III CLINICAL APPLICATIONS: NEUROMUSCULAR DISEASES

The Guillain-Barré syndrome: plasma exchange or immunoglobulins intravenously

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The Guillain-Barré syndrome (GBS) is an immune mediated subacute polyneuropathy. The predominant pathology is demyelination resulting in conduction block. The nadir is usually reached within two weeks but certainly by four weeks.¹ The majority of the patients become bedridden and a substantial proportion (15–30%) need artificial ventilation.

The prognosis for GBS was originally recorded as good, but it is now known that as many as 5% may die and 15% may have persistent functional deficits.¹³ In a severely afflicted group of 75 patients that required prolonged artificial respiration only one third made a full recovery.⁴ The muscular endurance of patients who seem to be cured may be limited for many years.³ In general, improvement may continue for at least two years before a plateau is reached.

In a number of studies prognostic factors have been identified that may help to predict outcome.^{7 10–12 16} In general, they show that a severe, fulminant course increases the risk of poor outcome. Severity has been indicated by: duration less than four days before becoming bed bound, admission within seven days of onset, needing artificial respiration, prolonged plateau phase or—as a laboratory marker of severe damage of nerves—low compound muscle action potential (CMAP) amplitudes. In addition, age has been shown to have a strong prognostic significance in the majority of studies. The patients in the North American trial who were randomised after day seven were 30 years of age, did not need artificial respiration, received plasma exchange and had CMAPs above 20% of normal and were all independently ambulant at six months. In contrast if patients were 60 years of age or more and had all the other negative factors, the proportion of patients independently ambulant at six months was only 19%.¹⁰ Similar results were obtained in the UK.¹⁶ In our own studies we distinguished between biological prognostic factors and factors related to the clinical condition, such as, EMG parameters and clinical deficit. Biological factors such as age above 50 years, Campylobacter infection and GM1 antibodies were related to a more severe course. If these factors are present only 10% of the patients may be able to walk two months after onset; if absent 75% will be able to walk.¹⁴ This analysis reinforces the importance of

these biological factors in the disease. The usually severe course of the disease and the unsatisfactory outcome in at least 20% of the patients has stimulated a search for effective specific therapy.

Specific treatment

In recent years attention has been focused on specific treatment. However, supportive treatment is at present still the mainstay in the care of patients with Guillain-Barré syndrome. The problems that should be anticipated are listed in the table.

The first specific treatment that has proved to be effective has been plasma exchange (PE) if applied early.^{6 8} Morbidity is decreased and outcome improved. Moreover, time spent on ventilation is shortened. PE is, however, a cumbersome procedure and many problems may occur.² High dose immunoglobulins, intravenously given (IVIg) are much more practical. Recently we published the results of a bias controlled randomised study in 150 GBS patients.¹⁵ Three patients were excluded, 74 received 2 g IVIg per kg in five days (Gammagard, Baxter) and 73 were plasma exchanged. In the plasma exchange group 34% showed functional improvement, in the IVIg group 53%, the 19% difference, was statistically significant ($p = 0.024$). Also, secondary outcome criteria were in favour of IVIg: time until independent locomotion, time until functional improvement, rate of multiple complications and proportion of patients needing artificial respiration early in the disease. As the trial was aimed at proving a similar effect of IVIg compared with PE we concluded that IVIg is at least as effective as PE, but may be superior.

As the two treatments – IVIg and PE – are used world wide, neurologists may be confronted with a new dilemma: what to do if a

Guillain-Barré syndrome

The following need monitoring and supportive care:

- respiratory complications
- thromboembolic complications
- cardiovascular instability
- compression neuropathies
- pain, primarily due to the neuropathy and secondary to lying paralysed
- contractures
- urinary tract infections
- obstipation/ileus
- decubitus
- psychological decompensation

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patient deteriorates after starting one of the two treatments. About a quarter of the IVIg treated patients and a third of the PE treated patients will continue to deteriorate in the first two weeks during treatment if the treatment is started early, both with PE and IVIg (unpublished observations). It raises the important question of how to evaluate the treatment effect in the individual patient.

The size of the clinical trials needed to demonstrate an effect in Guillain-Barré syndrome gives a clear hint that it is very difficult to assess in the individual patient what the effect of treatment is. This is caused by the variability of the natural course in Guillain-Barré patients. There are four possible clinical situations: 1) During and after treatment a patient continues to deteriorate. In which case it would be impossible to assess whether without treatment, deterioration would have been worse; in other words treatment may be effective in slowing down the progression. In this situation one may consider changing the therapy. Two points are important here: the effect of treatment may take up to a week (as in the treatment for chronic inflammatory polyneuropathy) and by that time the progressive phase may be over. We have learned from the North American plasma exchange trial, that starting the treatment in the third week of the disease did not lead to continued benefit.⁸ The appropriate time therefore to start further treatment has usually passed when the initial treatment has been sufficiently evaluated. 2) In our study no factors predict a better response to IVIg or PE; any change between the two treatments must be empirical. Furthermore, any combination of the two treatments has no scientific basis. It is not known whether they may act synergistically or antagonistically.

The third and fourth possibilities are that a patient stabilises or improves during or after treatment. Here also it is difficult to assess the benefit of the treatment.

Finally, a situation exists, in which a patient stabilises or improves during treatment, but deteriorates again after a therapy free interval of one or more weeks. This "treatment related clinical fluctuation" is caused by a temporary beneficial effect of the treatment and it occurs both with IVIg or with PE. A similar second treatment, if indicated by the clinical severity, will show a further improvement.⁹

Based on these considerations some practical treatment guidelines may be proposed: 1) Give a full dose of IVIg or alternatively a full course of PE; 2) Withdraw patients with "treatment related clinical fluctuations" with a similar treatment; 3) At present there is no scientific place for switching treatment modality; 4) Wait for further scientific information concerning improvement of therapy.

Future treatment perspectives

IVIg treatment has not only practical advantages for the patient and the hospital, but it also has the advantage of other medications being given simultaneously. In other words, it

lacks the disadvantage of PE, where co-medication is removed jointly with the unknown adverse disease factors. A first step in our Dutch study group was to explore whether the combination of IVIg and high-dose methylprednisolone (MP-IVIg) might have synergistic effects.⁵ Twenty five patients have been treated with 500 mg methylprednisolone and 0.4 g/kg IVIg during five days. These patients were followed up using a similar protocol as in the previous IVIg/PE trial. Comparing these 25 patients with the historical 74 IVIg treated patients resulted in significant differences in favour of combined treatment. Functional improvement after four weeks occurred in 76% of the MP-IVIg group and in 53% in the IVIg group ($p = 0.04$). The time until independent locomotion was achieved was also better in the MP-IVIg group, but not significant ($p = 0.10$).

These very promising results stress the advantage of IVIg treatment and prompted a randomised study to compare MP-IVIg with IVIg more formally. This study started in 1994.

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