

Lower Limbs Axonal Neuropathy in Polyarteritis Nodosa with Onset of Neuropathic Symptoms

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Abstract

Objective

The retrospective study aimed to investigate the most common electrophysiological changes in patients with polyarteritis nodosa (PAN) of peripheral neuropathy onset and supply some clinical data to neurologists to pay attention to PAN.

Methods

We reviewed the records of all PAN patients with peripheral neuropathy as the initial symptom who attended The Second Hospital of Hebei Medical University from December 2019 to December 2020. Finally, ten patients and thirteen healthy controls were clinical and electrophysiologically investigated in our study.

Results

Disease onset was subacute or acute style, with asymmetric clinical onset. Nine patients (90%) presented clinical onset from lower limbs, one (10%) from both lower and upper limbs. Symptoms of distal limbs were more severe than those of proximal ones in seven patients (70%). Nerve conduction studies revealed motor and sensory axonal neuropathy with a predilection for peroneal and sural nerves in the lower limbs.

Conclusions

Asymmetric motor and sensory axonal neuropathy, especially severe involvement of lower and distal limbs is the most electrophysiological changes in patients with PAN of peripheral neuropathy onset, which is consistent with clinical manifestation.

Introduction

Polyarteritis nodosa (PAN) is a necrotizing vasculitis involving medium and small arteries^{1,2}. PAN is a systemic disease and affects patients of any sex or ethnic background. Before vaccination against hepatitis B virus (HBV) was available, more than one third of adults with PAN were infected by HBV. The incidence rate of PAN decreased significantly^{3,4}, as there is widespread vaccination all over the world and increased awareness and improved diagnostic techniques to help doctors to recognize other systemic necrotizing vasculitis (i.e., ANCA-associated vasculitis, cryoglobulinemic vasculitis) as distinct entities. Although PAN is not fully understood, available evidence suggests that the pathogenesis is different than 30 years ago. Necrotizing inflammation of the blood vessels probably involve both the innate and adaptive immune systems⁵, induced by chronic viral infections⁶, paraneoplastic syndrome⁷, immune

deficiencies^{8,9}, gene mutant (*DADA2*^{10,11}, *SAVI*¹², *FMF*¹³) etc. The most widely implicated mechanism is the development of lesions induced by immune complexes. PAN is becoming a rare disease, together with the highly variable clinical presentation of PAN, prompt identification of PAN is important because they are associated with an increased risk of mortality.

Peripheral neuropathy is often the most frequent and earliest symptom of PAN¹⁴. Vasculitis neuropathy as a usual manifestation of PAN occurs in 50–75% of PAN patients^{15,16}. Nerve conduction studies (NCS) are an essential tool in the evaluation of the peripheral nervous system. Although it is well known that axonal neuropathy affects one or more nerves in system vasculitis neuropathy, more detailed peripheral nerve injury needs to be determined to identify PAN more quickly. Therefore, we conducted the retrospective study to investigate the most common electrophysiological changes in patients with PAN of peripheral neuropathy onset and supply some clinical data to neurologists to pay attention to PAN.

Methods

Study population

We reviewed the records of all PAN patients who attended The Second Hospital of Hebei Medical University from December 2019 to December 2020. Patients who met the following standards were included in the study: (1) The final diagnosis was PAN by a rheumatologist in accordance with American College of Rheumatology (ACR)/CHCC criteria. (2) Initial symptom was peripheral neuropathy and first visited to a neurologist. (3) On admission, the physical examination revealed one or more symptoms of peripheral neuropathy. (4) None of patients received immunotherapy or other treatments before neurophysiological assessment. (5) Nerve conduction examination was performed immediately after the first neurology outpatient visit. (6) Patient was excluded due to other etiologies of neuropathy at any time. Totally, 10 PAN patients were included in our study. Clinical characteristics and electrophysiological findings were extracted from the medical records. And 13 matched healthy controls were recruited from volunteers and all wrote informed consents.

Electrophysiological Assessment

Electrophysiological assessment was performed with a Dantec Keypoint EMG machine and done following standard procedures¹⁷. Nerve conduction studies (NCS) were performed on the more severe side, if abnormal involved both sides in PAN patients. In addition, the right side was a routine option for patients with normal extremities and healthy controls. Sensory nerve action potential (SNAP) by anterograde recording method in all subjects were performed on median, ulnar and sural nerves. Motor NCS were conducted on median, ulnar and peroneal nerves. While recording the compound muscle action potential (CMAP), the median nerve was stimulated at the wrist and elbow; the ulnar nerve was stimulated at the wrist and proximal elbow; and the peroneal nerve was stimulated at the ankle and above fibula head. Measurements included distal latency, nerve conduction velocity (NCV) and amplitude

(value from baseline to negative peak). The F-wave latency (FWL) and frequency (FWF) were calculated after 20 stimulations on median, ulnar and peroneal nerves. Room temperature was maintained to ensure that the skin temperature remained at $> 31^{\circ}\text{C}$ during all recording time.

Statistical Analysis

Patient characteristics are reported as the number and percentage for categorical variables. Continuous variables were expressed as mean \pm standard deviation (SD), whereas categorical data were presented as proportions. Differences in data between the 2 groups were analyzed by Mann–Whitney U-test. Two-tailed P value < 0.05 was statistically significant. All analyses were conducted with IBM SPSS Version 21 (Ehningen, Germany).

Results

Clinical characteristics

The 10 PAN patients included 6 females, and clinical characteristics were shown at Table 1. The median age on visit was 55.8 ± 15.47 years. Time from disease onset to electrophysiology examination was 3.77 ± 2.34 months. The frequent onset pattern was subacute (80%) followed by acute type (20%). In 9 cases (90%), onset symptoms of neuropathy were confirmed at low limbs by history or examination, and in only 1 (10%) case, symptoms were start from both upper and lower limbs. All patients suffered asymmetric peripheral neuropathic symptoms, and 7 patients (70%) had more severe symptoms in the distal limb than the proximal. There were 13 matched-healthy persons in the control group, including 5 males and 8 females, with a mean age of 55.17 ± 9.67 years.

Table 1
Characteristic of PAN patients.

| Characteristics | N = 10 |
|--|---------------|
| Age (median ± SD) | 55.80 ± 15.47 |
| Female (n, %) | 6 (60%) |
| Fever ahead of or during symptoms | 8 (80%) |
| Types of onset (n, %) | |
| acute | 2 (20%) |
| subacute | 8 (80%) |
| chronic | 0 (0) |
| Months from onset to electrophysiology examination (\bar{x} ± SD) | 3.77 ± 2.34 |
| Site of disease onset | |
| Lower limb (n, %) | 9 (90%) |
| Lower & upper limbs (n, %) | 1 (10%) |
| Upper limb (n, %) | 0 (0) |
| Clinical manifestations of onset | |
| Asymmetric (n, %) | 10 (100%) |
| The distal symptoms are more severe than the proximal. (n, %) | 7 (70%) |
| PAN: polyarteritis nodosa | |

Electrophysiology Measurement

All the 10 PAN patients and 13 healthy controls underwent electrophysiology examination. Values of CMAP and SNAP amplitudes of nerves were shown in Table 2. Compared with controls, CMAP amplitudes were significantly decreased ($P < 0.01$) at wrist and elbow points of median nerve and at ankle and above Fibula head points of peroneal nerve in PAN patients (Fig. 1A). No difference of CMAP amplitudes was found at both distal and proximal points of ulnar nerve (Fig. 1A). In addition, sensory nerves were more damaged than motor nerves, SNAP amplitudes of median, ulnar and sural nerves were all much significantly decreased in PAN patients compared to controls ($p < 0.001$, Fig. 1B). Only 2 cases (10%) had abnormal amplitude of CMAP of median nerve in upper limbs, yet the abnormal rate of peroneal nerve (6 cases, 60%) and sural nerve (5 cases, 50%) in lower limb was much higher than that in upper limb (Table 2), suggesting more severe changes in the lower limb. Besides, there were no significant

changes in the values of NCV and distal latency of all recorded motor and sensory nerves, and the similar results were observed in FWL and FWF of motor nerves (Supplement Table 1–3).

Table 2
Comparison amplitudes and occurrence of abnormal rates of SMAP and SNAP of motor and sensory nerves between PAN patients and controls.

| Site of detection | PAN patients | controls | P | Abnormal number of PAN | PAN patients (%) |
|---|------------------|------------------|----------|------------------------|------------------|
| Motor Nerves (CMAP, $\bar{x} \pm SD$, mv) | | | | | |
| Median | | | | 2 | 20 |
| wrist | 5.23 \pm 1.34 | 7.13 \pm 1.64 | < 0.01 | | |
| elbow | 4.81 \pm 1.27 | 6.61 \pm 1.56 | < 0.01 | | |
| Ulnar | | | | 0 | 0 |
| wrist | 6.74 \pm 1.59 | 6.57 \pm 0.78 | 0.71 | | |
| elbow | 6.09 \pm 1.39 | 6.12 \pm 0.66 | 0.59 | | |
| Peroneal | | | | 6 | 60 |
| ankle | 1.74 \pm 1.54 | 4.39 \pm 1.16 | < 0.001 | | |
| above Fibula head | 1.58 \pm 1.49 | 4.01 \pm 1.13 | < 0.001 | | |
| Sensory Nerves (SNAP, $\bar{x} \pm SD$, μ v) | | | | | |
| median Digit II | 14.00 \pm 6.22 | 22.53 \pm 7.81 | < 0.001 | 0 | 0 |
| ulnar Digit V | 12.00 \pm 5.24 | 19.65 \pm 5.76 | < 0.0001 | 0 | 0 |
| sural ankle | 3.42 \pm 2.19 | 6.68 \pm 2.07 | 0.002 | 5 | 50 |
| CMAP: the compound muscle action potential; SNAP: sensory nerve action potential SNAP; PAN: polyarteritis nodosa. | | | | | |

Discussion

PAN can affect almost any visceral organ, but it targets the peripheral nerves more often than other organ systems^{3,18}. So far, few studies focused on peripheral neuropathy due to PAN. Some of them concentrated on peripheral neuropathy in systemic vasculitis. According to our study, all PAN patients

suffered asymmetric peripheral neuropathy at onset stage, which were in accord with mononeuropathy or multiplex mononeuropathy^{3,19}. As the disease progress, multiple nerves were rapidly involved resulting in generalized symmetric polyneuropathy, just like previous studies on primary systemic vasculitis^{20–22}. Fever is not part of the ACR diagnostic criteria nor the three indices proposed by the French Vasculitis Study Group (FVSG)²³. Most patients with PAN develop organ involvement within weeks of developing fever²⁴. In our study, 80% of patients had fever before the onset symptoms or as an accompanying symptom. Thus, PAN need to be kept in mind when patient with mononeuropathy or multiplex mononeuropathy presented weeks of fever.

In our study, the characteristics of peripheral neuropathy in PAN patients are consistent with asymmetric axonal neuropathy that has a predilection for the lower extremities, affects distal limbs more severely than proximal, and involves both motor and sensory nerves. Previous studies have shown that sensorimotor abnormalities on NCS and the presence of a pure axonal neuropathy were most consistent with pathologically confirmed vasculitis^{25,26}, which is consistent with our findings. The lower limb is the most susceptible to nerve injuries in PAN patients, since the high frequent of disease onset rate appeared at lower limb in the clinical data and the abnormal amplitudes of peroneal and sural nerve were detected in NCS. Despite the less rates of site of disease onset and abnormality of CMAP amplitude of median nerve, the mean values of CMAP amplitude of median nerve and SNAP amplitude of median and ulnar nerves were significantly declining, which are considered to exist subclinical changes in upper limbs of patients with PAN. Ulnar motor nerve was selectively spared in our result, which need to be further verified through enlarging the sample size of patients.

PAN can make arterial aneurysm and thrombosis in many organs, including brain²⁷, heart²⁸, kidney²⁹, extremities³⁰ etc., due to inflammatory lesions of the blood vessels and necrosis of the vessel wall. It's associated with an increased risk of mortality, understanding the outstanding features of nerve conduction might enable us to quickly recognize PAN to start specific treatments as early as possible.

Our findings suggest that the asymmetric motor and sensory axonal neuropathy is the most common style, lower limbs are the most frequent site of involvement, and the severity of peripheral nerve involvement is more significant in the distal limb than in the proximal in patients with PAN of peripheral neuropathy onset. It is advisable for neurologists to consider PAN in the face of patients demonstrating above clinical and nerve conductive features as well as weeks of fever.

Declarations

Ethics approval and consent to participate

The study was approved by the central institutional review board at The Second Hospital of Hebei Medical University. All participants or their legal guardians gave written informed consent to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

Qi Liu contributed to data acquisition and analysis and prepared the manuscript. Xiaomeng Zhou and Yao Tian contributed to data acquisition, Ping Lv, Xueqin Song and Yaling Liu contributed to design and supervised of the study and revised the report. Hui Dong contributed to data acquisition and analysis, supervised the study, and revised the manuscript. All authors performed a critical review of the manuscript.

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Figures

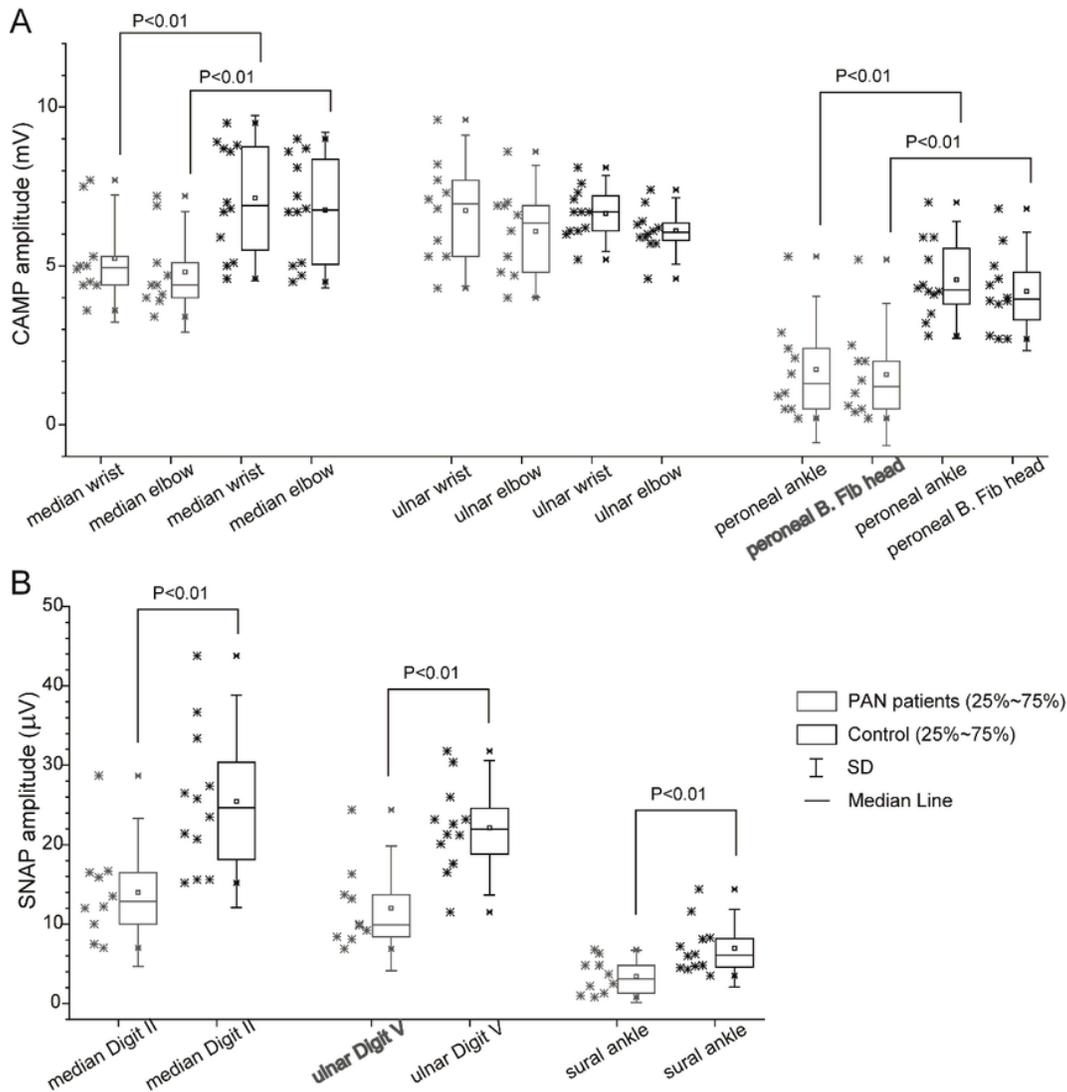


Figure 1

The compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes of motor nerves and sensory nerves in patients with PAN and controls. (A) CMAP amplitudes of median and peroneal nerves in patients with are significantly lower than those of controls. (B) SNAP amplitudes of median, ulnar and sural nerves in patients with PAN are also significantly lower than those of controls. Star scatters on the left of boxes are the values of each person, the bars show the \pm SD, the boxes show the values ranged from 25% to 75%, the dots inside boxes showed the mean value of each group, and the lines inside boxes showed the median value of each group.

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