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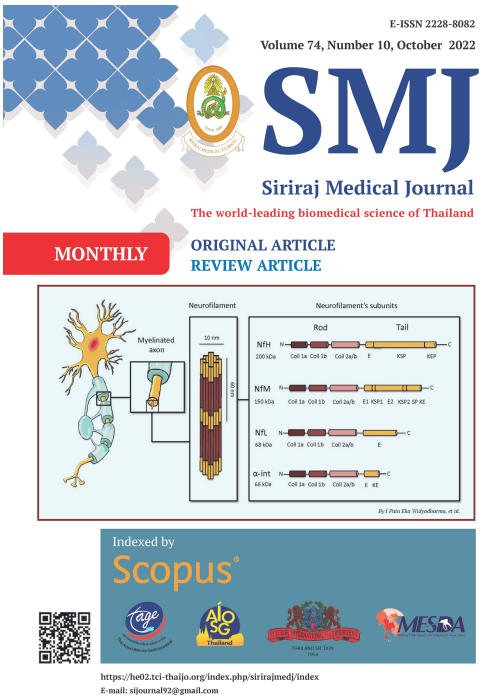

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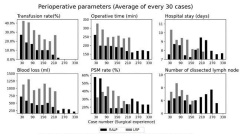

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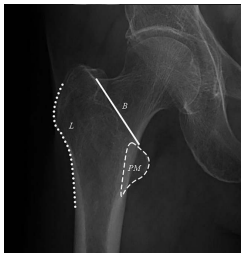

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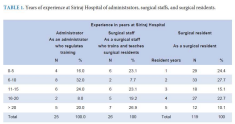

TABLE 1: Years of experience at Siriraj Hospital of administrators, surgical staffs, and surgical residents.

	Experience in years at Siriraj Hospital							
	Administrator		Surgical staff		Surgical resident			
	As an administrator who regulates training		As a surgical staff who trains and teaches surgical residents		As a surgical resident			
	N	%	N	%	Resident years	N	%	
0-5	4	16.0	6	23.1	1	29	24.4	
6-10	8	32.0	2	7.7	2	30	27.1	
11-15	6	24.0	6	23.1	3	18	15.1	
16-20	2	8.0	5	19.2	4	27	22.7	
>20	5	20.0	7	26.9	5	12	10.1	
Total	25	100.0	26	100	Total	118	100	

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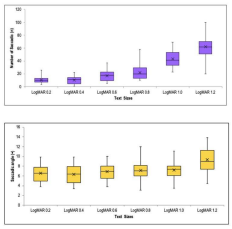

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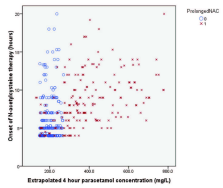

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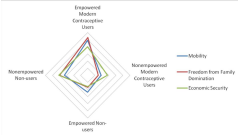

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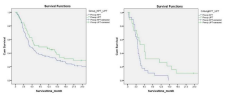

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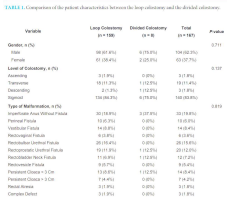

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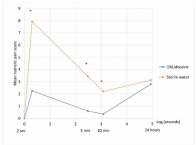

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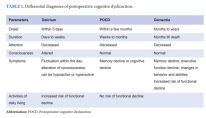

TABLE 1. Differential diagnosis of postoperative cognitive dysfunction.

Parameters	Delirium	POCD	Dementia
Onset	Within 2-days	Within a few months	Months to years
Duration	Days to weeks	Weeks to months	Months till death
Attention	Decreased	Decreased	Decreased
Consciousness	Altered	Normal	Normal
Symptoms	Fluctuation within the day; alteration of consciousness; can be hypoactive or hyperactive	Memory decline or cognitive decline	Memory decline; executive function decline; changes in behavior and abilities; increased risk of functional decline
Activities of daily living	Increased risk of functional decline	No risk of functional decline	

Abbreviation: POCD, Postoperative cognitive dysfunction

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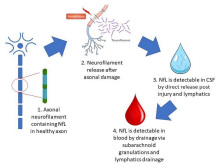

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Serum Neurofilament Light Chain: A Potential Biomarker for Peripheral Neuropathy

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ABSTRACT

In some neurological diseases, advanced examinations can be used as diagnostic tools. Several indicators have also been discovered that can be used to assess the severity of neuronal damage and neurological disease progression. Neurofilament light chain (NfL) is a cytoskeleton protein that makes up the structure of neuron axons and is released when a neuron is injured, allowing it to assess neuronal injury severity. NfL was first used to diagnose central nervous system disorders like dementia, multiple sclerosis, and other neurodegenerative diseases. But, NfL levels have also been elevated in peripheral nervous system disorders, like in several neuropathic conditions, including amyloid neuropathy, HIV-associated neuropathy, diabetic peripheral neuropathy, leprosy neuropathy, and other neuropathy, according to various investigations. Theoretically, all abnormalities induced by axonal injury will increase blood NfL levels, allowing NfL testing to be utilized as a measurement tool. NfL levels can also be a predictive indicator to monitor treatment efficacy and peripheral neuropathy progression.

Keywords: Biomarker; neurofilament light chain; peripheral neuropathy; prognostic (Siriraj Med J 2022; 74: 714-720)

INTRODUCTION

In recent years, neurology has made significant technological innovations. A variety of neuroimaging methods can generate accurate images of the brain. Moreover, various biomarkers have been developed which may be used in clinical trials to estimate the level of neuronal damage. One of them is the neurofilament light chain (NfL). NfL is released into the CSF and bloodstream whenever there is damage to neurons.[1]

Since it is an indicator of axonal damage, the serum neurofilament light chain (NfL) is a potential diagnostic in neurological diseases. Previously, NfL has only been detected in CSF. The NfL can still be detected in the blood due to the new advanced technologies, making it simpler to detect and avoiding traumatic procedures like a lumbar puncture. A neurologist can use NfL as a prospective diagnostic as an accurate sign of nerve injury. If the cardiologist has troponin, the neurologist has the neurofilament light chain (NfL).[2]

NfL concentrations in the normal population are rarely reported. Tobias et al revealed that NfL levels in normal populations are 7.3 (±3) pg/mL in serum and 416 (±191) pg/mL in CSF. In patients with Multiple Sclerosis, NfL levels are 16.4 (±14.4) pg/mL in serum and 2368 (±1947) pg/mL in CSF. The levels of NfL are affected by age, BMI, and renal function. The association between age and NfL concentration was positive ($r = 0.325$; p-value <0.0001), while the correlation between BMI and NfL concentration was negative ($r = 0.227$; p-value <0.0001). No significant differences exist between NfL concentration and gender. In addition, there was a strong correlation between NF-L levels and renal function. NfL concentration and eGFR were also found to have a very strong connection ($r = -0.492$; p-value <0.0001).[3-5]

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CSF and serum NfL levels were higher in patients with a central or peripheral nervous system injury. This increase has been linked to neurological diseases, according to certain studies. The NfL can also be used to predict future outcomes. Because it can be easily detected and non-invasively in the blood, NfL is a promising biomarker for monitoring the progression of neurological diseases and evaluating the efficacy of therapy.[6]

Peripheral neuropathy affects approximately 2.4 percent of the population, with symptoms varying depending on what type of nerve fiber is affected, the type of neuron injury, and the severity of the injury. Peripheral neuropathy is most commonly caused by diabetes. However, HIV can also directly or indirectly induce peripheral neuropathy through antiretroviral (ARV) medications. Systemic disease, infection, and malnutrition are also all potential causes of peripheral neuropathy.[7]

A neurologist might conduct an electrophysiological evaluation of nerve conduction velocity to diagnose peripheral neuropathy. However, nerve conduction velocity may not be able to accurately assess the severity and progression of neuropathy in some conditions, requiring the use of additional biomarkers to determine prognostic value. On the other hand, NfL has lately undergone massive research and can be utilized as a biomarker for peripheral nerve injury. Serum NfL levels are known to be elevated in cases of peripheral neuropathy and correlate with disease severity.[8] In this review, we provide the role of the neurofilament light chain (NfL) as a biomarker of peripheral neuropathy.

Neurofilament light chain (NfL)

The essential features of neurons are neurofilaments, built up of protein triplets and present on nerve axons (Fig 1). The neurofilament core cannot functionally work without the neurofilament light chain (NfL) subunit. Almost every neuron component contains the protein neurofilament light chain (NfL). The diameter and speed of nerve conduction from peripheral nerves are determined by NfL accumulation, linked to axon growth during myelination.[9] Depending on the severity of axonal damage in peripheral nerves, NfL can be released into the extracellular space and bloodstream. An apophagocytotic process releases NfL into the CSF and bloodstream when neurons in the central nervous system are damaged. NfL will enter the CSF through direct drainage and then enter the bloodstream through arachnoid granulation and lymphatic flow in the subarachnoid space, making it detectable in both the CSF and the blood.[10] According to some studies, the amount of NfL in CSF is 500 times higher than in blood because CSF is directly related to the central nervous system. NfL concentrations in the blood are too low to be detected by an ELISA test. Thanks to recent technological advancements, a new method, SIMOA (Single-Molecule Assay (SiMoA), has been developed to detect NfL down to a single-digit picogram per millimeter unit.[11]

NfL in neurological cases

Axonal damage in the central and peripheral nervous systems, such as stroke, head trauma, multiple sclerosis, ALS, Alzheimer's disease, frontotemporal dementia,

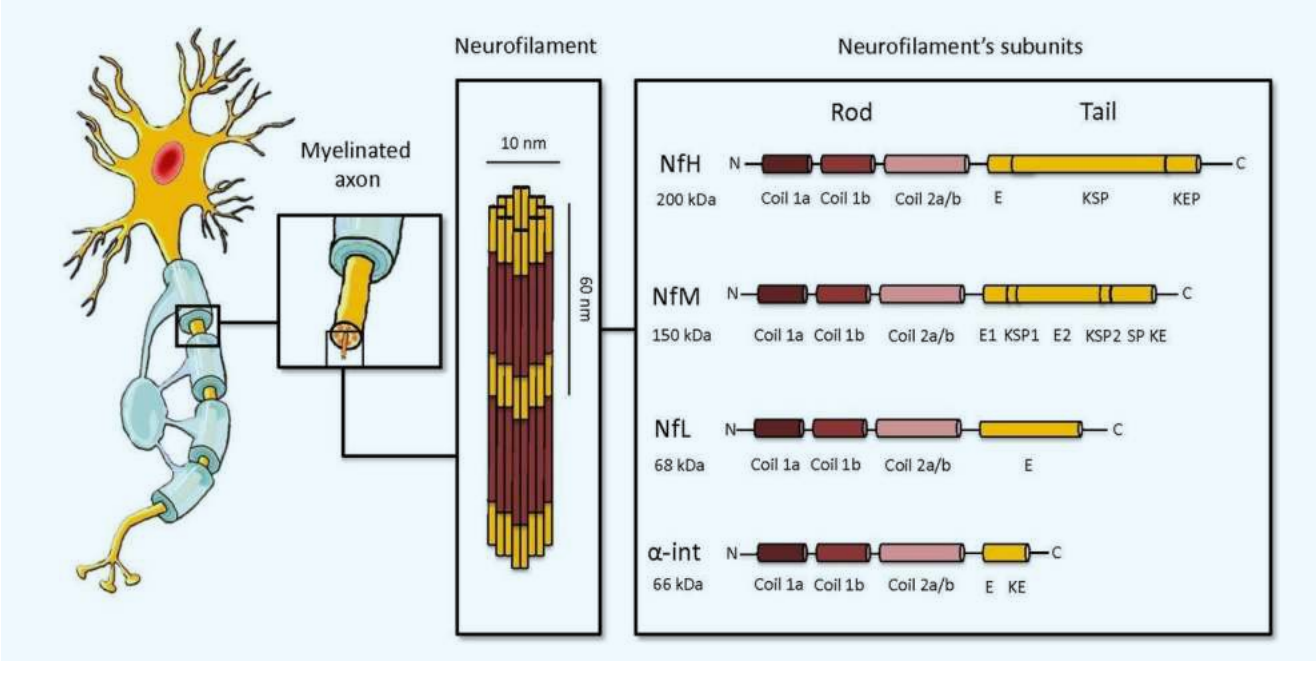

Fig 1. Structure of neurofilament.[6]

and peripheral neuropathy, can be identified by NfL measurement. Previous studies linked increased NfL levels in CSF and serum to neurodegenerative and neuroinflammatory processes, indicating demyelination and axonal damage.[12-16]

Neurological patients have much greater NfL levels in their CSF and blood than healthy or non-neurological patients. NfL is a test that can identify neurological problems caused by axonal damage. It can tell the difference between varying degrees of axonal damage, progression, and whether or not it is a neurodegenerative condition. As a result, the NfL examination is utilized as a biomarker to validate the diagnosis after a full neurological examination or other biomarker and neuroimaging procedures.[6] In the event of peripheral neuropathy, NfL can be utilized as a non-invasive diagnostic technique to determine therapy success and progression.[8]

It is unclear how long the duration of NfL levels increases in patients with peripheral neuropathy. In studies on multiple sclerosis, traumatic brain injury, and stroke, NfL levels peak 3–4 weeks after a clinical relapse and remain elevated for 6–12 months. Further studies on how long NfL levels increase in peripheral neuropathy need to be done for prognostic purposes.[17]

NfL in peripheral neuropathy

Peripheral neuropathy has become a global health concern, affecting 2.4 percent of the world's population, or around 10 million people in the European Union and 7 million in the United States. Measurement of nerve conduction velocity is the gold standard for diagnosing peripheral neuropathy. However, it cannot be used as a monitor for the success of therapy or disease progression in some cases. As a result, a peripheral nerve damage biomarker is required. On the other hand, NfL has recently undergone extensive research and can be used as a biomarker for peripheral nerve damage. NfL levels have been shown to increase in peripheral neuropathy patients' blood and correlate with disease severity, implying that the NfL is involved in disease progression and can be used as a prognostic factor in peripheral nerve damage.[8,18]

Neuronal neurofilament breakdown is thought to use a combination of ubiquitin-mediated proteasomal and apophagocytotic mechanisms. Based on the transport of other CNS-degraded proteins, it is likely that neurofilament fragments drain directly into CSF and blood via numerous pathways. These include lymphatic outflow into subarachnoid and perivascular regions and direct draining into CSF and blood via arachnoid granulations. Once NfL enters the bloodstream, the half-life is a crucial factor with consequences for disease activity monitoring frequency. In a longitudinal study of NfL levels before and after implantation of an intrathecal catheter, NfL levels in both CSF and serum peaked one month after surgery and returned to baseline six to nine months later.[2]

Other biomarkers besides NfL can be used to diagnose peripheral neuropathy, including Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), and other inflammatory markers such as IL-1, 6,10, 18, and TNF-alpha. Low BDNF levels were correlated with CIPN in 91 multiple myeloma patients treated

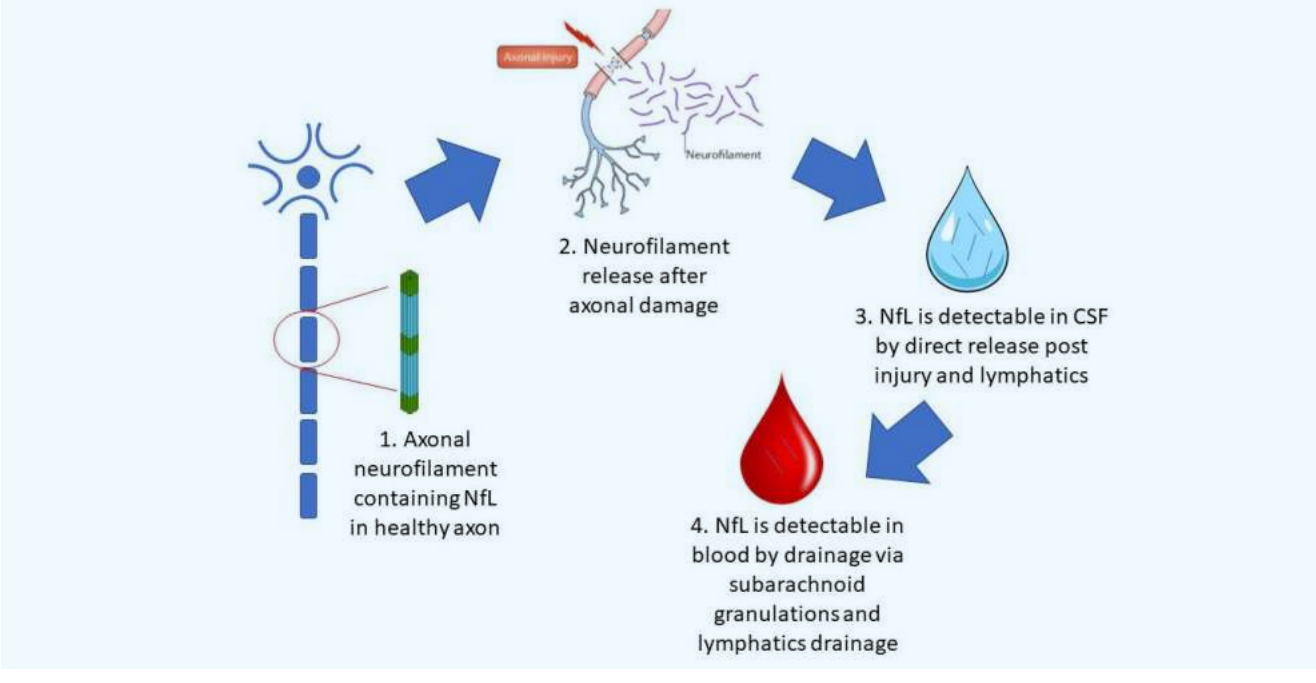

Fig 2. Pathophysiology of neurofilament light chain in cerebrospinal fluid (CSF) and blood.

with bortezomib, and a cut-point of 9.11 ng/ml was 76% sensitive and 71% specific for identifying Chemotherapy-induced Peripheral Neuropathy (CIPN). Nonetheless, another study found no correlation between BDNF and the incidence of CIPN. In one investigation, a correlation was shown between decreasing NGF and the severity of neuropathy as measured by nerve conduction velocity testing. High levels of IFN-, IL-1, and IL-8, but low levels of IL-10 and IL-6, were linked to peripheral neuropathy symptoms. Due to the inconsistency and expense of these biomarkers, NfL testing is recommended to monitor peripheral neuropathy.[19]

Sandelius et al. suggested that the cut-off value of NfL for peripheral neuropathy was 20 pg/mL with a sensitivity of 71% and specificity of 75%. Increased serum NfL concentration is not specific to peripheral neuropathy because other neurological disorders such as multiple sclerosis, Alzheimer's disease, stroke, and Amyotrophic Lateral Sclerosis (ALS) also reported increases. NfL is not useful for diagnosis, but it may be useful to measure axonal damage and could serve as a biomarker of progressivity of the disease for monitoring and response to treatment. NfL is sensitive to detecting axonal damage and correlates with disease severity and progressivity.[18]

Several studies have reported elevated levels of NfL in amyloid neuropathy, HIV-associated neuropathy, diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, and pyridoxine-induced sensory neuropathy.

Amyloid neuropathy

Amyloidosis patients with polyneuropathy experience axonal degeneration, which results in elevated serum NfL levels. Axonal degeneration is caused by the accumulation of amyloid fibrils in the endoneurium and direct toxicity to the nerve's prefibrillar oligomers.[20-22] Patients with symptomatic polyneuropathy, as well as those who are asymptomatic, have elevated serum NfL levels. Serum NfL levels can be used as a marker for early-stage axonal damage in asymptomatic or subclinical amyloidosis, making it essential to diagnose, treat, and monitor the progress and success of amyloidosis therapy.[23] The AUC between asymptomatic and symptomatic amyloid neuropathy patients was 0.99 (p .001), and a NfL concentration of 10.6 pg/mL distinguished these individuals with a sensitivity of 96.2% and a specificity of 93.8%.[20] Serum NfL levels increase the most in patients with abnormal EMG results. This demonstrates that serum NfL is a sensitive marker for early detection of polyneuropathy and is strongly associated with the disease.[14]

HIV-associated neuropathy

HIV-associated neuropathy manifests as distal symmetrical polyneuropathy and toxic antiretroviral neuropathy (ATN), which is difficult to distinguish clinically and electrophysiologically regardless of the use of antiretroviral drugs or the onset of symptoms. HIV-associated neuropathy is linked to the patient's viral load and CD4+ cell count. The use of dNRTIs like stavudine, didanosine, or zalcitabine has been linked to ATN. After antiretroviral therapy, the symptoms of HIV-related polyneuropathy improve as the viral load decreases. After a year of ARV treatment, the symptoms of ATN will worsen.[24]

NFL is a structural component of myelinated axons that have been used as a marker of axonal damage in neurodegenerative diseases in several studies. Axonal damage also occurs in HIV-associated neuropathy, but research on elevated serum NfL levels in HIV-associated neuropathy is uncommon. The HIV in Dementia study is the most widely conducted. Compared to HIV patients without dementia, NfL levels were significantly higher in HIV patients with dementia. The levels of plasma NfL and CSF NfL did not differ significantly. Damian et al. conducted a study to see if NfL levels were elevated in HIV-associated neuropathy patients. The researchers discovered an increase in NfL levels in both CSF and serum in 26 of 54 patients with neuropathy, which correlates to the severity of the neuropathy.[25] NfL levels are not only used as markers of damage to the central nervous system but also in the peripheral nervous system, such as neuropathy, according to these studies.[26]

Chemotherapy induced peripheral neuropathy (CIPN)

CIPN is a side effect of chemotherapy in some cancers. Proper diagnosis, treatment, and dosage adjustments are required to avoid permanent nerve damage. Because CIPN is an axonopathy, it can mimic the symptoms of polyneuropathy. Previous research has discovered that elevated serum NfL levels are linked to peripheral neuropathy and the severity of nerve damage, allowing NfL levels to be measured in CIPN patients. In a mouse model given the cytostatic drug vincristine (VCR) 0.2 mg/kg intravenously four times per week, serum NfL levels increased fourfold, with signs of axonopathy on neurophysiological and pathological examinations. The presence of the NfL in the blood can determine the severity of CIPN.[27-29]

Other chemotherapy drugs, such as oxaliplatin, can cause neuronal cell death and neuropathy in the dorsal ganglion. One study found a link between serum NfL levels and changes in nerve amplitude after treatment with

oxaliplatin. Serum NfL levels were significantly higher in 5 patients with grade 3 OIPN (oxaliplatin-induced peripheral neuropathy) than in grades 0-2 (80 percent sensitivity and 86 percent specificity with a cut-off value of 195 pg/mL). Based on the findings of these studies, serum NfL can be used as a monitor for the severity of OIPN.[30]

Diabetic peripheral neuropathy (DPN)

An observational study used Serum NfL as a non-invasive diagnostic tool to detect diabetic peripheral neuropathy and its progression. NfL levels are related to the neuropathy disability score (NDS) and decreased nerve conduction velocity in some nerves. The AUC for serum NfL was 0.564, and the DPN cut-off point was 12.6 pg/ml. NfL is also associated with the hyperalgesia phenotype and is positively correlated with the severity of DPN.[31,32]

NfL mRNA levels have also been elevated in prediabetic patients with peripheral neuropathy. This supports the hypothesis that NfL mRNA levels are significantly higher in prediabetic patients when small-diameter nociceptive afferent C fibers are interfered with in hyperglycemic conditions, causing axon damage and neuropathic pain symptoms. This level is positively correlated with DN4 questionnaire score.[9,33]

Leprosy neuropathy

Mycobacterium leprae can damage both myelinated and unmyelinated nerve fibers. Patients with leprosy may develop painful neuropathy symptoms. The pathogenesis of neuropathy in leprosy includes infection of the Schwann cells, demyelination, and damage to the axons, leading to atrophy. In tuberculoid and borderline leprosy, axon damage is caused by inflammation of the endoneurial membrane, which destroys nerve structures and causes nerve damage. According to the results of a nerve biopsy, axons and myelin are lost in patients with leprosy. Electromyography also revealed axonal polyneuropathy. Axon damage is a focus of research into the mechanism of leprosy neuropathy. Biomarkers such as NfL can be used with other tests to help determine prognosis and treatment success.[35,36]

Post-herpetic neuralgia

After the reactivation of the varicella-zoster virus, which damages the cell body and axons, post-herpetic neuralgia (PHN) develops. The pathology of PHN is associated with peripheral axonal damage, sensory neuron degeneration, and dorsal horn atrophy. However, several theories suggest that after viral reactivation, axonal damage occurs due to inflammation in PHN. The role of NfL in post-herpetic neuralgia has rarely been studied. More research on the NfL as a biomarker of post-herpetic neuralgia is needed.[37]

Pyridoxine-induced sensory neuropathy (PISN)

According to a study, NfL levels in the CSF and blood increased on day four after rats received pyridoxine therapy. Pyridoxine's primary target is the cell body of

TABLE 1. Summarize how NfL is used in various peripheral neuropathy diseases.

Disease	NfL levels	Indication	Sensitivity	Specificity	AUC	Reference
Peripheral neuropathy	20 pg/mL	Prognostic	71%	75%	0.755	18
Amyloid neuropathy	10.6 pg/mL	Prognostic	96.2%	93.8%	0.99	20
CIPN	195 pg/mL	Prognostic, treatment response	80%	86%	N/A	30
Diabetic peripheral neuropathy	12.6 pg/ml	Prognostic, treatment response	77.6%	86.3%	0.564	32
ALS	93 pg/ml	Prognostic	80.5%	90.9%	0.85	38
Post-stroke cognitive impairment	46.12 pg/ml	Prognostic	71%	81.5%	0.785	39

DRG neurons, which is followed by secondary nerve fiber degeneration. NfL is released directly from the DRG to the CSF via the subarachnoid space from the neuronal cell body and surrounding nerve fibers.[34]

Summarize

As described above, NfL can help determine the progression and response to peripheral neuropathy treatment. Here we provide a table summarizing how NfL is used in various peripheral neuropathy diseases discussed in the manuscript (Table 1). We also compared diseases such as ALS and post-stroke cognitive impairment. No studies determine the cut-off value for some types of peripheral neuropathy. Further research on cut-off NfL levels needs to be done.

CONCLUSION

Serum NfL can be used as a diagnostic tool for peripheral neuropathy after a careful history and physical examination. In addition, NfL levels can also be used as a monitor for the success of therapy and the progression of peripheral neuropathy to be used as a prognostic value. Further studies regarding when serum NfL levels begin to elevate, how long they last, and clear cut-off points for each type of peripheral neuropathy are needed to strengthen the diagnostic value and specificity of serum NfL.

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