

# The Effect of Plasmapheresis on Post-Thymectomy Ocular Dysfunction

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**SUMMARY:** *Five myasthenia gravis patients with post-thymectomy residual ocular signs were treated with plasmapheresis. Despite a significant reduction in AChR antibody titer, there was no clinical improvement. Subsequently, there was a dramatic response to prednisone. The AChR antibody titer did not correlate with the clinical state of the individual patient. It is suggested that plasmapheresis may operate by removing a thymic factor and that prednisone acts by a different mechanism.*

**RÉSUMÉ:** *Nous avons traité cinq patients souffrant de myasthénie grave, mais avec signes oculaires résiduels après thymectomie, avec plasmaphérèse. Malgré une diminution significative du titre des anticorps au récepteur cholinergique (AChR), il n'y eut aucune amélioration clinique. Par la suite il y eut réponse dramatique à la prednisone. Le titre AChR ne correspond en rien à l'état clinique d'un patient donné. Il est suggéré que la plasmaphérèse agit en enlevant le facteur thymique et que la prednisone agit par un mécanisme différent.*

## INTRODUCTION

Plasmapheresis has recently been employed in the treatment of myasthenia gravis (Behan et al., 1979; Dau et al., 1977; Pinching et al., 1976). It has generally been reserved for more severely affected patients who have failed to respond to other forms of therapy. Improvement is usually temporary and therefore it has been combined with either steroids and/or immunosuppressive agents in the attempt to obtain long term benefit.

Circulating acetylcholine receptor (AChR) antibodies have been found in the serum of 90% patients with myasthenia gravis (Lindstrom et al., 1976). They have been implicated in the pathogenesis of this disorder by passive transfer studies (Toyka et al., 1977), in vitro degradation of receptors in myotube tissue culture (Kao & Drachman, 1977), and by a myasthenic syndrome induced by monoclonal antibody directed to the AChR receptor (Lennon & Lambert, 1980).

Plasmapheresis is presumed to operate by removing a circulating humoral factor which is essential to the pathogenesis of myasthenia gravis (Newsom-Davis et al., 1978). Clinical improvement has been reported to be associated with a reduction in the AChR antibody titer suggesting this may be the specific circulating factor (Newsom-Davis, et al., 1979).

In our clinic, we have used plasmapheresis to prepare myasthenic patients for thymectomy. Anticholinesterase agents and steroids are avoided. If patients have already been started on medication prior to referral, attempts are made to discontinue them during plasmapheresis (Wechsler & Olanow, In Press). Thymectomy is then performed by a sternal splitting approach. We attempt a total thymectomy by removing all mediastinal

fat and searching carefully for any ectopic foci of thymic tissue (Wechsler & Olanow, 1980). Post-operative medications are not employed, if possible. Clinical follow-up studies with serial AChR antibody levels have suggested that a thymic factor may be essential in the pathogenesis of myasthenia gravis (Olanow & Roses, in press (c)). We have failed to demonstrate a direct correlation between the antibody titer and the clinical course of individual patients (Roses et al., In Press). Furthermore, patients who have undergone thymectomy with no other therapy have shown dramatic improvement, but continue to maintain elevated AChR antibody levels (Olanow et al. (a), In Press; Olanow et al. (b), In Press).

While the majority of our patients became asymptomatic following early thymectomy, some had residual ocular dysfunction. Prior to the institution of any other medical therapy, plasmapheresis was performed in 5 patients with residual ocular dysfunction to determine whether a reduction in AChR antibody titer in this population would improve these signs. We report the failure of plasmapheresis to influence residual post-thymectomy dysfunction in any of these patients despite significant AChR antibody reduction.

## MATERIAL AND METHODS

Five myasthenia gravis patients who had undergone previous thymectomy were entered into the study (Table I). Diagnosis was based on clinical, electrical, pharmacological and serological criteria. Thymectomy was performed within 6 months of onset of symptoms. Each patient improved but had some persistent ocular dysfunction. Each was responsive to edrophonium chloride and was receiving no medication.

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TABLE I

*Characteristics of Patients with Post-Thymectomy Ocular Dysfunction*

Patients	Age	Pre-Op* Grade	Post-Op= Grade	Interval Thymectomy-Plasmapheresis
A	44	IIa	I	13 mos.
B	63	IIa	I	30 mos.
C	32	IIa	I	26 mos.
D	58	IIa	I	5 mos.
E	61	IIc	I	31 mos.

\*Graded according to Osserman (1972).

Plasmapheresis, using an IBM Cell Separator, was carried out 5 to 31 months following thymectomy. Three to 4 liters of plasma were removed per exchange and replaced isovolemically with 2-3% albumin in Ringer's lactate. Four to 11 procedures were performed on each patient. AChR antibody titers were serially measured using a radioimmunoassay technique with human antigen (McAdams & Roses, 1980). AChR antibody titers were elevated in each case ranging from 0.194 to 14.8 nM (0.1 nM is diagnostic and greater than 1 nM is highly abnormal in our laboratory).

Following plasmapheresis, no medications were introduced during the subsequent 3 weeks. Thereafter, prednisone therapy in gradually increasing doses was begun. Ocular dysfunction was quantitated using a clinical grading system illustrated in Table II.

RESULTS

The results are summarized in Table

III. Plasmapheresis was well tolerated by all patients. A significant but temporary reduction in AChR antibody titer was obtained in all patients ranging from 58 to 100%. No significant improvement in ocular function was demonstrated in any patient despite a drop in antibody titer which exceeded 90% in 3 of the patients.

Prednisone therapy, by contrast, resulted in striking clinical improvement in all patients. Three of the 5 patients became asymptomatic and had normal eye examinations. Improvement occurred within 2 to 8 weeks following the institution of therapy. A comparison of the effect of plasmapheresis and prednisone on post-thymectomy residual ocular dysfunction is illustrated in Figure I. Figure II represents the serial AChR antibody levels and the clinical response of a typical patient treated with plasmapheresis and subsequently prednisone. Clinical improvement was not associated with a reduction in the

TABLE II

*Clinical Scoring System for Grading Ocular Dysfunction*

Score	Test
0 Normal	Ptosis — Left Eye
1 Mild Dysfunction	Ptosis — Right Eye
2 Moderate Dysfunction	External Ocular Muscle Function
3 Severe Dysfunction	Orbicularis Ocular Function

Score is determined by physical examination for each of the tests described above. Maximal score of three of each of the four tests would result in a clinical grade of 12. Less severe involvement in any of the tests would lower the grade appropriately.

AChR antibody titer, and a reduction in the AChR antibody titer did not result in clinical improvement.

DISCUSSION

Five myasthenia gravis patients with residual ocular features following thymectomy failed to respond to plasmapheresis. These patients were receiving no other medical therapy. Subsequently, relatively small doses of prednisone resulted in striking ocular improvement in each patient.

Differences in the technique and timing of thymectomy, and in the management of drugs during the pre- and post-thymectomy stages, make it difficult to directly compare the effect of plasmapheresis on patients described in the literature with those we report who have been treated only with early thymectomy. Most studies of plasmapheresis have been performed on patients receiving concomitant steroids and/or immunosuppressive agents. While these medications cloud

TABLE III

*Results of Treatment with Plasmapheresis and Steroids*

Patients	No. Runs of P.P.	Pre P.P. ACH R AB Titre (nM)	% Drop IN ACH R AB Titre	Max. Steroid Dose	Pre P.P. Grade*	Post P.P. Clinical Grade*	Post Steroid Clinical Grade*
I	4	0.43	80%	30/30	(6)	(6)	(1)
II	5	1.87	92%	30/15	(4)	(4)	(0)
III	5	0.27	100%	30/00	(5)	(5)	(0)
IV	4	0.20	100%	20/20	(5)	(5)	(0)
V	11	14.80	58%	40/00	(5)	(5)	(2)

\*Grading of ocular dysfunction as described in Table II.

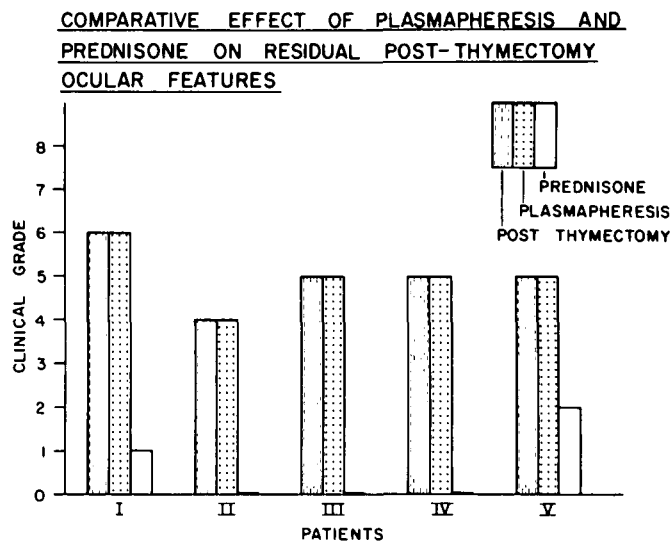


Figure 1 — A comparison of the effects of plasmapheresis and prednisone on residual post-thymectomy ocular dysfunction. Ocular dysfunction is scored according to Table II.

an evaluation of the role of plasmapheresis, it seems likely that improvement is due to plasmapheresis, since when medications are employed alone benefit is relatively delayed (Newsom-Davis, et al., 1979). Many of the reported patients have also had thymectomies. They are, however, severely affected with myasthenia gravis and it is possible that the thymic influence was not totally eradicated, due to incomplete or delayed thymectomy. This might occur for the severity and progression of symptoms despite thymectomy and the subsequent beneficial effect of plasmapheresis.

It is questioned whether plasmapheresis acts by removal of the AChR antibody. Despite a dramatic reduction in AChR antibody titer induced by plasmapheresis, no clinical improvement was detected in our patients. The possibility that there are subsets of antibodies to the AChR which are not currently detected, seems unlikely in view of the dramatic response to plasmapheresis we observe when preparing our patients for thymectomy. The possibility that the antibody may bind more tightly to the AChR of eye muscles and thus be less responsive to plasmapheresis is con-

sidered. More prolonged plasmapheresis theoretically may have led to some benefit. This also seems unlikely, however, since no such delay is noted in the response of the ocular features of myasthenia gravis to plasmapheresis prior to thymectomy.

The failure of a plasmapheresis induced reduction in the AChR antibody titer to improve *post-thymectomy* ocular dysfunction suggests that plasmapheresis may operate by the removal of other factor(s), independent of or in addition to the AChR antibody. The beneficial effect of plasmapheresis *prior to thymectomy* suggests that these factor(s) may be of thymic origin. It is known that thymic-derived T-lymphocytes can regulate the intensity of virtually all immune reactions (Reinhez & Schlossman, 1980). This study casts further doubt on the AChR antibody being the sole causative basis of myasthenia gravis and suggests that factors of thymic origin are of critical importance in the development of clinical symptoms. The mechanism by which prednisone operates is unknown but appears to be different than plasmapheresis.

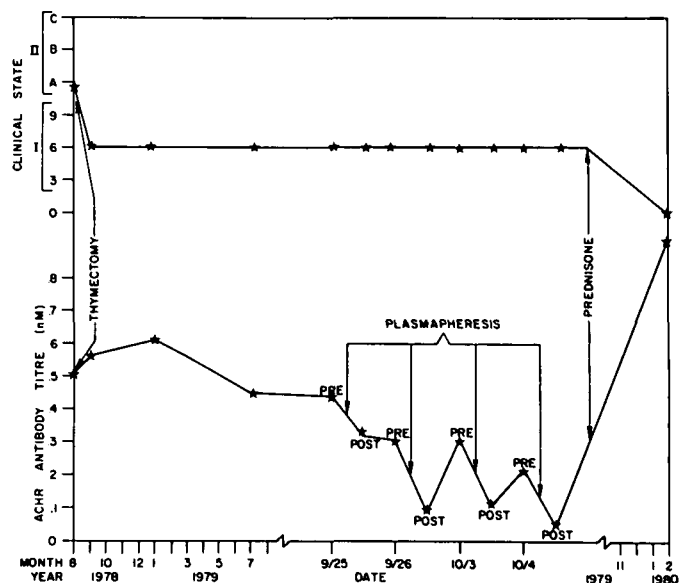


Figure 2 — Effects of thymectomy, plasmapheresis and prednisone on the clinical course and AChR antibody levels of a representative patient. The clinical state is classified according to Osserman (1972). Ocular dysfunction (Grade I) is further subdivided according to a scoring system outlined in Table II.

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