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Plasma Immunoadsorption Therapy for Guillain-Barré Syndrome: Critical Day for Initiation

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Abstract

Immunoadsorption plasmapheresis (IAPP) is a method of removing circulating immune factors that is used to treat Guillain-Barré syndrome (GBS). We retrospectively analyzed the data on our GBS patients. In 21 patients treated with IAPP, linear regression analysis showed that the time from the onset of symptoms to the initiation of IAPP was correlated with the time required for improvement by one Hughes functional grade. We investigated the critical day for initiating treatment, which we defined as the day when initiation of IAPP was significantly more likely to improve function by at least one Hughes grade when compared with the outcome in patients receiving supportive therapy (non-IAPP group). The critical day was found to be day 6 after the onset of GBS. (J Nippon Med Sch 2002; 69: 557–563)

Key words: immunoadsorption plasmapheresis, Guillain-Barré syndrome, timing of therapy, clinical improvement, regression analysis

Introduction

Guillain-Barré syndrome (GBS) is defined as an inflammatory polyradiculoneuropathy with a monophasic course that is characterized by rapidly progressive symmetrical muscle weakness and loss of tendon reflexes, followed by gradual remission. Pathological studies have suggested that this disease involves an autoimmune response directed against the peripheral nerves. Antibodies against gangliosides, which are cell surface components of nerves and other tissues, are often detected in patients with GBS, and an anti-ganglioside antibody has been demonstrated to cause motor nerve dysfunction in vitro[1]. Campylobacter jejuni infection is one of the well-known antecedents of GBS. Interestingly, C. *jejuni* possesses a lipopolysaccharide component that structurally resembles GM1 ganglioside[2]. Recent studies have demonstrated that immunoadsorption plasmapheresis (IAPP) to remove autoantibodies is an effective treatment for GBS. The immunoadsorbents currently used are tryptophan or phenylalanine immobilized on polyvinyl alcohol gel. The latest time during the course of GBS at which initiation of IAPP can still be effective has not been clarified by previous studies, so we attempted to define this critical day in the present study.

Materials and Methods

A retrospective analysis was performed of the medical records and work histories of 38 patients with GBS. In all cases, the diagnosis of GBS was made by a neurologist whose evaluation included examination of the cerebrospinal fluid. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) diagnostic criteria

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for GBS were used.[3] Patients with Fisher syndrome, Bell's palsy, Crow-Fukase syndrome, or a paraneoplastic syndrome were excluded. Five patients who underwent plasma exchange were also excluded (3 men and 2 women aged from 21 to 45 years). IAPP was performed in 21 GBS patients from 1985 to 1999 (IAPP group; 14 men and 7 women aged from 18 to 68 years). In all of these patients, IAPP was started within 2 days of admission. Although the duration from the onset of symptoms to initiation of IAPP tended to be longer in patients who were transferred to our hospital after a relatively long period, it was never deliberately delayed. Vascular access was obtained via a percutaneous transfemoral approach. During IAPP, plasma was separated from the cellular component using a membrane-type plasma separator (OP-05; Asahi Medical, Tokyo, Japan). The plasma was then passed through a TR 350 unit (Asahi Medical) containing a column of tryptophan immobilized on polyvinyl alcohol (PVA) gel to remove autoantibodies before it was returned to the blood. The volume of plasma processed during each IAPP session was 2 to 3 L, and the plasma flow rate was 18 to 25 mL/min. The mean number of IAPP sessions per patient was 6.3 ± 1.7. No patient suffered from complications such as hypotension during IAPP or the development of a bleeding tendency, and no patient discontinued treatment prematurely.

Twelve untreated patients were admitted with GBS before 1984, when IAPP was not an established therapy (9 men and 3 women aged from 16 to 74 years) (non-IAPP group). All of the patients in both groups were classified functionally according to a grading scale proposed by Hughes et al (**Table 1**)[4]. There were no significant differences in sex, age, or clinical grade between the IAPP group and the non-IAPP group.

We defined improvement of GBS as a decrease of one grade on the Hughes scale. In the IAPP group the relationship between the time from the onset of GBS to the initiation of IAPP and the time until improvement by one grade was investigated by linear regression analysis using the least-squares method. A p value < 0.05 was defined as indicating statistical significance. In the non-IAPP group, the mean ± 1.96 SD of the time until improvement by one grade was also calculated. In the treated group, we used linear regression analysis to determine the critical days, which were defined as the longest time from the onset of symptoms to initiation of IAPP that still permitted improvement by one grade in less time than the mean minus 1.96 SD for the non-IAPP group (the lower limit of the 95% confidence interval). Patients receiving IAPP were then divided into early treatment and delayed treatment subgroups relative to the critical day, after which the time until improvement by one grade was compared between the early treatment subgroup, the delayed treatment subgroup, and the non-IAPP group by analysis of variance (ANOVA) with a post hoc Scheffe's test.

Results

Tables 1 and 2 list clinical information for the IAPP and non-IAPP groups. Among 21 patients recieving IAPP, one was classified as Hughes grade 1, 5 as grade 2, 3 as grade 3, 8 as grade 4, and 4 as grade 5. Among the 12 patients in the non-IAPP group, 4 were grade 2,4 were grade 3, and 4 were grade 4.

A significant correlation was observed between the interval from the onset of symptoms until the initiation of IAPP and the day until improvement by one grade ($P < 0.05$; $r = 0.449$) in the patients receiving IAPP (**Fig. 1**). The regression line was defined by the following equation: $y = 0.923x + 11.920$. In the non-IAPP group, the mean time ± 1.96 SD until improvement by one grade was 38.17 ± 20.71 days. According to regression analysis, the critical day was day 6 after the onset of GBS (**Fig. 1**). This means that symptomatic improvement of the patients treated with IAPP was faster than that of patients receiving supportive therapy alone when IAPP was started within 6 days of the onset. When the IAPP group was divided into patients treated within 6 days of the onset (early treatment subgroup) and those treated after more than 6 days (delayed treatment subgroup), the day until improvement by one grade was significantly shorter in the early treatment subgroup than in the non-IAPP group or the delayed treatment subgroup, while the delayed treatment subgroup did not differ significantly from the non-IAPP group (**Fig. 2**).

Table 1 Clinical features of the IAPP group

Case	Sex	Age	Sessions	Duration from onset to intiation of IAPP (days)	Clinical grade (Hughes)	Days needed to improve by one grade	Cranial nerve involvement	Sensory disturbance	Autonomic disturbance	Preceding event	Intial symptom
1	M	54	6	2	4	10	—	−	−	−	Muscle weakness of upper extremities
2	M	54	7	2	5	15	—	+	−	+	Muscle weakness of lower extremities
3	F	32	7	3	4	7	—	+	−	+	Numbness of four extremities
4	M	37	4	4	4	7	Dysphasia/Dysarthria	+	−	+	Muscle weakness of four extremities
5	F	25	9	4	3	8	—	+	−	+	Hypoesthesia of four extremities
6	F	26	3	4	3	8	—	+	−	+	Muscle weakness of lower extremities
7	M	48	7	8	2	19	—	+	−	+	Muscle weakness of lower extremities
8	M	46	7	3	5	21	Dysphasia	+	−	+	Dysphasia
9	M	43	5	5	3	12	—	−	−	+	Muscle weakness of four extremities
10	M	33	9	5	5	13	Dysphasia	−	−	−	Muscle weakness of four extremities
11	M	28	7	7	2	13	Facial palsy	−	−	+	Facial palsy
12	M	43	4	8	4	22	Facial palsy	+	−	−	Hypoesthesia of upper extremities
13	F	35	3	8	2	25	—	−	−	+	Muscle weakness of upper extremities
14	M	43	8	9	2	23	Dysarthria	−	−	−	Muscle weakness of lower extremities
15	F	58	7	9	4	45	—	+	−	−	Muscle weakness of lower extremities
16	M	68	5	17	4	79	—	−	−	−	Muscle weakness of four extremities
17	F	27	7	36	4	26	Facial palsy	−	−	−	Muscle weakness of four extremities
18	F	37	7	4	5	14	Facial palsy	+	−	+	Numbness of upper extremities
19	M	24	7	2	4	7	—	+	−	+	Numbness of lower extremities
20	M	25	7	12	1	14	Facial palsy/Dysarthria	−	−	−	Muscle weakness of lower extremities
21	M	18	7	20	2	21	—	−	−	+	Numbness of four extremities

IAPP, immunoadsorption plasmapheresis.

Clinical grade (Hughes)

Grade 0; Healthy

Grade 1; Shiwing minor signs or symptoms of neuropathy but capable of manual work

Grade 2; Able to walk without support of a care but incapable of manual work

Grade 3; Able to walk with a care, appliance, or support

Grade 4; Conifined to bed or chairbound

Grade 5; Requiring assisted ventilation

Grade 6; Dead

Table 2 Clinical features of the non-IAPP group

Case	Sex	Age	Clinical grsde (Hughes)	Day needed to improve by one grade	Cranial nerve involvement	Sensory disturbance	Autonomic disturbance	Preceding event	Intial symptom	Treatment
1	F	23	4	41	Dysarthria	+	−	−	Muscle weakness of lower extremities	prednisolone/Vitamines
2	F	27	2	39	—	+	−	+	Paresthesia of four extremities	prednisolone/Vitamines
3	M	36	2	12	—	−	−	+	Numbness of lower extremities	prednisolone/Vitamines
4	M	35	3	38	—	−	−	+	Muscle weakness of four extremities	prednisolone/Vitamines
5	M	57	4	42	—	+	−	+	Muscle weakness of four extremities	prednisolone/Vitamines
6	M	16	3	50	—	−	−	+	Muscle weakness of lower extremities	Vitamines
7	M	70	3	45	Facial palsy	+	−	+	Facial palsy	Vitamines
8	M	20	2	37	—	+	−	+	Muscle weakness of four extremities	Vitamines
9	M	21	3	45	—	−	−	+	Muscle weakness of lower extremities	Vitamines
10	M	74	4	45	—	−	−	−	Muscle weakness of lower extremities	Vitamines
11	M	37	4	41	Facial palsy/Dysarthria	+	−	+	Muscle weakness of lower extremities	Vitamines
12	F	20	2	23	—	+	−	+	Muscle weakness of lower extremities	Vitamines

Discussion

Immunological mechanisms are fundamental to the development of GBS, which is considered to be an autoimmune disease that targets the peripheral nerves. GBS often occurs between 1 and 6 weeks after a respiratory tract infection or gastroenteritis, which is frequently caused by Epstein-Barr virus, cytomegalovirus[5], or C. *jejuni*[6]. Yuki[2] demonstrated that autoantibodies to GM1 ganglioside in serum from patients with GBS following C. *jejuni* infection react with an oligosaccharide protruding from the lipopolysaccharide core of the organism that is identical to the terminal tetrasaccharide of GM1 ganglioside, making this shared determinant a cross-reactive antigen. Anti-GM1 ganglioside antibody is likely to cause peripheral nerve dysfunction, since it can bind with GM1, GD1b, and asialo GM1[7]. Moreover, Takigawa[8] showed that purified anti-GM1 antibodies block sodium channels at the nodes of Ranvier in the presence of complement. The GM1 epitope is mainly present on the nodes of Ranvier, the presynaptic membranes, and the motor neurons of the spinal cord[9,10]. Patients who develop GBS following mycoplasma infection frequently have serum anti-galactocerebroside antibodies[11], while patients developing GBS after cytomegalovirus infection often have anti-GM2 antibodies[12]. Moreover, serum from patients with GBS often contains antibodies directed against various gangliosides, including GD1a, GD1b, GT1b, LM1, and asialo GM1 as well as GM1 or GM2[13−16].

After the treatment of GBS with prednisolone was first attempted by Shy[17], prednisolone was frequently used to treat this disease. However, Hughes subsequently found no significant difference between GBS patients treated with prednisolone and an untreated control group[4], later extending these observations to high-dose intravenous methylprednisolone therapy with a similarly negative result[18]. Brettle[19] was the first investigator to report on the use of plasma exchange for GBS. The French Cooperative Group then demonstrated the efficacy of plasma exchange for GBS in a large-scale controlled trial[20]. Plasma exchange is currently recognized as effective for GBS and is often used as the initial therapy[21,22]. However, plasma exchange may have

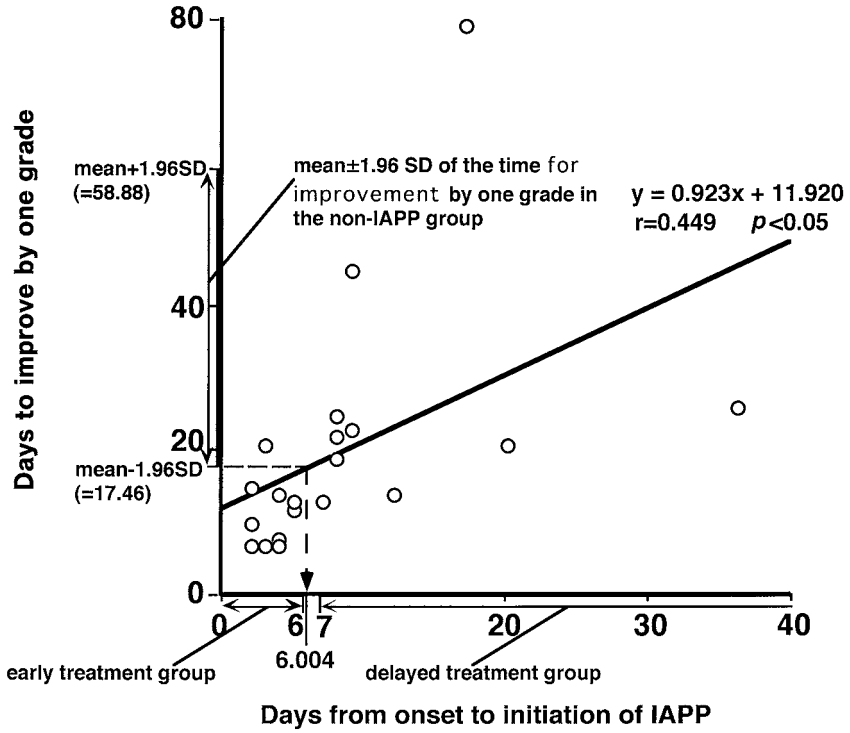

Fig. 1 Scatter plot of the time from the onset of symptoms to the initiation of plasmapheresis versus the time required for clinical improvement by one Hughes grade. A linear correlation is evident between the time until treatment and the time required for improvement by one grade. Data of case 5 overlays that of case 6. The regression line was defined by the following equation: $y = 0.923\ x + 11.920$. Using this equation, improvement by one grade in the IAPP group occurred significantly faster than the mean minus 1.96 (the lower limit of the 95% confidence interval) of the time for the same improvement in the non-IAAP group, when IAPP was started within 6.004 days. Therefore, the critical day was day 6 from the onset of GBS.

numerous adverse effects, including allergic reactions or the transmission of infections such as hepatitis or acquired immunodeficiency syndrome when using fresh frozen plasma, and this therapy requires large volumes of replacement fluid. If albumin is used instead of fresh frozen plasma, the risk of transmitting infections during plasma exchange is probably reduced.

IAPP is an alternative method for removing circulating factors, such as IgG, IgM, IgA, and complement components[2], which does not require the used of a replacement fluid (such as fresh frozen plasma or albumin in saline) because the separated plasma is returned to the blood after removal of circulating factors.

We chose a PVA gel column containing tryptophan rather than one containing phenylalanine. While both kinds of column can selectively adsorb autoantibodies or immune complexes, Yuki found that the tryptophan column was more effective for adsorbing anti-ganglioside antibodies[23], probably because of the increased hydrophobicity contributed by the side chains of tryptophan.

The present study showed that IAPP should be initiated within 6 days of the onset of GBS. The GBS study group found that clinical improvement of patients treated with plasmapheresis was significantly faster than that of patients given supportive therapy alone when treatment was started within 7 days of the first symptoms. Although the reason why 7 days was the cut-off time was not discussed, this finding is similar to the present results[24]. Tagawa demonstrated that more immunoglobulins and C3 were removed by plasma exchange than by IAPP using a tryptophan-immobilized polyvinyl alcohol gel column[25]. Therefore, there is a possibility that the critical period might be extended by using plasma exchange instead of IAPP. We defined the critical day for initiating IAPP based on the premise that the time

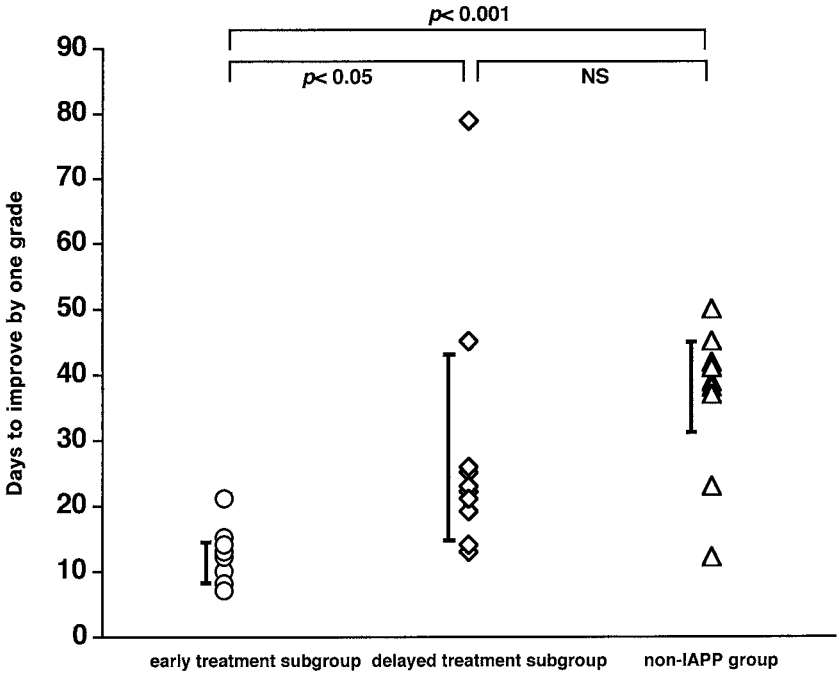

Fig. 2 Early and delayed treatment subgroups were defined relative to the critical day (day 6). Each scatter plot represents the time required for one Hughes grade of clinical improvement. Each bar represents the mean ± SD of the time for improvement by one grade. Improvement was slower in the delayed treatment subgroup and the non-IAPP group than in the early treatment subgroup. Columns represent the mean values and bars show the standard deviation. NS, not significant.

for improvement by one grade had to be shorter than the 95% confidence interval (mean ± 1.96 SD) in untreated patients to provide a clear and consistent benefit. During the development of GBS, anti-GM 1 antibodies block sodium channels at the nodes of Ranvier in the early stage[8], and damage to peripheral nerves occurs subsequently. It is desirable to prevent the progression of GBS before such pathologic changes occur, because it takes a certain amount of time to recover from these changes. The fact that the critical day for initiating IAPP is 6 days after the onset of GBS may reflect the occurrence of pathologic changes in the nurves. Birchem showed by electron microscopy that acute-phase serum from GBS patients was cytolytic for myelin-related Schwann cells and could damage peripheral myelin in an experimental setting free of leukocytes or mononuclear cells[26]. These findings suggest that antibodies and complement may play an important role in the acute pathology of GBS. Pathologically, GBS is categorized into acute demyelinating polyradiculopathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN). In AIDP, Haymaker and Kernohan detected edema during the initial 3 to 4 days, followed by the onset of swelling and irregularity of the myelin sheath and axis cylinders on day 5, the appearance of a few lymphocytes on day 9, and phagocytosis on day 11[27]. In the acute axonal pattern of GBS, the pathologic features are wallerian-like degeneration of fibers with little demyelination[28-30].

Although there are relatively few macrophages in the spinal roots on day 7, endoneurial macrophages become numerous and foamy by day 18 in patients with this type of GBS. IAPP seems to prevent immunoglobulins and complement from causing direct damage to myelin sheaths or axons. There is also a possibility that IAPP may prevent lymphocyte cytotoxicity mediated by antigen-antibody reactions, or may prevent macrophages from binding immunoglobulins by removing antibodies.

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