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Eczematous skin reaction after intravenous immunoglobulin therapy in axonal Guillain-Barré syndrome

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Abstract

Background: Intravenous immunoglobulin (IVIG) treatment in Guillain-Barré syndrome (GBS) is relatively easy to administer and safe due to infrequent, non-severe side effects. Adverse effects can include skin reactions, the causes of which have not been fully elucidated. In this study, we investigated skin reactions following IVIG treatment for acute inflammatory neuropathy. We examined the relationship between the clinical results in the neuropathy and the clinical profile of skin reactions. *Methods:* We retrospectively analyzed patients with skin reactions that developed after IVIG treatment in acute immune-mediated or inflammatory neuropathy [GBS or Miller Fisher syndrome (MFS)] based on the dermatologic evaluation. *Results:* Ninety-six patients with acute inflammatory neuropathy were treated with IVIG during the study period. Thirteen cases (13.5%), with age at onset ranging from 22–69 years (mean, 50.3 years), developed skin reactions after IVIG treatment. The features accompanying skin reactions were hand eczema, including pompholyx (9/13, 82%), generalized eczematous eruption (2/13, 15.4%), and contact dermatitis, including folliculitis. The electrophysiological classification of 11 patients with classical GBS showed that nine patients (81.8 %) had axonal neuropathy, and one (9.1 %) had acute inflammatory demyelinating polyradiculoneuropathy.
Conclusions: Eczematous skin reactions or pompholyx are the most common skin reactions following IVIG treatment in axonal GBS. These reactions were relatively minor and recovered well. Although adverse skin reactions to IVIG were usually benign and the precise mechanism of this cutaneous eruption remains unknown, its occurrence within days of IVIG treatment can be managed effectively if recognized by neurologists.

Keywords: Intravenous immunoglobulin, Guillain-Barré syndrome, skin reaction, eczema, pompholyx, adverse effect

INTRODUCTION

Guillain-Barré syndrome (GBS) is the most representative acute inflammatory peripheral neuropathy and most common disease causing acute flaccid paralysis.[1-3] GBS is used as an umbrella term; it appears as a variety of regional variants due to heterogenous patterns, such as Miller Fisher syndrome (MFS) or other GBS variants.[4-6] Medical history, neurophysiological, neurophysiological, and cerebrospinal fluid examination are important in its diagnosis and treatment. Further, the measurement of serum anti-ganglioside antibodies is helpful for diagnosis.[1,3,7]

The standard treatment in GBS is mainly *via* intravenous immunoglobulin (IVIG) or plasma exchange (PLEX).[3,7] The treatment effects are identical; therefore, the choice of these treatments is decided based on cost, accessibility, or side

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effects. Consequently, their use can depend on the country, institution, and researcher.[7-9]

IVIG does not require specialized equipment; therefore, it is relatively safe during pregnancy. Additionally, side effects are uncommon. As such, it is widely used in various neuroimmunological diseases, such as chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, myasthenia gravis, and GBS.[10] It is also used in various immune-mediated skin diseases, such as Steven-Johnson syndrome, toxic epidermal necrolysis, and bullous pemphigoid.[11,12]

Thrombotic events, renal failure, anaphylaxis, and meningismus may occur during or after IVIG treatment.[9,13,14] Among these side effects, adverse skin reactions are relatively uncommon.[12-14]

This study aimed to analyze the clinical characteristics related to neuropathy and skin reactions in patients with GBS after IVIG treatment. Further, we sought to explain the relationship between related variables and skin reactions.

METHODS

Patients

This retrospective study involved adult patients with acute inflammatory neuropathy, such as GBS, MFS, other GBS variants from January 2010 to June 2020 admitted to the Department of Neurology of Inje University Busan Paik Hospital in Korea. The Ethics Committees of the Inje University Busan Paik Hospital approved the study (IRB No. 2020-11-005). During this period, 96 patients clinically compatible with GBS, MFS, or a GBS variant met the defined criteria (treated with IVIG); therefore, they were selected as study subjects.[5,7] Patients who consulted with a dermatologist due to skin reactions during or after IVIG treatment during hospitalization were investigated.

Patients were excluded with the following features: (1) those who were administered concurrent plasmapheresis or plasma exchange; (2) did not meet the diagnostic criteria for acute inflammatory neuropathy, including chronic inflammatory demyelinating polyradiculoneuropathy; (3) or had a history of suffering from long-term sequelae of neurologic disease, which would make it hard to evaluate the severity of GBS.

Clinical and laboratory assessments

Patients' age, sex, type of preceding infection, presenting symptoms, neurological signs, treatment, and cerebrospinal fluid (CSF) findings were analyzed. Albuminocytologic dissociation, defined as the combination of increased protein concentration and cell count of <50 cells/μl.[15] The GBS disability score, as defined by Hughes *et al*., was used in this study.[16] Demographic data, preceding infection, involved systems (cranial, sensory, motor, and autonomic), laboratory parameters and investigations performed to exclude the secondary causes, intensive care unit (ICU) complications if treated in the ICU, electrophysiological studies, anti-ganglioside antibodies profiles, treatment details, and the other outcome parameters, such as rapidity of progression to nadir, administration of ventilator, duration of ICU stay, Hughes scale at admission, 1 month, and 6 months were recorded.[16] We defined poor outcomes as a GBS disability score of ≥3 at 6 months, which corresponds with the inability to walk 10 m independently.[17] Conventional nerve conduction studies (NCS) were performed in the upper and lower extremities. An enzyme-linked immunosorbent assay (ELISA) was performed to detect various anti-ganglioside antibodies, including immunoglobulin G (IgG) and IgM antibodies against the gangliosides GM1, GM2, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and GB1b, as described previously.[1]

Dermatologic analysis

Dermatological symptoms, sites, duration to first eruption after IVIG administration, underlying dermatologic diseases, treatment, and skin biopsy results were collected. Clinical severity of eczematous reaction was defined according to the hand eczema severity index (HESCI) and eczema area and severity index (EASI). The range of the HESCI score is 0–360 and severity strata presented in the 2019 study was set as a reference value (for clear, 0; almost clear, 1–16; moderate, 17–37; severe, 38–116; very severe, ≥ 117).[18] The range of the EASI score is 0-72 and severity index presented in the 2017 study was set as a reference value (0.0, clear; 1.0-5.9, mild; 6.0-22.9, moderate; 23.0-72.0; severe).[19]

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences, Version 22.0 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for each variable using frequencies and means for categorical and continuous variables, respectively.

RESULTS

Demographic and clinical findings for the enrolled patients

Between January 2010 to June 2020, 96 patients with GBS, MFS, and other GBS variants treated with IVIG were admitted at Inje University Busan Paik Hospital. Thirteen patients with GBS (13.5%) met the inclusion criteria of the study. Four (33.3%) patients were female. The age ranged from 35–69 years (mean age, 52.7 years). Most (84.6%; 11/13) patients had a preceding infection: three patients (23.1%) had an upper respiratory infection and seven patients (61.5%) had a gastrointestinal infection. Furthermore, 11 (84.6%) patients were diagnosed with classical GBS and two (16.7%) were diagnosed with MFS. According to the electrophysiological classification of patients with classical GBS, six (66.7%) had acute motor ataxic neuropathy (AMAN), two (22.2%) had acute motor and sensory ataxic neuropathy (AMSAN), and one (11.1%) had acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Most of the enrolled cases (9/10) with classical GBS initially manifested with limb weakness or sensory symptoms as the predominant symptom. The onset to nadir ranged from 3–9 days (mean, 6.3). Time from symptom onset to IVIG treatment ranged from 1–8 days (mean, 3.4). The infusion rate was 0.4 g/kg/day over 5 days for all patients.

Clinical course and prognosis for the enrolled patients

Three patients were treated in the ICU and required a mechanical ventilator (Table 1). Eleven patients (84.6%) had good outcomes (GBS disability score <3) and two patients (16.6%) had poor outcomes at 6 months. Three patients (23.1%) reported systemic adverse effects after IVIG, such as tachycardia and hypokalemia, hot flush, flu-like symptoms, hyponatremia, chest discomfort, and hypokalemia [Case 2: hot flush, flu-like symptom; Case 6: hot flush, flu-like symptom, hyponatremia; Case 13: chest discomfort, hypokalemia].

Laboratory and electrophysiological findings

In five out of 13 patients (38.5%), there were albuminocytologic dissociations (Table 2). Five (50.0%) were positive for IgG antibodies against various types of gangliosides. Of these, three patients had IgG anti-GM1 antibodies, followed by one patient with IgG anti-GT1a and patient with IgG anti-GQ1b antibodies, and one patient with IgG anti-GD1b antibody.

Dermatological findings

Among 96 patients, 13 (13.5%) complained about dermatological side effects. The most common disease was hand eczema (9/13, 69.2%), including pompholyx, and two cases of generalized eczematous eruption. Each case of contact dermatitis and folliculitis was observed. Hand eczema associated with IVIG occurred in the form of erythematous scaly patches accompanied by slight discharge, which was not different from typical hand eczema (Figure 1, Case 9). The pompholyx after IVIG administration showed sterile vesicles; however, no pustule was observed.

The mean onset time of dermatological symptoms after IVIG administration was 7.38 ± 4.14 days. Most patients had no underlying skin disorders, such as allergic reactions, history of drug eruption, and atopic dermatitis, except for one patient (Case 1: atopic dermatitis).

In the case of hand eczema, clinical severity was evaluated where possible by clinical picture. Five patients (5/7, 71.4%) showed moderate severity and two patients showed almost clear severity, as measured by the hand eczema severity index (HECSI).[18] All patients with a generalized eczematous reaction showed mild severity, as measured by the eczema area and severity index (EASI).[19] All patients were treated with topical steroids. One patient complained of itching and was administered with antihistamines. Improvement of skin lesions over time was confirmed in five patients and lasted for an average of 18.2 days (Range: 4–51); however, the exact timing was unknown in eight patients. None required drug treatment for more than three months, and there were no sequelae due to skin reaction.

DISCUSSION

This study analyzed patients after IVIG treatment in GBS, GBS variant, and MFS who had undergone a dermatological examination. Skin reactions to IVIG in GBS were not rare (15.7%); however, patients showed mostly good outcomes after 6 months. Additionally, most skin reactions recovered relatively well. IVIG therapy is generally considered as a safe treatment for autoimmune disorders and the incidence of reported adverse reactions varies from 1–81%.[13] Most reactions are mild and reversible. There are several reports of the occurrence of skin reactions

Table 1: Demographic and clinical characteristics of the enrolled patients

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at onset, years	66	42	45	64	69	36	55	53	65	35	43	22	59
Sex	M	F	F	M	M	F	M	M	M	M	M	M	F
Antecedent infection	None	GI	GI	GI	GI	GI	GI	None	URI	GI	URI	GI	URI
Initial subjective symptoms	Limb tingling sense (U, L)	Leg weakness	Leg paresthesia	Hand weakness	Dysarthria, hoarseness	Limb tingling sense (U, L)	Leg weakness	Limb weakness (U, L)	Limb tingling sense (U, L)	Arm weakness	Diplopia	Arm weakness	Diplopia, dysarthria
Classification	AIDP	AMAN	AMSAN	AMSAN	AMSAN	AMSAN	AMAN	AMAN	AMAN	Unclassified	MFS	AMAN	MFS
Involved system													
Cranial	-	+	-	+	+	-	-	-	-	+	+	+	+
Motor	+	+	+	+	+	+	+	+	+	+	+	+	-
Sensory	+	-	+	+	+	+	+	-	+	-	+	-	+
Autonomic	-	+	+	+	-	-	-	-	-	+	+	-	-
Hyporeflexia/areflexia	+	+	+	+	+	+	+	+	+	+	+	+	+
Ataxia	-	-	-	-	+	-	-	-	+	-	-	-	-
Treatment & outcome													
Onset to nadir (days)	8	5	9	7	4	9	5	7	3	7	4	8	7
Time from symptom onset to IVIG Tx (days)	6	2	4	1	3	8	2	5	1	3	3	3	3
ICU admission, (days)	-	+ (55)	-	+(32)	-	-	-	-	-	+(17)	-	-	-
Ventilator care	-	+	-	+	-	-	-	-	-	+	-	-	-
Prognosis (Disability scale)													
At admission	1	5	4	5	2	2	3	4	4	1	4	3	3
At 1 month	2	5	2	5	2	4	1	2	3	4	3	3	2
At 6 months	1	4	1	1	1	1	0	1	1	3	2	2	0

IVIG, intravenous immunoglobulin; GI gastrointestineunal infection; URI, upper respiratory infection

Table 2: Laboratory and electrophysiological findings of the enrolled patients

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13
Laboratory tests													
CSF													
Time from symptom onset, in days	7	3	5	2	4	9	2	6	1	3	3	3	1
CSF protein, mg/dL	**45.5**	30.7	21.9	36.9	**148.2**	**63.4**	29.3	**55.2**	34.2	34.1	20.9	34.3	**46.2**
CSF leukocyte, count/μL	0	1	0	0	0	7	0	0	0	0	1	1	19
Albuminocytological dissociation	+	–	–	–	+	+	–	+	–	–	–	–	+
Anti-ganglioside antibodies	Neg	Neg	IgG GD1b	IgG GM1	N/C	IgG GM1	IgG GM1	Neg	Neg	Neg	IgG GT1a, IgG GQ1b	N/C	N/C

CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; Neg, negative; N/C, not checked

after IVIG treatment in inflammatory neuropathy, including GBS.[12-14,20-23] Some skin reactions are common during IVIG administration and typically resolve within several hours; however, treatment with antihistamines and corticosteroids is effective.[13] In addition to GBS, Cohen Aubart *et al*. have reported the occurrence of eczematous eruptions in multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, and other diseases for which IVIG is used.[23] In this study, skin disease often recurred after re-administration. In these cases, eruption occurred faster and was more generalized. Further, Cohen Aubart *et al*. suggested that switching the type of IVIG may be successful in avoiding further eruptions.[23]

GBS patients who had skin reactions were mainly classified with axonal type GBS. Most patients suffered from antecedent infections compared with MFS patients. Only patient skin reactions were investigated in this study; however, three patients reported systemic adverse effects that improved within a few days without serious complications. During hospitalization, three patients received intensive care, including ventilator treatment, and no patients died. When the prognosis was evaluated at 6 months, most patients had a good outcome (GBS disability score <3). Two out of three patients who received intensive care treatment had a disability score of 4 and 3, respectively.

Taken together, these data suggest that is difficult to predict whether skin reactions will occur more frequently in patients receiving intensive care. Further, the prognosis associated with GBS was not serious in most cases.

Five patients showed an increase in protein in CSF analysis; all showed albuminocytologic dissociations.[15] The anti-ganglioside antibody test was positive in five patients, which accounted for 50% of classical GBS cases. Similar to test results reported in previous studies in Korea,[1] GM1, GT1, GQ1b, and GD1b were found. No other antibodies were found.

The pathogenesis of the eczematous skin reaction to IVIG is unknown.[24] Various B cell responses and epidermal complement deposits that occur after IVIG treatment have been partially explained.[24] Furthermore, IVIG is associated with T-cell modulation. Another hypothesis is that the delayed hypersensitivity skin reaction is due to the activation of drug specific CD4+ and CD8+ T cells, which triggers these eczematous reactions.[25] It is conceivable that the various immune reactions necessary for the formation of these antibodies

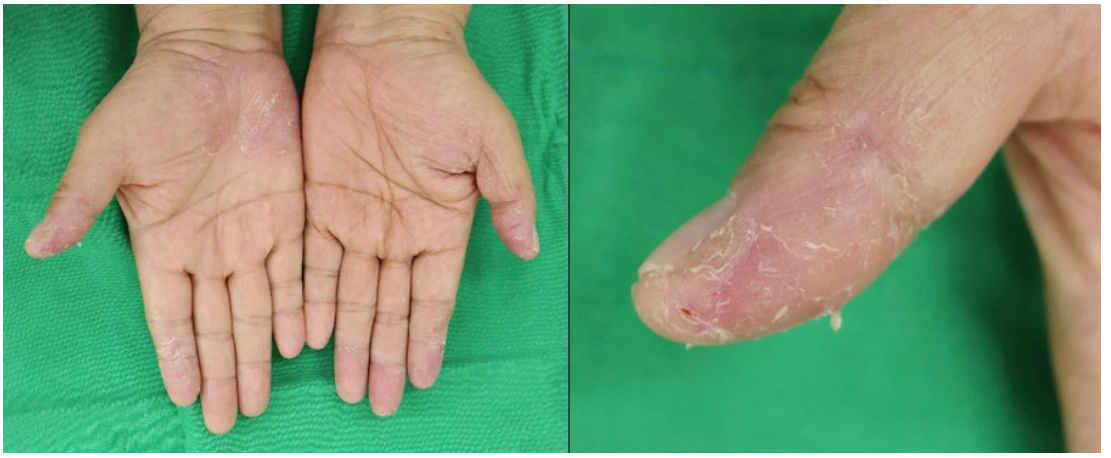

Figure 1. Clinical photographs of patient (Case 9). Photographs showed skin-colored to erythematous scaly patches on both hands.

may affect different cytokines and immune cells; therefore, these immunity-forming processes may trigger skin reactions.[25] Additionally, this may be a hypersensitivity reaction to unidentified substances within IVIG.[26] Some studies have suggested that IVIG-related eczematous eruptions are a high dose-dependent or infusion rate-dependent side effect.[20,27] Dermatologically, hand eczema, including pompholyx, was the most common lesion in nine patients and generalized eczematous eruption was found in two patients. The clinical severity of skin reactions in all patients was mild to moderate; skin lesions were improved without any sequelae by applying topical steroids with emollients. None of the patients required pharmacologic intervention, including long-term drug therapy for more than three months. Underlying skin diseases were rare and most of the symptoms occurred within two weeks' treatment. Symptoms occurred mainly in the upper limbs, lower extremities, and body; however, there were some facial occurrences (Table 3). There was no correlation between the severity of neurological symptoms, IVIG dose, and the severity of skin reaction. Pompholyx has been reported in some studies.[20-23] In this study, additional dermatologic treatment was not required because most patients showed improvements through simple medication or observation without any significant side effects. No serious complications or sequelae were observed.

The skin biopsy (Case 5, Figure 2) of the patient who presented with hand eczema showed a typical manifestation of subacute spongiotic dermatitis characterized by hyperkeratosis, acanthosis, spongiosis, vesicle formation in epidermis and vascular ectasia and proliferation, and perivascular lymphocytic infiltration in the superficial dermis. This suggested that the pathologic findings of hand eczema after IVIG administration were not different from typical hand eczema.

This study has several limitations. First, it was conducted in a small number of patients in a single tertiary hospital. Second, only patients who had consulted with a dermatologist were enrolled; therefore, this may not include mild skin reactions that did were not reported. Lastly, we focused on skin reactions limited to the hospitalization period; therefore, it was difficult to include skin reactions with subacute onset or that continued with a chronic clinical course after discharge.

In conclusion, we retrospectively investigated skin reactions that occurred after IVIG treatment in patients with GBS. Most patients had a good prognosis for GBS and the skin reactions. Neurologists who treat GBS can be less interested in skin reactions because of the severity of GBS when compared with these side effects; however, consultations with dermatologists might improve their understanding.

Research into skin reactions following IVIG remains insufficient and the association with the disease has not been identified; therefore, further studies should focus on the mechanism underlying the occurrence of skin reactions and its association with diseases. Furthermore, additional skin biopsies will be required.

DISCLOSURE

Financial support: This work was supported by 2022 Inje University Busan Paik Hospital Research Grant.

Table 3: Dermatologic findings after IVIG treatment of the enrolled patients

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13
Days to first skin reactions from IVIG (days)	8	9	9	1	4	13	9	4	6	16	7	9	1
Underlying disease	HTN	-	Angina	BPH, prostate cancer	HTN, BPH, angina	HLD	-	HTN	HLD		HTN, BPH	-	HBV
Skin reaction characteristics	Whitish vesicles, scaly patches	erythematous patches	erythematous papules	erythematous to hyperpigmented scaly patches	skin-colored vesicles	skin-colored vesicles	skin-colored vesicles	skin-colored scaly patches	Skin-colored to erythematous scaly patches	erythematous papules, pustules	erythematous scaly patches	erythematous scaly patch, tiny pustules	erythematous patches
Dermatologic diagnosis	pompholyx	Generalized eczematous eruption	pompholyx	Generalized eczematous eruption	pompholyx	pompholyx,	pompholyx,	hand eczema	Hand, foot eczema	folliculitis	hand eczema	pompholyx	Contact dermatitis
Site of symptom	Both hands	Whole body	Both hands, feet	Whole body	Both hands	Both hands, feet	Both hands	Both hands	Both hands, feet	Forehead	Both hands	Both hands, feet	Back
HECSI score	30		N/A		22	14	11	24	30		21	N/A	
EASI score		9.5		4.6									
Treatment for skin reaction													
- Topical steroids	1	1	1	1	1	1	0	1	1	1	1	1	1
- Systemic steroids	0	0	0	0	0	0	0	0	0	0	0	0	0
- Anti-histamines	0	1	0	0	0	0	0	0	0	0	1	0	0
- Moisturizer	0	1	0	0	0	0	0	1	1	0	0	0	1

N/A, not available; IVIG, intravenous immunoglobulin; HTN, hypertension; BPH, benign prostatic hyperplasia; HLD, herniated lumbar disc; HBV, hepatitis B virus; HECSI, hand eczema severity index; EASI, Eczema Area and Severity Index

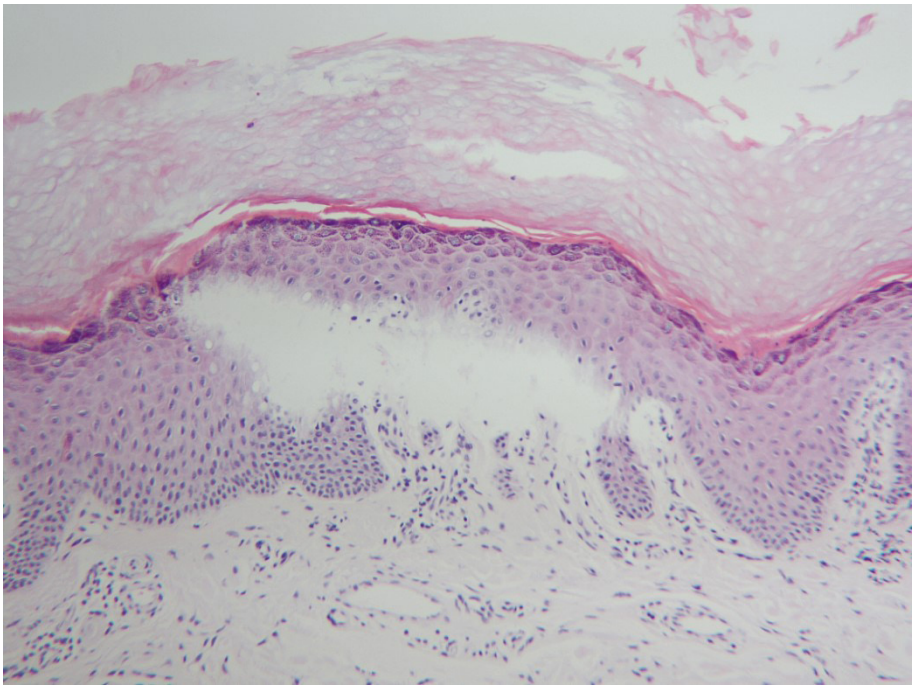

Figure 2. Histologic changes in skin lesions (Case 8). Histologic findings showed hyperkeratosis, acanthosis, spongiosis intraepidermal vesiculation, perivascular, interstitial infiltration composed mainly of lymphocytes (H&E ×100).

Conflict of interest: None

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