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Acute therapeutic effects and pathophysiology of eosinophilic granulomatosis with polyangiitis neuropathy

Nanami Yamanaka ,[1] Yukio Takeshita,[2,3] Ryota Sato ,[1] Takashi Nawata,[4] Tatsuya Okafuji,[2] Susumu Fujikawa,[1] Miwako Fujisawa,[1] Kinya Matsuo,[1] Joe Nemoto,[1] Yuki Mizumoto,[1] Hideaki Nishihara,[1] Masaya Honda,[1] Mariko Oishi,[1] Toshihiko Maeda,[1] Fumitaka Shimizu ,[1] Michiaki Koga ,[5,6] Takashi Kanda,[7] Masayuki Nakamori [1,8]

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NY and YT contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Yukio Takeshita;
takeshy@yamaguchi-u.ac.jp

ABSTRACT

Objective This study investigated the effects of early treatment and pathophysiology on eosinophilic granulomatosis with polyangiitis neuropathy (EGPA-N).

Methods Twenty-six consecutive patients with EGPA-N were diagnosed and treated within a day of admission and underwent clinical analysis. Peripheral nerve recovery rates were evaluated after early treatment by identifying the damaged peripheral nerve through detailed neurological findings.

Results The eosinophil count at onset was significantly correlated with the total number of damaged nerves. There was a strong correlation between the timing of treatment and the recovery rate in patients who started treatment within 50 days, as the recovery rate did not increase after 50 days of treatment. Antineutrophil cytoplasmic antibodies (ANCA)-negative cases showed significantly higher recovery rates than ANCA-positive cases. Vasculitis was detected in 67% of ANCA-positive and 29% of ANCA-negative patients in the sural nerve and skin biopsy specimen. In addition, infiltration of eosinophils into peripheral nerve tissues was observed in 40% of ANCA-negative patients, whereas it was absent in ANCA-positive patients. Intrafascicular oedema was found in 95% of all patients.

Discussion Our results suggest three pathological pathways: (1) ischaemic peripheral nerve due to vasculitis mainly in ANCA-positive cases, (2) direct infiltration and degranulation of eosinophils in ANCA-negative cases and (3) progression of axonal ischaemia due to intrafascicular oedema in both cases. The study also found that ANCA-negative cases exhibited better responsiveness to acute-phase treatment than ANCA-positive cases. It is essential to treat patients with EGPA-N as early as possible because the patients could recover time-dependently within 50 days of the onset.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Eosinophilic granulomatosis with polyangiitis (EGPA) patients may exhibit different pathophysiology depending on their antineutrophil cytoplasmic antibodies (ANCA) status. However, the efficacy of acute-phase treatments for EGPA, including differences between ANCA-positive and ANCA-negative subgroups, remains unclear.

WHAT THIS STUDY ADDS

⇒ This study demonstrated a strong correlation between the timing of treatment initiation and neurological recovery, showing that patients who started treatment more than 50 days after symptom onset did not achieve recovery. Furthermore, ANCA-negative cases showed a higher recovery rate compared with ANCA-positive cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlighted the importance of early treatment for EGPA neuropathy. It also demonstrated differences in treatment responsiveness and pathological findings between ANCA-positive and ANCA-negative cases, contributing to a better understanding of the disease mechanisms.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a type of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) and caused by inflammation of the small blood vessels. Bronchial asthma and eosinophilic sinusitis usually precede EGPA, and about 90% of patients with peripheral blood eosinophilia develop neuropathy.[1 2] Churg and Strauss *et al* first reported this in 1951.[3] This disease was called as Churg-Strauss syndrome or allergic granulomatous angiitis, and relabelled as EGPA in 2012.[4] While granulomatosis with polyangiitis (GPA) and microscopic polyangiitis have high ANCA-positive rates, the rate is lower for EGPA—50% or less.[5 6] EGPA patients may exhibit different

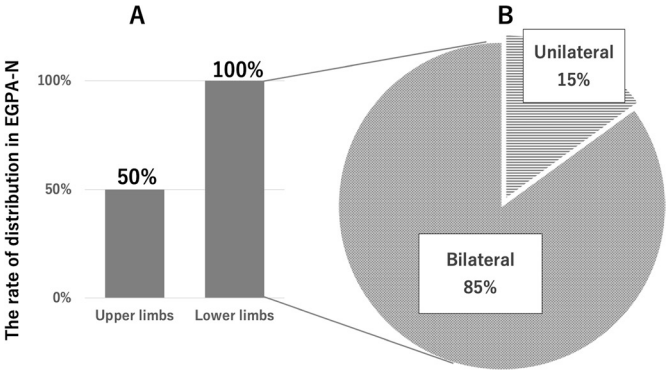

Figure 1 Evaluation of EGPA neuropathy site distribution. Of the 26 patients with EGPA, 50% showed neurological symptoms in the upper limbs, while 100% showed neurological symptoms in the lower limbs (A). 85% of patients who experienced neurological symptoms in the lower limb showed bilateral involvement (B). EGPA, eosinophilic granulomatosis with polyangiitis.

pathophysiology depending on their ANCA status, due to reported differences in genetic background between ANCA-positive and ANCA-negative patients.[7]

EGPA neuropathy (EGPA-N) usually causes distal-predominant multiple mononeuropathies,[8] potentially leading to irreversible neurological problems. Previous studies have suggested that EGPA neuropathy is primarily caused by an arterial blockage secondary to vasculitis, which results in ischaemic axonopathy. However, few studies have examined the acute-phase of EGPA-N,[9 10] making it difficult to determine the exact pathway of EGPA-N. Additionally, the efficacy of treatments administered during the acute-phase is unknown due to the limited number of early-treated patients.

Our institution established a plan to evaluate EGPA-N patients within 12 hours of admission to address these issues. This study included 26 consecutive patients with

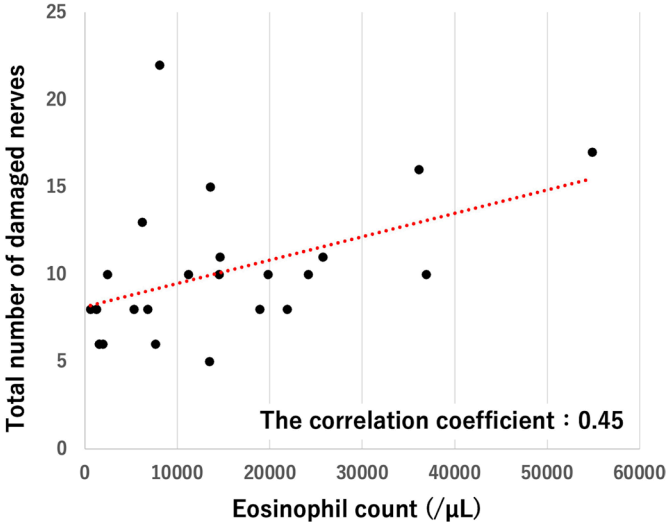

Figure 2 Correlation between pretreatment eosinophil count and the total number of damaged nerves. The correlation coefficient between the pretreatment eosinophil count and the number of damaged nerves was 0.45.

EGPA-N and involved neurological, haematological, pathological and therapeutic analyses to determine the pathophysiological pathway and the efficacy of acute interventions.

METHODS

Patients

Between 2005 and 2023, we examined 26 patients consecutively diagnosed with EGPA[11 12] based on neurological, haematological and therapeutic retrospective-analyses. We recorded each patient's age, sex, impaired nerves, ANCA-positivity, time from neuropathy onset to treatment commencement, eosinophil count before treatment and peripheral nerve recovery rate 4 weeks after treatment. Of the 26 cases, 92% (24/26) had no prior treatment interventions with immunosuppressants, biologics, intravenous immunoglobulin (IVIg) or glucocorticoid therapies before visiting our hospital. The acute-phase treatment for 88% of the patients (23/26) was methylprednisolone pulse therapy, while the remaining patients received moderate-to-high-dose oral prednisolone (PSL). Additionally, intravenous cyclophosphamide was used in 8% (2/26) of cases. On the other hand, there were no cases where IVIg or mepolizumab was used during the acute phase. The Institutional Review Boards of Yamaguchi University Graduate School of Medicine approved all study protocols.

Patient and public involvement

No 'Patient and public involvement'.

Identification and analysis of peripheral neuropathy and peripheral nerve recovery rate

Neurological symptom onset was defined as follows: sensory disturbances were identified as the sensory symptoms (such as paresthesia or hypoesthesia) that were consistent with the distribution of the peripheral nerve, and the motor disturbances were described as the muscle weakness that was compatible with the distribution of the peripheral nerve. We evaluated 12 nerves in the upper and lower limbs, including the median, ulnar, radial, musculocutaneous, axillary, femoral, saphenous, tibial, common peroneal, superficial peroneal, deep peroneal and sural nerves. The damaged nerves were identified by assessing muscle weakness in the dominant muscle and sensory impairment in the dominant region. The manual muscle testing (MMT) scores in the innervating muscles and the sensory impairment scale in sensory areas of the damaged nerves were compared before and 4 weeks after treatment. Nerves that had recovered by at least 1 point on the MMT score in innervating muscles and at least 2 points on a 10-point sensory impairment scale in sensory regions were considered as 'recovered' nerves. These indications were chosen because they represent the minimal reproducible changes in objective neurological findings. The peripheral nerve recovery rate was calculated by dividing the number of peripheral nerves

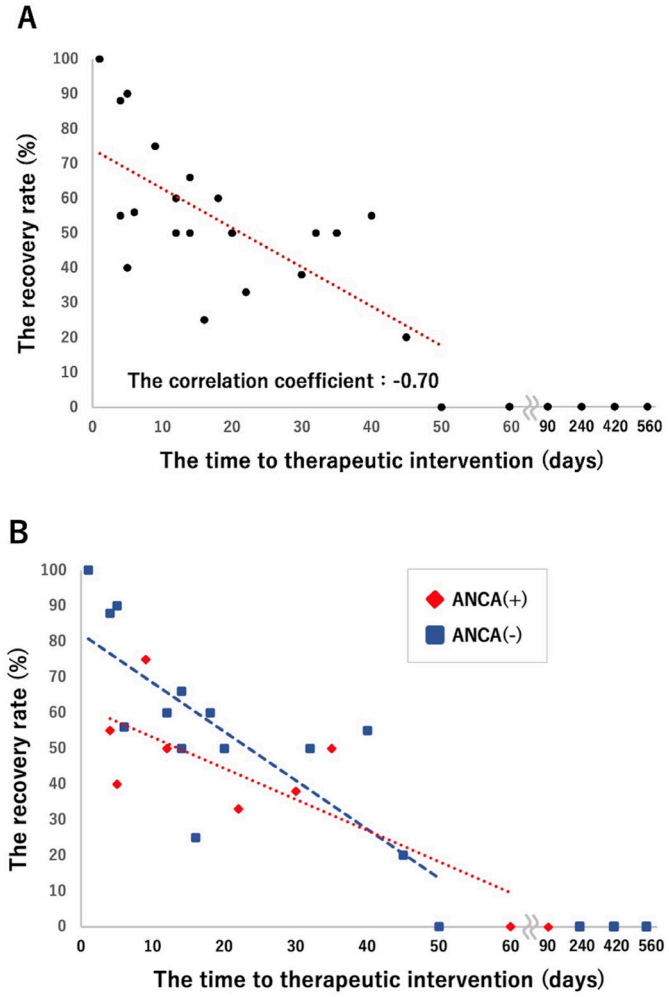

Figure 3 Correlation between the time from the onset of neuropathy to the commencement of treatment and the peripheral nerve recovery rate. The correlation coefficient between the recovery rate 4 weeks after treatment initiation and the time to therapeutic intervention within first 50 days was −0.70 (A). Patients who underwent therapeutic intervention 50 days or more after the onset of neuropathy showed a peripheral nerve recovery rate of 0%. A significant difference was observed in the regression line between ANCA-positive and ANCA-negative patients ($p<0.05$) (B). ANCA, antineutrophil cytoplasmic antibodies.

with muscle and sensory impairment recovery by the total number of impaired peripheral nerves. In cases where a sural nerve biopsy was performed, the sural nerve was excluded from the total number of impaired nerves used in the calculation of the recovery rate.

Biopsies and neuropathological studies

Twenty patients underwent sural nerve biopsy. In addition to routine H&E staining, epon-embedded toluidine blue staining was performed to determine the degree of oedema and neurological deficits within the nerve bundles. Some patients' specimens underwent electron microscopic analyses. The following pathological findings (1) perivascular inflammatory cell infiltration, (2) vascular occlusion, (3) vascular recanalisation and/or (4) fibrinoid degeneration of blood vessels implied vasculitis.

Statistical analysis

Statistical analyses were performed with GraphPad Prism V.10.0 software (GraphPad, San Diego, CA). The correlation between the pretreatment eosinophil count and the number of damaged nerves, and between the recovery rate and the time to treatment intervention, was quantified by reporting the correlation coefficient. Generally, a correlation coefficient |0.1–0.3| is considered a small effect, |0.3–0.5| a medium effect and >|0.5| a large effect. Two regression lines of ANCA-positive and ANCA-negative patients were compared by analysis of covariance. Statistical significance was defined as a two-sided $p<0.05$.

RESULTS

Clinical and haematological analyses of EGPA neuropathy

The department provided a definitive diagnosis and commencement of treatment within 24 hours of presentation, with a sural nerve biopsy rate of 77%. Of all the patients, 35% tested positive for ANCA (89% of ANCA-positive patients were MPO-ANCA); 77% were female, and the median age was 62.5 years (range: 39–77). In their medical history, 85% of the patients had a history of asthma, 31% had purpura, 19% had sinusitis, 15% had eosinophilic pneumonia, 12% had otitis media and 4% had nephritis.

Distribution of EGPA neuropathy

After analysing the distribution of EGPA sites across the 26 patients, we found that 50% showed upper limb neurological symptoms. In contrast, 100% showed symptoms in the lower limb (figure 1A). Eighty-five per cent of patients with lower limb presentation showed bilateral symptoms (refer to figure 1B).

Correlation between the pretreatment eosinophil count and the degree of nerve damage

The median baseline pretreatment eosinophil count was 12 326/μL, and, on average, 9.8 peripheral nerves were damaged. The correlation coefficient between the pretreatment eosinophil count and the number of damaged peripheral nerves was 0.45, indicating a significant, positive and moderately strong correlation with the extent of nerve damage (figure 2).

Correlation between treatment intervention duration and the peripheral nerve recovery rate

The time from the beginning of peripheral neuropathy to initiating therapy varied from 1 to 560 days, with a median of 19 days. Patients who began initial therapeutic intervention more than 50 days after the onset of neuropathy had a recovery rate of 0%. In ANCA-positive patients in this study, those who started treatment more than 60 days after onset showed a 0% recovery rate. Similarly, among ANCA-negative patients, those who started treatment more

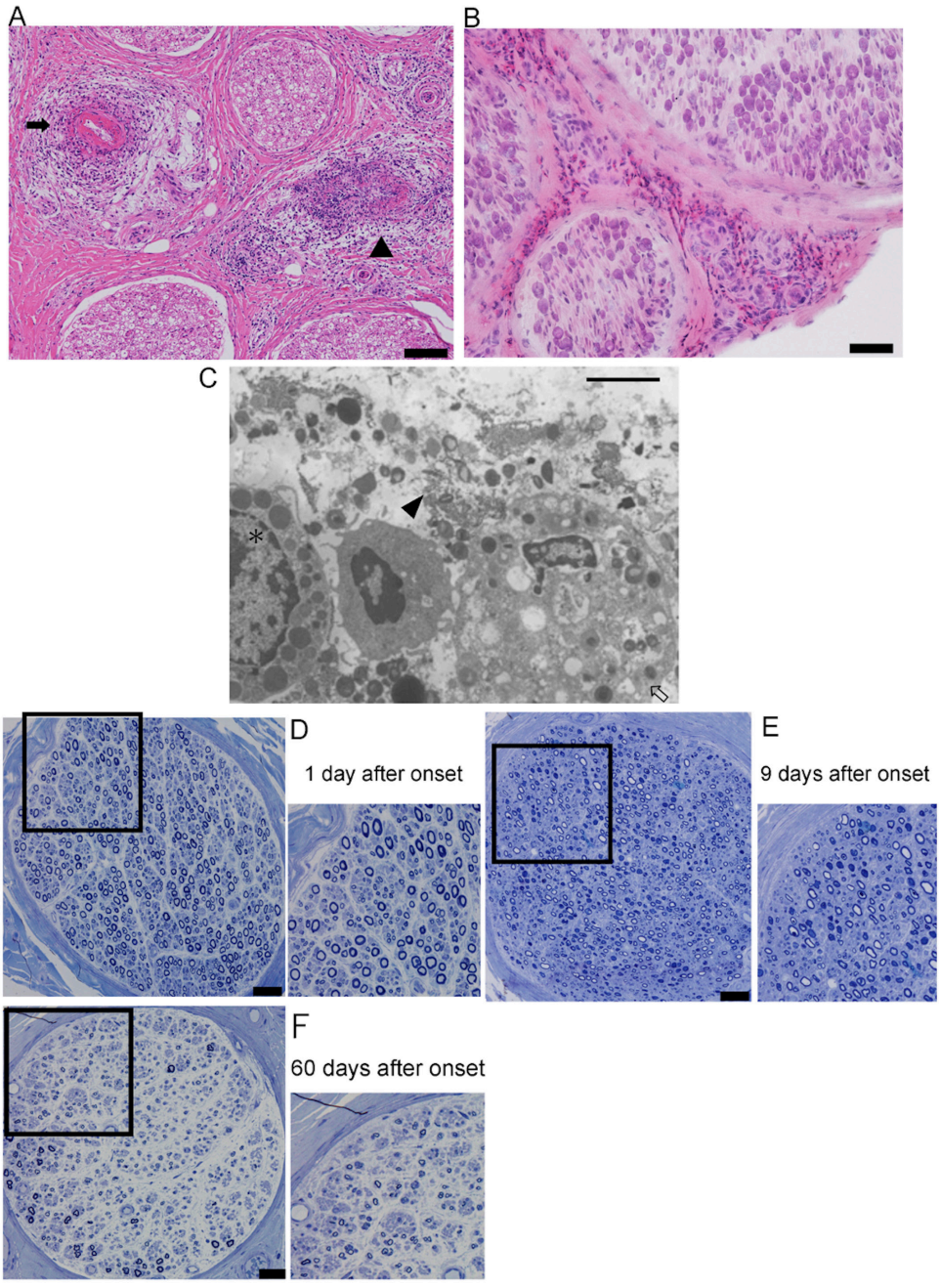

Figure 4 Pathologic features in the sural nerve of EGPA neuropathy. The image of vasculitis via H&E staining for EGPA neuropathy (A: ANCA-positive patient) showed perivascular inflammatory cell infiltration (black arrow) and vascular occlusion due to vasculitis (black arrowhead) (bar: 100 µm). The image of eosinophilic infiltration into peripheral nerve tissues in H&E staining for EGPA neuropathy (B: ANCA-negative patient) showed eosinophil degranulation in peripheral nerve tissues by electron microscopic analysis (C: ANCA-negative patient). Eosinophils with granules inside (*), degranulated eosinophils (arrow) and released granules (arrowhead) were observed (bar: 5 µm). Sural nerves in EGPA-N patients on days 1, 9 and 60 of the onset of neuropathy were stained with epon-embedding toluidine blue staining (D: 1 day after onset (ANCA-negative patient), (E): 9 days (ANCA-positive patient), (F): 60 days (ANCA-negative patient)). Myelin ovoids and an inhomogeneous loss of nerve fibres in nerve fascicles proceeded in a time-dependent manner (D–F) bar: 50 µm. ANCA, antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis.

than 50 days also had a 0% recovery rate. A strong inverse correlation was observed between the peripheral nerve recovery rate and the timing of therapy initiation, evidenced by a correlation coefficient of −0.70 within the first 50 days (figure 3A). Further, the correlation coefficient between recovery rate and the time from onset of neuropathy to treatment intervention was −0.77 for ANCA-positive patients, while for ANCA-negative patients, it was −0.79. A significant difference was revealed in the regression lines between ANCA-positive and ANCA-negative patients ($p<0.05$) (figure 3B).

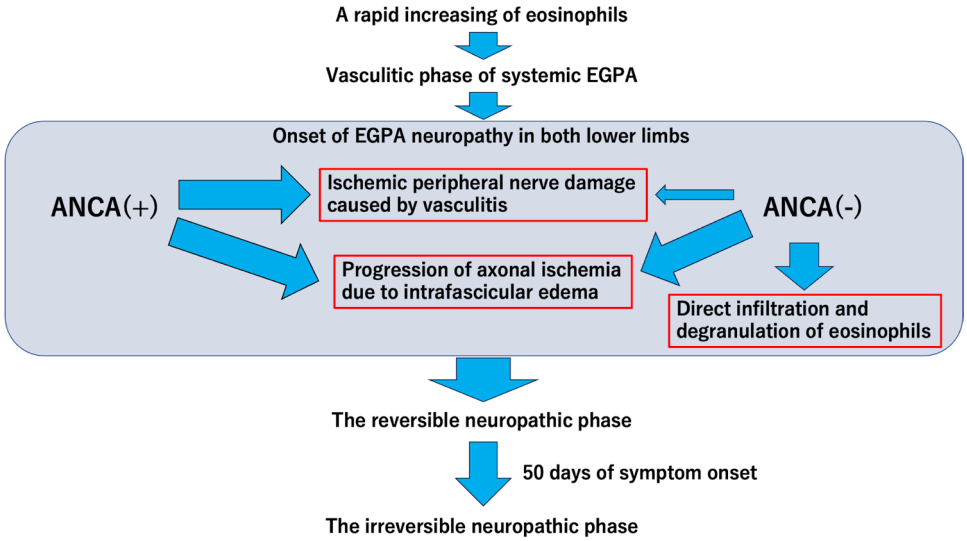

Figure 5 Pathophysiology of EGPA neuropathy. In patients with eosinophilic granulomatosis with polyangiitis (EGPA) neuropathy, multiple mononeuropathies were induced in both lower limbs during the vasculitic phase due to the following three conditions: (1) ischaemic peripheral nerve due to vasculitic arterial occlusion in peripheral innervation vessels in ANCA-positive patients, (2) direct infiltration and degranulation of eosinophils into peripheral nerves in ANCA-negative patients and (3) progression of axonal ischaemia due to intrafascicular oedema. There is a reversible neuropathic phase within 50 days after the onset of EGPA neuropathy. ANCA, antineutrophil cytoplasmic antibodies.

Pathological analysis of EGPA neuropathy

Peripheral nerve pathology indicated vasculitis in 40% of patients who underwent biopsy (figure 4A); 67% of ANCA-positive patients showed vasculitis, while only 29% of ANCA-negative patients. Eosinophilic infiltration into peripheral nerve specimens was seen in 40% of patients (figure 4B). Interestingly, none of the ANCA-positive patients showed eosinophil infiltration. In 95% of cases (19/20), intrafascicular oedema was observed. Electron microscopy analysis revealed infiltration and degranulation of eosinophils in ANCA-negative patients (figure 4C). Epon-embedded toluidine blue staining showed a time-dependent loss of nerve fibres and myelin ovoids in ANCA-positive and ANCA-negative patients (figure 4D–F). On the first day of onset, only mild oedema was identified in the sural nerve pathology (figure 4D). On the 9 days after onset, a few losses of nerve fibres and some myelin ovoids were seen (figure 4E). Finally, on the 60 days after onset, few nerve fibres were observed (figure 4F).

DISCUSSION

This is the first study to investigate the relationship between the time from neuropathy onset to treatment commencement and the therapeutic response to early intervention in EGPA-N. This study revealed four major findings: (1) almost all patients (95%) had multiple mononeuropathy in the lower limbs; (2) there was a correlation between the number of eosinophils and the total number of damaged peripheral nerves at the onset of neuropathy; (3) patients treated more than 50 days after the onset of neuropathy had a peripheral nerve recovery rate of 0%. Whereas, those treated within 50 days showed a strong correlation between the timing of treatment and the recovery rate. Moreover, higher recovery rates were observed in ANCA-negative cases compared with ANCA-positive cases; (4) pathological analysis revealed that vasculitis occurred mainly in ANCA-positive patients, and that eosinophil infiltration and degranulation into peripheral nerve tissues were observed in ANCA-negative patients, while intrafascicular oedema was seen in almost all patients.

Based on these neurological, haematological, pathological and therapeutic findings, we speculate on the effects of acute EGPA-N intervention and the pathophysiological pathways.

Acute intervention for ANCA-positive and ANCA-negative EGPA neuropathy

This study identified a connection between the recovery rate and the time from onset to treatment commencement for EGPA-N. The recovery rate showed an inverse correlation with the time to treatment within the first 50 days of onset. This suggests that nerve dysfunction may still be reversible during the acute phase within the initial 50-day period. Additionally, ANCA-negative cases respond more effectively to treatment in the acute phase than ANCA-positive cases.

Depending on ANCA-positivity in EGPA-N, this different pathophysiology may be caused by genetic factors like HLA-DQ and IL-5 mutations.[7] Pathological analyses have confirmed that ANCA-positive patients showed frequent vasculitis findings. These findings indicated that vasculitic inflammation and occlusion occurred in the terminal arteries of peripheral nerves. As a result, ANCA-positive patients suffer from ischaemic peripheral neuropathy because of the lack of blood supply from the collateral circulation. In contrast, ANCA-negative patients showed

direct infiltration of eosinophils into peripheral nerve tissues. Eosinophil granules contain cytotoxic proteins such as eosinophil cationic proteins and monocyte chemoattractant protein,[13] which can damage peripheral nerve tissues and cause EGPA neuropathy. Based on the above, it is suggested that ANCA-positive patients are more susceptible to irreversible damage due to ischaemia of the terminal arteries. There are two possible reasons for the absence of eosinophilic pathology in ANCA-positive cases. First, the number of ANCA-positive cases that underwent biopsy was small. Second, we also think that eosinophilic pathology depends on the tissue specificity of the peripheral nerve itself. Thus, not eosinophilic pathologies but vasculitic pathologies in ANCA-positive cases could be a critical factor in the mechanism of EGPA neuropathy.

Pathophysiological pathway of EGPA neuropathy

The previous section has highlighted that vasculitis is the leading cause of ANCA-positive patients, whereas eosinophilic infiltration is the leading cause of ANCA-negative patients. Moreover, regardless of ANCA-positivity, almost all EGPA-N patients demonstrated severe intrafascicular oedema. It is believed that this oedema can cause ischaemic injury due to the nerve bundles' anatomical characteristics. Specifically, nerve haemodynamics in the peripheral area are linked to the vasa vasorum's flow, which goes through the epineurium and the nerve sheath into the nerve bundles. It is important to note that the perineurium is reached through an oblique pathway rather than a direct one.[14] When the pressure inside the nerve sheath increases, the blood vessels that enter through an oblique route are compressed like a check valve to prevent peripheral nerve herniation caused by oedema. When inflammation induces severe swelling, the check valve mechanism further reduces blood flow in the feeding vessels, leading to severe ischaemia in the nerve bundles.

Finally, we propose three pathological pathways for acute EGPA-N, as shown in figure 5: (1) ischaemic peripheral nerve damage caused by arterial occlusion in peripheral innervation vessels, (2) peripheral neuropathy due to direct infiltration and degranulation of eosinophils into peripheral nerves and (3) progression of axonal ischaemia due to intrafascicular oedema. Then, it is crucial to treat patients as early as possible because the reversible neuropathic phase can be seen during acute intervention of EGPA-N, regardless of ANCA-positivity.

This study has some limitations. First, it was a retrospective study with a small number of cases; hence, the potential selection bias was not eliminated. Second, the evaluation of peripheral nerve recovery rate was inaccurate because the sensory impairment scale was subjective.

Author affiliations
[1]Department of Neurology and Clinical Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, Japan
[2]Blood-Brain Barrier Research Center, Yamaguchi University School of Medicine, Ube, Japan
[3]Department of Neurotherapeutics, Yamaguchi University School of Medicine, Ube, Japan
[4]Division of Cardiology Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan
[5]Department of Neurology and Clinical Neuroscience, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan
[6]Faculty of Medicine and Health Sciences, Yamaguchi University School of Medicine Graduate School of Medicine, Ube, Japan
[7]Department of Neurology, Neuromuscular Center Yoshimizu Hospital, Shimonoseki, Japan
[8]Research Institute for Cell Design Medical Science, Yamaguchi University, Ube, Japan

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Contributors YT is the guarantor of this work and accepts full responsibility for the overall content, the conduct of the study, access to the data, and the decision to publish. The study was conceptualised and designed by YT, TK and MN. YT, TO and NY contributed to drafting the article and calculated the peripheral nerve recovery rates. RS, JN and MF analysed the pathological data. YM, KM, SF, HN, MH, MO, TN, TM, FS and MK selected the eosinophilic granulomatosis with polyangiitis (EGPA) patients from all patients at Yamaguchi University Hospital. I used ChatGPT-4 to proofread part of the English text.

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Competing interests The authors declare the following conflicts of interest. YT affiliates with Endowed Department (Neuromuscular Center Yoshimizu Hospital). YT has received research funding from Takeda Pharmaceutical Company, Daiichi Sankyo Company, Chugai Pharmaceutical Company and Japan Blood Products Organization. There are no conflicts of interest for the other coauthors.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Center for Clinical Research. Yamaguchi University Hospital: 2021-073. Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Nanami Yamanaka http://orcid.org/0009-0007-5017-8711
Ryota Sato http://orcid.org/0000-0003-1691-1776
Fumitaka Shimizu http://orcid.org/0000-0003-4163-2939
Michiaki Koga http://orcid.org/0000-0002-1356-955X
Masayuki Nakamori http://orcid.org/0000-0003-4714-3044

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