Intravenous immunoglobulin therapy for Miller Fisher syndrome

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Abstract—We analyzed clinical recovery of 92 patients with Miller Fisher syndrome who had been treated with IV immunoglobulin (IVIg; n = 28), plasmapheresis (n = 23), and no immune treatment (n = 41). IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia, but the times of the disappearances of those symptoms were similar among three groups. In Miller Fisher syndrome, IVIg and plasmapheresis seem not to have influenced patients' outcomes, presumably because of good natural recovery.

NEUROLOGY 2007;68:1144–1146

Both plasmapheresis[1] and IV immunoglobulin (IVIg) therapy[2] have beneficial effects on Guillain–Barré syndrome (GBS). Because Miller Fisher syndrome (MFS) is closely linked to GBS, these treatments have been tried in patients with MFS.[3-5] Moreover, removal of the anti-GQ1b antibody, a major pathogenetic factor in MFS, by plasmapheresis has been thought to ameliorate symptoms. The efficacy of immunomodulating treatments on MFS has been reported, as patients showed good recovery after these treatments.[3-5] However, because patients with MFS usually have a natural good recovery over time,[6] the efficacy of such treatments must be carefully judged. Because of the rarity of MFS, prospective randomized control trials are difficult to design. We therefore reviewed records of 92 consecutive patients with MFS to determine whether IVIg or plasmapheresis affected the speed of recovery.

Methods. *Patients.* We reviewed medical records of 92 patients with MFS, seen at Chiba University Hospital or affiliated hospitals between 1979 and 2005. Fifty of the patients were described in our previous investigation of the natural course of MFS.[7] Comparison of recoveries in patients treated with plasmapheresis and those not given immune-modulating therapy are described elsewhere.[8] Inclusion criteria for the current study were the presence of the clinical triad of MFS (ophthalmoplegia, ataxia, and areflexia) and acute onset without major limb weakness or other signs indicative of CNS involvement.

Treatments. Twenty-eight patients with MFS were treated with IVIg (400 mg/kg/day s-sulfonated human immunoglobulin) for 5 consecutive days (the IVIg group). Twenty-three underwent plasmapheresis with a second filter (Evaflux 3A, Kuraray Co. Ltd., Kurashiki, Japan, or Immusorber TR-350, Asahi medical Co. Ltd., Tokyo, Japan) (the PP group) and received it every other day 2 to 6 times (mean 4.1 times). All patients gave informed consent to the treatments. The 41 patients who did not receive immune-modulating therapy served as controls. Whether patients were given plasmapheresis, immunoglobulin, or neither depended on differences in the practices of neurologists and differences in when MFS was diagnosed. Plasmapheresis was not in wide use before 1985, and some did not receive IVIg because until 2000 it was not approved in Japan as a health insurance treatment for immune-mediated neuropathies. Therefore, patients were frequently treated with PP between 1985 and 1999 and with IVIg between 2000 and 2005.

Assessments. The clinical course was charted monthly until symptoms and signs disappeared, with focus on amelioration of ophthalmoplegia and ataxia. We did not assess areflexia because it did not affect patients' daily living activities and is difficult to assess by retrospective analysis. All of the patients were asked about the times between onset of ataxia and the start of its amelioration of symptoms. Time between onsets of ophthalmoplegia and ataxia and the time taken for their disappearance were judged by the various neurologists.

Statistical analysis. The significance of differences in percentage was determined by the Fisher exact test. The time to recovery was analyzed by the Kaplan–Meier method, and the log-rank test was analyzed by means of an SPSS statistical package (version 11.0.1J, SPSS Japan Inc., Tokyo, Japan). Comparisons between the two patient groups were evaluated by the Steel–Dwass test. A p value < 0.05 was considered significant.

Results. *Baseline study.* The table shows the clinical features of the three patient groups. There were no significant differences among the IVIg, PP, and control groups in age, sex, antecedent events, frequency of limb weakness, or frequency of the inability to walk independently. The frequency of complete external ophthalmoplegia was higher in the IVIg than the control group ($p = 0.007$), but was similar in the PP and control groups and in the PP and IVIg groups. Time from onset to initial treatment did not differ significantly between the IVIg and PP groups.

Follow-up study. The figure shows Kaplan–Meier curves for the periods between ophthalmoplegia and ataxia onset and the start of alleviation in each patient subgroup. Those were more likely to alleviate faster in the IVIg group

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Supported in part by a Neuroimmunological Disease Research Committee grant from the Ministry of Health, Labor and Welfare, Japan.

Disclosure: The authors report no conflicts of interest.

Received June 14, 2006. Accepted in final form November 27, 2006.

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Table *Clinical features of the subgroups of patients with Miller Fisher syndrome according to treatment*

	Immunoglobulin (n = 28)	Plasmapheresis (n = 23)	Control (n = 41)
Age, median (range), years	44.5 (21–68)	41.0 (13–66)	42.0 (10–78)
Men:Women	16:12	15:8	31:10
Previous infection (R:G:O)	17:3:8	16:2:5	30:1:10
Limb weakness	5 (18%)	5 (22%)	5 (12%)
Inability to walk independently at nadir	9 (32%)	9 (39%)	9 (22%)
Complete ophthalmoplegia at nadir	15 (54%)*	8 (35%)	9 (22%)
Time from onset to initial treatment, median (range), days	4.0 (0–11)	5.0 (0–17)	

* $p < 0.05$, compared with the control group.

R = respiratory infection; G = gastroenteritis; O = others or none.

than in the control group (ophthalmoplegia, $p = 0.04$; ataxia, $p = 0.027$), whereas those between the PP and control groups and those between the IVIg and the PP groups did not significantly differ. The median (range) days between ophthalmoplegia onset and the start of amelioration was 12.0 (3 to 39) days for the IVIg group, 11.5 (3 to 44) days for the PP group, and 13.5 (1 to 87) days for the control group. The median (range) days between ataxia onset and the start of amelioration was 8.0 (2 to 23) days for the IVIg group, 9.0 (1 to 36) days for the PP group, and 10.0 (1 to 59) days for the control group. Kaplan–Meier curves for the periods between ophthalmoplegia and ataxia onset and the disappearance of ophthalmoplegia and ataxia were similar for each patient group. The median (range) days between ophthalmoplegia onset and the disappearance was 82.0 (5 to 170) days for the IVIg group, 92.0 (8 to 466) days for the PP group, and 76.0 (45 to 164) days for the control group (table E-1 on the *Neurology* Web site at www.neurology.org). The median (range) days between ataxia onset and the disappearance was 39.0 (10 to 254) days for the IVIg group, 21.0 (5 to 101) days for the PP group, and 31.0 (4 to 270) days for the control group.

In the subgroup analyses of patients who had severe disability (complete ophthalmoplegia or unable to walk due to ataxia), the times for the disappearance of ophthalmoplegia and ataxia did not differ significantly among IVIg, PP, and control groups.

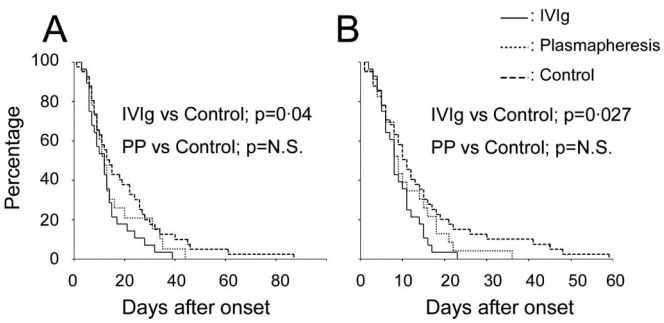

Figure. Kaplan–Meier curves show the percentage of patients with Miller Fisher syndrome by group whose symptoms (ophthalmoplegia [A], ataxia [B]) were not alleviated. IV immunoglobulin therapy (IVIg) slightly hastened the time between symptom onset and the start of alleviation of ophthalmoplegia ($p = 0.04$) and ataxia ($p = 0.027$). Plasmapheresis (PP) did not. N.S. = not significant.

One year after the onset of neurologic symptoms, except for areflexia, only four (4%) patients with MFS had residual symptom(s) (three diplopia, one both diplopia and ophthalmoplegia; one [4.3%] in IVIg group, two [8.6%] in PP group, and one [2.4%] in control group); 96% were free of all symptoms and signs, whether or not they received IVIg therapy or plasmapheresis.

Discussion. We found that for patients with MFS, IVIg therapy seems not to influence patient outcomes, though it slightly hastens the periods between ophthalmoplegia and ataxia onset and the start of the alleviation of these symptoms. Natural recovery was excellent; almost all the patients were free from ophthalmoplegia and ataxia 1 year after onset, whether or not they received immune modulation treatment.

Some reports have suggested the possible efficacy of plasmapheresis on MFS, but none have compared its clinical effects in treated and nontreated patients.[3] In a previous report, we showed that the time required for the lessening of ataxia and ophthalmoplegia to start and the chance of recovery from them did not differ significantly for patients treated or not treated with plasmapheresis.[8] We suggested that this probably was mainly due to patients' good spontaneous recovery from MFS symptoms. In our current study, we enrolled more patients who had or had not been treated with plasmapheresis, and included analyses by the log-rank test. We found no efficacious effect of plasmapheresis on the speed of recovery of patients with MFS.

Whereas this study was retrospective, and some bias could have played in selecting patients for IVIg, plasmapheresis, or no treatment, our findings suggest that IVIg slightly hastens the alleviation of ophthalmoplegia and ataxia but does not affect recovery outcome. Presumably, this is because MFS follows a good, natural course. Theoretically, removing or neutralizing pathogenetic autoantibodies would benefit in immune-mediated disorders,[9,10] but it seems that there are only slight effects of IVIg on the speed of recovery. Considering the high cost of IVIg, its use would not be necessary for patients with MFS unless there is overlapping GBS or Bickerstaff brainstem

encephalitis. However, IVIg treatment could remain an option for patients with MFS overlapping these disorders.

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