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REVIEW ARTICLE

Blood biomarkers of peripheral neuropathy

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Traditionally, neurophysiology is the primary diagnostic and prognostic biomarker in peripheral neuropathy clinical practice; however, it may lack responsiveness in the context of slowly progressive neuropathies and where there is significant axonal damage. The development of ultrasensitive platforms for measuring serum proteins at the lower limit of detection of traditional ELISA techniques has transformed the field of blood biomarkers of peripheral neuropathy. A variety of blood biomarkers have been identified from inflammatory cytokines and apokines in diabetic neuropathy through to neuron-specific proteins such as neurofilament light chain, Schwann cell-specific proteins such as TMPRSS5 and microRNAs in other acquired and hereditary neuropathies. In this article, we review blood biomarkers of disease activity for the common subtypes of peripheral neuropathy including inflammatory demyelinating neuropathies, vasculitic neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy and Charcot–Marie–Tooth disease and related disorders including TTR amyloidosis.

KEYWORDS
Biomarkers, Blood, Peripheral neuropathy

1 | INTRODUCTION

Historically, biomarkers of peripheral nerve disease have focused on neurophysiological parameters such as nerve conduction studies and electromyography. Although these remain the cornerstone of peripheral nerve diagnosis, due to the high skill levels required, inter-operator variability and lack of sensitivity and responsiveness over a desirable time frame (e.g. weeks in acute vasculitic neuropathy and 1–2 years in hereditary neuropathies), its use as a biomarker of peripheral nerve disease progression over time is limited. Whilst CSF and blood biomarkers have rapidly evolved in central nervous system disease, their use and development in peripheral nerve disease has lagged behind.[1]

Biomarkers of peripheral nerve disease have a role in diagnosis, clinical management and in research where much attention is focused on their use in natural history studies and clinical trials.[2,3] They have relevance for a broad range of peripheral nerve diseases including inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and vasculitic neuropathy, toxic neuropathies such as chemotherapy-induced painful neuropathy (CIPN), diabetic neuropathy and also genetic neuropathies such as Charcot–Marie–Tooth disease (CMT) and hereditary TTR amyloidosis (ATTR). This review will primarily focus on the use of blood biomarkers of peripheral neuropathy for clinical management and as outcome measures in clinical trials (See Table 1). The review will not focus on diagnostic blood biomarkers for peripheral neuropathy such as anti-ganglioside antibodies in CIDP that have been reviewed extensively elsewhere.[4]

2 | INFLAMMATORY NEUROPATHIES

Inflammatory peripheral neuropathies can be divided into those that are demyelinating (the most common of which are Guillain–Barre syndrome [GBS] and CIDP) and those that are axonal, for example peripheral neuropathy due to vasculitis. Treatment of these

TABLE 1 Summary of blood biomarkers of peripheral nerve disease

Disease	Subtype	Biomarker	Change	Responsive
Inflammatory neuropathies	CIDP	NFL GFAP	Increased	Possibly UK
	GBS	NFL	Increased	UK
	Vasculitis	NFL VEGF		Yes UK
CIPN	Oxaliplatin	NFL	Increased	Yes
Diabetic neuropathy		Cytokines	Increased	UK
		NGF and BDNF	Decreased	UK
		NSE	Increased	UK
		NFL	Increased	UK
		MPZ circ mRNA	Increased	UK
CMT and Related Disorders	CMT	NFL	Increased	UK
	CMT	GDF15	Increased	UK
	CMT	NCAM1	Increased	UK
	CMT1A	TMPRSS5	Increased	UK
	CMT1A	MicroRNA	Increased	UK
	hATTR	NFL	Increased	Yes
	CMT2	PFN2	Decreased	UK
	CMT2	GAMT	Decreased	UK

Abbreviations: BDNF, Brain Derived Neurotrophic Factor; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; CIPN, Chemotherapy Induced Peripheral Neuropathy; CMT, Charcot–Marie–Tooth disease; GAMT, Guanidinoacetate methyltransferase; GBS, Guillain–Barre Syndrome; GDF15, Growth Differentiation Factor 15; GFAP, Glial Fibrillary Acidic Protein; hATTR, Hereditary Transthyretin Amyloidosis; MPZ, Myelin Protein Zero; NCAM1, Neural Cell Adhesion Molecule 1; NFL, Neurofilament Light Chain; NGF, Nerve Growth Factor; NSE, Neuron-Specific Enolase; PFN2, Profilin 2; TMPRSS5, Transmembrane Serum Protease 5; UK, Unknown; VEGF, Vascular Endothelial Growth Factor.

conditions requires acute or long-term immune-modulation or immunosuppression. Monitoring response to treatment in neuropathies needing long-term immunosuppression is challenging as clinical improvement often lags behind disease remission. For example, if there is significant axonal damage, as seen in vasculitis, a neurophysiological response to treatment may not be seen for several months up to a year following successful treatment aimed at suppressing disease activity. An early and accessible blood biomarker of disease activity, that is able to identify when patients are in remission, would be invaluable in clinical practice.

2.1 | Inflammatory demyelinating peripheral neuropathies

One of the first studies of blood biomarkers of inflammatory demyelinating neuropathy examined Glial fibrillary acidic protein (GFAP), a cytoskeletal intermediate filament protein.[5] In this study, serum GFAP was significantly increased in chronic axonal neuropathy, CIDP and multifocal motor neuropathy compared to controls; however, there was no longitudinal data examining the responsiveness of serum GFAP over time.[5]

The majority of recent studies examining blood biomarkers of inflammatory demyelinating neuropathy have focused on serum neurofilament light chain (NFL).[6–8] Neurofilaments are the major cytoskeletal proteins of both the central and peripheral nervous systems and are composed of neurofilament heavy, medium and light chains. In a study comparing serum and CSF NFL concentrations in a cohort of CIDP, Guillain–Barre syndrome (GBS), anti-MAG and vasculitis patients, there was a 50-fold increase in CSF NFL in GBS patients compared to controls.[7] This is perhaps unsurprising as GBS predominantly affects nerve roots within the intrathecal space. In the cohort of patients with CIDP, NFL was increased in both the CSF and serum compared to controls but again there was no longitudinal data to evaluate its responsiveness over time.[7] In a subsequent Dutch study of 81 patients with CIDP, of which a third were new diagnoses receiving induction therapy, a third on maintenance therapy and a third in remission, there was a modest increase in NFL in the initial treatment group of 41.9 pg/ml compared to 27.2 pg/ml in those on maintenance therapy and 20.6 pg/ml in those in remission.[6] Although there was no longitudinal data, the study supports raised serum NFL as a biomarker of disease activity in CIDP, a notion supported by a similar study of 11 newly diagnosed CIDP patients in whom serum NFL was increased at treatment induction and declined over time suggesting that NFL falls with treatment as patients enter remission.[8]

Serum NFL has also been shown to be a predictor of poor prognosis in patients with GBS. In a study of 27 patients with GBS, serum NFL was significantly increased at baseline and predicted a poor clinical outcome.[9]

2.2 | Peripheral nerve vasculitis

Peripheral nerve vasculitis is an aggressive disease with active axonal loss resulting in significant disability. Initial studies identified vascular endothelial growth factor (VEGF) as a potential candidate that could discriminate vasculitis from multifocal motor neuropathy and CIDP and was shown to be responsive to successful treatment.[10] VEGF has now gone out of favour in vasculitis given its very strong association with POEMS syndrome. Studies of blood biomarkers in peripheral nerve vasculitis are sparse, and there are limited data to support their use; however, a small study of 11 patients with peripheral nerve vasculitis showed a significant increase in serum NFL up to 2364 pg/ml that fell by at least 50% following treatment, suggesting that it is potentially both a sensitive and responsive biomarker in this disease.[11]

3 | CHEMOTHERAPY-INDUCED PAINFUL NEUROPATHY (CIPN)

Painful peripheral neuropathy is a common complication of many chemotherapy drugs, particularly platinum-containing drugs such as cisplatin and oxaliplatin. Although the diagnosis is often easy to make and treatment symptomatic, there can sometimes be diagnostic uncertainty when symptoms progress following completion of treatment especially when other causes of neuropathy are present, for example diabetes, amyloid. A blood biomarker able to demonstrate a clear temporal relationship to chemotherapy would therefore be of benefit in clinical practice.

Initial studies of blood biomarkers of CIPN centred on concentrations of neurotrophic factors and lipid metabolites.[12] Blood concentration of nerve growth factor in CIPN patients has given conflicting results, demonstrating a fall during treatment in some studies of platinum-containing chemotherapy drugs[13,14] but also an increase in other studies.[15] BDNF, another neurotrophic factor, has been shown to be reduced in the plasma of patients receiving chemotherapy with bortezomib, paclitaxel and vincristine compared to controls.[16–18] Abnormalities of sphingolipids have also been observed in patients receiving paclitaxel and oxaliplatin.[19,20] This is of relevance as these are also deregulated in the painful neuropathy, hereditary sensory neuropathy type I.[21]

As with the inflammatory neuropathies, NFL has shown promise in CIPN. In rats treated with either cisplatin, which is known to cause a neuronopathy, or vincristine which causes an axonopathy, there was a significant rise in serum NFL in rats treated with these drugs for 4 weeks which correlated with the severity of the neuropathy as determined by neurophysiological and morphometric parameters.[22] In humans, serum NFL has been shown to increase during chemotherapy with oxaliplatin based regimes, before falling four to 6 months after completion of treatment. Furthermore, the concentration was highest in those with more severe neuropathy.[23] This suggests that serum NFL may be a suitable biomarker for monitoring patients with CIPN. There is insufficient evidence at present to support the use of serum NFL or any of the other blood biomarkers described above to guide treatment decisions following the development of CIPN.

4 | DIABETIC PERIPHERAL NEUROPATHY

Blood biomarkers in diabetes have concentrated on the most common subtype of diabetic peripheral neuropathy, distal painful sensory neuropathy in patients with type 2 diabetes. Much of the work has concentrated on metabolic biomarkers and neurotrophic factors, given their role in nerve regeneration and repair.[24]

There have been a multitude of large case–control studies of patients with type 2 diabetes, with and without neuropathy, in which inflammatory and metabolic markers have been measured using cytokine and apocrine arrays.[24] These studies have consistently shown an increase in a number of inflammatory markers in type 2 diabetic patients with neuropathy compared to those without neuropathy; these include TLR 4, TNF alpha, TGF beta, CXCL10, MCP-1, adhesion molecule E-selectin and interleukins including IL-6 IL-1, IL12p70, IL-13 and IL-17A.[25–29] All of these inflammatory or metabolic biomarkers have been shown to be raised in patients with type 2 diabetes with neuropathy compared to those without but there is no longitudinal data or evidence to suggest that these markers change dynamically with the severity of neuropathy. These are important attributes that need to be demonstrated if these biomarkers are to be used for clinical trials or to assess response to treatment.

Compared to other types of peripheral neuropathy, there has been less research on neuronal protein biomarkers in blood. Plasma concentration of phosphorylated neurofilament heavy chain (pNFH) has been shown to be marginally increased in patients with diabetic peripheral neuropathy compared to controls.[30] The lack of a significant increase may reflect difficulties encountered in quantifying pNFH encountered in other types of neuropathy such as CMT.[31] Plasma NFL has been shown to be significantly elevated in a cohort of diabetic patients with neuropathy versus controls, but was unable to differentiate diabetics with and without neuropathy. In the same cohort of patients, myelin protein zero circulating mRNA was able to differentiate diabetic neuropathy patients from both controls and diabetic patients without neuropathy.[32]

Neuron-specific enolase is a soluble intracellular enzyme principally expressed in neural cells, the concentration of which increases in blood after nerve injury. It has a long history of use as a prognostic marker in hypoxic ischaemic brain injury. Studies in both type1 and 2 diabetic patients show that it is increased in patients with neuropathy versus those without neuropathy; however, there have been no longitudinal studies to show that it is responsive to changes in the severity of neuropathy over time.[33]

There have a handful of studies examining blood concentrations of neurotrophic factors in diabetes. These have tended to show a reduction in the neurotrophic factor BDNF and nerve growth factor in patients with neuropathy.[34] In common with many other studies of blood biomarkers of diabetic peripheral neuropathy, the

lack of longitudinal data has limited their use in clinical practice and research.

5 | CHARCOT–MARIE–TOOTH DISEASE AND OTHER HEREDITARY NEUROPATHIES

In contrast to inflammatory peripheral neuropathies, research into blood biomarkers of peripheral neuropathy in the hereditary neuropathies has focused on their use as outcome measures in clinical trials.[2] This is particularly important for the common forms of CMT that are slowly progressive and for which clinical outcome measures lack sufficient sensitivity to detect clinical progression over the normal one to 2 years of a trial. With the recent introduction of highly effective gene silencing therapies for ATTR amyloidosis, there is also increasing interest in the use of blood biomarkers to monitor disease activity in patients receiving treatment.[35–37]

5.1 | Charcot–Marie–Tooth disease

The most common type of genetic peripheral neuropathy is CMT; a collection of inherited diseases in which peripheral neuropathy is the predominant feature. In some types of CMT, the disease-causing gene is solely expressed in Schwann cells whereas in others the pathology originates in the axon.[38] The most common subtype of CMT, CMT1A, is due to a duplication of the short arm of chromosome 17 which includes the *PMP22* gene which is solely expressed in Schwann cells. There have therefore been attempts to identify both Schwann cell and axon-specific biomarkers of peripheral nerve degeneration, although it has been shown that even for those subtypes in which the pathology begins in the Schwann cell, the degree of disability relates to the subsequent axonal loss.[39]

Research on blood biomarkers in CMT has focused on the commonest subtype, CMT1A and have concentrated on measurement of neuron-specific proteins. The first such study measured plasma pNFH but failed to show an increase in patients with CMT versus controls.[31] Subsequent studies using a more sensitive SIMOA platform measuring NFL have shown a significant albeit small difference (10 pg/ml compared to 51.3 pg/ml in ATTR amyloidosis) in patients with CMT (both axonal and demyelinating) versus controls.[37,40–43] Subgroup analyses have shown significant NFL increases in the CMT1A, CMT1X and hereditary sensory neuropathy cohorts.[40] Encouragingly, there was also a significant correlation between plasma NFL and the clinical outcome measure, the CMT examination score version 2.[40] The demonstration of significantly increased plasma NFL in patients with CMT1A, and CMT1B has been replicated by other groups,[43,4441]; however, the correlation between plasma NFL and the CMT neuropathy and examination scores has been replicated in some but not all studies.[40,41,43]

In the only longitudinal study of plasma NFL in CMT, there was no significant change over 6 years follow-up period.[41] Subgroup analysis revealed a trend towards a reduction in plasma NFL over time in CMT1A and a significant reduction in CMT1X. Unfortunately, for the use of plasma NFL as an outcome measure in clinical trials in CMT, the intra-subjective variability over 6 years was 11 pg/ml which is significant when one considers that plasma NFL is only increased in patients with CMT by 10 pg/ml compared to healthy controls. If one employs this effect size and intra-subject variability, use of plasma NFL as a primary outcome measure in a clinical trial of CMT1A would require more than 7000 patients in each arm of a trial to detect a 50% reduction in the rate of axonal degeneration over 2 years.[45]

One of the criticisms of the studies of plasma NFL in CMT is the disproportionate inclusion of older patients with a mean age of 40–50 years. Murine models of CMT including CMT1X and CMT2D show changes in plasma NFL concentration throughout the lifespan of the animal.[41,45] For example, in one severe model of CMT2D, there was a significant increase in plasma NFL the first few months of life that then returned to similar concentrations to controls. These studies of mouse models of CMT challenge the view that there is a constant rate of axonal degeneration in CMT throughout the lifetime of the individual.

Although plasma NFL shows promise in several forms of hereditary neuropathy, there has also been an effort to identify Schwann cell-specific biomarkers that may signify early disease in the commonest type of CMT, CMT1A. A treatment responsive Schwann cell biomarker may identify target engagement of a trial drug, much earlier than any blood biomarker of axonal degeneration. In one large, unbiased study of blood samples collected from two CMT1A patient cohorts and analysed using the OLINK PCR platform, TMPRSS5, a Schwann cell-specific protein was found to be significantly elevated in patients with CMT1A versus controls, although there was no correlation with the disease severity scores, the CMTES and CMTNS.[43] The increase in TMPRSS5 was not replicated in samples from patients with CMT1B implying this biomarker is specific to CMT1A.

Small circulating microRNAs are non-coding RNAs that regulate gene expression and have shown promise as potential biomarkers of disease activity in other diseases such as ALS.[46] Encouragingly, blood micro-RNAs specific to Schwann cells and muscle have been shown to be elevated in two separate CMT1A patient cohorts with good reproducibility.[47] It is hoped that these microRNAs are closely linked to the early pathogenic processes involved in the disease. If this were the case, they may prove to be highly sensitive blood biomarkers for use in clinical trials although further work validating their significance and responsiveness is required.

5.2 | Biomarkers of target engagement in CMT

In addition to biomarkers of disability, there has been considerable work in identifying blood biomarkers of pathogenesis that can be used to demonstrate target engagement in clinical trials of CMT. This is particularly relevant for those inherited neuropathies interrupting metabolic pathways, the most well established being hereditary sensory neuropathy type I due to mutations in *SPTLC1* and 2 in which mutations in these components of the enzyme serine palmitoyl

transferase result in the production of toxic deoxysphingolipids which are thought to be central to the disease pathogenesis.[21,48,49] Ongoing trials investigating L-serine supplementation, that correct this pathway and lead to a reduction in deoxysphingolipids, allow quantification of these sphingolipids to be used as a biomarker of target engagement.

More recently, recessive mutations in *SORD*, encoding sorbitol dehydrogenase have been identified as one of the commonest causes of axonal hereditary motor neuropathy. In all patients, plasma sorbitol concentrations are increased and this is thought to contribute to the disease.[50] This allows plasma sorbitol concentrations to be used as a biomarker of target engagement for potential therapies that inhibit upstream pathways reducing its concentration. Finally, in mouse models of CMT2D, activation of the integrated stress response has been proposed as a biomarker of disease activity. Interestingly, elevated blood concentrations of the integrated stress response marker GDF15 were also seen in patients with not only CMT2D but also mutations in other genes known to cause CMT.[51,52] In the same study, serum concentrations of neural cell adhesion Molecule 1 were also elevated in patients with CMT versus healthy controls.[52]

5.2.1 | ATTR amyloidosis

The most compelling evidence for the use of a blood biomarker in the management and trial evaluation of patients with peripheral neuropathy has come from studies of patients with hereditary ATTR amyloidosis.[37] ATTR is a hereditary disease caused by point mutations in *TTR* encoding transthyretin. Patients with ATTR develop a multisystem disease from early to late adulthood with variable involvement of the peripheral nervous system depending upon their ethnic background and genotype. In contrast to CMT, the disease is rapidly progressive and often fatal if untreated.[53] ATTR amyloidosis is also one of the first genetic conditions for which a licensed gene therapy has entered clinical practice.[35,36] These drugs utilize either antisense oligonucleotide or silencing RNA technology to suppress production of both wild-type and mutant TTR.[54] In two randomized double-blind placebo-controlled trials, these drugs were shown to be effective in preventing progression of peripheral neuropathy in patients with ATTR.[36,37] In the clinical trial of the siRNA Patisiran, blood was collected from patients in both arms and at several time points throughout the study.[37] Using an unbiased approach to identify sensitive protein biomarkers of axonal damage, blood samples were analysed using the OLINK platform, able to analyse more than 1000 proteins thought to be associated with polyneuropathy. Of the 66 proteins significantly changed with successful treatment with Patisiran, NFL had the strongest correlation.[37] This corroborated findings in uncontrolled patient cohorts showing an increase in plasma NFL in patients with ATTR and peripheral neuropathy versus healthy controls (and patients with ATTR amyloidosis and no peripheral neuropathy).[55–57] Furthermore, plasma NFL showed a significant reduction in those patients successfully treated with Patisiran versus those with placebo and correlated with improvement in clinical scores of peripheral neuropathy.[37] This study was pivotal in demonstrating that plasma NFL is a responsive biomarker of peripheral neuropathy, is responsive to effective treatment and correlates with FDA approved clinical outcome measures.

6 | CONCLUSION

The concept that a blood test might be used to diagnose and monitor peripheral nerve damage until relatively recently would have seemed fanciful, however, with the development of ultrasensitive protein assays with a lower limit of detection above that of traditional ELISA techniques, has allowed markers of neuronal damage such as NFL to be accurately measured in blood. One of the key setbacks, however, is the inability to distinguish central from peripheral nerve degeneration. Nevertheless, these protein biomarkers appear to be effective at identifying patients with peripheral neuropathy compared to controls and also show efficacy as a marker of disease activity in patients with rapidly progressive peripheral neuropathy such as vasculitis and amyloidosis. The use of axonal protein biomarkers such as NFL in slowly progressive diseases without significant axonal loss such as CMT, CIDP and multifocal motor neuropathy is less certain. Measurement of relevant circulating microRNAs shows great promise, as the technology for quantification is well established and specific microRNAs may be selected that are specific to disease processes.

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CONFLICT OF INTEREST

There are no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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