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【 ORIGINAL ARTICLE 】

Neurological Complications in Eosinophilic Granulomatosis with Polyangiitis (EGPA): The Roles of History and Physical Examinations in the Diagnosis of EGPA

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Abstract:

Objective To investigate the clinical symptoms, the physical and neurological findings, and the clinical course of neurological complications in eosinophilic granulomatosis with polyangiitis (EGPA).

Methods A retrospective chart review of EGPA cases managed by two referral hospitals was performed, with a focus on the neurological findings. The study analyzed the symptoms at the onset of EGPA and investigated their chronological relationship. The patient delay (the delay between the onset of symptoms and the initial consultation), and the physician delay (the delay from consultation to the initiation of therapy) were determined and compared. The involved nerves were identified thorough a neurological examination. The cases with central nervous system (CNS) involvement were described.

Results The average duration of symptoms prior to the initiating of therapy for sensory disturbances, motor deficits, rash, edema, and fever was 23, 5, 21, 18, and 24 days, respectively. Among the EGPA-specific symptoms, sensory disturbance was often the first symptom (63%), and was usually followed by the appearance of rash within four days (63%). The average physician delay (32.9±38.3 days) was significantly longer than the average patient delay (7.9±7.8 days; p=0.010). Reduced touch sensation in the superficial peroneal area, and weakness of dorsal flexion of the first toe secondary to deep peroneal nerve involvement, were highly sensitive for identifying the presence of peripheral nerve involvement in our series of patients with EGPA. Two cases, with CNS involvement, had multiple skin lesions over their hands and feet (Janeway lesions).

Conclusion Japanese physicians are not always familiar with EGPA. It is important for us to consider this disease, when an asthmatic patient complains about the new onset of an abnormal sensation in the distal lower extremities, which is followed several days later by rash.

Key words: eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, peripheral neuropathy, ANCA

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is one of the three anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which include granulomatosis with polyangiitis, and microscopic polyangiitis. EGPA is characteristically associated with asthma and eosinophilia (1), and has a higher incidence of peripheral nerve and central nervous system (CNS) involvement in comparison to the other two ANCA-associated vasculitides. However, the details of these complications have

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not been well studied. We herein investigate the history, and the results of physical and neurological examinations of these complications in patients with EGPA.

Materials and Methods

Consecutive patients who were newly diagnosed with EGPA (Churg-Strauss) according to the American College of Rheumatology classification criteria (2) and who were initially treated by one of the authors (H.O., M.F., and K.K.) at their respective institutions were included in the present study. The eligible patients must have visited the Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital between July 2009 and March 2012, or the Department of Rheumatology, Hiroshima City Hiroshima Citizens Hospital, between April 2012 and August 2015. This study was approved by the institutional review boards of both hospitals.

We conducted a retrospective chart review of these cases with a focus on the neurological findings. Clinically, peripheral neuropathy was classified as mononeuropathy, mononeuropathy multiplex or polyneuropathy by a rheumatologist and/or a neurologist. The classification was subsequently confirmed (retrospectively) by a neurologist (T.M.) specializing in nerve conduction studies.

A medical interview was conducted in which an attempt was made to determine the nerve responsible for the first neurological symptom, based on the cutaneous fields of peripheral nerves in a textbook figure (3). Next, to investigate the chronological relationship between the different symptoms of EGPA, data were collected on each case (including the onset of sensory and motor disturbance, rash, edema and fever) and the history of each case was carefully obtained at the first visit. We tried to determine the date of the onset of each symptom. In cases in which it was difficult to determine the date of a symptom's onset, an "approximate" date was assumed; for example, if the patients described the onset of an EGPA symptom in the middle of a month, the date of the onset was recorded as the 15th of that month. Subsequently, the duration between the onset of EGPA-specific symptoms (neuropathy and skin lesions) and first medical consultation (patient delay), and the duration between the first consultation and initiation of therapy (physician delay) were calculated, and compared. We statistically verified whether the inappropriate use of glucocorticoids contributed to the delay in cases in which the physician delay exceeded 14 days, and the reasons for the physician delay were described.

On neurological examination, sensory disturbance was evaluated based on touch sensation, while motor disturbance was graded as ≤2, 3, 4 or 5 by manual muscle testing (MMT). Weakness was defined by an MMT score ≤4, and serious weakness was defined by an MMT score of ≤3. Although there was no specific protocol for the muscles to be tested, the dorsal and plantar flexion of the ankle and toes were frequently tested: the dorsal and plantar flexion of the first toe was evaluated alone, while the dorsal and plantar flexion of the second to fifth toes were evaluated in combination. The MMT scores of these movements at baseline and the last visit were compared. Data related to the tests, treatment, and outcomes were also collected. In cases of EGPA with CNS involvement, a case description was included.

Statistical analyses

The differences in patient and physician delay were analyzed using the Mann-Whitney U test. Fisher's exact test was used to analyze the correlation between the inappropriate use of glucosteroids and physician delay (>14 days vs. <14 days). P values of <0.05 were considered to indicate statistical significance. All of the statistical analyses were performed using the Microsoft Excel software program (2013).

Results

Patient characteristics

A total of 12 cases were analyzed in this study (Table 1). The mean age of the study population was 52 years [standard deviation (SD), ±13] and the male:female ratio was 5:7. All of the patients had a history of bronchial asthma (mean duration of 7.5±9.0 years). Five patients were inappropriately treated with oral prednisolone (PSL) before establishing a diagnosis of EGPA; however, four of them had stopped taking oral PSL before the first visit, while the other (Case 10) had taken prednisolone (10 mg/day) for 17 days.

Peripheral neuropathy was present in all 12 patients (100%), while only two (17%) had CNS involvement. Mononeuropathy multiplex and mononeuropathy were identified in 10 of 12 (83%) and 2 of 12 (17%) patients, respectively. One patient (Case 11) did not have peripheral neuropathy at the first visit, but had mononeuropathy a month later; this case was also included in the analysis.

The mean eosinophil count was 14,332±9,208 cells/μL, and the IgE levels were elevated in all 10 cases. The myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA levels were elevated in 6 of 12 (50%) and 1 of 12 (8%) cases, respectively.

The history of peripheral neuropathy

In their medical interviews, all 12 patients (100%) complained of sensory deficits, while nine (75%) reported motor weakness. Three cases (25%) experienced falls, while four (33%) could not walk by themselves at the initial visit. The initial sensory disturbance was described as painful paresthesia in 6 of 11 patients (55%), decreased sensation in 3 of 11 (27%), and numbness in 2 of 11 (18%). The initially-involved nerve was thought to be the superficial peroneal nerve in 4 of 11 patients (36%), the superficial or deep peroneal nerve in 1 of 11 (9%), the plantar branches of the tib-

Table 1. Patient Characteristics.

No.	Age/Sex	Patient delay	Physician delay	Neurologic findings	Glucocorticoid use*	Follow-up period (weeks)
1	46 F	23	10	MM	None	20#
2	68 M	1	13	MM	None	116
3	66 F	3	10	MM	None	61
4	36 F	21	9	MM	None	53
5	49 F	3	4	MM	None	45
6	22 M	5	31	M	"-30 days to -16 days; PSL 15 mg and tapered dose"	45
7	60 F	8	50	MM	"-41 days to-11 days; PSL 30 mg and tapered dose"	26
8	65 F	7	129	MM	"-126 days to -94 days; PSL 20 mg and tapered dose"	33
9	59 M	6	56	MM	none	257
10	53 F	2	17	MM	"-17 day to visit; PSL 10 mg"	235
11	39 M	NA	NA	CNS, (M)	None	264
12	73 M	NA	NA	CNS, MM	For asthma, until 3 months previously	14#

NA: not available, MM: mononeuropathy multiplex, M: mononeuropathy, CNS: central nervous system involvement, PSL: prednisolone

*Inappropriate glucocorticoid use before starting therapy for EGPA.

#Lost to follow-up.

Table 2. The Duration of Symptoms (in Days) before the Initiation of Therapy.

Case	Sensory	Motor	Rash	Edema	Fever
1	4	NA	<u>30</u>	NA	8
2	<u>24</u>	0	20	20	NA
3	<u>13</u>	3	12	12	NA
4	10	3	30	NA	<u>56</u>
5	<u>7</u>	3	4	3	2
6	35	NA	31	<u>36</u>	34
9	<u>75</u>	3	21	NA	NA
10	19	17	19	17	<u>22</u>
mean±SD	23±23	5±6	21±10	18±12	24±22

NA: not available

The underlined values indicate the initial symptom.

ial nerve in 3 of 11 (27%), the sural nerve in 2 of 11 (18%), and the median nerve in 1 of 11 (9%).

In the analysis of the chronological relationship of the disease symptoms in the evaluable cases, the initial symptom was sensory disturbance in 4 of 8 patients (50%), rash or edema in 2 of 8 (25%), and fever in 2 of 8 (25%). Among the EGPA-specific symptoms, sensory disturbance was the initial symptom in 5 of 8 patients (63%). The average duration of symptoms before the initiation of therapy for sensory disturbance, motor weakness, rash, edema, and fever was 23, 5, 21, 18, and 24 days, respectively (Table 2). Additionally, in 5 of 8 patients (63%), sensory disturbance was followed by the onset of rash within four days. Edema, when present, occurred almost simultaneously with rash. A typical case presentation included sensory disturbance, rash, or both, three weeks prior to the initial visit. Lower limb weakness, when present, appeared several days before the initiation of therapy.

The patient and physician delay could be analyzed in 10 cases, after excluding the cases of two patients with CNS involvement for whom the history was unreliable. The average (± SD) physician delay of 32.9±38.3 days was significantly longer than the patient delay of 7.9±7.8 days ($p=0.010$). Each of the patients visited an average of 3.7 physicians (median, 4) before the start of EGPA-specific therapy. Four of the five cases with physician delays exceeding 14 days were inappropriately treated with glucocorticoids before the diagnosis of EGPA was established. None of the patients with physician delays of <14 days were inappropriately treated with glucocorticoids ($p=0.046$).

The reasons for physician delays exceeding 14 days were diagnostic errors in two cases (anaphylactoid purpura in Case 6, and eosinophilic pneumonia in Case 8), and a lack of knowledge about EGPA in three cases (Cases 7, 9 and 10).

Neurological examination

Neurological examinations were performed in 11 cases, except for one case with CNS involvement (Case 12). The involved nerves, judged according to sensory impairment, included the superficial peroneal nerve in 10 patients (91%), the plantar branches of the tibial nerve in 8 (73%), the sural

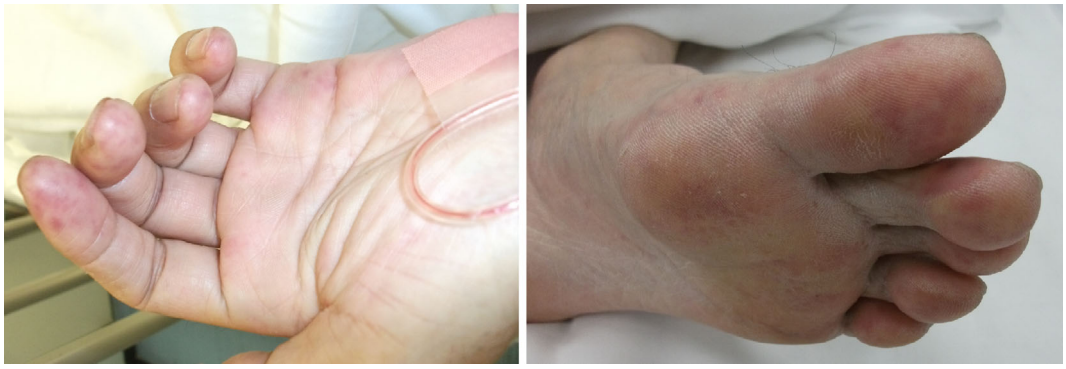

Figure 1. **Erythematous macules on the palms and soles (Janeway lesions), in Case 12.**

nerve in 7 (64%), the lateral sural cutaneous nerve in 6 (55%), the deep peroneal nerve in 4 (36%), the median nerve in 3 (18%), and the ulnar nerve, saphenous nerve, and lateral cutaneous nerve of the thigh in 1 patient each (9%). The involved nerves, judged according to motor disturbance, included the deep peroneal nerve in 9 (82%) patients, the tibial nerve in 8 (73%), and the median nerve in 2 (18%). One of the two patients with median nerve involvement showed thumb flexion weakness, while the other showed second finger flexion weakness. The plantar and dorsal flexion of the ankle and the toes, which reflects the deep peroneal and the tibial nerve, respectively, was assessed in 11 patients. The incidence of dorsal flexion weakness of the ankle, first toe and other toes was 73% (8/11), 82% (9/11) and 50% (5/10), respectively, while the incidence of serious dorsal flexion weakness of the ankle, first toe and other toes was 45% (5/11), 55% (6/11) and 50% (5/10), respectively. The incidence of plantar flexion weakness of the ankle, first toe and other toes was 27% (3/11), 50% (5/10) and 50% (5/10), respectively; while the incidence of serious plantar flexion weakness of the ankle, first toe and other toes was 18% (2/11), 40% (4/10) and 40% (4/10), respectively.

Nerve conduction studies (NCSs)

NCSs were performed in 7 cases involving patients with mononeuropathy multiplex. The results of the tests were consistent with the axonal involvement of the tested nerves, and mononeuropathy multiplex was suggested in 3 cases (43%), and normal findings in two (29%) patients. In the other two cases, the test results could not distinguish between mononeuropathy multiplex and polyneuropathy, due to severe nerve damage in one case, and technical issues in the other. The NCS was not available in the two cases with mononeuropathy; thus, both of them were diagnosed as mononeuropathy based on the clinical findings alone.

The treatments and outcomes

Individual treatment plans were determined by the respective physicians with reference to the standard strategy followed in Europe (4). For induction therapy, intravenous methyl-prednisolone (IVMP) was indicated in three patients with poor prognostic factors, and eight patients with significant motor dysfunction, whereas high-dose PSL was initially indicated in the remaining case with sensory disturbance. Intravenous cyclophosphamide (IVCY) was indicated in two patients with cardiomyopathy, and one patient with severe motor disturbance due to peripheral neuropathy.

During a median follow-up period of 57 weeks (mean ± SD, 114±99 weeks), two (20%) of the 10 cases (two cases were lost to follow-up) relapsed. Both were minor relapses that were characterized by an increased eosinophil count, and were successfully treated using incremental doses of PSL combined with azathioprine. Inhaled corticosteroids were required to achieve the control of asthma in 7 cases (70%). PSL was stopped in only one case (Case 11).

MMT, in which the plantar and dorsal flexion of the toes and the ankle were reassessed, was performed at the last visit in 8 cases, with a median follow-up period of 49 months (80±79). Baseline MMT values of ≤2, 3, 4, and 5 were recorded in 21, 16, 12, and 41 muscles, respectively. A total of 17 of the 21 muscles (81%) with an MMT of ≤2 improved to 3-5 at the last observation, and in four (19%), the MMT remained unchanged; 9 of the 16 muscles (56%) with an MMT score of 3 improved to 4-5, 2 (13%) remained the same, and 5 (31%) worsened to ≤2; 9 of the 12 muscles (75%) with an MMT score of 4 improved to 5, and 3 (25%) remained unchanged; 39 of the 41 muscles (95%) with an MMT score of 5 remained unchanged, while 2 (5%) worsened to 4.

CNS involvement

Two cases showed significant CNS involvement (Cases 11 and 12). One (Case 11) has been reported previously (5). The patent had no recollection of the events that occurred within the previous two weeks, and appeared slightly confused and disoriented to time. He had peripheral skin lesions, including Janeway lesions. The other (Case 12) was transported by an ambulance due to altered consciousness. The patient was severely confused and uncooperative during the neurological examination; however, the muscles of the right upper extremity appeared obviously weak. He had multiple purpura, including Janeway lesions, over the trunk and lower extremities (Fig. 1). In both of the two, the results of diffusion-weighted magnetic resonance imaging

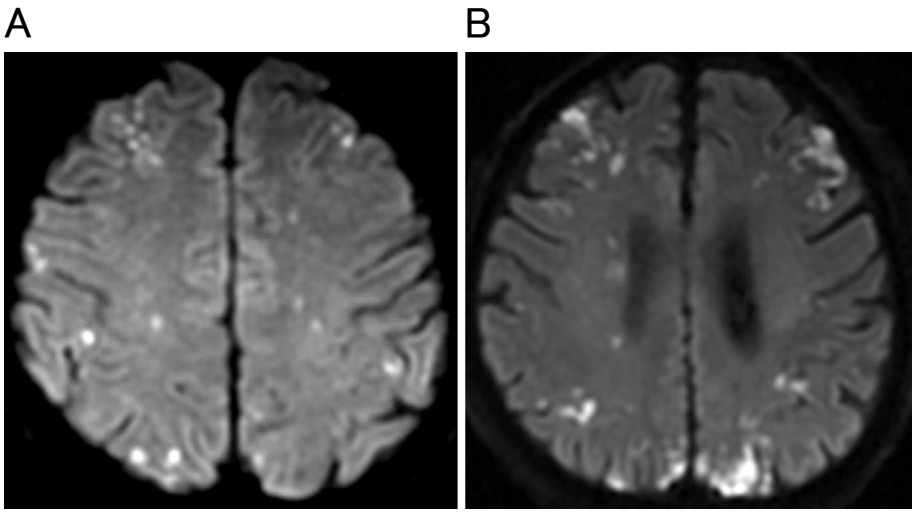

Figure 2. **Diffusion-weighted magnetic resonance imaging (MRI) of the brain. (A) Multiple high-intensity lesions are identified in the cortical and subcortical regions of the brain (Case 11). (B) Multiple high-intensity lesions are identified in the brain cortex (Case 12).**

(MRI) of the brain revealed multiple high-intensity lesions in the brain and cerebellum (Fig. 2). NCS was performed for one of these cases (Case 12); the results were consistent with mononeuropathy multiplex.

Discussion

This case-series study, which focused on the neurological complications of EGPA, demonstrated several important features concerning peripheral neuropathy in patients with EGPA. In general, patients with EGPA initially noticed sensory disturbance, which was followed several days later by rash and/or edema, before they finally developed motor deficits. The common initial areas of sensory deficits corresponded to the cutaneous fields that are supplied by the superficial peroneal or the plantar branches of the tibial nerves. Decreased touch sensation over the superficial peroneal area, and dorsal flexion weakness of the first toe, secondary to the involvement of the deep peroneal nerve, were highly sensitive for identifying the presence of peripheral nerve involvement in our series of patients with EGPA.

In an earlier study analyzing neuropathy in EGPA, painful paresthesia initially appeared over the legs (82%) or hands (18%), in association with local edema (6). The initial area with abnormal sensation in our series was consistent with the peripheral area of the legs. Longer nerves more frequently showed vasculitic damage of the vasa nervorum, and the peripheral area of the legs, which is supplied by the longest nerves in the body, may tend to be affected first. Additionally, sensory disturbance was often followed by rash and/or edema. These observations suggest that in the early stages, local vasculitis simultaneously results in neuronal ischemia and subcutaneous inflammation. It is important for physicians to investigate the eosinophil count in patients who present with abnormal sensation (of new onset), followed by skin lesions within several days.

Patient delay was reported as an important factor that influences the cancer stage at presentation (7); it is also represents a serious public health problem in the management of tuberculosis (8, 9). On the other hand, physician delay, which reflects diagnostic delay, may occasionally be longer than patient delay (7, 8). Our study is the first to introduce these concepts in the diagnosis of vasculitis. This study demonstrated that physician delay exceeded patient delay in cases with EGPA. A physician delay of >14 days was likely to be associated with inappropriate glucocorticoid use, which may mask the early signs of EGPA. These data emphasize that physicians should consider consulting specialists in this disease before attempting glucocorticoid therapy.

The frequency of nerve involvement at the initial examination varies according to the method of evaluation. In a previous study analyzing both sensory and motor disturbances, the CP nerve was the most frequently involved nerve (84%) (10), whereas a more recent study reported that the sural nerve was the most frequently involved (69%) nerve, followed by the CP, tibial, and median nerves (50% each). When considering sensory impairment alone, the CP nerve is reported to be the most frequently involved nerve (96%), followed by the tibial, sural, ulnar and median nerves (6). In our study, sensory deficit most commonly occurred due to the involvement of superficial peroneal nerve (91%) while motor deficits were frequently related to the deep peroneal nerve (82%). These findings may be useful in screening for peripheral neuropathy in patients with EGPA.

Two of our patients showed impaired consciousness due to multiple ischemic lesions in the brain and cerebellum. Follow-up MRI taken within two weeks after the initiation of treatment revealed that these lesions regressed significantly with treatment. This suggests that they represented reversible vascular lesions, rather than irreversible infarction. Similar multiple ischemic lesions were previously reported in at least 9 cases (11-17), 6 (66%) of which occurred in pa-

tients who presented with altered consciousness. Chen et al. reported a unique case with multiple cerebral infarctions and multiple purpura involving the trunk, fingers of both hands, and the soles (14), which resembled Janeway lesions in our cases. These findings suggest that skin lesions may serve as indicators of CNS vasculitis.

Our study is associated with some limitations. It was a retrospective study of a relatively small study population; thus, it was subject to potential bias, especially in regard to the reporting of the disease severity and outcomes. However, we believe that our study contributes to clarifying the clinical course of the neurological complications of EGPA.

In conclusion, the first symptom in EGPA is usually sensory disturbance of the distal lower extremities. This is followed, several days later, by rash and/or edema. The EGPA patients with CNS involvement had skin lesions over their hands and feet, similar to Janeway lesions. Japanese physicians were not always familiar with the disease, and an awareness of the course of EGPA-related neurological complications might aid in its early recognition.

The authors state that they have no Conflict of Interest (COI).

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