Pathological spontaneous activity as a prognostic marker in chronic inflammatory demyelinating polyneuropathy

T. Grüter\textsuperscript{a,b,*}, J. Motte\textsuperscript{a,b,*}, A. L. Fisse\textsuperscript{a,b}, Y. Bülut\textsuperscript{a,b}, N. Köse\textsuperscript{a}, D. Athanasopoulos\textsuperscript{a,b}, S. Otto\textsuperscript{a}, M.-S. Yoon\textsuperscript{b,c}, C. Schneider-Gold\textsuperscript{a}, R. Gold\textsuperscript{a,b} and K. Pitarokili\textsuperscript{a,b}

\textsuperscript{a}Department of Neurology, St Josef-Hospital, Ruhr University Bochum, Bochum; \textsuperscript{b}Immunmediated Neuropathies Biobank (INHIBIT), Ruhr University, Bochum; and \textsuperscript{c}Department of Neurology, Evangelisches Krankenhaus Hattingen, Hattingen, Germany

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Background and purpose: Monitoring of the disease course of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) remains challenging because nerve conduction studies do not adequately correlate with functional disability. The prognostic value of pathological spontaneous activity (PSA) in needle electromyography (EMG) in different CIDP subgroups in a longitudinal context has, to date, not been analysed. We aimed to determine whether PSA was a prognostic marker or a marker of disease activity in a cohort of patients with CIDP.

Methods: A total of 127 patients with CIDP spectrum disorder were retrospectively analysed over 57\textsuperscript{±}47 months regarding the occurrence of PSA (fibrillations and positive sharp waves). The presence of PSA at diagnosis, newly occurring PSA, and continuously present PSA were longitudinally correlated with clinical disability using the Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) and CIDP subtype.

Results: Pathological spontaneous activity occurred in 49.6\% of all CIDP patients at first diagnosis. More frequent evidence of PSA was significantly associated with a higher INCAT-ODSS at the last follow-up. Continuous and new occurrence of PSA were associated with higher degree of disability at the last follow-up. The majority of patients with sustained evidence of PSA were characterized by an atypical phenotype, higher degree of disability, and the need for escalation of treatment.

Conclusions: Pathological spontaneous activity was associated with a higher degree of disability and occurred more frequently in atypical CIDP variants according to the longitudinal data of a large cohort of patients with CIDP. Our results showed that EMG examination was an adequate marker for disease progression and should be evaluated during the disease course.

Introduction

Several studies have examined the pathogenesis of chronic inflammatory demyelinating polyneuropathy (CIDP), demonstrating subgroups with different pathoanatomical features, such as distal acquired demyelinating symmetric neuropathy (DADS) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) [1]. Because more than 25\% of CIDP patients do not adequately respond to first-line treatment and are at risk of disease progression, monitoring the disease course is of great importance [2]. Nerve conduction studies and needle electromyography (EMG) are classic diagnostic and monitoring tools in addition to neurological examination. Nevertheless, whether nerve conduction studies correlate with functional disability is still under discussion. Especially in severe disease courses, this correlation was not found [3]. Signs of secondary axonal
involvement in nerve conduction studies have been associated with incomplete improvement after immunotherapy with steroids and immunosuppressants [4]. However, the prognostic value of pathological spontaneous activity (PSA) in needle EMG in different CIDP subgroups in a longitudinal context has not yet been analysed. In the present paper, we report the longitudinal PSA data of a cohort of 127 CIDP patients over 57 ± 47 months and correlate these with clinical progression in order to dissect the role of PSA in CIDP.

**Methods**

**Whole cohort**

The longitudinal data of 127 patients with typical and atypical CIDP were retrospectively analysed regarding the occurrence of PSA during the disease course. A total of 82 patients were diagnosed in our department for the first time. The remaining 45 patients were treated in our department after an external initial diagnosis. All patients were recruited from the Department of Neurology of St Josef-Hospital Bochum, Ruhr University Bochum, between 2004 and 2019.

Patients with typical CIDP were diagnosed in accordance with the diagnostic criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) [5]. Atypical CIDP was diagnosed in accordance with Doneddu et al. [6] and included the following subgroups: DADS; pure motor CIDP; and Lewis-Sumner syndrome (MAD-SAM). We retrospectively analysed how often PSA had occurred since the initial visit to our hospital and correlated these results with the documented degree of disability using the Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) [7]. The decision to perform an EMG examination was made independently of this study in all patients.

**Subgroup analysis**

In addition to analysing the whole cohort, we performed a subgroup analysis of patients with the following: (1) no evidence of PSA during the whole disease course (NO-PSA group); (2) fluctuation of PSA during the disease course, defined as the occurrence of both PSA-positive and PSA-negative EMG examinations during the disease course (independent of whether PSA occurred at initial diagnosis; FLUCTUATING-PSA group); and (3) evidence of PSA in every EMG examination during the whole disease process (CONTINUOUS-PSA group).

**Outcome variables**

To evaluate the role of PSA as a prognostic, activity and differentiation marker in CIDP, as well as the effect of immunotherapy on PSA, we performed the analyses described below.

**Prognostic value of PSA**

To assess the prognostic value of PSA, we correlated (1) the evidence of PSA at initial diagnosis of CIDP to the clinical status (INCAT-ODSS) at the time of diagnosis and at the last follow-up, (2) the individual frequency of PSA-positive EMG examinations to the last INCAT-ODSS and (3) the need for escalation therapy depending on the occurrence of PSA. Escalation immunotherapy was defined as cyclophosphamide, rituximab or bortezomib. The decision to intensify treatment was made independently from this study.

**Association of new occurring PSA with disease activity**

To investigate whether new occurrence of PSA implied disease activity, we compared the patients’ clinical status (INCAT-ODSS) before, after and at the time of the new occurrence of PSA.

**Association of PSA with different CIDP subtypes**

To evaluate the association of PSA with the different subtypes of CIDP, we analysed for the likelihood of an atypical variant depending to the occurrence of PSA.

**Prevalence of PSA after induction of second-line escalation immunotherapy**

Finally, the alteration of the prevalence of PSA after the induction of second-line escalation immunotherapy (cyclophosphamide, rituximab, bortezomib) was assessed 6 months after therapy induction and at the last follow-up for all escalated patients to evaluate PSA as a marker of therapy monitoring.

In all examinations (if not otherwise stated), at least three EMG examinations per patient were required for inclusion in the study.

**Electromyographic examination**

All needle electromyographic examinations were performed with the same device (Medtronic 4 canal electromyography device; Medtronic, Meerbusch, Germany) and equal disposable concentric monopolar needle electrode (50 × 0.46 mm, 0.07 mm² recording area, Value Line DCN, Natus, Ireland) in standardized conditions. PSA was sampled in the tibialis anterior muscle or the first dorsal interosseous muscle. If data were available, we analysed results from the left tibial anterior muscle to exclude selection bias regarding the muscle selection. The
instrument sensitivity to evaluate for electrical activity was initially performed at 100 µV/div, with a sweep speed of 10 ms/div. High- and low-frequency filters were set to 10 Hz and 10 000 Hz. Only discharges with a regular discharge rate approximating 1–15 Hz were assessed. According to the standard protocol of our neurophysiology laboratory, the needle electrode was inserted in at least three directions (approximately 45°/90°/45° to skin), with different depth of needle insertion (10–45 mm) in each muscle, and thereby at least 10 different muscle locations were analysed. The number of needle positions demonstrating PSA was counted. PSA was considered only if fibrillations and positive sharp waves occurred in more than 10% of the analysed needle positions [8]. Evidence of fibrillation and no positive sharp waves or vice versa in a single needle position were not considered to be reliable detection of PSA.

Statistics
Statistical analysis was performed using GraphPad Prism version 6.01 for Windows (GraphPad Software, La Jolla, CA, USA). Clinical outcomes (INCAT-ODSS) were compared using the Mann–Whitney test for two groups. The Kruskal–Wallis test was used for the analysis of more than two groups. The Friedman test was used for longitudinal data. The prognostic value was analysed using simple linear regression and odds ratio (OR) analysis. Non-numeric variables were compared with the chi-squared test. As a diagnostic accuracy test, we evaluated the area under the receiver-operating characteristic (ROC) curve (AUC). As a measure of variation, we used standard deviation. For ORs, we reported the 95% confidential interval (CI). For all analyses, statistical significance was defined as a P value < 0.05.

Ethical standards
All procedures performed were in accordance with the ethical standard of the institutional research committee (Ruhr University Bochum, vote-no. 18-6407) and with the World Medical Association Declaration of Helsinki published on the website of the Journal of the American Medical Association. The study was approved by the local ethics committee.

Results

Epidemiology
We included 127 patients (age at diagnosis 55.2 ± 12.7 years; women:men ratio 1:1.53) fulfilling the EFNS/PNS criteria for CIDP (n = 110, definite CIDP; n = 12, probable CIDP; n = 5, possible CIDP). The follow-up time was 57 ± 47 months. We identified nine patients with monoclonal gammopathy of unspecific significance; two with monoclonal IgM and seven with monoclonal IgG. Patients with evidence of myelin-associated antibody or antibodies associated with paranodopathy were excluded from the study. Most patients had typical CIDP (n = 105, typical CIDP; n = 22, atypical CIDP, including n = 5 DADS, n = 1 pure motor CIDP, n = 13 MADSAM). The epidemiological data of the cohort are presented in Table 1.

For subgroup analyses, we compared patients with no PSA (n = 21, all definite CIDP), fluctuating PSA (n = 50, 45 definite CIDP, four probable CIDP, one possible CIDP), and continuous PSA (n = 22, 19 definite CIDP, three probable CIDP) during the disease course. The CONTINUOUS-PSA group included two DADS and five MADSAM patients, the FLUCTUATING-PSA group included four DADS and two MADSAM patients, and the NO-PSA group included only one MADSAM patient.

Fibrillation and no positive sharp waves or vice versa occurred only in three patients in single needle positions. During the whole study, there were no differences in analysing fibrillations or positive sharp waves. At first visit, needle EMG was analysed in 106 patients from the left tibialis anterior muscle, in

Table 1 Epidemiological data of the cohort

| Variable               | Total       | Typical CIDP | Atypical CIDP |
|------------------------|-------------|--------------|---------------|
| Patients, n            | 127         | 105          | 22            |
| Age at initial diagnosis, years | 55.2 ± 12.7 | 54.7 ± 13.0 | 57.0 ± 11.9 |
| Women: men ratio       | 1:1.53      | 1:1.51       | 1:1.60        |
| INCAT-ODSS at initial diagnosis | 2.4 ± 1.9   | 2.4 ± 1.7    | 2.6 ± 1.6    |
| Mean follow-up, years  | 4.8 ± 3.9   | 5.0 ± 4.0    | 3.8 ± 3.6    |
| EFNS/PNS criteria      | 110 x definite CIDP (87%) | 93 x definite CIDP (89%) | 17 x definite CIDP (77%) |
|                        | 12 x probable CIDP (9%)   | 8 x probable CIDP (8%)    | 4 x probable CIDP (18%)  |
|                        | 5 x possible CIDP (4%)    | 4 x possible CIDP (4%)    | 1 x possible CIDP (5%)   |

CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS); INCAT-ODSS, Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score.
15 patients from the right tibialis anterior muscle, and in six patients from the first dorsal interosseous muscle.

Needle EMG revealed PSA in 50.0% of the CIDP patients at first diagnosis, in 39% of whom PSA was evident for more than five of 10 needle positions. The CIDP subtypes were similarly distributed with respect to the occurrence of PSA at the time of diagnosis (no PSA: 82.9% typical CIDP; PSA: 78.0% typical CIDP). PSA diminished continuously from the time of diagnosis during the disease course, with 50.0% of patients (n = 82) showing PSA at the time of diagnosis, 46.4% (n = 56) at months 1 to 6 after diagnosis, 44.6% (n = 56) at months 7 to 12, 36.6% (n = 71) at months 13 to 24, 31.5% (n = 54) at months 25 to 36, and 30.6% (n = 62) after 36 months.

Subgroup analysis

Pathological spontaneous activity as a marker for disease severity and its prognostic value

Evidence of PSA at diagnosis was associated with a significantly higher INCAT-ODSS at the time of diagnosis [no PSA: 1.54 vs. PSA: 3.12, Mann–Whitney test, U = 422.5, P < 0.0001, n = 82 (Fig. 1a)] and at the last follow-up [no PSA: 2.5 vs. PSA: 3.3, Mann–Whitney test, U = 627.5, P < 0.05, mean follow-up 3.3 vs. 3.5 years, n = 82 (Fig. 1b)].

We correlated the frequency of PSA-positive EMG examinations with the patients’ disability. The proportion of PSA-positive EMG examinations relative to all EMG examinations was significantly associated with last INCAT-ODSS in regression analysis [F(1, 85) = 12.3, P < 0.001, R² = 0.126, follow-up 6.0 years; n = 87 (Fig. 1c)].

Of the patients who showed PSA in the EMG examination at diagnosis (n = 41), 31.7% received escalation therapy, whereas only 19.5% of the patients without PSA (n = 41) required this; however, a single first EMG examination was not enough to definitively predict the need for escalation therapy (OR = 1.9, 95% CI 0.69–5.28; n = 82).

Compared to the NO-PSA group and the FLUCTUATING-PSA group, the CONTINUOUS-PSA group had a significantly higher INCAT-ODSS at the time of diagnosis [1.6 vs. 2.5 vs. 3.3, respectively; P < 0.05, Kruskal–Wallis test (Fig. 2a)] and at the last follow-up [2.4 vs. 3.1 vs. 5.6, respectively; P < 0.01, Kruskal–Wallis test; follow-up 5.5 vs. 5.4 vs. 5.5 years, respectively (Fig. 2b)].

Moreover, the CONTINUOUS-PSA group included the highest proportion of patients requiring escalation therapy compared to the other groups [NO-PSA: 28.6% vs. FLUCTUATING-PSA: 24.0% vs. CONTINUOUS-PSA: 68.2%, χ² (2) = 13.6; P < 0.01, chi-squared test (Fig. 2c)]. This finding persisted when...
only typical CIDP patients were considered (NO-PSA: 20.0% vs. FLUCTUATING-PSA: 22.7% vs. CONTINUOUS-PSA: 60.0%; \( \chi^2(2) = 7.3; P < 0.05 \), chi-squared test). Continuous PSA was a predictor of need for escalation therapy (\( n = 22; \) OR = 6.2; 95% CI 2.3–16.7).

**Pathological spontaneous activity as a marker of disease activity**

We analysed the data on patients who were clinically evaluated between 3 and 12 months before and after new occurrence of PSA (on average, 9 months before and 7 months after new PSA). Before new detection of PSA, the INCAT-ODSS did not significantly increase. After new evidence of PSA in the disease course, the INCAT-ODSS at the last follow-up was significantly increased compared to that at the first visit and compared to that at the time of new evidence of PSA [first visit: 2.7 vs. new PSA: 2.8 vs. last follow-up (6.3 years): 4.0, Friedman test, Friedmann value 18.08, \( P < 0.01; n = 22 \) (Fig. 3)].

**Pathological spontaneous activity as a marker of differentiation**

Compared to patients with typical CIDP, patients with atypical CIDP had a significantly higher individual proportion of PSA-positive EMG examinations relative to all EMG examinations [typical: 0.38 vs. atypical: 0.68, Mann–Whitney test, \( U = 230.5, P < 0.01; n = 87 \) (Fig. 4a)]. Therefore, the individual proportion of PSA-positive EMG examinations serves as a fair indicator for an atypical phenotype [ROC curve analysis: AUC 0.77, \( P < 0.01, 95\% \) CI 0.61–0.93; \( n = 87 \) (Fig. 4b)] and there was a tendency for an atypical variant even if only the first EMG examination demonstrated PSA (OR = 2.5, 95% CI 0.96–6.8; \( n = 127 \)).

The CONTINUOUS-PSA group included the highest proportion of atypical CIDP patients compared to the FLUCTUATING-PSA group and the NO-PSA group.

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**Figure 2** Comparison of Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) in patients with evidence of pathological spontaneous activity (PSA) in every electromyographic (EMG) examination during the whole disease process (CONTINUOUS-PSA group, \( n = 22 \)) with INCAT-ODSS in those with fluctuation of PSA during the disease course (FLUCTUATING-PSA group; \( n = 50 \)) and in those with no evidence of PSA during the disease course (NO-PSA group; \( n = 21 \) ) at (a) diagnosis and (b) last follow-up. (c) Percentage of patients in the CONTINUOUS-PSA group that required escalation therapy compared to those of the FLUCTUATING-PSA and the CONTINUOUS-PSA groups. *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \).

**Figure 3** Association of new evidence of pathological spontaneous activity (PSA) with long-lasting increase in Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS; \( n = 22 \)). *\( P < 0.05 \).
group [31.8%, 12.0% and 4.8%, respectively, \( \chi^2 (2) = 6.9, P < 0.05 \), chi-squared test (Fig. 4c)]. Evidence of continuous PSA was associated with an atypical variant (n = 22; OR = 3.0, 95% CI 1.05–8.7) and had a positive predictive value of 31.8%.

**Impact of second-line escalation therapy on PSA**

As continuous PSA was significantly associated with the need for therapy escalation, we assessed the prevalence of PSA-positive EMG examinations at the first visit, at the time of induction therapy, at 6 months after induction, and at the last follow-up (4.6 years after the first visit and 2.2 years after induction of immunotherapy; n = 28). At the first visit, the percentage of PSA-positive EMG examinations of patients requiring escalation therapy was higher in comparison to the non-escalated group (45.5%, n = 99 vs. 64.3%, n = 28). In the active inflammation phase 6 months after the induction of escalation therapy, the percentage of PSA-positive patients increased by approximately 12.4% compared to the therapy induction time point (Fig. 5). By contrast, the whole cohort demonstrated a constant reduction in the percentage of PSA-positive patients. The induction of escalation therapy was able to reduce the percentage of evidence of PSA of the escalated group in the long term by 14.3% when comparing the values at the last follow-up to those at the time of therapy induction. This finding was similar to that observed in the group of patients without escalation therapy [19.4%, first visit vs. last follow-up; n = 99 (Fig. 5)].

**Discussion**

In the present study, we show for the first time in a large cohort of CIDP patients that frequent PSA in EMG examinations was associated with a higher degree of disability and the need for escalation therapy and occurred more frequently in atypical than in typical CIDP. We showed that evidence of PSA at the time of diagnosis, new occurrence of PSA, and continuously present PSA were associated with an elevated INCAT-ODSS. We were able to show a significant association between the frequency of the occurrence
of PSA and the individual outcome. Thus, PSA was a useful marker for estimating prognosis, disease activity and disease severity. Frequent and continuous PSA was associated with atypical forms of CIDP spectrum disorder.

The finding of PSA at the time of diagnosis indicates axon loss even after a short disease duration in CIDP spectrum disorder [8]. Axonal damage is relevant for disease progression and outcome, which has been demonstrated for autoimmune disease of the peripheral nervous system [4,9–12]. Axonal loss was evident in 78.9% of all sural nerve biopsies analysed in patients with suspected autoimmune neuropathy [12]. In a study of 20 patients with multifocal motor neuropathy, axonal loss detected by needle EMG (and not conduction block) was the prominent independent variable correlating with the degree of weakness [11]. Electrophysiological signs of axonal involvement were previously related to a worse treatment response to immunotherapy in patients with CIDP [4]; however, the amount of PSA did not correlate with the efficiency of therapeutic plasmapheresis in CIDP patients in another study, which may be related to the time course of de- and reinnervation or the small number of patients included in the study [13]. In a magnetic resonance imaging study of patients with CIDP, PSA was correlated with significant L5 root enlargement and the need for escalation of treatment [14]. Inflammation and demyelination are the main pathophysiological mechanisms in CIDP spectrum disorders, leading to secondary axonal loss and disease progression [15]. Neurodegeneration and axonal loss, as represented by PSA in EMG examinations, seem to predict long-term disability immediately from the beginning of the disease. Therefore, persistent evidence of PSA should increase physician vigilance and might support early therapy intervention.

The identification of PSA as a prognostic disease marker of CIDP demonstrates the importance of preventing mechanisms leading to axonal loss in the progression of disability. This aspect is increasingly important, as more than 25% of patients with CIDP do not adequately respond to first-line therapy and are at risk of disease progression [2]. Immunomodulating/immunosuppressive therapy acts on demyelination and inflammation but does not primarily affect neurodegeneration and irreversible axon loss. Therefore, neuroprotection and regeneration should be a further goal in the development of new treatment options in CIDP. Recently, it has been demonstrated that Schwann cells cultured with sera from CIDP patients support regenerating axons less effectively than Schwann cells conditioned with control sera due to a lower expression of granulocyte-macrophage colony-stimulating factor and other neurotrophins [16]. Furthermore, intrathecally applied steroids seem to have a protective role against oxidative stress in Schwann cells [17]. In experimental autoimmune neuritis and chronic experimental autoimmune neuritis, the classic animal model of CIDP, fingolimod had a beneficial effect on the disease course and reduced axonal damage [18,19]. Because of the huge impact of axonal loss on the development of disability, currently available therapies should be evaluated for their neuroprotective or regenerative potential.

Interestingly, PSA was more frequent in patients with atypical CIDP. Therefore, the persistence of PSA could be an important diagnostic hint implying an atypical CIDP. Even though PSA occurs in both axonal and demyelinating polyneuropathies, [20] among others, it has been reported that the number of fibrillation potentials differentiates CIDP patients from POEMS syndrome patients [21]. DADS and MAD-SAM patients, who made up the largest part of our atypical CIDP group, respond less often to intravenous immunoglobulin therapy than typical CIDP patients [6]. This could possibly be attributable to the higher proportion of axonal damage that we found in
the EMG examinations in atypical CIDP patients. Therefore, frequent occurrence of PSA should lead to extended diagnostic evaluation to differentiate CIDP subtypes. However, alternative diagnosis (lymphoma, POEMS syndrome, amyloidosis) should also be considered in patients with an aggressive course and prominent spontaneous activity, even when nerve conduction studies seem concordant with EFNS/PNS criteria for CIDP.

Because of the retrospective nature of the present analysis, several circumstances might have led to a selection bias. Firstly, because decisions on treatment interventions were made independently of this study, we cannot exclude the possibility that the occurrence of PSA could have been a reason for intensifying treatment. Secondly, we routinely performed myographic examination of the left tibial anterior muscle in all admitted CIDP patients; nevertheless, in some patients the opposite was examined due to amputation and open wounds and some patients were not examined due to anticoagulation or refusion of the patient. Thirdly, as we detected long-lasting PSA in a large number of patients (>36 months, n = 19/62), we cannot exclude the presence of bias attributable to recruitment from a single specialized centre for inflammatory neuropathies. However, the analysis highlights valuable information, especially given that long-lasting longitudinal data of an invasive method performed in a large cohort of CIDP patients are difficult to generate.

In conclusion, we found that EMG examination was a possible prognostic marker and marker for disease progression and could help to differentiate CIDP subtypes. Needle EMG should be performed during the disease course to evaluate the degree of axonal damage. We recommend close monitoring and extended diagnostic evaluation for patients with continuous evidence of PSA in needle EMG.

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**Patient and public involvement**

All information from patients is sufficiently anonymized. Patients cannot be traced.

**Data availability statement**

The data that support the findings of this study are available from the corresponding author (thomas.grueter@rub.de) upon reasonable request.

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