphocytes supported the role of cellular mechanisms in pathogenesis.

The rationale for the use of plasma exchange (PE) in GBS is based on the presence of serum antibodies which can be removed by PE.

Brettle, et al. (15), first reported the successful use of PE in acute GBS in 1978. An abrupt and dramatic improvement was seen in this case. This report was published shortly after Hughes, et al. (63), reported a poor response to steroids in a controlled clinical trial of acute GBS. With evidence against the use of steroids established in a controlled clinical trial and with evidence of a dramatic improvement with plasma exchange, many centers throughout the world began to experiment with and report their results of PE therapy.

The existing literature includes many case reports and small series of cases in which apheresis or more specifically PE was used in the treatment of acute GBS.

In reviewing this literature one must appreciate several factors repeatedly emphasized by the authors and critics.

1. As an experimental therapy initial use of the therapy was not standardized. The timing, quantity, duration, and type of PE varied considerably. In some patients the therapy was used concurrently with steroid treatment and in others after steroids had failed. Some patients were treated after extended respirator and intensive care therapy while others were treated in an effort to avoid the need for such care.
2. The measures of assessment of outcome also varied enormously. Some investigators reported obvious and at times dramatic clinical improvements while others reported changes in nerve conduction tests and immunological changes which preceded or were unassociated with a clinical response.
3. The reported studies are all case reports without any concurrent control groups, blinding, randomization, or other techniques used in controlled clinical trials.
4. The documentation of adverse effects was not systematic and may have been biased by the tendency to report successful uses of a new therapy.
5. The natural history of acute GBS with its tendency for spontaneous and occasionally abrupt improvement makes the interpretation of therapy related results more difficult.

Despite these difficulties much has been learned from the initial studies and reports on the use of PE in GBS. The following section summarizes the reported evidence on efficacy.

Efficacy

The reported individual cases repeatedly refer to striking or dramatic change which occur within minutes to hours after plasma exchange.

One report (134) stated: "the improvement after the exchanges was so abrupt and striking that it induced us to believe that the plasma exchanges were essentially responsible for this development. Particularly in our case with ventilator insufficiency and bulbar palsy, which worsened day by day, the course of the disease seemed to have been reversed by plasma exchange inducing an immediate amelioration. The response was quicker in those nerves which had deteriorated the latest, which is in accordance with clinical experience in cases of spontaneous recovery."

Other cases of dramatic improvements after plasma exchange includes the following:

Littlewood and Bajada (77) report: "On day 8 of our patient's illness respiratory vital capacity fell to 1.41 and was accomplished by complete ophthalmoplegia and iridoplegia. A dramatic improvement in vital capacity followed the first session and was subsequently maintained." Similarly, Corachan, et al. (27), report a case of: "... dramatic improvement after ... (apheresis) ... " Levy, et al. (76), report that "clinical improvement was dramatic" in a patient with chronic relapsing disease.

Not all investigators have reported success. Cook, et al. (26), reported a series of five patients only one of whom had a "significant clinical improvement." Maisey and Olczak (78) reported two patients who failed to respond to PE. Gross, et al. (45), have argued that Maisey's use of 1.5 liters per day of plasma exchange was "small compared with those used by other operators for the same disease and in other disease processes." They further argue that one would not expect all cases to respond. They write: "Cases of inflammatory polyneuropathy probably constitute a heterogeneous group and it would be surprising if every patient proved to benefit from plasma exchange."

Several larger series have also been recently reported. Ruml, et al. (119), reported eight cases of successful treatment with PE. They report: "Recovery was abrupt in all cases after the first PEs. Improvement was more marked, when ... (apheresis) ... was performed on three successive days with plasma exchanges of 2.0-3.0l each ... Recovery seemed to be delayed in cases when plasma exchanges were reduced to 0.5-1.5l each and were spread over several days or weeks, even when the number of plasma exchanges was increased."

Durward, et al. (33), reported their experience with six cases all of whom improved to some degree after

PE. They conclude "Our experience to date (11 incidents in six patients) is of recovery beginning or accelerating immediately after plasma exchange ... We started exchanges fairly early—usually about one week after onset—and exchanged more than 10—1 on each occasion (except in case 3)."

Dau, et al. (31), report on 13 patients with acute GBS who underwent 2 to 3 weeks of PE with 4 or 5 exchanges of 4 liters. Seven patients, all of whom were still progressing or stable "stopped progressing on the day of the first ... (apheresis) ... and had discernible clinical improvement within 48 hours." Among the other patients two continued progressing, three were already slowly improving and apheresis "did not seem to accelerate recovery." In these patients apheresis was started "relatively late after disease onset." In the last patient there was progressive deterioration. The report concluded that factors associated with a good outcome were:

1. Institution of apheresis early in the course of the illness.
2. Normal evoked muscle action potential.
3. Little electromyographic evidence of denervation.
4. Age less than 50 years.

Schooneman, et al.'s (123), series of 10 patients with acute GBS is the only reported series in which no patients received steroids and in which a control group was attempted. In addition, the authors performed extensive neurological testing before and after each exchange. Respiratory impairment was assessed by clinical examination and blood gas determinations.

In 9 of their 10 cases patients showed improvement within 24 hours after the first exchange. The authors believe that "the progressive phase of the disease was halted." They term their results "spectacular." In comparing their 10 patients to 258 historical control patients with GBS they conclude that apheresis appeared to shorten the duration of paralysis, reduce the need for tracheotomy, and shorten the hospital course. They did not demonstrate reduced mortality since one patient died in each group. They also did not demonstrate or claim that these patients represented comparable study and control groups.

Safety

Plasma exchange carries inherent risks in all patients. Samtleben, et al. (120), reporting on 100 consecutive PE procedures, observed allergic reactions to albumen in 10 percent, hypocalcemic symptoms in 6 percent, and vasovagal reactions in 5 percent. Other side effects have included massive extracorporeal blood clotting, hypercoagulation states with vascular thrombosis, hemorrhagic tendencies, changes in serum lipid

fractions, cardiac arrhythmias, and pulmonary emboli (93).

Rumpl, et al. (119), reported that in their experience with plasma exchange for GBS, cardiovascular problems, coagulation difficulties, and allergic reactions made it necessary to interrupt PE and influenced the amount of exchanged plasma.

Patients with severe GBS may have an unstable autonomic nervous system predisposing them to problems with blood pressure control and cardiac arrhythmias. The need to perform the procedure on respirator dependent patients may further complicate PE.

In light of these considerations Mayr, et al. (81), who have successfully used PEs in GBS, conclude: "The considerable risks and high technical requirements may limit this therapy to the severe course of Guillain-Barré syndrome."

Need for Controlled Clinical Trials

A controlled trial is not a trial of a treatment. It is a trial of a specific means of administering a therapy; thus it requires agreement on the timing, extent, and duration of therapy.

The performance of a controlled clinical trial should be preceded by enough research to establish an agreed upon method for administering the therapy. In addition, before going to the expense of a well-performed controlled clinical trial, it is important that preliminary evidence exists of the effectiveness and additional benefit of the treatment. These two prerequisites to a controlled clinical trial have been adequately fulfilled by the existing literature.

Despite the controversy in the reported literature over the efficacy and safety of PE in GBS, both the advocates and the skeptics appear to agree on the need for controlled clinical trials. A sampling of their comments should demonstrate this point.

Irvine and Tibbles (64) in their report of an apparently successful treatment with exchange transfusions conclude: "In the future it will be important to document failures as well as success to place this treatment in its proper perspective. It is likely that the organization of a prospective controlled trial of this costly form of management will be necessary."

During 1981 a series of letters appeared in the *British Medical Journal* reporting dramatic improvement, evidence of subtle response, and cases without measurable improvement. All three reports agreed on the need for a controlled trial. The group (78) reporting no response wrote: "If anecdotal reports are relied on, publication bias ensures that apparently successful results dominate the literature." The group (62) reporting success

wrote: "... a controlled trial of plasma exchange is necessary in acute inflammatory polyradiculoneuropathy before its value can be assessed. Since patients with this condition begin to improve after a variable time after the onset of symptoms and usually recover completely, it is not surprising that each new treatment has been hailed with enthusiasm on the basis of anecdotal reports." The group (33) reporting subtle responses concurred, stating: "These data only re-emphasize the need for a controlled clinical trial, especially in the early phase, in order to delineate the role of plasma exchange in acute Guillain-Barré syndrome."

In their advocacy of their forthcoming controlled clinical trial Asbury, et al. (10), wrote in the October 1980 issue of *Neurology* that apheresis of "an acutely ill patient with respiratory depression and autonomic instability is not a benign procedure. Until this study is completed anecdotal reports of the efficacy of ... (apheresis) ... in the Guillain-Barre syndrome should be interpreted with caution. At present, it is not possible to state the therapeutic role that ... (apheresis) ... plays for this disease,"

Controlled Clinical Trials in Progress

In December 1980, the National Institute of Neurological and Communicative Disorders and Stroke funded a 3-year multiple site cooperative study of apheresis treatment of acute GBS (87).

The primary study question is: Does apheresis effect a significant beneficial change in the early course of severely ill patients with GBS? Secondary study questions include the following:

1. Are there clinical, epidemiologic, laboratory, or electrodiagnostic factors associated with a good outcome of GBS? If so, how does apheresis interact with these factors?
2. Is there a subgroup of patients with GBS for whom apheresis can be expected to be of value and a subgroup for whom it cannot?
3. Can apheresis reduce the incidence of long-term complications (assessed at 6 months) in the 15 to 20 percent of GBS patients destined to have some lasting deficits?

The study uses generally accepted criteria for the diagnosis of GBS. Patients must be within 30 days of onset of definitive neuropathic symptoms. They must require a walker or support to walk 5 meters or be more severely affected. Steroid treatment is not given to study patients. The quantity and timing of the PE are consistent with that reported for successful uses of PE in GBS.

The study protocol provides standard methods for assuring randomization, informed consent, termination, monitoring of followup, and statistical analysis.

The study is designed to include about 240 patients. This number is adequate to provide an 80-percent chance of demonstrating a statistically significant improvement if apheresis actually provides a 50-percent improvement over conventional therapy. As of July 1, 1982, 102 patients had been enrolled in the study.

An interim analysis of the data is planned when approximately 120 patients have been entered into the study. The interim analysis is designed to determine whether the study should continue. This analysis will consider the following three possibilities:

1. The evidence is overwhelming that the apheresis patients are doing better, and if the study were to continue with little or no advantage to the exchange protocol over the second half of the study, a statistically significant difference would still exist.
2. the exchange protocol patients are doing worse or no better than the other patients and continuation of the study could not, even with an extreme reverse of results in the second half, demonstrate a beneficial effect of apheresis.
3. Neither extreme exists.

The endpoints considered in this analysis will be measures of clinical improvement 4 weeks after entry into the study as well as time spent on a respirator. If the interim report reaches conclusion 1 or 2, the study will be stopped and presumably the results released and reported. Otherwise the study will continue and the results presumably will not be released by the National Institutes of Health (NIH).

The NIH study appears to be adequately designed to answer the basic questions regarding efficacy of apheresis. The results should largely determine whether evidence exists for moving PE from an experimental status to that of a conventional therapy for acute GBS.

A second randomized controlled clinical trial is currently underway in Great Britain (87). This study also includes patients who require support to walk 5 meters or who are more severely affected. The findings on the first 19 randomized patients were reported in May 1982. A "decided trend in favor of plasma exchange was noted at 4 weeks after randomization which did not reach statistical significance."

NIH will not currently release preliminary results of the American study. The interim analysis should be completed by early 1983, but unless the results of the interim analysis clearly answer the efficacy question, a full report may not be available until 1984.

Conclusions

1. Case reports and small-scale, mostly uncontrolled trials provided suggestive evidence that plasma exchange may be efficacious for some patients with acute GBS.
2. Because of the low mortality and good prognosis for most patients with Guillain-Barré syndrome, the safety of the procedure and indications for its use should be delineated prior to nonexperimental use of plasma exchange in GBS.
3. The conditions for use of plasma exchange in acute Guillain-Barré syndrome have been sufficiently standardized to enable a controlled clinical trial of the procedure.
4. The potential cost saving and potential for shortened disability make well-designed controlled studies of this therapy important.
5. Controlled studies of the efficacy, safety, and indications for plasma exchange in acute GBS are currently in progress. These studies should be adequate to provide data which address the essential clinical questions. Until the results of these studies are available, the use of plasma exchange in GBS should be considered an experimental procedure.