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Neurofilament Light Chain (NfL) as A Potential Biomarker of Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Cervical Cancer Patients

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ABSTRACT

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a complication of chemotherapy observed in several types of cancer, including cervical cancer. The pathomechanism of CIPN is multifactorial and depends on the type and dosage of chemotherapy administered. CIPN is an axonopathy that can lead to clinical manifestations of polyneuropathy. Proper diagnosis, management, and dose adjustments are necessary to prevent permanent nerve damage. However, no gold standard diagnostic test for CIPN currently exists. One biomarker that has recently gained attention is the neurofilament light chain (NfL). NfL is the most abundant filament in neurons and axons, playing a crucial role in the assembly and maintenance of the axonal cytoskeleton. Disruption of the axonal membrane results in the release of neurofilaments into the interstitial fluid, which subsequently enters the cerebrospinal fluid (CSF) and blood serum. Due to its lowest molecular weight and highest solubility among neurofilaments, NfL diffuses more readily from the parenchyma into the CSF following axonal degeneration, neuronal death, or neuronal damage. Therefore, elevated NfL concentrations in the blood serum serve as a marker of axonal degeneration. The potential role of NfL as a biomarker for neurologists should be a point of interest, which may aid in the clinical diagnosis of CIPN in the future.

Keywords: cervical cancer; chemotherapy; chemotherapy-induced peripheral neuropathy; neurofilament light chain; biomarker.

INTRODUCTION

Cervical cancer remains a significant public health issue in Indonesia, ranking second among the ten most common cancers according to Anatomical Pathology data from 2010, with an incidence rate of 20%.[1] Chemotherapy is one of the effective therapeutic options to suppress cancer progression. However, chemotherapeutic agents also exert adverse effects on normal cells and structures, including the nervous system. Chemotherapy agents can damage neural structures, leading to various types of neuropathy.[2] The neurotoxic effects of chemotherapy vary across drug classes, depending on the specific physicochemical properties and their single or cumulative doses.[3] One of the most common neuropathies induced by antineoplastic agents is chemotherapy-induced peripheral neuropathy (CIPN).[4]

The prevalence of CIPN varies depending on the chemotherapeutic agent, with reported rates ranging from 19% to over 85%. The highest prevalence is observed with platinum-based agents (70–100%), taxanes (11–87%), thalidomide and its analogs (20–60%), and ixabepilone (60–65%). Neurotoxicity can occur with either high single doses or cumulative exposure over time.[2] The symptoms of CIPN vary in intensity and duration, ranging from transient acute thermal sensations to permanent peripheral nerve alterations, chronic pain, and irreversible nerve damage. CIPN can manifest not only during chemotherapy administration but may also persist for months or even years after treatment cessation. The highest prevalence occurs within the first month following chemotherapy, with a rate of 68.1%. This rate subsequently declines to 60% at three months post-chemotherapy. In some individuals, CIPN persists even after six months post-treatment, with a prevalence of 30%.[5]

Several quantitative biomarkers have been associated with CIPN due to axonal damage, including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurofilament Protein

(NF), and MicroRNAs.[6] One promising biomarker for predicting CIPN is Neurofilament Light Chain (NfL). NfL is an intermediate filament primarily expressed by large myelinated axons and is released into the cerebrospinal fluid (CSF) during neuronal or synaptic degeneration.[7] A study by Huehnchen et al., evaluating NfL levels in breast and ovarian cancer patients undergoing paclitaxel chemotherapy demonstrated a significant increase in serum NfL (sNfL) levels among those who developed CIPN.[8] Another study involving 190 ovarian cancer patients receiving paclitaxel/carboplatin chemotherapy reported a substantial increase in sNfL levels during treatment, with significant interindividual variability (Mortensen et al., 2023). Additional research also supports the potential of sNfL as a predictor of CIPN.[9]

Cervical cancer patients undergoing chemotherapy are at risk of developing CIPN due to peripheral nerve damage. This damage is characterized by the release of NfL into the bloodstream, leading to elevated serum NfL levels. Given the potential of NfL as a biomarker for CIPN, this literature review will provide an in-depth discussion of its role in chemotherapy-induced neurotoxicity.

Overview of CIPN

CIPN is peripheral nerve damage that occurs as a side effect of neurotoxic antineoplastic agents.[10] CIPN is commonly observed in cancer patients undergoing chemotherapy. The prevalence and incidence of CIPN vary depending on several factors, including the type of chemotherapy agent, dosage, treatment duration, and the methods used for assessment.[11] The chemotherapeutic drug classes most frequently associated with CIPN include platinum-based agents, taxanes, ixabepilone, as well as thalidomide and its analogs. Platinum-based chemotherapy can induce CIPN in 70–100% of patients, while taxanes affect 11–87% of patients. Thalidomide and its analogs contribute to CIPN in 20–60% of patients, whereas ixabepilone leads to CIPN in 60–65% of cases.[2,12]

A study involving 754 cancer patients at the National Institute of Cancerology in Mexico found that 30.9% of participants experienced CIPN. Patients at the highest risk of developing CIPN were those receiving paclitaxel chemotherapy (OR=8.3; $p < 0.01$), followed by platinum-based chemotherapy (OR=4; $p<0.01$), vincristine (OR=1.5; $p = 0.01$), and thalidomide (OR=1.1; $p=0.01$).[13]

A meta-analysis encompassing 31 studies with a total of 4,179 patients found that the prevalence of Chemotherapy-Induced Peripheral Neuropathy (CIPN) was approximately 68% within the first month after chemotherapy, decreasing to 60% after three months and 30% after six months.[5] CIPN-related symptoms often persist for more than six months following chemotherapy cessation, with evidence linking neuropathy severity to quality of life (QoL).[14] Further research evaluating the long-term consequences of docetaxel treatment in breast cancer and oxaliplatin treatment in colorectal cancer patients reported that 42% and 84% of patients, respectively, experienced CIPN symptoms two years post-treatment.[15] Additionally, a systematic review found that between 11% and over 80% of breast cancer patients studied reported persistent CIPN symptoms one to three years after chemotherapy.[14]

CIPN symptoms may be sensory, motor, or autonomic, though sensory complaints are the most common. These sensory symptoms result from damage to peripheral sensory nerve fibers. Injury to small nerve fibers, such as myelinated Aδ fibers and unmyelinated C fibers, contributes to neuropathic pain.[16,17] Several risk factors have been identified as being associated with an increased risk of CIPN; however, the causal relationships between these factors and CIPN remain unclear. These risk factors include: (1) older age, (2) the use of cardiovascular medications such as beta-blockers, (3) comorbid conditions such as diabetes, HIV, alcohol consumption, and smoking, (4) increased body mass index, which may be linked to the pro-inflammatory state associated with obesity, (5) low serum albumin levels, and (6) opioid use.[18]

Molecular Pathomechanism of CIPN

Neuroimmune activation plays a crucial role in the development of Chemotherapy-Induced Peripheral Neuropathy (CIPN). Peripheral nerve cells contain various glial cells, where dorsal root ganglion (DRG) neurons are surrounded by satellite glial cells, and axons are ensheathed by Schwann cells. Chemotherapeutic agents trigger a response from Schwann cells and satellite glial cells, leading to phenotypic changes and the secretion of inflammatory mediators that enhance neuronal excitability and pain hypersensitivity. Schwann cells are the first to respond to neuronal damage by activating the extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) signaling pathway, which induces the expression of inflammatory mediators and recruits immune cells. Additionally, Schwann cells experience disturbances in differentiation and degeneration of the myelin sheath. Mast cells undergo degranulation and release inflammatory mediators such as histamine, serotonin, growth factors, and leukotrienes, which sensitize nociceptors and contribute to neutrophil recruitment. Neutrophils, in turn, release mediators that further sensitize nociceptors and recruit macrophages and T cells to the injured nerve. Infiltrating macrophages merge with resident macrophages and Schwann cells, phagocytizing degenerated axons and myelin sheaths while also releasing pro-inflammatory cytokines and chemokines.[19]

Schwann cells produce pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and PGE2, as well as the anti-inflammatory cytokine IL-10 to counterbalance nerve injury processes. Macrophages and T cells induce the secretion of various cytokines (TNF-α, IL-1β, IL-6, and IL-8), chemokines (CCL2 and CXCL), growth factors (GF), and inflammatory mediators, including bradykinin, prostaglandins, serotonin, and nitric oxide (NO).

Chemokines play a crucial role in activating and infiltrating macrophages involved in neuropathic pain. TNF-α, IL-1β, bradykinin, and nerve growth factors increase action potential generation by enhancing Na+ and Ca2+ influx at peripheral nociceptor terminals, thereby increasing membrane excitability, lowering pain thresholds, and promoting peripheral sensitization in myelinated Aδ fibers and unmyelinated C fibers.[20,21]

Chemotherapy Agent-Induced CIPN

The pathomechanism of CIPN is multifactorial, with the effects of chemotherapeutic agents on the peripheral nervous system depending on the characteristics, mechanisms of action, and dosage of the drug (Table 1). This neurotoxicity may occur either directly through drug interactions with neuronal cells or indirectly through glial damage, inflammation, and other mechanisms.[22] The process involves microtubule damage, mitochondrial dysfunction, and oxidative stress, as well as alterations in ion channel activity, damage to the myelin sheath, DNA damage, and immunological and neuroinflammatory processes. The chemotherapeutic drug classes most frequently associated with CIPN include platinum-based agents, taxanes, ixabepilone, as well as thalidomide and its analogs.[2]

TABLE 1: Chemotherapy Doses Causing Peripheral Neuropathy.[23]

Type	Class	Dose threshold	Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paclitaxel	Taxane	>300 mg/m2	Predominance of sensory neuropathy	At higher doses, myalgia and myopathy	Infrequently
Docetaxel	Taxane	>100 mg/m2	Predominance of sensory neuropathy	At higher doses, myalgia and myopathy	Infrequently
Oxaliplatin	Platinum	>550 mg/m2	Symptoms of acute and chronic sensory neuropathy	Acute cramps and fasciculation	Infrequently
Cisplatin	Platinum	>350 mg/m2	Predominance of sensory neuropathy	Infrequently	Infrequently
Vincristine	Vinca alkaloids	>2-6 mg/m2	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes
Thalidomide	Immunomodulators	>20 g	Sensory neuropathy	Mild distal weakness and muscle cramps	Infrequently
Bortezomib	Protease inhibitor	>16 mg/m2	Pain, sensory neuropathy	Infrequently	Yes

Platinum-based chemotherapy agent

Drugs in this class include cisplatin (first-generation), carboplatin (second-generation), and oxaliplatin (third-generation).[24] Platinum-based drugs are commonly used in the treatment of solid tumors, including those of the ovaries, uterus, lungs, head and neck, bladder, and gastrointestinal tract. All platinum-based compounds specifically bind to guanosine and adenosine, creating DNA cross-links that inhibit replication and transcription, ultimately leading to cell cycle arrest and programmed cell death. Additionally, platinum agents can permanently bind to mitochondrial DNA (mtDNA), triggering mitochondrial depletion. This results in a reduction in mitochondrial numbers within neuronal cell bodies, an increase in reactive oxygen species, and heightened oxidative stress.[22,24]

Cisplatin tends to cause more severe neuropathy compared to carboplatin and oxaliplatin. Unlike other platinum-based agents, oxaliplatin does not influence macrophage infiltration or accumulation, and macrophage-reducing agents do not alleviate oxaliplatin-induced neuropathic symptoms. Oxaliplatin interacts with voltage-gated potassium channels (VGKCs) expressed in peripheral motor neurons. This interaction is associated with the acute phase of oxaliplatin-induced neuropathy, during which patients may experience symptoms resembling neuromyotonia, such as prolonged depolarization, increased neurotransmission, and nerve hyperexcitability.[24]

Antimicrotubule chemotherapy agent

• Taxane

Antimicrotubular agents include paclitaxel, docetaxel, and cabazitaxel. These drugs serve as first-line treatments for breast, ovarian, lung, pancreatic, bladder, and prostate cancers, as well as other solid tumors. These agents induce neuropathy in a dose-dependent manner by targeting microtubules, which are essential cytoskeletal proteins involved in various cellular functions, including cell shape regulation, mitosis, chromosome segregation, and retrograde and anterograde intracellular transport.[24,25]

Microtubules function based on the dynamic balance between permanent aggregation and disassembly of α- and β-tubulin subunits. Taxanes promote microtubule polymerization (by inhibiting tubulin depolymerization) through their binding to β-tubulin subunits. This action disrupts mitotic spindle formation, inhibits normal mitosis, and induces apoptosis. Research has shown that paclitaxel alters tubulin acetylation; however, tubulin expression returns to normal levels rapidly following discontinuation of the drug.[24]

Mitochondrial dysfunction has also been proposed as a mediator of paclitaxel-induced pain. By disrupting the mitochondrial permeability transition pore, paclitaxel induces mitochondrial dysfunction, which reduces mitochondrial respiration and impairs ATP production in neurons. Rodents administered taxanes exhibit increased levels of reactive oxygen species (ROS) and oxidative stress, along with decreased mitochondrial metabolic activity, membrane potential, and bio-antioxidant availability. Furthermore, taxanes upregulate Toll-like receptor 4 (TLR4) expression and enhance the production of pro-inflammatory cytokines.[24]

In vitro studies have shown that co-administration of paclitaxel and probiotics can normalize TRPV4 expression and acetylated α-tubulin levels. This finding is further supported by evidence that probiotic-treated rodents did not develop mechanical hypersensitivity during treatment with paclitaxel.[22]

• Vinca alkaloid

Vinca alkaloids, including vincristine, vinblastine, and vinorelbine, are primarily used in the treatment of hematologic malignancies, either as monotherapy or in combination with other drugs. These agents induce sensorimotor neuropathy, with vincristine exhibiting the highest neurotoxicity among them. Similar to taxanes, vinca alkaloids target microtubules; however, instead of stabilizing their structure, they bind to β-tubulin subunits and inhibit microtubule formation, specifically microtubule aggregation. They disrupt the polymerization of α-tubulin, preventing the formation of the mitotic spindle. Recent studies suggest that SARM1 (sterile alpha and TIR motif containing 1), a protein involved in Wallerian degeneration, plays a crucial role in vincristine-induced axonal degeneration.[22]

Bortezomib

Bortezomib, a proteasome inhibitor, is a relatively newer chemotherapeutic agent compared to other chemotherapy drugs and has been used in the management of various hematologic malignancies. Bortezomib exerts its anticancer effects by inhibiting the 20S core proteasome, suppressing the unfolded protein response, accumulating ubiquitinated proteins, stabilizing tumor suppressor proteins such as p21, p27, Bax, and p54, and increasing reactive oxygen species (ROS). Additionally, bortezomib is associated with intracellular calcium dysregulation, leading to apoptosis induction. It has been shown to alter nerve action potentials and reduce nerve conduction velocity in peripheral nerves. However, the exact mechanism by which bortezomib induces peripheral neuropathy remains unclear.[24]

Thalidomide

Thalidomide is used to treat several types of cancer, including multiple myeloma, glioblastoma, melanoma, renal cell carcinoma, breast cancer, prostate cancer, colorectal carcinoma, and lung cancer. The precise mechanism by which thalidomide exerts its anticancer effects remains unclear. However, it has been implicated in promoting cell death by inhibiting NF-κB activation and TNF-α production. The underlying mechanisms of thalidomide-induced chemotherapy effects have also been proposed as a contributing factor to thalidomide-induced neuropathy.[24]

5-Fluorouracil (5-FU)

5-Fluorouracil (5-FU) can bind to DNA and alter nucleotide sequences. At higher doses, it can cause RNA dysfunction, disrupt cellular protein synthesis, and induce apoptosis, ultimately leading to chemotherapy-induced peripheral neuropathy (CIPN).[22]

Cyclophosphamide-alkylating agent

The mechanism of action of cyclophosphamide is similar to that of platinum compounds. Cyclophosphamide forms cross-links between two DNA strands at the N-7 position of guanine. This prevents DNA replication and repair, ultimately leading to cell death.[22]

Physiology and Pathophysiology of Neurofilament

Neurofilaments are the most prominent structural components of nerve cells, composed of triplet proteins and found in the axons of neurons. The neurofilament light chain (NfL) is the most abundant protein component in neurons (Figure 1). The accumulation of NfL is associated with axonal growth during the myelination process, thereby determining the diameter and conduction velocity of peripheral nerves. Neurofilaments are classified as intermediate filaments with a diameter of approximately 10 nm. They are subdivided into: a) Human neurofilament heavy chain (NfH) with a molecular weight of 112.5 kDa based on DNA sequence and 200-220 kDa based on polyacrylamide gel electrophoresis; b) Neurofilament medium chain (NfM) with a weight of 102.5 kDa and 145-160 kDa; c) NfL with a weight of 61.5 kDa and 70-86 kDa; d) α-internexin with a weight of 55.4 kDa and 58-66 kDa; and e) Peripherin with a weight of 53.7 kDa and 57-59 kDa.[26,27]

Neurofilament proteins contain intrinsically disordered regions. One of the primary features of these disordered regions is their composition, which is primarily composed of lysine residues. Lysine and serine are the dominant amino acids in the neurofilament tail domain. Additionally, there is a short variable head domain at the amino terminal and a highly variable tail at the carboxy terminal, which are characteristic of the neurofilament protein subunits. The head domain contains serine and threonine residues, as well as O-linked glycosylation and phosphorylation sites. The tail domain is composed of glutamate and lysine, with varying lengths and several serine phosphorylation sites. The central rod domain contains hydrophobic repeats that facilitate the formation of coil-to-coil dimers (Figure 1).[28]

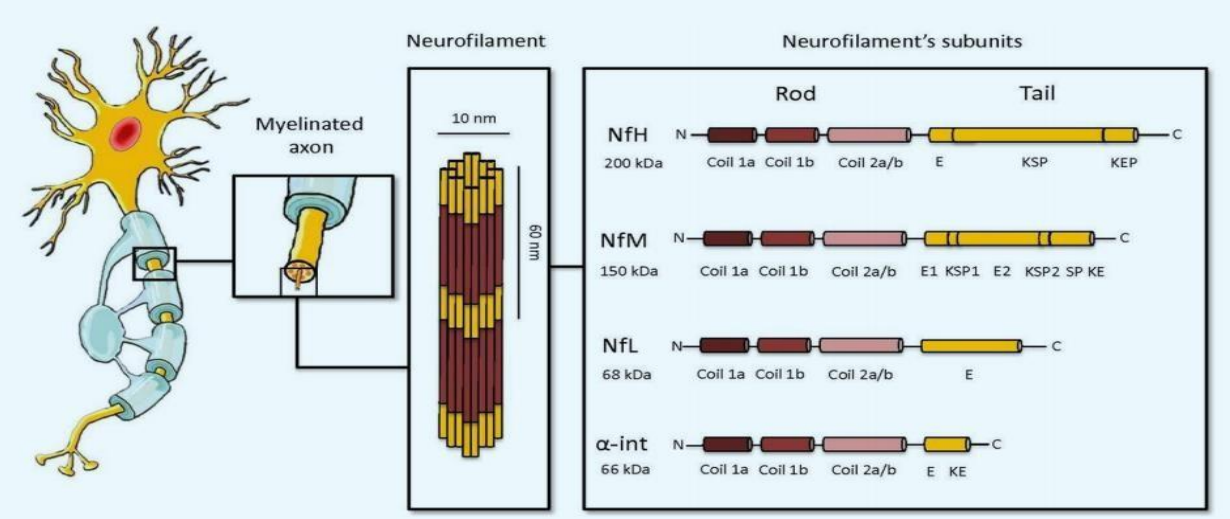

FIGURE 1: The structure of neurofilament.[27]

The formation of neurofilament protein dimers is the first step in the assembly of heteropolymers. The antiparallel aggregation of these dimers results in the formation of a tetramer, and eight laterally associated tetramers subsequently form the cylindrical structure of the unit-length filament (UFL).[26,29] The annealing process of UFL results in the longitudinal elongation of the neurofilament, followed by radial compaction, which forms the final neurofilament with a diameter of 10 nm (Figure 2).[28,29]

Post-translational modifications of neurofilaments include the addition of O-linked N-acetylglucosamine (O-GlcNAc) to serine and threonine residues, as well as nitration, oxidation, ubiquitination, and phosphorylation.[26] All subunits are phosphorylated at the head domain. However, only NfM and NfH are extensively phosphorylated at the carboxy-terminal domain, and this phosphorylation enhances the resistance of these subunits to proteases.[30]

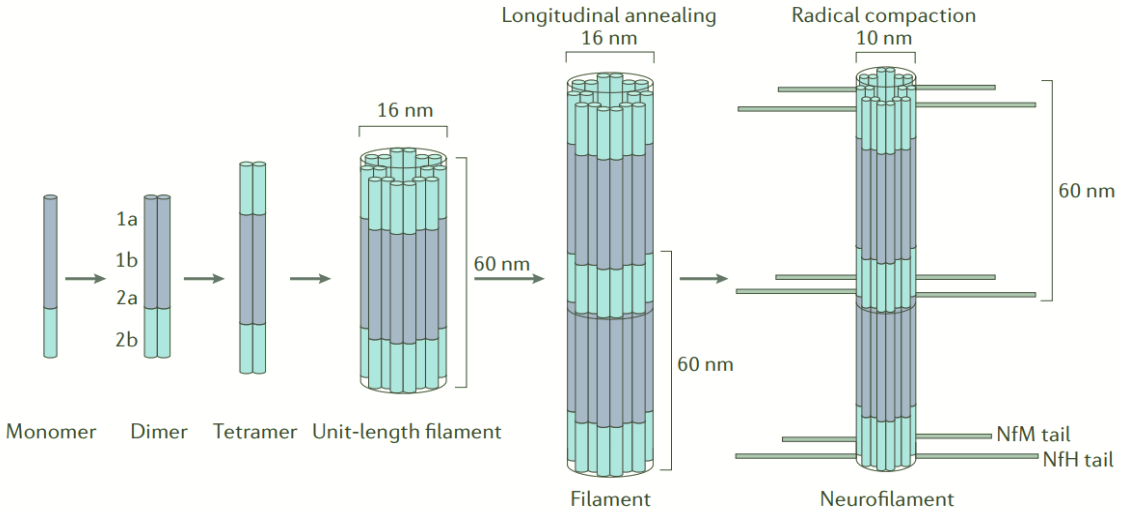

FIGURE 2: Physiological structure of neurofilament construction.[28]

Under normal conditions, neurofilaments are highly stable within axons, and their regeneration is relatively low.[31] Neurofilaments play a crucial role as part of the neuroaxon structure, enabling it to withstand external pressure, determining axon diameter, indirectly moderating conduction velocity, and serving as a site for the attachment of organelles and other proteins. Several reports suggest that neurofilaments interact with other proteins and organelles, including mitochondria and microtubules, indicating that they have functions beyond maintaining axonal stability.[26].Beyond their structural role in axons, increasing evidence suggests that the unique collection of synaptic neurofilament proteins has dynamic functions beyond static structural support.[32] Neurofilaments can form liquid crystal gel networks in diseases such as amyotrophic lateral sclerosis (ALS), dementia with Lewy bodies (DLB), or Parkinson's disease (PD); neurofilament accumulation is related to subunit stoichiometry and phosphorylation levels.[30]

Damage to neurons in the central nervous system (CNS) and axons in peripheral nerves leads to the release of neurofilaments. This results in an increase in their levels in cerebrospinal fluid (CSF) and eventually in the blood, where neurofilament concentrations reflect the rate of neurofilament release from neurons (Figure 3). Physiological degradation of neurofilaments in neurons occurs through a combination of proteasomal pathways and ubiquitin-mediated autophagy.[33]

Degraded neurofilament fragments partially flow directly into CSF and blood through several routes. These routes include direct drainage to CSF and blood via arachnoid granulations as well as lymphatic drainage to the subarachnoid and perivascular spaces.[34] Some literature suggests that testing in cerebrospinal fluid (CSF) is more sensitive because it is directly related to the central nervous system, with NfL levels in CSF being approximately 500 times higher than in blood. However, several studies have demonstrated a strong correlation between NfL levels in blood and cerebrospinal fluid (CSF), with correlation coefficients typically ranging from 0.7 to 0.8.[31]

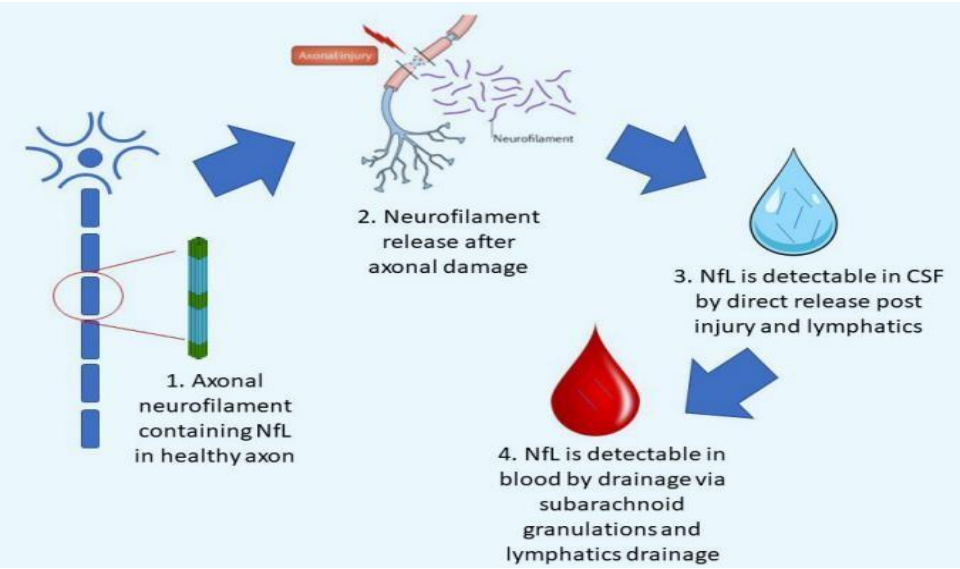

FIGURE 3: The pathophysiology of Nfl in cerebrospinal fluid and blood serum.[27]

The permeability of the blood-brain barrier (BBB) can act as a disruptor, where the neurofilament levels in blood compared to cerebrospinal fluid (CSF) can be selectively increased during inflammatory periods, as seen in relapsing multiple sclerosis (MS), thereby positively influencing blood NfL levels. After NfL enters the bloodstream, the half-life becomes a key consideration, with implications for the frequency of disease activity monitoring. In longitudinal studies examining NfL levels before and after intrathecal catheter placement, NfL levels in both CSF and serum peak at 1 month post-operation, returning to baseline levels within 6 to 9 months.[35] In MS patients sampled longitudinally around the time of relapse, levels were elevated 5 months prior, peaked at the clinical onset, and recovered within 4–5 months.[36]

Age is a significant physiological covariate for NfL levels. NfL levels in healthy controls increase by 2.2% per year.[37,38] Furthermore, an inflection point can be observed above the age of 60, after which sNfL levels, along with inter-individual variability, rise significantly.[39] These changes are believed to be due to aging itself, along with the accumulation of subclinical comorbidities. Other factors, such as neurological diseases, BMI, and vascular risk factors, can also influence neurofilament levels.[40,41]

Neurofilament Detection and Its Potential Marker for CIPN

The detection of neurofilaments has undergone significant technological advancements. First-generation immunoassays are best described as semi-quantitative. Protein separation-based immunoblots, such as electrophoresis or dot blot, although limited, consistently demonstrate the presence of neurofilament isoforms in cerebrospinal fluid (CSF) and blood of patients with various diseases. Second-generation sandwich ELISA technology provides reliable quantitative data for the first time, enabling the prognostic and diagnostic evaluation of NfH and NfL in CSF for disease assessment. This technique also enables analysis across various compartments of human body fluids, including interstitial fluid, extracellular fluid, serum, plasma, amniotic fluid, and vitreous humor. Meta-analysis studies and international validation indicate that expert laboratories can achieve high precision, yet also emphasize the need for better test standardization.[28]

Third-generation electrochemiluminescence (ECL) technology has significantly improved analytical sensitivity. ECL-based assays are known to be highly sensitive, with a broad dynamic range and requiring small sample volumes. However, fourth-generation SiMoA (single molecule array) technology offers 126 times greater sensitivity than ELISA and 25 times higher sensitivity compared to ECL assays in quantifying NfL. This technology enhances analytical sensitivity to such an extent that NfL quantification in the blood becomes feasible across the entire concentration range observed in both pathological and physiological conditions. This advanced method utilizes single-molecule arrays and simultaneous counting, utilizing sandwich antibody complexes (two antibodies and one antigen). This analytical sensitivity is significantly higher than that of ELISA, which is designed for CSF measurement, enabling the reliable detection of low NfL concentrations in blood samples from healthy young individuals. This enables the monitoring of small protein concentration changes, primarily due to physiological aging or mild injury.[42,43]

A strong correlation between NfL levels in serum or plasma and those in CSF has been demonstrated in various studies across different neurological diseases. This correlation enables the assessment of moderate axonal damage solely through blood analysis, eliminating the need for CSF collection via lumbar puncture. Research on NfM remains limited, but commercial SiMoA kits for detecting phosphorylated NfL and NfH are now available.[44]

NfL, a neuronal cytoskeletal protein, is a promising biomarker in neurodegenerative disorders and has garnered significant attention as a serum biomarker for axonal degeneration. Abnormal levels of NfL in both CSF and blood reflect axonal damage in various neurological, inflammatory, vascular, and traumatic conditions. Recent studies have highlighted the utility of NfL as a biomarker for neuroaxonal damage in patients treated with oxaliplatin and paclitaxel.[45] It is well-established that elevated serum NfL levels are associated with peripheral neuropathy and correlate with the severity of nerve damage, making NfL measurement a useful diagnostic tool in patients with chemotherapy-induced peripheral neuropathy.[7,45]

NfL has been studied in animal models, including a mouse model exposed to vincristine. NfL levels in vincristine-exposed mice showed a four-fold increase compared to controls, consistent with signs of axonopathy and loss of intraepidermal nerve fibers (IENF). Other studies have also confirmed this finding, where exposure to cisplatin and paclitaxel elevated NfL levels, and the increase was associated with the severity of morphological and functional changes in axonal structures, highlighting its utility in detecting chemotherapy-induced peripheral neuropathy (CIPN) and the linear association between the signs and symptoms of CIPN and its morphological changes.[7]

Plasma NfL concentration increased significantly in animals treated with the highest dose of paclitaxel (15 mg/kg) as early as day 7 after the study began, compared to control animals and those treated with doses of 5 and 10 mg/kg. Furthermore, the increase in plasma NfL levels in paclitaxel-treated animals correlated with histopathological findings in peripheral nerve tissue, demonstrating a strong relationship between NfL concentration and peripheral nerve lesions.[46]

Numerous studies have linked NfL levels in blood to the occurrence of peripheral neuropathy, both in animal and human studies. In a Wistar female rat model of CIPN, serum NfL rapidly increased after administration of paclitaxel (10 mg/kg, intravenous injection once a week for 4 weeks), cisplatin (2 mg/kg,

intraperitoneal injection twice a week for 4 weeks), and vincristine (0.2 mg/kg, intravenous injection once a week for 4 weeks). In all three animal models, serum NfL concentrations significantly increased from the first week of treatment to the end of the experiment compared to control animals. Peripheral neuropathy was confirmed with morphological and neurophysiological changes in the caudal nerve.[7]

Lucarini et al. reported an increase in plasma NfL concentration in rats following repeated paclitaxel injections (2 mg/kg, intraperitoneal injections on days 1, 3, 5, and 8) compared to control animals. NfL concentrations were assessed on day 18, and the authors observed intraepidermal nerve fiber loss, a reduction in myelin area in the sciatic nerve, and an increase in multinucleated neurons in the dorsal root ganglia of paclitaxel-treated rats compared to controls. Furthermore, paclitaxel-treated rats developed cold and mechanical allodynia, as well as mechanical hyperalgesia.[47]

NfL has also been studied among colorectal cancer patients receiving oxaliplatin and monitored for oxaliplatin-induced peripheral neuropathy (OAIPN). NfL levels were significantly higher in those with more severe OAIPN, and levels decreased significantly six months after chemotherapy cessation. Another study observed that NfL levels increased linearly with the severity of chemotherapy-induced peripheral neuropathy (CIPN), with significantly lower levels in individuals without symptoms compared to those with active symptoms, highlighting the dynamic and linear association between NfL levels and disease progression and severity. This underscores the utility of NfL in detecting early CIPN and monitoring ongoing axonal injury.[6]

A clear positive correlation between NfL levels and changes in sensory nerve amplitude also supports the relationship between neuronal damage and NfL concentrations. NF-κB is primarily associated with neuronal cell damage and death, offering a key advantage over other biomarkers. In 2018, Meregalli et al. reported increased blood NfL levels closely associated with axonopathy, which was pathologically confirmed in rats treated with vincristine.[7]

Oxaliplatin causes damage to the ganglion root nuclei, leading to neuronal apoptosis.[48] The elevated serum NfL levels in patients with oxaliplatin-induced peripheral neuropathy (Oxaliplatin-Induced Peripheral Neuropathy, OAIPN) and the significant correlation between serum NfL levels and disease severity support the role of NfL as a biomarker of severity in OAIPN.[49]

A study conducted by Huehnchen et al. evaluated NfL levels in patients with breast or ovarian cancer undergoing paclitaxel chemotherapy, breast cancer control patients without chemotherapy, and healthy controls. Subjects were recruited in a cohort study and examined before chemotherapy (V1) and after 28 weeks (V2, post-chemotherapy). Chemotherapy-induced peripheral neuropathy (CIPN) was assessed using the validated Total Neuropathy Score reduced (TNSr), which combines patient-reported symptoms with data from clinical examination. Serum NfL (sNfL) concentrations were measured at both visits using single-molecule array technology. The results showed a significant increase in sNfL in patients treated with paclitaxel who developed CIPN, but not in patients undergoing chemotherapy without CIPN or in controls. The sensitivity and specificity were 86% and 87%, respectively. An increase in sNfL of +36 pg/mL from baseline was associated with a probability of CIPN greater than 0.5.[8]

Another study measured serum NfL (sNfL) levels in 190 patients with ovarian cancer who received paclitaxel/carboplatin chemotherapy, with measurements taken at baseline and after two or six subsequent chemotherapy cycles. sNfL levels increased significantly during paclitaxel/carboplatin chemotherapy, with considerable interindividual variability. Patients with sNfL levels greater than 150 pg/mL after the first cycle had a higher risk of discontinuing paclitaxel early (unadjusted HR: 2.47 [95% CI 1.16–5.22]; adjusted HR: 2.25 [95% CI: 0.88–5.79]). A similar trend was observed for the risk of severe paclitaxel-induced peripheral neuropathy (PIPN) and dose reduction of paclitaxel due to PIPN. The median half-life of sNfL elimination was 43 days (IQR 27-82 days).[50]

Other studies support the potential of sNfL as a reliable biomarker for PIPN. sNfL levels increased during paclitaxel treatment in all patients. After two, four, and six cycles, patients with grade 3 PIPN had higher average sNfL levels compared to those with grades 0–2 PIPN ($p = 0.004$, $p = 0.001$, and $p < 0.001$, respectively). For sNfL levels ≥124 pg/mL after two chemotherapy cycles, the sensitivity and specificity for predicting grade 3 PIPN at the end of treatment were 80% and 79%, respectively.[9]

CONCLUSION

NfL shows potential as a translational biomarker for chemotherapy-induced peripheral neuropathy (CIPN). Current evidence supports NfL as an objective biomarker in in vitro assays and preclinical rodent models. This may enable future in vitro screening, potentially leading to the discovery of new therapies for the unmet medical needs of CIPN. In animal models, NfL offers an objective and easily obtainable means of studying chemotherapy-induced neurodegeneration, potentially in combination with other relevant functional or behavioral measurements. In clinical trials, NfL shows promise as a potential diagnostic biomarker for CIPN. Some knowledge gaps regarding this biomarker remain, necessitating further research before clinical implementation can occur.

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