BRAIN
ORIGINAL ARTICLE

Plasma periaxin is a biomarker of peripheral nerve demyelination

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Assessing disease progression and informing clinical trials in peripheral neuropathy would benefit from objective and responsive fluid biomarkers closely linked to disease biology. This is particularly important in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain–Barré syndrome (GBS), the most common inflammatory neuropathies, where reliable biomarkers of peripheral demyelination would help identify, and potentially measure, active disease and responses to treatment. We postulated that periaxin, a protein exclusively expressed by myelinating Schwann cells, could serve as a fluid biomarker of demyelinating peripheral neuropathy.

We developed a single molecule array (Simoa)-based immunoassay to measure plasma periaxin in patients with CIDP ($n = 45$, including longitudinal samples across a discovery cohort and a validation cohort, for a total of 77 time points), GBS ($n = 30$, 66 time points), Charcot–Marie–Tooth disease (CMT, $n = 20$), CNS disease controls with multiple sclerosis ($n = 30$) and healthy controls ($n = 30$). We also evaluated whether periaxin is released in myelinating co-cultures following immune-mediated demyelination and axonal damage, comparing results with uninjured cultures.

Plasma periaxin effectively distinguishes peripheral from CNS diseases, with significantly elevated levels in CIDP, GBS and CMT, but not in CNS disease or healthy controls (all $P < 0.01$). In CIDP, periaxin discriminates patients with active disease from those with inactive disease ($P < 0.0001$), and plasma levels decrease following treatment with intravenous immunoglobulin (IVIg). Elevated periaxin strongly predicts clinical worsening at 1 year [sensitivity 99%, specificity 72%, area under the curve (AUC) 0.86 (95% confidence interval, CI: 0.67–1)]. In GBS, peak levels of plasma periaxin and the ratio of periaxin to axonal biomarkers [neurofilament light chain (NfL) and peripherin] discriminate most cases of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) from acute motor axonal neuropathy (AMAN), as classified by electrophysiology (sensitivity 100%, specificity 86%, AUC = 0.94, 95% CI: 0.81–1). Serial measurements showed that plasma periaxin levels peak 2 to 3 weeks after GBS symptom onset, followed by a gradual decline in the weeks thereafter. *In vitro*, periaxin is higher following immune-mediated demyelination compared with axonal damage and control conditions.

Plasma periaxin is a biomarker of peripheral nerve demyelination. Combined with axonal fluid biomarkers and existing clinical scales, periaxin has the potential to improve the clinical management of peripheral neuropathies, accelerating advances in care and experimental research.

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Introduction

Macrophage-associated demyelination, directed by antibodies, T cells and complement, is the primary immunopathological process in the majority of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain–Barré syndrome (GBS). The pathophysiological mechanisms of CIDP and GBS are well understood but not entirely characterized.[1,2] However, no reliable blood or CSF biomarkers of peripheral nerve demyelination for clinical use have been identified. The diagnosis of GBS remains clinical, and both GBS and CIDP are confirmed and subsequently monitored with neurological examination and a combination of basic CSF analysis (total protein and cell counts), electrophysiology and clinical scales, whilst peripheral nerve imaging plays a limited role. These tests are indirect measures of nerve damage, somewhat removed from the cellular pathology. Clinical examination remains important for recording longitudinal disease progression but correlates imprecisely with the underlying pathology and ongoing disease activity. The lack of valid, direct biomarkers of peripheral nerve demyelination potentially limits clinical management as it is not possible to determine if the disease process is still active. This uncertainty can lead to overtreatment-related side effects or excess disability as a result of undertreatment. Furthermore, as demand, consumption and cost of immunomodulation in the inflammatory neuropathies continue to increase, objective and responsive biomarkers are urgently needed to measure peripheral nerve demyelination, individually tailor therapies and improve their cost-effectiveness.

The introduction of ultrasensitive technologies for biomarker measurement has driven growing interest in fluid biomarkers of peripheral nerve diseases.[3] Neurofilament light chain (NfL) is an important but generic biomarker of axonal damage in the CNS and peripheral nervous system (PNS).[4,5] In CIDP, plasma NfL is marginally higher before treatment with intravenous immunoglobulin (IVIg) compared with healthy control subjects and in patients with active versus stable disease. Although NfL may decrease in some after treatment, it does not increase again with relapse after treatment withdrawal.[6-8] In GBS, serum NfL levels correlate with disease severity and axonal neurophysiology, and high baseline levels in early disease are associated with worse functional outcomes.[9,10] As such, NfL could contribute to improved clinical measures and prognostic models in CIDP and GBS. However, due to the ubiquitous expression of NfL throughout the nervous system, it is not specific to any one disease,[11] and high levels of NfL can be found in over 80 PNS and CNS conditions, as well as some non-neurological disorders. The difference between plasma NfL in active or untreated disease compared with controls is marginal and often not definitive in indicating disease activity or progression in individual patients. We have previously demonstrated that peripherin, a type III intermediate filament protein, rises selectively in GBS and not in inflammatory or degenerative CNS disorders, and can differentiate acute axonal injury from slowly progressive demyelination.[12] Although NfL and peripherin have shown potential in identifying nerve injury and correlating with disease activity, both are axonal cytoskeletal proteins and neither can identify primary demyelination in the PNS. As such, there remains an unmet need for a biomarker that is both specific to peripheral nerves and capable of distinguishing demyelinating from axonal neuropathy.

Periaxin is exclusively expressed by myelinating Schwann cells.[13-15] In the PNS, periaxin contributes to the development and regeneration of myelin after injury.[14] Mutations in the periaxin gene (*PRX*) cause CMT4F, a severe, demyelinating, autosomal recessive form of Charcot–Marie–Tooth (CMT) disease. We postulated that periaxin could serve as a biomarker of peripheral nerve demyelination, and developed a Simoa (single molecule array)-based assay to measure periaxin in patient plasma and in myelinating culture systems. In this study, we describe periaxin as the first peripheral nerve-specific biomarker of demyelination in CIDP and GBS, and discuss its potential clinical applications, limitations and future developments.

Materials and methods

Detailed protocols for immunohistochemistry on frozen human CNS and PNS tissue and affinity chromatography purification of periaxin are provided in the Supplementary material.

Development of a periaxin Simoa assay

A full-length recombinant periaxin protein, purified from transiently transfected human embryonic kidney (HEK293T) cells, was used to select the antibody combination that produced the best signal-to-noise ratio across a range of periaxin concentrations (1 to 20 000 pg/ml). Antibodies that had previously been used for western blot, ELISA, immunocytochemistry and/or immunohistochemistry were chosen for screening with electrochemiluminescence (ECL). The combination G-5 capture mouse monoclonal antibody (sc-515672, Santa Cruz) and detector rabbit polyclonal antibody (orb413079, Biorbyt) was deemed suitable for assay development. An ECL-based assay was initially developed for periaxin measurement, with details of the assay protocol provided in the Supplementary material. The assay lower limit of detection (LLOD) was 30 pg/ml, corrected to 240 pg/ml when accounting for the minimum required sample dilution. Preliminary testing in a subset of plasma samples from GBS patients ($n = 10$) revealed

periaxin levels below the LLOD in all cases, prompting the transition to Simoa technology (Supplementary Fig. 3).

For Simoa, the capture antibody was buffer exchanged into the recommended bead conjugation buffer using Amicon Ultra-0.5 50 kDa centrifugal filters (Merck), as per the Simoa Homebrew Assay Development Guide (Quanterix®). Paramagnetic dyed single-plex assay beads (TECH-0143 488, Quanterix) were washed and prepared to provide a supply of 1.4×10^9 beads/ml of capture antibody solution. Beads were activated using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) with the addition of N-hydroxysulfosuccinimide (Sulfo-NHS) allowing the formation of a stable amine-reactive Sulfo-NHS ester intermediate, and capture antibodies were then conjugated to those beads with incubation at room temperature for 30 min on a rollator (HulaMixer, Thermo Fisher). Conjugated beads were washed and blocked with blocking solution for 45 min at 2°C–8°C. Following three washes, the conjugated beads were resuspended and stored at 4°C. The detection antibodies were buffer exchanged into Quanterix® biotinylation reaction buffer using Amicon Ultra-0.5 50 kDa filters. Antibody concentration was adjusted prior to biotinylation with NHS-PEG4-biotin (A39259, Thermo Fisher Scientific) at a 40:1 challenge ratio, and incubated for 30 min at room temperature. The bead-conjugated capture antibody and biotinylated detector were then tested to detect recombinant periaxin protein across a range of concentrations from 0 to 50 000 pg/ml.

For analyte quantification, a two-step protocol (incubation of capture beads with sample and detection antibody in the first step prior to washing, followed by enzyme labelling with streptavidin β-galactosidase) was chosen over a three-step protocol, as the former displayed higher dose-response and lower background noise. The final calibration curve was optimized from 0 to 10 000 pg/ml, expected to cover the plausible range of plasma periaxin concentrations (Supplementary Fig. 2A). Parallelism, dilution linearity and spike-recovery were used to choose the diluent and define the minimum required dilution (1:8). The assay's LLOD was 0.2 pg/ml, functionally equating to 1.6 pg/ml given the 1:8 minimum required dilution: this represented a 150-fold increase in sensitivity compared with the ECL assay, allowing measurement of periaxin in 50% of the previously tested GBS samples where levels of the analyte had fallen below the LLOD (Supplementary Fig. 3). Consequently, Simoa was selected for further analysis.

Myelinating cell cultures and immunocytochemistry

We generated myelinating co-cultures of human induced pluripotent stem cell (IPSC)-derived sensory neurons and rodent Schwann cells, and induced antibody-mediated and complement-dependent demyelination and axonal injury. IPSC from healthy control subjects were obtained through the IMI/EU sponsored StemBANCC consortium via the Human Biomaterials Resource Centre, University of Birmingham, UK. To induce demyelination, we applied a serum with previously established IgG myelin reactivity to the cultures[16] at 1:50 concentration. To induce axonal injury, we used anti-GD2 monoclonal antibody (14G2A) at 10 μg/ml in neurobasal media supplemented with N2 (Cat. No. 17502-048), B27 (Cat. No. 12587-010), GlutaMAX™ (Cat. No. 35050-038) and an antibiotic-antimycotic (penicillin, streptomycin and amphotericin) mixture (Cat. No. 15240-062) (all Gibco, Life Technologies) ('complete' neurobasal medium) plus recombinant human β-nerve growth factor (β-NGF) (rhNGF) at 25 ng/ml (Cat. No. 450-01, Peprotech). One hour after incubation with antibody or serum, normal human serum 20% (NHS 20%) was added to induce complement-mediated demyelination and axonal injury. Culture supernatants were collected from three wells per condition [demyelination, axonal damage, control (complete neurobasal medium + β-NGF)] at each time point (before injury, 4 h, 24 h, 48 h).

For immunocytochemistry, coverslips were transferred to PBS, fixed in 4% paraformaldehyde for 30 min, washed three times in PBS then permeabilized in ice-cold methanol for 20 min. Following three PBS washes, cells were blocked using PBS with 5% normal goat serum (NGS), washed in PBS and incubated with primary antibodies [chicken anti-neurofilament heavy chain antibodies at 1:10 000 for axons and rat anti-myelin basic protein (MBP) antibodies at 1:500 for myelin] overnight at 4°C. Cells were then washed with PBS and incubated with the secondary antibodies [goat anti-chicken Biotin (1:500) Life Tech BA9010, and goat anti-rat Alexa Fluor 546 (1:1000) Life Tech A11081] for 1 h on an orbital shaker (500 rpm) covered in tin foil. The secondary antibody was washed off with PBS, followed by incubation with Streptavidin-Pacific Blue (1:500, Life Tech S11222). Finally, the coverslips were mounted onto SuperFrost® Plus microscope slides (Thermo Scientific) in Vectashield mounting medium (Vector Laboratories). Confocal microscopy was used to confirm axonal degeneration and quantify myelination, and objective sampling across the coverslip was ensured through systematic random sampling on a spinning disc microscope. The thresholded MBP signal was used to quantify myelin fragmentation in ImageJ, and the percentage of myelin fragmentation was calculated as (myelin fragment area) / [(total myelin area) (non-specific particle area)] × 100. Images were acquired on an Olympus SpinSR10 spinning disc confocal microscope.

Participants and clinical samples

Two cohorts of plasma samples were collected from patients with CIDP: a discovery cohort ($n = 15$) and an independent validation cohort ($n = 30$). In the discovery cohort, eight patients (53%) had multiple longitudinal samples collected, totalling 36 samples. In the validation cohort, 9 of the 30 patients (30%) were sampled at more than one time point, resulting in 41 samples. In total, 77 CIDP plasma samples were analysed across both cohorts. Samples were also collected from 30 patients with GBS, of whom 18 (60%) had multiple samples collected longitudinally (66 GBS samples in total). For the CIDP discovery cohort, samples were collected from patients presenting to the Manchester Centre for Clinical Neurosciences at Salford Royal Hospital, through an observational study and biobank established at the John Radcliffe Hospital in Oxford, or from the Department of Neurology at the University of KwaZulu-Natal in Durban, South Africa. The CIDP validation cohort was distinct and comprised samples from patients presenting to the National Hospital for Neurology and Neurosurgery in London. All patients had been evaluated by neurologists and electrophysiologists, and the diagnosis of CIDP or GBS had been confirmed by standard published clinical and neurophysiological criteria.[17,18] CIDP patients had samples taken at variable intervals, up to 28 weeks apart. In the majority of GBS patients with multiple samples, these were collected at Week 1, 2, 3, 4 and in some cases Weeks 5, 6, 7 or 8. Single blood samples were also collected from 20 patients with CMT disease, including 13 with CMT1 and 7 with CMT2, as well as from 30 CNS controls with multiple sclerosis (MS) and 30 healthy control subjects.

Blood samples were centrifuged at 3000*g* for 5 min and frozen at −80°C within 5 h of collection. Both serum and plasma samples (collected in EDTA tubes) were available for patients in the GBS and

CIDP discovery cohorts, and both biofluids were tested in all cases. Periaxin was consistently measured in plasma, with very few exceptions among the serum samples. A direct comparison between lithium heparin (LiH) and EDTA plasma samples was performed, and periaxin was only measured in EDTA plasma. Consequently, EDTA plasma was selected for subsequent analyses. Samples were tested for periaxin, peripherin (as previously described[12]) and NfL using the Quanterix NF-light® Advantage Kit. Demographic information (age, sex) was available for all CIDP, GBS, CMT, MS patients and healthy controls. Electrophysiology was available for 44/45 (98%) CIDP patients in the discovery and validation cohorts, and 23/30 (77%) GBS patients. The Inflammatory-Rasch-built Overall Disability Scale (I-RODS) and Overall Neuropathy Limitations Scale (ONLS) were available for 18/30 (60%) GBS patients, whereas I-RODS and Medical Research Council Sum Score (MRC-SS) were linked to 41/45 (91%) CIDP patients. Treatment details were obtained for all CIDP patients and 26/30 (87%) GBS patients.

CIDP was classified as clinically active in 17/45 patients (38%) who demonstrated objective evidence of end-of-dose fluctuations between pre- and post-treatment with IVIg or during interval assessments between consecutive clinical reviews. A minimal clinically important difference (MCID) was defined as a change of at least four centile I-RODS points or two ONLS points. Patients who did not meet these criteria, as well as those in remission for at least 6 months, were classified as having inactive CIDP (16/45, 36%). Patients with discordant clinical outcome measures that prevented clear classification were categorized as indeterminate and were not assigned to either the active or inactive CIDP groups (12/45, 26%). All patients with active CIDP were receiving treatment: 15 were on IVIg, one on corticosteroids, and one on a combination of corticosteroids and cyclophosphamide. Among the 16 patients with inactive disease, two had achieved remission and were off treatment, while the remaining 14 had stable disease and were either on no treatment, or on maintenance IVIg or subcutaneous immunoglobulin (SCIg).

Statistical analysis

Statistical analysis was performed using R (R Core Team, version 4.3.3, 2024). The Mann–Whitney U-test and Kruskal–Wallis test were used to compare demographic and clinical data between the different groups. Spearman's correlation coefficient was used to assess the reciprocal correlations of periaxin, peripherin, NfL and their correlation with age, as well as the correlation between biomarker levels (and their ratios) and clinical scales. Additionally, levels of periaxin, peripherin, NfL, their ratios and disability scales were categorized into low, intermediate and high groups by identifying the minimum and maximum values and dividing each range into quartiles, with the lower and upper cut-offs defined by the 25th and 75th percentiles, respectively. The relationships between each categorical variable and the respective disability scores, as well as between peak values and nadir disability scores, were analysed for associations using Fisher's exact test. This approach ensured a balanced distribution, enhanced the detection of non-linear relationships between biomarkers and clinical scales, and reduced the impact of outliers, thereby minimizing the risk of type II errors. To evaluate the relationship between periaxin and clinical scale changes in GBS and CIDP, summary statistics were used rather than correlation analyses due to the limited sample sizes. A linear mixed-effects model was fitted to assess the association between plasma periaxin levels, CIDP classification (active versus inactive), and time since the most recent treatment. The model included CIDP classification and days since treatment as fixed effects, with patient ID included as a random intercept to account for repeated measures.

For biomarker comparisons between GBS electrophysiological subtypes, plasma concentrations were log-transformed to normalize their distribution and stabilize variance. Medians of the log-transformed values were calculated for each group within each comparison. Pairwise comparisons between axonal and demyelinating groups were performed using the two-sample *t*-test. Empirical receiver operating characteristic (ROC) curves were used to assess the diagnostic utility of plasma periaxin, peripherin, NfL and reciprocal ratios to discriminate between electrophysiological subtypes, and only the three with the highest area under the curve (AUC) are shown, including 95% confidence interval (CI) and cut-off optimizing Youden Index.

To minimize the risk of false associations (type I error) when comparing levels across different groups, any samples with concentrations below the LLOD were assigned values of 1.6 pg/ml (periaxin), 1.1 pg/ml (peripherin) or 0.34 pg/ml (NfL), corresponding to the assays' respective detection limits. To investigate whether periaxin is associated with age, sex or body mass index (BMI), two separate linear regression analyses were performed. In the first model, restricted to healthy controls, age and sex were included as covariates. In the second model, combining data from CIDP, CMT1, CMT2 and healthy controls, age, sex, BMI and disability (measured through clinical outcome measures), were included as covariates. Model fit and variability explained were assessed using the coefficient of determination (R^2) and adjusted R^2 values. A significance value of $P < 0.05$ was used throughout, with Bonferroni correction for multiple comparisons where appropriate.

Ethics

Samples obtained from the Manchester Centre for Clinical Neurosciences at Salford Royal Hospital and from the National Hospital for Neurology and Neurosurgery in London were collected and tested according to the Queen Square Research Ethics Committee 190929 (REC: 16/LO/1852). Samples obtained via the Oxford paranodal antibody testing service were collected in accordance with the ethically approved Biomarker Investigation & Study of Pathology in Neuropathy (Bio-SPiN) protocol (reference 14/SC/0280). Collection and testing of the samples from South Africa were approved by the University of KZN Biomedical Research Ethics Committee (BREC/00005861/2023).

Results

Distribution of periaxin in the nervous tissue

Immunohistochemistry of human nervous tissue across the whole neuroaxis demonstrated that periaxin is strongly expressed in the PNS and has minimal background or is absent in the brain cortex, cerebellum, optic nerve and spinal cord (Fig. 1). The lack of co-expression with β-tubulin confirmed that periaxin is expressed by myelinating Schwann cells and not axons.

Periaxin in cell culture models of immune-mediated demyelination

Functional evidence of periaxin release was obtained in a cell culture model of complement-mediated demyelination. Myelin fragmentation was confirmed morphologically using immunocytochemistry

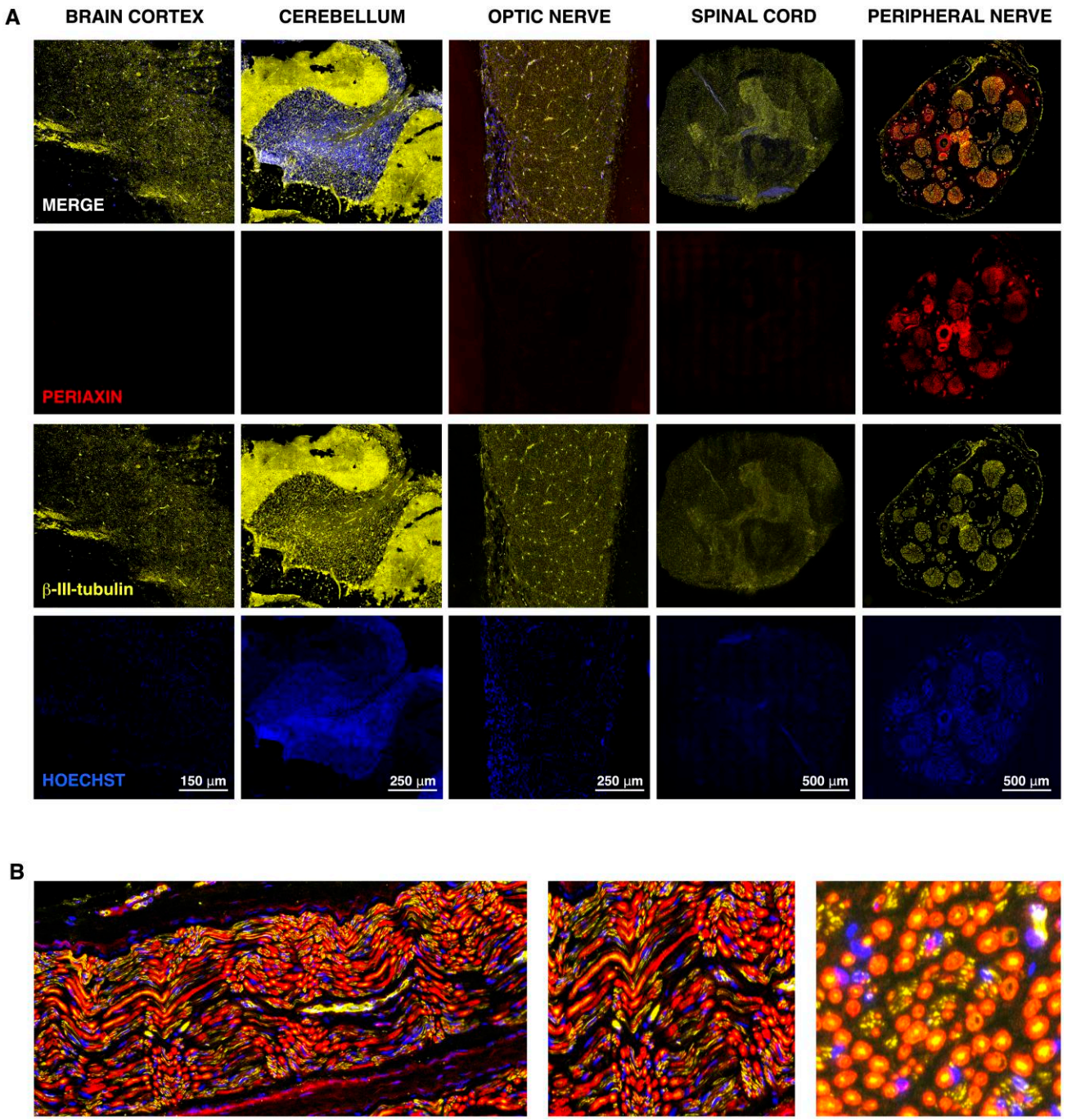

Figure 1 Differential expression of periaxin in central and peripheral nervous tissue. (**A**) Immunohistochemistry of the human brain cortex, cerebellum, optic nerve, spinal cord and peripheral nerve cross-sections. Periaxin (in red) is absent in the CNS but is strongly expressed in peripheral nerve tissue. In contrast, β-tubulin (yellow), an axonal marker, is robustly expressed in both central and peripheral tissues. (**B**) Longitudinal section of peripheral nerve tissue (*left*) showing that periaxin is located within the Schwann cells, surrounding each axon, with greater detail visible in the enlarged-section (*middle*). The *right* panel presents a magnified view of the peripheral nerve transverse cross-section shown in **A**. Scale bars as indicated.

and confocal imaging (Fig. 2A) and quantified at 4 h (15%) and 48 h (30%), as shown in Fig. 2B. Following antibody and complement-mediated demyelination, *in vitro* supernatant levels of periaxin were higher (8275.5 ± 155.6 pg/ml, mean ± standard deviation) compared with axonal damage (3803.0 ± 727.0 pg/ml, unpaired *t*-test $P = 0.003$) and control conditions (728.8 ± 161.8 pg/ml, $P = 0.0009$) at 48 h (Fig. 2C and D). The ratio of periaxin to peripherin was higher in cultures with primary demyelination compared with axonal injury and control conditions at 4, 24 and 48 h, whereas peripherin levels increased over time but were higher after primary axonal injury compared with demyelination (Fig. 2D), consistent with our previous findings.[12]

Periaxin and peripherin levels were also assessed during myelination and axonal formation, respectively (Supplementary Fig. 4). Periaxin progressively increased in the weeks following Schwann cell seeding into newly differentiated cultures of

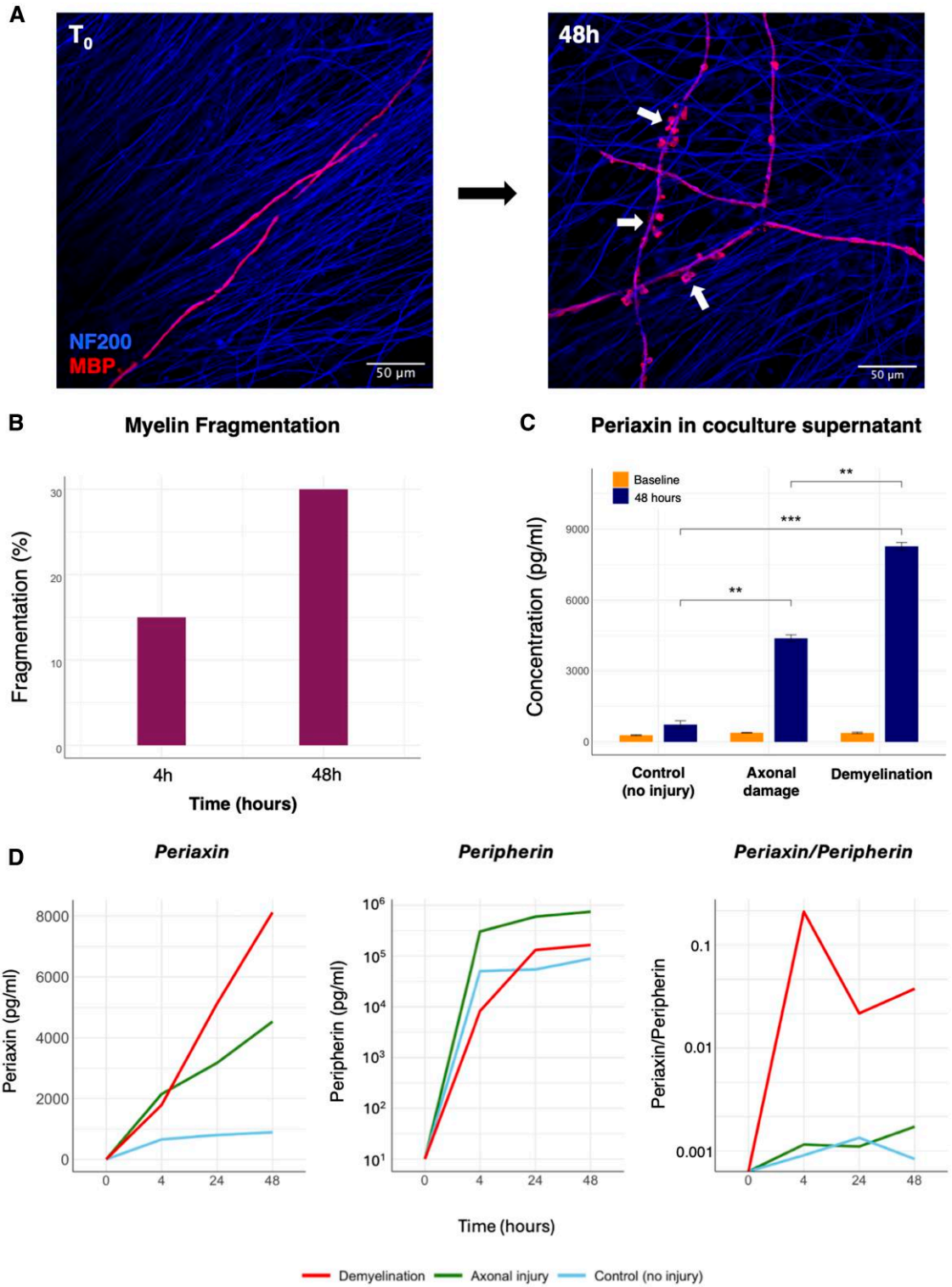

Figure 2 ***In vitro*** **models of immune-mediated demyelination and axonal injury.** (**A**) Immunocytochemistry and confocal imaging of myelinating co-cultures with antibody and complement-mediated demyelination at baseline and 48 h. (**B**) Percentage of myelin fragmentation increased from 4 to 48 h. (**C** and **D**) Periaxin levels in co-culture supernatants increased gradually and were higher following demyelination compared with axonal damage (unpaired *t*-test, $P = 0.003$) and uninjured control conditions ($P = 0.0009$) at 48 h. Similarly, peripherin levels rose rapidly and increased over time, but were higher after primary axonal injury compared with demyelination. The ratio of periaxin to peripherin was consistently higher in cultures with primary demyelination compared with axonal injury and control conditions at 4, 24 and 48 h (**D**).

IPSC-derived sensory neurons (Supplementary Fig. 4A). Similarly, peripherin rose gradually during the differentiation of both sensory and motor neurons from IPSCs (Supplementary Fig. 4B). However, in both processes, levels were markedly lower compared with injury conditions: periaxin concentrations were approximately 1000 times lower during myelination than during demyelination,

Table 1 Baseline cohort demographics

	CIDP	GBS	CMT	MS	HC
Total case number	45	30	20	30	30
Total sample number	77	66	NA	NA	NA
Median age, years (IQR)	57 (19)	49 (17)	57	36 (14)	37 (27)
Male:female ratio (% female)	2:1 (34%)	1.7:1 (37%)	–	0.6:1 (63%)	1:1 (50%)
Median follow-up duration in days (IQR), [min–max]	106 (69), [1–205]	25 (25), [5–109]	NA	NA	NA
Cases with available demographic info	45/45 (100%)	30/30 (100%)	NA	NA	NA
CIDP phenotype	–	–	NA	NA	NA
Typical	28/45 (62%)	NA	–	–	–
A-CIDP	4/45 (9%)	NA	–	–	–
DADS	5/45 (11%)	NA	–	–	–
Unknown	8/45 (18%)	NA	–	–	–
Cases with available electrophysiology	44/45 (98%)	23/30 (77%)	NA	NA	NA
Electrophysiology classification[a]	–	–	NA	NA	NA
Demyelinating	45/45 (100%)	13/30 (43%)	–	–	–
Axonal	NA	9/30 (30%)	–	–	–
Normal	NA	1/30 (3%)	–	–	–
Equivocal	NA	2/30 (7%)	–	–	–
Unavailable	NA	5/30 (17%)	–	–	–
Cases with available I-RODS	41/45 (91%)	18/30 (60%)	NA	NA	NA
Cases with available ONLS	–	18/30 (60%)	NA	NA	NA
Cases with available MRC-SS	41/45 (91%)	–	NA	NA	NA
Cases with available treatment details	45/45 (100%)	26/30 (87%)	NA	NA	NA

A-CIDP = acute CIDP; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMT = Charcot–Marie–Tooth disease; DADS = distal acquired demyelinating symmetrics variant of CIDP; GBS = Guillain–Barré syndrome; HC = healthy control subjects; IQR = interquartile range; I-RODS = inflammatory-rasch-built overall disability scale; MRC-SS = Medical Research Council sum score; MS = multiple sclerosis; NA = not applicable; ONLS = overall neuropathy limitations scale; – = not available.
[a]Hadden electrophysiological criteria.

and peripherin levels were around 15 000 times lower during axonal growth compared with axonal injury (Supplementary Fig. 4C and D).

Periaxin in clinical samples

Baseline characteristics and demographics of the clinical cohorts are summarized in Table 1.

Periaxin in CIDP

In CIDP, median levels of peak plasma periaxin were 239.7 pg/ml [interquartile range (IQR) = <LLOD to 1286 pg/ml] in the discovery cohort and 261.2 pg/ml (IQR = 14.1–920 pg/ml) in the validation cohort. In comparison, patients with MS and healthy controls had substantially lower periaxin levels: 19 pg/ml (IQR = <LLOD to 174 pg/ml) and 14.6 pg/ml (IQR = <LLOD to 126.9 pg/ml), respectively. Periaxin was significantly higher in CIDP compared with both MS ($P < 0.0001$) and healthy controls ($P < 0.0001$). Comparisons between groups are illustrated in Fig. 3.

Patients with active CIDP had substantially higher periaxin compared with those with inactive CIDP (median 522.4 versus 57.9 pg/ml, $P < 0.0001$, Wilcoxon rank-sum test; Fig. 4A). This difference remained significant in a linear mixed-effects model that accounted for repeated measures and included CIDP classification and time since the most recent treatment as fixed effects ($P = 0.0012$), with a mean reduction of 311.55 pg/ml in the inactive group. There was no significant association between plasma periaxin levels and time since the most recent treatment ($\beta = -3.90$, 95% CI: −10.0 to 2.2, $P = 0.196$).

Periaxin levels decreased following treatment with IVIg, with a median time to decline of 4 weeks (Fig. 4B). Notably, two patients experienced an increase in periaxin levels after treatment, both of whom had a clinical relapse weeks or months later.

To evaluate whether immunoglobulin could interfere with the technical measurement of periaxin in plasma, we spiked 11 mg/ml of 10% IVIg directly into samples with previously measured low, intermediate and high periaxin levels. This approach aimed to recapitulate the increase in IgG following IVIg treatment (delta IgG)[19] at an equivalent concentration of 2 g/kg. Periaxin levels remained stable, within 80%–120% of their pre-spike values, with no significant changes observed (Supplementary Fig. 5).

Plasma periaxin demonstrated strong predictive value for identifying patients with CIDP who experienced clinical worsening at 1 year. ROC curve analysis demonstrated a strong discriminatory ability, with an AUC of 0.81 (95% CI: 0.67–1), as shown in Fig. 5. The optimal periaxin cut-off value was 262.63, which achieved 100% sensitivity and 72.2% specificity, corresponding to a Youden index of 0.722. This cut-off correctly identified all patients who experienced worsening at 1 year, while 72.2% of those with stable or improved outcomes were appropriately classified. In comparison, peripherin and NfL showed weaker discriminatory ability, with AUC values of 0.63 (95% CI: 0.26–0.93) and 0.59 (95% CI: 0.32–0.82), respectively.

Periaxin and NfL exhibited significant negative correlations with I-RODS (Spearman's rho = −0.400, $P = 0.047$, and rho = −0.577, $P = 0.0025$, respectively). Conversely, no significant correlation was observed between peripherin and I-RODS. Neither periaxin, peripherin nor NfL showed a significant correlation with MRC-SS.

Periaxin in Guillain–Barré syndrome

Median peak periaxin levels in GBS (190.5 pg/ml, IQR = <LLOD to 964 pg/ml) were higher compared with both MS and healthy controls (GBS versus healthy controls, $P < 0.01$, GBS versus MS, $P < 0.01$).

Peak periaxin was higher in acute inflammatory demyelinating polyradiculoneuropathy (AIDP) compared with acute motor axonal neuropathy (AMAN): 451 versus 109 pg/ml ($P = 0.008$). Empirical ROC

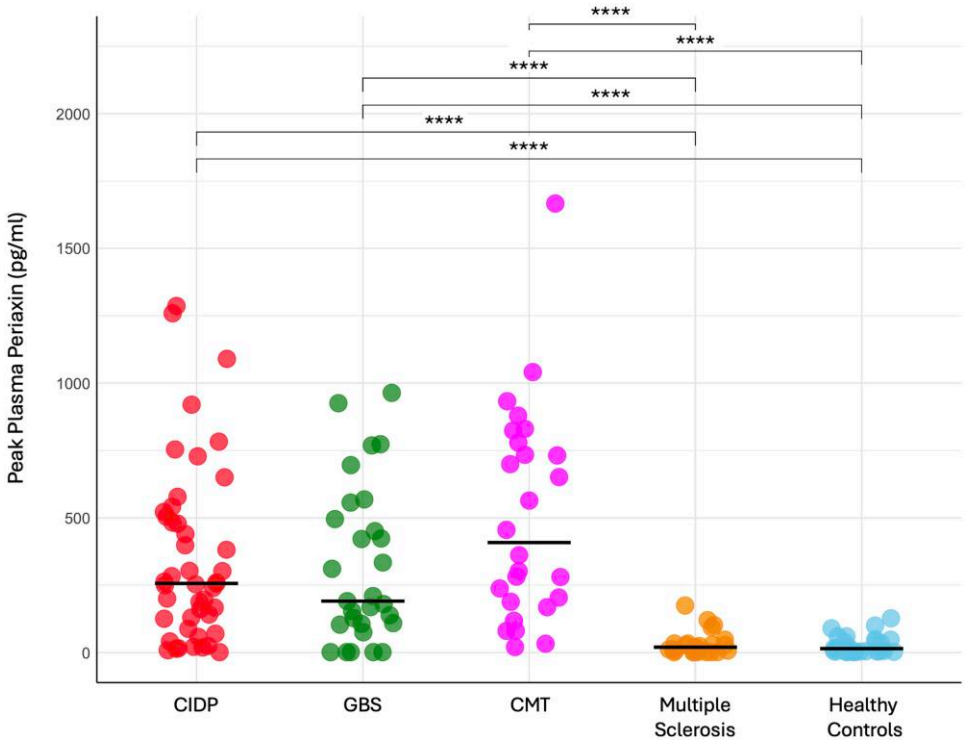

Figure 3 Peak plasma periaxin in neuropathy and control groups. Peak levels of plasma periaxin in the immune-mediated neuropathies chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain–Barré syndrome (GBS), and in Charcot-Marie-Tooth disease (CMT), compared with CNS controls (multiple sclerosis) and healthy controls. The solid bars indicate median periaxin levels. Mann–Whitney U-test: $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

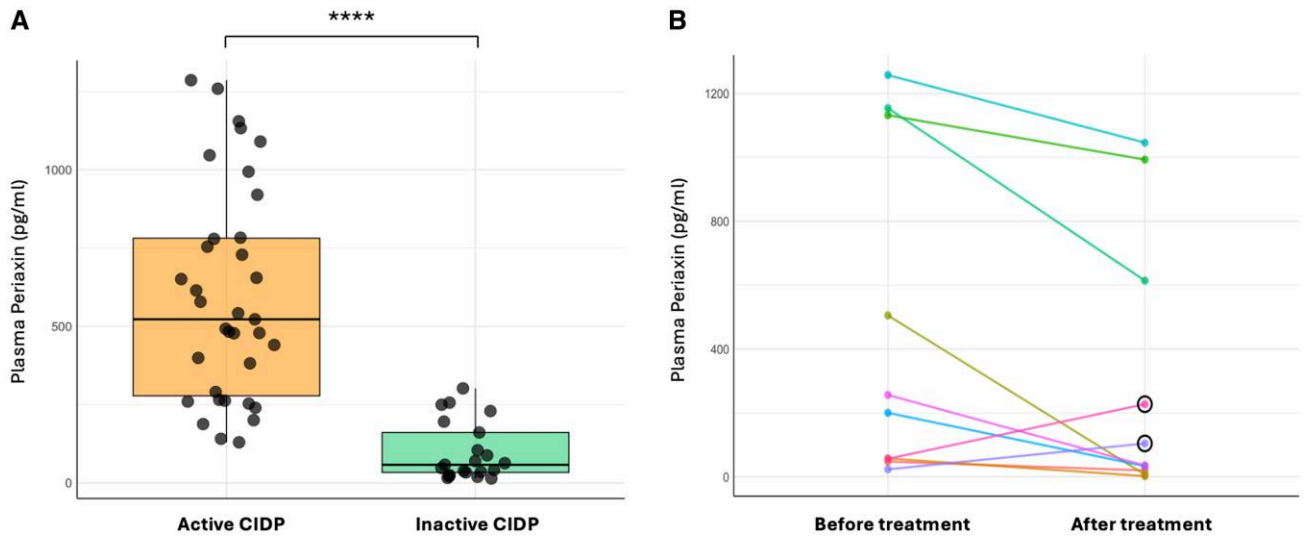

Figure 4 Plasma periaxin discriminates active from inactive CIDP and levels decrease after treatment with immunoglobulin. (**A**) Patients with active chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) had substantially higher periaxin compared with those with inactive CIDP (median 522.4 versus 57.9 pg/ml, $^{****}P < 0.0001$, Wilcoxon rank-sum test). Boxes represent the interquartile range (IQR; 25th to 75th percentile). The horizontal line inside the box denotes the median. The whiskers extend to the most extreme data-points within 1.5 × IQR from the quartiles. (**B**) Plasma levels of periaxin decrease following treatment with intravenous immunoglobulin (IVIg). The two circled patients with higher periaxin post-treatment had a subsequent clinical relapse.

curve analysis demonstrated that periaxin effectively discriminated between the two electrophysiological subtypes (AUC = 0.88, 95% CI: 0.72–1) with a Youden cut-off of 179.6 pg/ml, achieving 82% sensitivity and 86% specificity. Discriminatory performance improved with the ratio of peak periaxin to peak peripherin (AUC = 0.84, 95% CI: 0.64–1; cut-off = 11.38, sensitivity 100%, specificity 71%) and was highest for the ratio of peak periaxin to peak NfL (AUC = 0.94, 95% CI: 0.81–1; cut-off = 0.46, sensitivity 100%, specificity 86%), as shown in Fig. 6.

Longitudinal measurements showed that plasma periaxin peaked 2 to 3 weeks after symptom onset, followed by a gradual

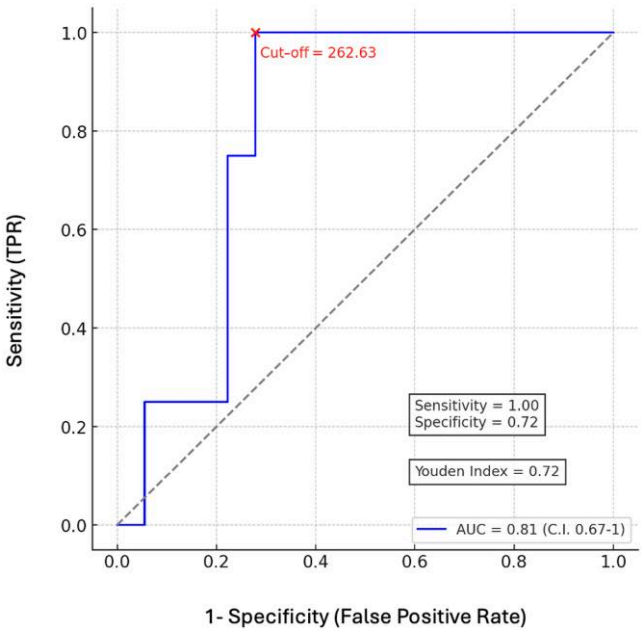

Figure 5 High levels of periaxin predict clinical worsening at 1 year in CIDP. ROC curve for periaxin predicting clinical worsening in patients with CIDP (defined as a 4-point change in the centile I-RODS or 2 in the ONLS). The ROC curve is shown in blue, with the diagonal reference line shown in grey. The optimal periaxin cut-off was 262.63 pg/ml, achieving 100% sensitivity and 72.2% specificity, corresponding to a Youden index of 0.722, indicating good discriminative performance. The AUC was 0.81 (95% confidence interval 0.67–1). AUC = area under the curve; I-RODS = Inflammatory-Rasch-built Overall Disability Scale; ONLS = Overall Neuropathy Limitations Scale; ROC = receiver operating characteristic.

decline over the following weeks (Fig. 7A). In contrast, peripherin peaked earlier, within the first week of disease onset, then decreased before rising again around Weeks 6 and 7; this secondary rise was more pronounced in patients with AMAN, consistent with our previous findings[12] (Fig. 7B). NfL levels remained elevated for several weeks (Fig. 7C). A minor secondary peak in periaxin levels was observed, resembling the pattern seen in peripherin, albeit with a slight delay (Fig. 7D). Periaxin, peripherin and NfL levels were consistently higher from disease onset in patients with axonal GBS compared with those with AIDP (Fig. 7D–F), but periaxin reached higher peaks compared with both axonal biomarkers in AIDP (Fig. 7D).

No significant Spearman's correlation was observed between periaxin and either I-RODS or ONLS across all time points or between peak levels and nadir disability scores. When fluid biomarkers and clinical scales were categorically classified (Supplementary Table 1), NfL showed significant associations with I-RODS and peak NfL with nadir ONLS (Fisher's exact test, $P < 0.001$). Peak levels of all three biomarkers showed strong and consistent associations with nadir disability scores of both scales (Supplementary Table 2).

Amongst the GBS patients with longitudinal samples, 10 had periaxin levels measured on admission (Week 1). Of these, seven remained clinically stable after 1 week, with six of them (86%) showing low or moderately elevated periaxin levels at baseline. Two patients who improved had high baseline periaxin levels. The one patient whose condition worsened after 1 week had intermediate periaxin levels. No clear associations or predictive patterns were identified for changes at 1 month.

Finally, we measured periaxin levels in the CSF of 10 patients with AIDP, and all samples were below the limit of detection. These samples had been collected from a separate group of patients and were not matched with any of the plasma samples included in our GBS cohort.

Periaxin in Charcot–Marie–Tooth disease

Periaxin strongly discriminated between CMT and healthy individuals without peripheral neuropathy. Median periaxin levels in CMT were 409 pg/ml (IQR = 20.4 to 1665 pg/ml), significantly higher compared with both healthy controls (CMT versus healthy controls, $P < 0.0001$) and patients with MS (CMT versus MS, $P < 0.0001$).

There was no significant difference in periaxin levels between CMT1 and CMT2. However, a trend toward a higher periaxin/NfL ratio was observed in CMT1 (median 49.24 pg/ml, IQR = 52.9) compared with CMT2 (median 35.42 pg/ml, IQR = 15.7), albeit without statistical significance. More extensive work is ongoing.

Periaxin was significantly higher in patients with moderate/severe disease [CMT Neuropathy Score (CMTNS) > 10][20] compared with patients with mild disease (CMTNS ≤ 10), $P = 0.014$, as shown in Supplementary Fig. 6. Peripherin ($P = 0.138$) and NfL ($P = 0.139$) levels showed no significant differences between the groups. Similarly, no significant difference was observed for the ratio of periaxin/peripherin. The ratio of periaxin/NfL approached significance, with a trend toward higher levels in the moderate/severe group compared with the mild group ($P = 0.051$).

Periaxin in healthy individuals

Most healthy controls (29/30, 97%) had measurable but low periaxin (median 14.5 pg/ml, IQR = 38.2). We evaluated whether periaxin levels were associated with age, BMI or sex through two separate linear regression analyses. The first included healthy controls only, with age and sex as covariates, and there was no statistically significant association ($F = 1.04$, $P = 0.376$), explaining only 11.5% of the variability in periaxin ($R^2 = 0.115$; adjusted $R^2 = 0.004$). Neither age ($P = 0.173$) nor sex ($P = 0.739$) was a significant predictor of periaxin in healthy controls. In a combined analysis including the disease groups, the model included age, BMI, sex, and disability as covariates and was also not statistically significant ($F = 0.948$, $P = 0.467$), explaining only 22.6% of the variability in periaxin ($R^2 = 0.226$; adjusted $R^2 = -0.012$). Age ($P = 0.482$), BMI ($P = 0.219$) and sex ($P = 0.807$) showed no significant associations with periaxin.

Discussion

We have developed a highly sensitive Simoa-based immunoassay to measure periaxin, which we demonstrate is a biomarker of demyelination in peripheral nerve disease. Our study shows that plasma periaxin can differentiate peripheral from CNS disease, with higher levels in CIDP, GBS and CMT compared with patients with inflammatory demyelinating CNS pathology or healthy controls. Periaxin discriminates active from inactive CIDP, and plasma levels decrease following treatment with intravenous immunoglobulin. In CIDP, high levels of periaxin strongly predict clinical worsening at 1 year. In GBS, periaxin and the ratio of periaxin to axonal biomarkers such as NfL and peripherin discriminate most cases of electrophysiologically classified demyelinating from axonal neuropathy. In cell-based models of neuropathy, levels of periaxin are higher following immune-mediated demyelination compared with axonal damage and control conditions. Thus periaxin, in combination with axonal fluid biomarkers and existing clinical scales,

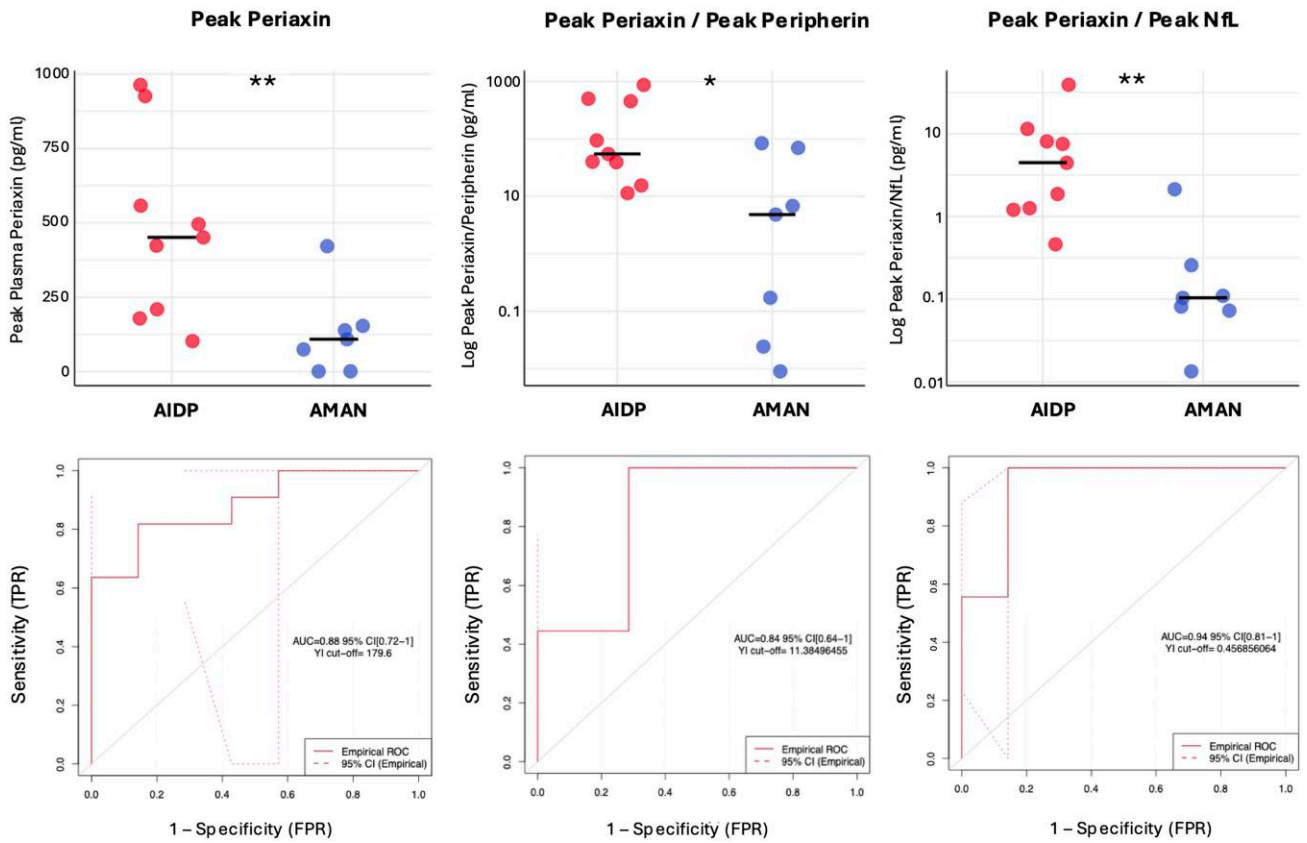

Figure 6 Peak periaxin, combined with axonal biomarkers, discriminates demyelinating from axonal Guillain–Barré syndrome. Peak periaxin was higher in AIDP compared with AMAN: 451 versus 109 pg/ml ($P = 0.008$). Empirical ROC curve analysis shows that periaxin discriminates between the two electrophysiological subtypes (AUC = 0.88, 95% CI: 0.72–1) with a Youden cut-off of 179.6 pg/ml, sensitivity 82% and specificity 86%. Discriminatory performance improved with the ratio of peak periaxin to peak peripherin and was highest for peak periaxin/peak NfL (AUC = 0.94, 95% CI: 0.81–1; cut-off = 0.46, sensitivity 100%, specificity 86%). AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AUC = area under the curve; CI = confidence interval; ROC = receiver operating characteristic.

has the potential to significantly improve diagnosis and management of demyelinating neuropathies.

Two glial proteins, transmembrane protease serine 5 (TMPRSS5) and glial fibrillary acidic protein (GFAP), as well as a myelin sphingolipid (sphingomyelin), have previously been proposed as biomarkers of peripheral demyelination. Plasma TMPRSS5 is higher in patients with CMT1A compared with healthy controls, but does not correlate with nerve conduction studies and is not significantly elevated in other genetic neuropathies such as CMT1B, CMT1X, CMT2A or CMT2E when compared with controls.[21] No data are currently available on TMPRSS5 in any immune-mediate neuropathies. GFAP, a CNS and PNS intermediate filament protein, has been shown to be higher in the serum of patients with some forms of chronic axonal neuropathy (diabetic, vasculitic, toxic-alcoholic and idiopathic) compared with CIDP, multifocal motor neuropathy (MMN) and healthy controls, and in MMN versus controls.[22] Higher levels of GFAP correlate with lower sensory nerve action potential amplitudes and disease severity. However, in the PNS, GFAP is expressed by non-myelinating Schwann cells and satellite glial cells, and not by myelinating Schwann cells.[23] For this reason, and in light of the limitations of the currently published data, GFAP would seem to have limited utility in directly measuring PNS demyelination. Sphingomyelin is higher in the CSF of patients with CIDP and demyelinating GBS compared with non-demyelinating CNS disease and healthy controls, whereas levels do not differ across groups when measured in the serum.[24] Together with its lack of PNS specificity, the clinical use of sphingomyelin is limited by the fact that it can only be measured in CSF. Ideal neuropathy biomarkers would be specific to peripheral nerves, detectable in plasma or serum, able to distinguish primary demyelinating versus axonal pathology, and have a wide dynamic range with lower levels in other diseases and healthy controls.

The ability to detect a significant rise in plasma periaxin in patients with demyelinating peripheral neuropathy as opposed to CNS demyelinating disease or healthy individuals has important clinical implications. Immunohistochemistry of the human brain, cranial nerves and spinal cord sections shows that periaxin is absent in the CNS and only expressed peripherally by myelinating Schwann cells. This is in contrast to NfL, which is abundantly expressed throughout the CNS, and peripherin, which is also found in the cell bodies of motor neurons in the anterior horns.[12] Thus, periaxin might have a key role in the ability to distinguish GBS from acute spinal cord disease, and may suggest a diagnosis of GBS in patients with rare initial hyperreflexia or sphincter disturbance.[25] Periaxin may also be used to quantitate the relative proportion of peripheral demyelination in conditions affecting both CNS and PNS such as combined central and peripheral demyelination (CCPD).

Over half of patients with CIDP require ongoing immunotherapy to maintain disease stability.[26] This typically involves treatment with immunoglobulin, corticosteroids, alternative immunosuppressive

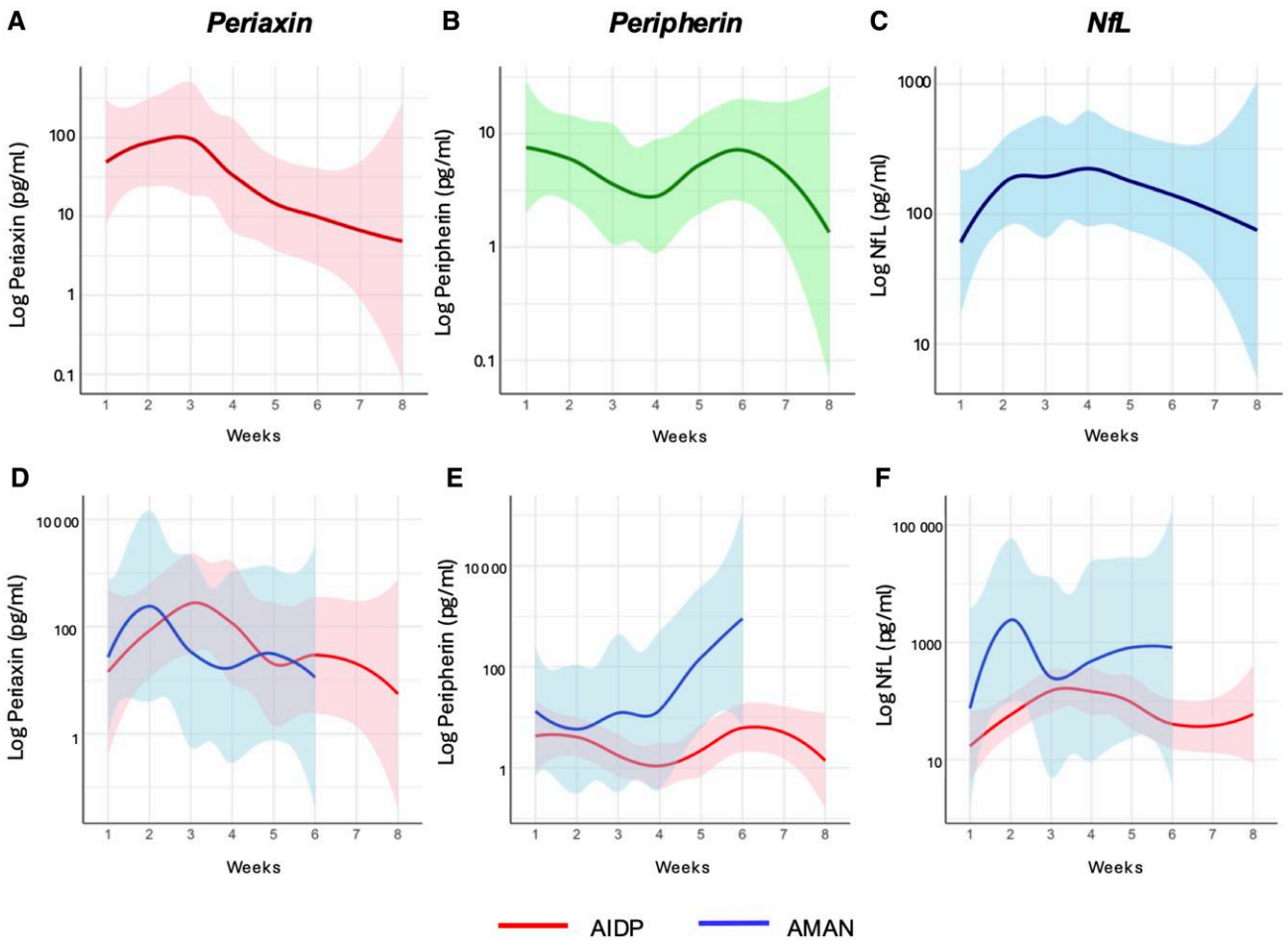

Figure 7 Periaxin and axonal fluid biomarkers over time in Guillain–Barré syndrome. Trends in plasma levels of periaxin (**A** and **D**), peripherin (**B** and **E**) and NfL (**C** and **F**) over time in patients with Guillain–Barré syndrome. Plots **A–C** show trends of the biomarkers for all patients combined, whereas plots **D–F** illustrate trends separately for patients with demyelinating versus axonal disease, as classified by nerve conduction studies. In all plots, solid lines represent smoothed trends over time (LOESS), with the shaded areas indicating 95% confidence intervals (based on the standard error of the LOESS fit). AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; LOESS = locally estimated scatter plot smoothing.

agents or plasma exchange. However, monitoring disease activity remains challenging, as clinicians rely on clinical assessments and neurophysiology, that are unable to identify ongoing damage. As a result, there is a risk of misjudging disease activity, potentially leading to unnecessary treatment escalation or insufficient therapeutic intervention. Meanwhile, the financial burden of immunotherapies continues to grow, with IVIg alone costing the National Health Service over £300 million annually. As such, a biomarker of disease activity, particularly demyelination, is urgently needed. Periaxin is the first PNS-specific biomarker to effectively discriminate clinically active from quiescent CIDP. Current outcome measures are limited to assessing clinical disease—that which is outwardly visible—whereas periaxin, a structural Schwann cell protein, provides a window into the underlying immunopathological process. Elevated or rising levels of periaxin likely reflect active peripheral nerve demyelination, and subsequent falling levels would suggest decay or removal of circulating periaxin, without further Schwann cell damage. Levels of periaxin are lower after treatment in patients with CIDP, and in some cases rise again, likely reflecting the short duration of action of IVIg.

The lack of strong correlation between periaxin and clinical scales, both at individual time points and peak disability, is not unexpected. Clinical scales are static measures of established functional disability, whilst fluid biomarkers are dynamic and inherently more responsive. Their imperfect correlation strengthens the argument for developing fluid biomarkers even further. Disability reflects the balance between injury and repair over the lifetime of the disease and, as such, combining clinical scales with fluid biomarkers may offer a more informative assessment of disease progression and treatment response.

Since Feasby *et al.*[27] GBS has been divided by neurophysiological findings into AIDP and AMAN/AMSAN. However, the 2023 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) GBS Guidelines[28] no longer endorse this clinical distinction. There is no gold standard to choose between the many published criteria and there are no unequivocal features distinguishing 'demyelinating' from 'axonal' GBS. Despite this, we find significantly different levels of periaxin between patients who would be neurophysiologically classed as AIDP and those with axonal nerve conduction studies. This may indicate a true pathological difference between AIDP and AMAN, with primary damage occurring in the Schwann cells and in the axons, respectively, ultimately leading to disruption of both. Our findings in patient plasma are consistent with our *in vitro* results: periaxin measured in culture supernatants is higher following demyelination compared with axonal damage, and levels rise gradually over time.

The biological significance of the delayed peripherin peak remains unclear, similar to the near-concomitant minor peak in periaxin (Fig. 7D). The secondary peaks could be due to a lag in axonal injury with secondary demyelination, or axoglial regeneration: both hypotheses are plausible. Using *in vitro* myelinating culture systems to investigate whether remyelination could influence plasma levels of periaxin, we found that low levels of periaxin are released for a short period during myelin development, prior to any injury, similar to peripherin release during axonal growth. It is not inconceivable that some periaxin may also be released during myelin repair following damage. However, the levels associated with myelination were substantially lower than those observed post-injury. Wallerian degeneration, the process of axonal and myelin breakdown distal to the site of nerve injury, may contribute to elevated plasma periaxin levels by releasing myelin-associated proteins into the circulation. Periaxin levels during advanced or chronic phases of nerve degeneration might reflect this process rather than active primary demyelination or repair. Longitudinal studies investigating the mechanisms of periaxin release, as well as its relationship with Schwann cell pathology and axonal degeneration, will be crucial to better understand its significance and optimize its clinical use as a biomarker.

In GBS, early diagnosis allows prompt treatment, reduces long-term disability and improves prognosis. On a research level, accurately distinguishing between demyelinating and axonal GBS may improve patient classification and recruitment to experimental studies. On a more general level, fluid biomarkers of neuropathy could serve as surrogate outcome measures for primary or secondary end points, improving the efficiency of clinical trials.

Used together, periaxin, NfL and peripherin appear to discriminate between GBS electrophysiological subtypes. The area under the ROC curve for distinguishing demyelinating versus axonal GBS was highest for the ratio peak periaxin/peak NfL, demonstrating the superiority of biomarker panels over individual biomarkers in enhancing accuracy and precision of neuropathy classification. Further work is needed to elucidate whether composite fluid biomarkers can improve current prognostic models.

We tested a small cohort of CSF samples to evaluate whether periaxin in patients with acute radiculoneuropathy would selectively identify demyelination in the spinal roots. All samples were negative and this may be due to small tissue volume (short segments of nerve roots releasing tiny amounts of protein), reduced structural stability of periaxin in the CSF matrix compared with plasma and/or protein distribution in the subarachnoid space. This could be evaluated in future studies. However, venepuncture is safer, more accessible and better tolerated than lumbar puncture, which is invasive and may result in complications. Blood-based biomarkers appear better suited for longitudinal monitoring of diseases primarily affecting the PNS, and are likely to increase patient compliance in both clinical and research settings.

Whilst periaxin demonstrates specificity for peripheral nerve demyelination, other biomarkers such as NfL remain valuable for assessing overall axonal damage and prognosis. Similarly, GFAP and sphingomyelin may provide insights into glial activity or myelin integrity, but with limitations in PNS specificity. Together, these biomarkers could form a panel to comprehensively assess nerve injury, inflammation and repair across diverse neuropathies.

Limitations

One limitation of this study is the relatively small sample size of the groups and the limited number of populations studied. GBS and CIDP are both relatively rare diseases and homogeneous patient cohorts with longitudinal plasma biosamples are even rarer. Plasma is collected less frequently than serum in clinical practice, and this has constrained the size of our cohorts. Expanding cohort sizes and diversifying study populations whilst upholding these stringent criteria will be critical for confirming and generalizing our findings.

Future collaborative studies should aim to include different disease groups to confirm the reproducibility and generalizability of our findings across diverse patient populations and clinical settings. Such collaborations, leveraging larger and more heterogeneous datasets, will be crucial to provide robust evidence for the clinical utility of periaxin and to establish its role in diagnosing and monitoring demyelinating peripheral nerve diseases.

This study establishes periaxin as a putative biomarker of peripheral nerve demyelination but does not yet provide a comprehensive analysis of its prognostic utility. Nonetheless, it lays the foundation for understanding periaxin's clinical potential, with future research needed to explore its prognostic value and broader applications.

In conclusion, we have demonstrated that periaxin is a biomarker of demyelination in the PNS. Plasma periaxin differentiates peripheral from CNS disease, with higher levels in CIDP, GBS and CMT compared with CNS disease and healthy controls. Periaxin is a biomarker of clinical activity in CIDP, plasma levels decrease following treatment with intravenous immunoglobulin, and high levels predict clinical worsening at 1 year. In GBS, periaxin, used in combination with axonal biomarkers, discriminates most cases of electrophysiologically classified demyelinating from axonal disease, and levels of periaxin are higher following immune-mediated demyelination compared with axonal damage and control conditions in cell-based models of neuropathy. As such, periaxin has the potential to improve clinical management of peripheral neuropathies, enhancing experimental research and accelerating advances in care.

Data availability

Data are available on reasonable request to the corresponding author.

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Competing interests

M.P.L. reports speaker fees from BeiGene and Sanofi, conference travel fees from CSL Behring, *ad hoc* consulting fees from AstraZeneca, Roche, UCB Pharma and Polyneuron pharmaceuticals.

Supplementary material

Supplementary material is available at *Brain* online.

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