

SHORT REPORT

Risk factors for treatment related clinical fluctuations in Guillain-Barré syndrome

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Abstract

The risk factors for treatment related clinical fluctuations, relapses occurring after initial therapeutic induced stabilisation or improvement, were evaluated in a group of 172 patients with Guillain-Barré syndrome. Clinical, laboratory, and electrodiagnostic features of all 16 patients with Guillain-Barré syndrome with treatment related fluctuations, of whom 13 were retreated, were compared with those who did not have fluctuations. No significant differences were found between patients with Guillain-Barré syndrome treated with plasma exchange and patients treated with intravenous immune globulins either alone or in combination with high dose methylprednisolone. None of the patients with Guillain-Barré syndrome with preceding gastrointestinal illness, initial predominant distal weakness, acute motor neuropathy, or anti-GM1 antibodies showed treatment related fluctuations. On the other hand patients with fluctuations showed a trend to have the fluctuations after a protracted disease course. It is therefore suggested that treatment related clinical fluctuations are due to a more prolonged immune attack. There is no indication that the fluctuations are related to treatment modality. The results of this study may help the neurologist to identify patients with Guillain-Barré syndrome who are at risk for treatment related fluctuations.

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The effect of plasma exchange and intravenous immune globulins (IVIg) has been established in the treatment of Guillain-Barré syndrome.¹⁻³ One of the most important prognostic factors for the outcome of patients with Guillain-Barré syndrome is the severity of muscle weakness.⁴⁻⁵ In an effort to improve this outcome neurologists may be tempted to apply plasma exchange or IVIg at an earlier stage of the disease—for example, when the patients are still able to walk

independently.⁶ However, early relapses, treatment related fluctuations, occur in 8%-10% of the treated patients.⁷⁻⁹ It has been stated that especially patients with Guillain-Barré syndrome who are treated early in the course of their disease may be at risk for these relapses.⁸ The aim of this study involving 172 patients with Guillain-Barré syndrome was to identify risk factors for the occurrence of treatment related fluctuations.

Methods

All patients participated in either the Dutch Guillain-Barré syndrome trial, a multicentre clinical trial comparing the effect of IVIg and plasma exchange,³ or in the Dutch IVIg-methylprednisolone pilot study.¹⁰ The background, design, and results of these two studies have been published elsewhere.^{3,10} Briefly, 172 consecutive patients, fulfilling the criteria for Guillain-Barré syndrome, unable to walk 10 m independently, and within two weeks of the onset of weakness were included in these studies.

The motor function at randomisation and during follow up was assessed using a seven point functional scale (F score)³ and Medical Research Council sumscore (MRC sumscore) for six bilateral muscle groups.¹¹

At the time of randomisation the following features were determined: age, sex, antecedent episodes in the four weeks before onset of weakness, a gastrointestinal or upper respiratory tract infection, time from onset of weakness until randomisation, distribution of muscle weakness, F score, MRC sumscore, presence of sensory loss, and cranial nerve deficits. At study entry and during six months of follow up neurological examinations were performed. To assess the distribution of muscle weakness on entry to the study, the strength of some proximal and distal muscles was assessed according to the MRC sumscore as described earlier.¹²

Severity of sensory loss at the time of randomisation and during follow up was classified according to the method described elsewhere.¹³ For the 25 patients who participated in the IVIg-methylprednisolone pilot study no follow up data of the sensory system were available as this was not tested prospectively.

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Table 1 The clinical and laboratory data of patients with Guillain-Barré syndrome (GBS) with and without fluctuations related to treatment

Features	GBS patients without fluctuations (n=156)	GBS patients with fluctuations (n=16)	p Value*
Clinical characteristics			
Time from onset of weakness to treatment (in days, mean (95% CI))	5.6 (5.0 -6.2)	5.4 (3.6 -7.3)	NS†
Time until nadir (in days, mean (95% CI))	9.0 (8.2 - 9.7)	11 (8.4 -13.6)	0.08†
Predominant weakness (n (%)):			
Distal	59 (37)	0 (0)	0.003
Proximal	36 (23)	7 (44)	0.06
Global	47 (30)	8 (50)	0.09
Mixed	9 (6)	1 (6)	NS
MRC sumscore at entry (mean (95% CI))	36 (34-38)	40 (34-45)	NS†
MRC sumscore at nadir (mean (95% CI))	28 (26 -31)	31 (22-40)	NS†
Motor GBS group (n (%))	27/147 (17)	0 (0)	0.06
Antecedent infections (n (%)):			
URTI	61/155 (39)	7/14 (50)	NS
Gastrointestinal tract	29 (19)	0 (0)	0.06
Laboratory findings (n (%)):			
Positive <i>C jejuni</i> serology	45/140 (32)‡	4/14 (29)‡	NS
Positive CMV serology	18/148 (12)‡	4/15 (27)‡	0.1
Anti-GM1 antibodies	31/140 (22)‡	0/14 (0) ‡	0.05
Electrodiagnostic characteristics (mean (95% CI)):			
SNAP ulnar nerve (V entry):			
Week 1	12 (9-14)	8 (1-14)	NS
Week 4	14 (8-13)	4 (0-12)	0.06
SNAP median nerve (V entry):			
Week 1	11 (8-14)	6 (0-16)	0.006
Week 4	13 (10-16)	7 (0-16)	0.06
Week 1	12 (8-15)	4 (0-10)	0.02
Week 4	12 (8-15)	3 (0-9)	0.004

* p Values were derived from the χ^2 test, two tailed unless indicated otherwise.

† Wilcoxon-Mann-Whitney test, two tailed.

‡ Number tested.

F \geq 3 = not able to walk 10 m without support or worse; MRC = Medical Research Council score; motor GBS = patients with the Guillain-Barré syndrome, who did not have sensory loss on clinical examination during a follow up period of six months (acute motor neuropathy); URTI= upper respiratory tract infection; CMV = cytomegalovirus; *C jejuni* = *Campylobacter jejuni*; SNAP= sensory nerve action potential.

A treatment related fluctuation was defined as⁹:

(1) improvement in functional score of at least one grade or improvement in MRC sumscore of more than five points within four weeks, followed by a decrease in the MRC sumscore of more than five points or a worsening in functional score of at least one grade or:

(2) stabilisation of the clinical course for more than one week followed by a worsening of more than five points on the MRC sumscore or at least one grade of the functional score.

Campylobacter jejuni (*C jejuni*) and cytomegalovirus serology, and anti-GM1 antibody assays were performed as described earlier.¹³

Electrodiagnostic testing (EMG) was performed using standardised conventional techniques. The details of testing have been reported previously.¹⁴

Results

Treatment related clinical fluctuations were found in 16 (9%) of the 172 patients. Five patients were treated with plasma exchange (5/73, 7%), nine with IVIg (9/74, 12%), and two with IVIg-methylprednisolone (2/25, 8%). These differences between the treatment groups were not significant (p=0.53). The treating neurologists regarded the worsening in three patients as "mild" (although the worsening fulfilled the criteria) and these patients were therefore not re-treated. Thirteen (7%) of the 172 received a second treatment; four (5%) in the plasma exchange group, seven (9%) in the IVIg group, and two (8%) in the IVIg-methylprednisolone treated group (p=0.66). The second treatment was a repetition of either plasma exchange or IVIg.

The clinical, laboratory, and electrodiagnostic characteristics of the patients with treat-

ment related fluctuations were compared with the group of patients with Guillain-Barré syndrome without fluctuations. The table summarises the main results.

Age, sex, time of onset of muscle weakness until start of treatment, and presence of cranial nerve deficits at the time of start of treatment were not related to an increased incidence of treatment related fluctuations. At the start of treatment and during follow up there were no significant differences between the two groups in severity of muscle weakness, as assessed by the F score and MRC sumscore. The time until the nadir tended to be longer for the patients with fluctuations in comparison with the other patients (table). Interestingly, none of the patients with treatment fluctuations had predominant distal weakness, which was the most important factor for not getting fluctuations. Furthermore, treatment related fluctuations did not occur in the patients without sensory signs (the acute motor neuropathy group). This clinical observation was confirmed by the EMG data, which showed significant lower sensory nerve action potential amplitudes in the treatment related fluctuation group (table).

For antecedent infections, none of the patients with fluctuations had preceding diarrhoea; this was not related to a *C jejuni* infection as this occurred in similar proportions in both groups. On the other hand more patients with fluctuations tended to have a cytomegalovirus infection compared with the patients without fluctuations.

The EMG data did not show significant differences in mean compound muscle action potentials after distal stimulation of the ulnar or median nerve, ulnar and median motor and sensory conduction velocities, percentage of

conduction blocks, and distal motor latencies between the groups.

Discussion

We studied the risk factors for treatment related fluctuations in a group of 172 patients with Guillain-Barré syndrome treated with either plasma exchange, IVIg, or IVIg-methylprednisolone with the assumption that the nature of these fluctuations is the same for the applied immunomodulating therapies. Sixteen of 172 patients, five in the plasma exchange group, nine in the IVIg group, and two in the IVIg-methylprednisolone group showed fluctuations. This study gives more insight into the factors causing susceptibility to treatment related fluctuations. Those with preceding diarrhoea, distal onset of muscle weakness, a clinical pattern of acute motor neuropathy, or presence of anti-GM1 antibodies are not at risk. The data need to be carefully interpreted because of the small size of the treatment related fluctuation group and the many variables tested which can lead to false positive findings.

In our study treatment related fluctuations did not occur in the patients with Guillain-Barré syndrome with an acute motor neuropathy. The clinical and laboratory characteristics of patients with Guillain-Barré syndrome with acute motor neuropathy characterised by a rapid onset of weakness, an early reaching of nadir, a distal dominant weakness, lack of cranial nerve involvement, a preceding gastrointestinal illness caused by a recent *C jejuni* infection, and a presence of high titres of anti-GM1 antibodies have been described before.¹² Our present results give more substantial evidence that different pathophysiological mechanisms are involved in the Guillain-Barré syndrome subgroups we defined and that they are of therapeutic importance.^{12,13}

Insight into risk factors for fluctuations may lead to a better understanding of the underlying mechanisms involved. Theoretically, treatment related fluctuations may occur under two circumstances. Firstly, relapses after therapy may take place when treatment is applied early in the disease course. At that time the "disease process" is still very active and treatment arrests the progression only temporarily. Worsening of weakness occurs shortly after stopping therapy and theoretically treatment related fluctuations could have been prevented by applying therapy for a longer period. Secondly, relapses after treatment may occur when there is an ongoing immune (re)activation resulting in a more protracted clinical course. Factors which triggered the immune mediated demyelination more chronically activate or after a latent phase, induced by therapy, reactivate the immune system. Under these circumstances there may be a relatively long interval between the cessation of treatment and the occurrence of a relapse.

In our study, rapid onset or a relative short period of progression seems not to be a risk

factor for the occurrence of fluctuations, which argues against the first hypothesis and is in disagreement with the suggestion made by Ropper *et al* that early treatment may result in an increased risk of relapses.⁸ The fluctuations occurred more often in those who after start of treatment showed a more protracted disease process; the time until nadir tended to be longer in the patients with fluctuations. Also the time of onset of worsening was usually more than 10 days after the start of therapy.⁹ These findings argue in favour of the second theory. Moreover, Osterman *et al* studying relapses after plasma exchange reported a similar finding.⁷

Our findings are of importance for the patients with an acute motor neuropathy, as these patients may show a rapid progression after onset of muscle weakness and early treatment may improve outcome in these patients. Further studies are needed to resolve the underlying mechanisms involved in the patients with Guillain-Barré syndrome with fluctuations.

The participants of the Dutch Guillain-Barré syndrome trial have been listed elsewhere.⁵

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