



# Clinical Characteristics and Treatment Response of Peripheral Neuropathy in the Presence of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome): Experience at a Single Tertiary Center

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**Background and Purpose** Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small-vessel vasculitis accompanied by asthma, eosinophilia, and eosinophilic inflammation of various tissues including the peripheral nerves. This study investigated the clinical course and long-term outcomes of peripheral neuropathy in patients with EGPA.

**Methods** Seventy-one patients with physician-diagnosed EGPA were identified at Samsung Medical Center between January 1995 and April 2014. Sixty-one of these patients were followed-up for more than 1 year and received corticosteroid therapy with or without intravenous cyclophosphamide pulse therapy for 6 to 18 months. Medical records of the 61 patients including demographic data, clinical features, laboratory and pathological findings, treatments, and outcomes were reviewed.

**Results** Peripheral neuropathy as a manifestation of EGPA was present in 46 (75%) of the 61 patients. The mean follow-up duration of the patients with neuropathy was 6.4 years (range 1.2–18.8 years). The scores on the neurological functional disability scale before and after the combination treatment with corticosteroid and cyclophosphamide were  $2.43 \pm 0.86$  and  $0.54 \pm 0.95$  (mean  $\pm$  SD;  $p < 0.001$ ), respectively. The peripheral neuropathy relapsed in one patient.

**Conclusions** The long-term clinical outcome of peripheral neuropathy in patients with EGPA receiving initial corticosteroid and cyclophosphamide combination therapy was favorable with a very low relapse rate.

**Key Words** eosinophilic granulomatosis with polyangiitis, peripheral neuropathy, cyclophosphamide, prognosis.

## INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA; also called Churg-Strauss Syndrome) is a rare form of systemic vasculitis characterized by asthma, eosinophilia, and small-vessel vasculitis. Its rarity has resulted in few studies focusing on EGPA-associated peripheral neuropathy (PN), and they have involved relatively small numbers of subjects.<sup>1-6</sup> The mainstay in the treatment of EGPA is a corticosteroid (CS), while it is widely accepted that additional immunosuppressive agents such as cyclophosphamide (CY) are needed in cases with life- or organ-threatening manifestations. Several trials by the French Vasculitis Study group have employed the five-factor score (FFS) when determining the usefulness of immunosuppressive agents in the treatment of EGPA.<sup>7,8</sup> However, the FFS is designed to predict the

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mortality of heterogeneous necrotizing vasculitides (polyarteritis nodosa, microscopic polyangiitis, and EGPA), and it does not reflect common manifestations in the peripheral nervous system that may induce severe disability in patients with EGPA. This has prompted some clinicians to criticize the simple method of using the FFS.<sup>9</sup>

Based on our clinical experience, in 1995 we designed a protocol to treat EGPA-associated PN with CSs and CY. In the present study we analyzed the clinical features and long-term prognosis of EGPA-associated PN in patients treated with this protocol.

## METHODS

From January 1995 to April 2014, 71 patients were diagnosed with EGPA at Samsung Medical Center by specialized rheumatologists based on the American College of Rheumatology 1990 criteria. Sixty-one of these patients completed the treatment protocol and were followed up for more than 1 year. Demographic data, clinical features, laboratory findings, pathological findings, treatments, and outcomes were reviewed from the medical records of these 61 patients. Forty-six patients were diagnosed with PN by neuromuscular specialists after a neurological examination and nerve conduction study (NCS) using standard techniques. Additional analyses of the electrodiagnostic and neurological characteristics were performed. Biopsies were performed on various organs, most commonly the skin and sural nerve but also the gastrointestinal tract, nasopharynx, lung, kidney, and myocardium. The disability caused by EGPA involvement in the nervous system [including the central nervous system (CNS) and the peripheral nervous system] was assessed using the modified Rankin scale (mRS). As stated above, all patients were treated using a consistent treatment protocol. CSs were administered to all patients diagnosed with EGPA. Immediately after diagnosing a patient with EGPA, he or she was treated according to the protocol described below. Not only patients with an FFS of  $\geq 1$  but also those with peripheral nerve involvement received intravenous methylprednisolone pulse therapy at 1 g/day for 2 days, and then monthly intravenous CY pulse therapy for 6–18 months. The CS treatment was continued as oral prednisolone, with the dose determined according to the individual clinical course of each patient. A late responder was defined as needing monthly CY pulse treatment for more than 6 months or needing to receive long-term oral CY treatment. Complete recovery of PN was considered to have occurred when no symptoms and signs were found in the neurological examination. Azathioprine was used as a steroid sparing agent in two patients due to the temporary nonavailability of CY. Ethics approval was provided by the

institutional review board of Samsung Medical Center.

All statistical analysis was performed using SPSS software (version 20.0, IBM Corporation, Armonk, NY, USA). The Mann-Whitney U test and Fisher's exact test were used to compare the groups. Probability values of  $p < 0.05$  were considered to be indicative of statistical significance.

## RESULTS

### Comparison of clinical features according to the presence of PN

There were no significant differences between the patients with and without EGPA-associated PN in age at diagnosis, sex, laboratory and pathological findings, and organ involvement (Table 1). The mean age was 46.4 years (range 19–72 years) in PN(+) patients and 40.6 years (range 21–63 years) in PN(-) patients. At the time of EGPA diagnosis, 59 patients showed eosinophilia, whereas 2 had a normal eosinophil count after steroid use at other hospitals. Antineutrophil cytoplasmic antibody (ANCA) was detected in 11% of PN(+) patients, but was not detected in any of the PN(-) patients. A biopsy was performed in 44 patients, which revealed extravascular eosinophils in 80% and vasculitis in 77%, while no extravascular granuloma was observed.

More patients were treated with CY in the PN(+) group than in the PN(-) group (87% vs. 60%,  $p = 0.05$ ) since the protocol directs patients with PN to CY treatment. Although statistically nonsignificant, more patients had an FFS of  $\geq 1$  in the PN(+) group (33% vs. 9%,  $p = 0.75$ ).

There were three cases (5%) of CNS involvement: two with cerebral infarction and one with intracranial hemorrhage. Following the initial symptoms of PN, two had facial nerve involvement and one had vestibular nerve involvement. No CNS or cranial nerves were involved in the PN(-) patients. One PN(+) patient had central retinal artery occlusion associated with vasculitis.

### Clinical characteristics and NCS findings in PN(+) patients

Except one patient who presented only with skin lesions, all of the PN(+) patients showed peripheral neuropathic symptoms at the initial presentation of EGPA. Nonspecific constitutional symptoms such as fever, myalgia, and weight loss were seen in 11 (24%) of the 46 PN(+) patients. The mean interval from the diagnosis of asthma to the symptom onset of PN was 3.25 years, with a range from 0 to 53 years (Fig. 1). Fig. 2 shows the characteristics of EGPA-associated PN. Forty-four (95.6%) patients complained of neuropathic pain or dysesthesia. The sensory neuropathy was distributed mostly asymmetrically in the distal portion of the limbs, being more

common in the lower limbs than in the upper limbs (Fig. 2A). Motor neuropathy (regardless of sensory neuropathy) was seen in 24 (52.2%) patients, with similar distributions (Fig. 2B). Among the patients with motor neuropathy, 22 (92%) showed foot drop and 18 (75%) showed muscle weakness with a Medical Research Council grade of 3 or higher in at least one muscle.

The peroneal (67%) and sural (65%) nerves were the most commonly involved (Fig. 2C). The NCS revealed mononeuritis multiplex (MM) in 23 (54%) of 43 patients, mononeuropathy in 10 (23%), and symmetric axonal polyneuropathy in 7 (16%) (Fig. 2D).

### MM/mononeuropathy versus symmetric polyneuropathy

The sensory nerve action potential was absent in the bilateral sural nerve in all of the patients with symmetric polyneuropathy. Before treatment, patients with polyneuropathy exhibited lower amplitudes and slower conduction velocities in the sensory nerves (median, ulnar, and sural nerves) and motor nerves (tibial and peroneal nerves), as well as higher mRS scores (Table 2). However, there were no significant differences between the MM and polyneuropathy groups in laboratory and histological findings, rates of remission and relapse, and posttreatment mRS scores.

**Table 1.** Clinical and laboratory characteristics according to the presence of peripheral neuropathy (PN)

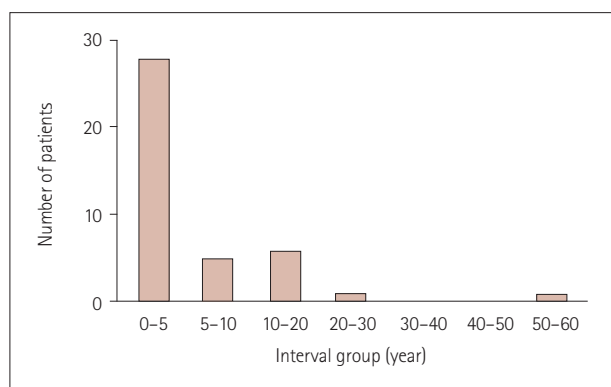
	EGPA patients with PN (n=46)	EGPA patients without PN (n=15)	p
Age at diagnosis, years; mean (range)	46.4 (19–72)	40.6 (21–63)	0.11
Males, n (%)	21, 46	7, 47	0.94
Follow-up duration, years; mean (range)	6.4 (1.2–18.8)	2.7 (1.7–5.2)	0.005
Duration of treatment with a corticosteroid and CY, months; mean (range)	9.7 (0–51.3)	6.2 (0–12.2)	0.19
Interval from the first symptom of EGPA to the beginning of treatment, months; mean (range)	4.9 (0–28.7)	3.09 (0–22.9)	0.43
FFS, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.62
FFS ≥ 1, n/total (%)	15/46 (33)	4/15 (9)	0.75
CY treatment, n/total (%)	40/46 (87)	9/15 (60)	0.05
Relapse rate, n/total (%)	5/46 (11)	1/15 (7)	1.0
Late responders, n/total (%)	24/46 (52)	6/15 (40)	0.55
Death, n/total (%)	2/46 (4)	0/15 (0)	1.0
Organ involvement, n/total (%)			
Lung	24/46 (52)	11/15 (73)	0.15
Skin	18/46 (39)	5/15 (33)	0.68
Gastrointestinal tract	4/46 (7)	3/15 (20)	0.34
Heart	10/46 (22)	2/15 (13)	0.71
Kidney	2/46 (4)	0/15 (0)	1.0
Central nervous system	3/46 (7)	0/15 (0)	0.56
Pathological findings, n/total (%)			
Eosinophil extravasation	26/31 (84)	9/11 (82)	1.0
Necrotizing vasculitis	27/31 (87)	7/11 (64)	0.17
Laboratory findings before initial treatment			
ANCA, n/total (%)	5/46 (11)	0/15 (0)	0.48
WBC count, median (IQR)	15.3 (11.6–23.2)	12.7 (11.7–18.3)	0.37
Eosinophil count, /μL; median (IQR)	2,045.0 (311.5–7,916.25)	2,850.0 (935.0–5,850.0)	0.90
Total IgE, U/mL; median (IQR)	634.0 (305.7–1,446.2)	743.0 (281.0–2,924.0)	0.46
CRP, mg/dL; median (IQR)	1.7 (0.5–5.5)	0.99 (0.2–6.1)	0.56
ESR, mm/hr; median (IQR)	21.0 (3.0–57.0)	32.0 (15.5–56.5)	0.26
ECP, median (IQR)	64.6 (23.4–201.0)	110.0 (54.5–283.5)	0.31

ANCA: antineutrophil cytoplasmic antibody, CRP: C-reactive protein, CY: cyclophosphamide, ECP: eosinophil cationic protein, EGPA: eosinophilic granulomatosis with polyangiitis, ESR: erythrocyte sedimentation rate, FFS: five-factor score, IQR: interquartile range, WBC: white blood cells.

**Treatment response and prognosis of EGPA-associated PN(+) patients**

Complete recovery of PN was observed in 66% of the patients with sensory neuropathy and 83% of those with limb weakness, and was associated with a lower age [logistic regression:  $\exp(B)=1.07, p=0.02$ ]. The mRS score improved by more than 1 point after treatment in 44 (95.6%) patients [ $2.43\pm 0.86$  vs.  $0.43\pm 0.95$  (mean $\pm$ SD)] before and after treatment, respectively;  $p<0.001$  (Fig. 3). Six of the 46 PN(+) patients did not receive CY treatment: three had very mild dysesthesia with normal NCS findings, and the other three received initial treatment with CSs at other hospitals. Five patients experienced relapse of EGPA, but relapse of neuropathy was seen in only one patient (with a worsened foot drop).

Twenty-four patients (52%) were late responders. There were two cases of mortality: one from pancreatic cancer unrelated to EGPA and the other from heart failure that was attributed to cardiac involvement of EGPA. The patient had severely depressed left ventricular systolic function at the time of initial presentation with EGPA. Adverse reactions to CS and CY combination treatment was observed in four patients: one developed hemorrhagic cystitis after 6 years of oral CY, one had transient alopecia, one visited our hospital with *Pneumocystis jirovecii* pneumonia after 13 cycles of CY treatment without prophylactic antibiotics, and one had a lung abscess due to *Klebsiella pneumoniae* related to alcoholism.

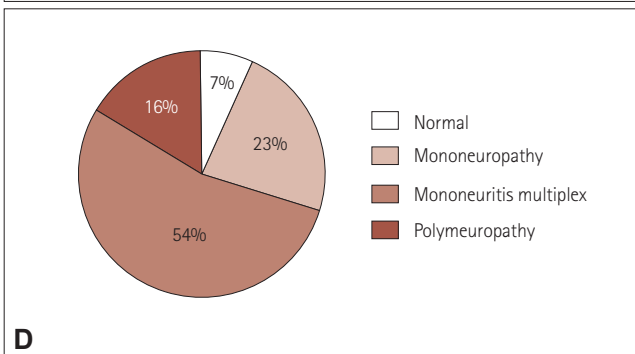
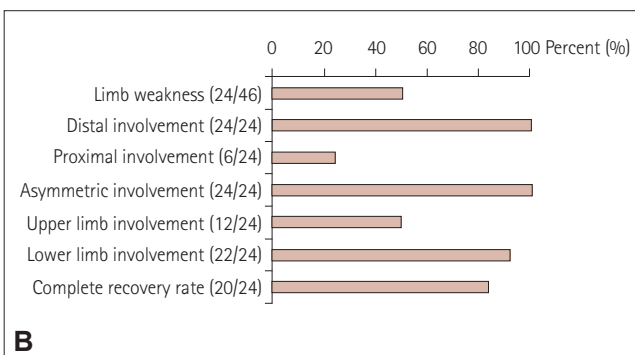
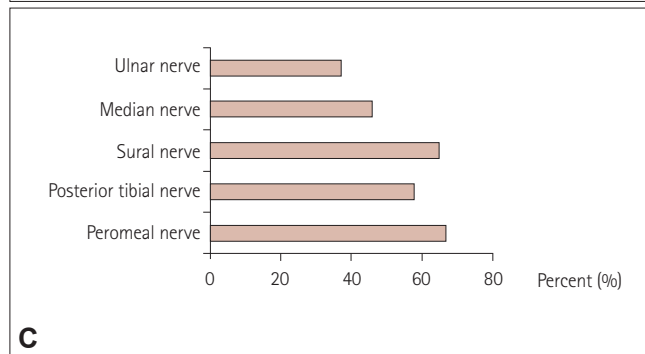
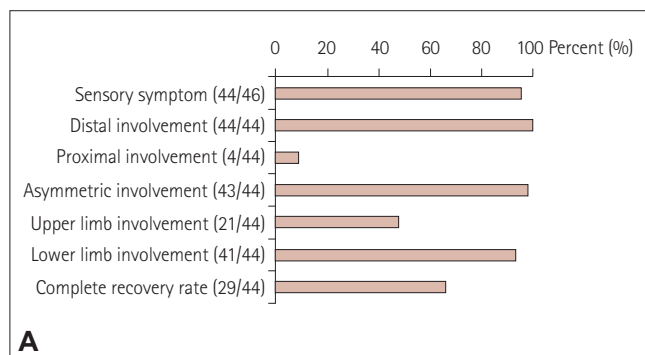


**Fig. 1.** Interval between the onset of asthma and peripheral neuropathy.

**DISCUSSION**

The present study has demonstrated that the prognosis of EGPA-associated PN can be excellent, with this being the first report of the complete recovery of neurological deficits in EGPA-associated PN. The mRS scores improved significantly after treatment, being less than 2 points in all except one patient who had intracranial hemorrhage.

Hattori et al.<sup>1</sup> found that the initial CS treatment induced definite improvement in the laboratory findings (including the eosinophil count) but no consistent functional neurological outcome. A particularly notable finding has been that patients who did not respond to CS treatment within 4 weeks



**Fig. 2.** Clinical and electrodiagnostic characteristics of patients with eosinophilic granulomatosis with polyangiitis-associated neuropathy. Characteristics of limb weakness (A), sensory symptom (B), nerve involvement (C), and PN pattern (D). PN: peripheral neuropathy.

reportedly showed poor long-term outcomes.<sup>6</sup> The excellent long-term outcomes in our patients are thought to be the result of aggressive CY treatment that was continued for 12 months or more in patients with unsatisfactory earlier responses.

The overall relapse rate was lower in this study than in previous studies.<sup>7,10</sup> Ribí et al.<sup>8</sup> reported failure in the remission induction or relapse in 42% of patients with an FFS of 0 who were initially treated only with CSs. Persistent or relapsed PN was observed in 37% of these patients, in contrast to 2% of cases with relapsed PN in the present study. It is notable that only 5 of 10 patients who received CY treatment in the study by Ribí et al.<sup>8</sup> achieved remission, with the other 5 (50%) requiring long-term oral immunosuppressive agents. The much lower rate of long-term immunosuppressive treatments (11%) in our study suggests that the early administration of CY treatment is important for inducing and maintaining EGPA remission. Moreover, the rate of treatment-related adverse reactions was low (8%), and adverse reactions due solely to CY were only observed in two patients taking oral CY for a long period. Consistent with a previous study finding fewer side effects with intravenous pulse CY than with daily oral CY,<sup>11</sup> no intravenous CY-related adverse reaction was observed in the present study. Although the French Vasculitis Study group found that 12-month CY pulse therapy was superior to 6-month CY pulse therapy in terms of the rates of complete remission and severe side effects,<sup>12</sup> our protocol of selectively continuing to 12-month CY pulse therapy based on assessing the response after 6 months of CY pulse therapy also showed favorable outcomes.

The rate of peripheral nerve involvement was high (75%) in this study, as also found in previous studies.<sup>7,10</sup> Some researchers have implicated that sex differences contribute to the variations in the reported rates of PN in EGPA (26.7% to 78.6%),<sup>3,6,13</sup> but the incidence rate of PN did not differ between male and female patients in the present study. The pattern of PN was similar to that found in previous studies, with MM being the most common manifestation. A study comparing MM and polyneuropathy in patients with Wegener's granulomatosis found greater functional disability in those patients with MM, but the final neurological outcomes did not differ between these two conditions at the end of the treatment follow-up.<sup>14</sup> In contrast, the patients with symmetric PN in the present study showed more severe findings in the NCS and mRS before treatment compared to those with MM. However, the laboratory findings, treatment response, and final functional outcomes did not differ between MM and polyneuropathy patients. One previous study found that MM generally progressed to polyneuropathy.<sup>6</sup> In the present study, MM progressed to polyneuropathy in only 1 of the 22 pa-

tients in whom follow-up NCS was performed. Among the patients with mononeuropathy, one progressed to MM and one recovered completely after treatment, with normal NCS findings. Another patient who had MM showed normal findings in the follow-up NCS, whereas there were few changes from the initial study in other patients.

As reported previously,<sup>6</sup> the peroneal nerve is the most frequently and severely involved nerve in the present study. Foot drop was observed in most of the patients with motor neuropathy, while CNS or cranial nerve involvement was infrequent. Although the symptoms due to cranial nerve involvement were completely reversed, one of the three patients with CNS involvement remained disabled with an mRS score of 4 after the completion of treatment. ANCA was found in 38–50% of patients with EGPA, and the antibodies for myeloperoxidase were detected frequently.<sup>15</sup> Other researchers have recently found that the presence of ANCA affects the pattern of nerve biopsy, clinical manifestations, and outcome of EGPA-associated PN.<sup>4,10,16</sup> In the present study, the overall rate of ANCA positivity was low (8%) and it tended to be present in the PN(+) group, which is compatible with previous reports of preferential PN involvement in ANCA-positive patients. However, no differences in the laboratory values, treatment response, and mortality rate were seen between ANCA-positive and ANCA-negative patients, although one of the ANCA-positive patients showed the most severe neurological disability (posttreatment mRS score of 4) with CNS involvement. Further larger scale studies are needed to clarify the clinical and pathological relationships between ANCA positivity and PN involvement in EGPA patients. Moreover, the low rate of ANCA-positive patients with EGPA in another study conducted in Korea indicates that racial differences might exist.<sup>17</sup>

A previous study observed an average interval of 10 years between the onset of asthma and the systemic symptoms of EGPA.<sup>10</sup> We saw a wide interval range of 0 to 53 years, with an average interval of 3.25 years (Fig. 1). The interval between the onset of asthma and EGPA was not associated with the severity of PN or the treatment response.

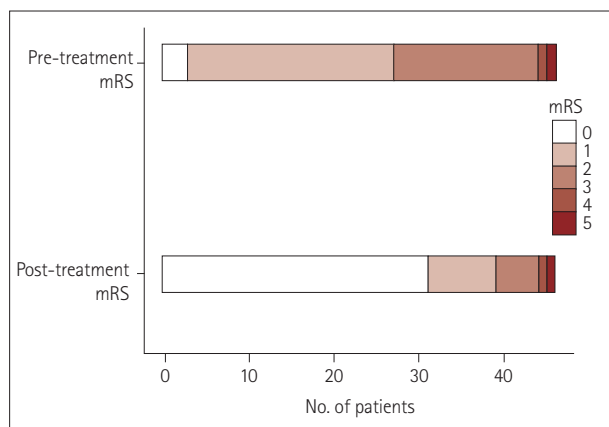
There is no treatment guideline for treating EGPA-associated PN despite this being the most frequent manifestation of the syndrome. In particular, the importance of PN when deciding the treatment strategy is often underestimated because it is not included in the FFS. The present study found excellent clinical outcomes without increasing the treatment-related adverse reactions by administering a CS in combination with CY in patients with EGPA-associated PN without involvement of the heart, kidneys, gastrointestinal tract, or CNS. In particular, the motor functions improved significantly in most patients after the treatment.



**Table 2.** Clinical features according to the pattern of PN

	Symmetric axonal polyneuropathy pattern group (n=7)	Mononeuritis multiplex group (n=23)	p
Age at diagnosis, years; mean (range)	51 (42–61)	16 (19–72)	0.45
Males, n (%)	3 (42)	17 (47)	0.94
ANCA, n (%)	2 (28)	3 (8)	0.08
Follow-up, years; mean (range)	8.62 (3.65–16.84)	5.63 (1.21–18.88)	0.23
FFS, median (IQR)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.59
FFS ≥1, n (%)	3 (43)	12 (33)	0.53
CY treatment, n (%)	7 (100)	32 (89)	0.05
Relapse, n (%)	1 (14)	4 (11)	1.0
Late responsiveness to CY treatment, n (%)	2 (28)	21 (58)	0.35
mRS score before treatment, median (range)	2.8 (2–5)	2.3 (1–4)	0.04
mRS score after treatment, median (range)	0.5 (0.0–4.0)	0.4 (0.0–4.0)	0.94
Death, n (%)	1 (14)	1 (3)	0.39
NCS findings, mean±SD			
Median nerve			
NCV (m/s)/CMAP (mV)	38.4±22.63/9.7±9.1	44.9±22.7/10.8±6.8	0.16/0.94
SCV (m/s)/SNAP (µV)	24.8±22.7/6.5±8.9	41.1±16.5/28.4±24.6	0.02/0.05
Ulnar nerve			
NCV (m/s)/CMAP (mV)	41.6±24.3/7.5±5.4	50.8±19.8/11.1±6.7	0.16/0.21
SCV (m/s)/SNAP (µV)	25.0±23.0/20.2±15.9	41.1±16.5/28.4±24.6	0.02/0.03
Tibial nerve			
NCV (m/s)/CMAP (mV)	22.0±20.9/4.0±5.6	34.6±19.7/9.7±12.1	0.08/0.33
Peroneal nerve			
NCV (m/s)/CMAP (mV)	13.0±18.6/1.1±1.5	32.3±22.1/2.9±3.2	0.04/0.23
Sural nerve			
NCV (m/s)/SNAP (µV)	0.0±0.0/0.0±0.0	29.0±19.8/5.73±6.5	0.01/0.01
Not evoked (%)	100	30	

ANCA: antineutrophil cytoplasmic antibody, CMAP: compound muscle action potential, CY: cyclophosphamide, FFS: five-factor score, NCS: nerve conduction study, NCV: nerve conduction velocity, NE: not evoked, mRS: modified Rankin scale, PN: peripheral neuropathy, SNAP: sensory nerve action potential, SVC: sensory conduction velocity.



**Fig. 3.** Neurological disability [modified Rankin scale (mRS) score] before and after the treatment.

This retrospective study had the limitation of being carried out in a single tertiary center. However, all of the patients had been diagnosed and treated under a consistent protocol since 1995 and all of them suspected of having PN were referred to

a specialized neurologist, which might have avoid the limitation of the study having a retrospective design. Considering the rarity of the disease, 61 patients from a single center is a large number to be able to include in a study on EGPA.

In conclusion, EGPA-associated PN causes great discomfort and disability in the everyday lives of the affected patients, and it occurs in a large proportion of patients with EGPA. However, PN rarely relapses, and shows an excellent functional outcome when treated early with CY in combination with a CS.

**Conflicts of Interest**

The authors have no financial conflicts of interest.

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