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Value of Neurofilament Light Chain as a Biomarker in Peripheral Neuropathy

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【**Abstract**】 Neurofilament light chain (NfL) has been identified as a biomarker of axonal injury in a variety of central nervous system diseases. The value of NfL as a biomarker in peripheral neuropathy has gainedincreasing attention. We reviewed the relationship of serum NfL with and the dynamics of axonal injury in various immune-mediated peripheral neuropathies (such as Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy), hereditary peripheral neuropathy, drug-induced peripheral neuropathies and diabetic peripheral neuropathy, and drew a conclusion after a comprehensive analysis: the quantified NfL may be used as a promising biomarker to monitor disease activity, assess short-and long-term prognosis, and also as a potential biomarker for clinical trials and monitoring treatment response.

【**Key words**】 Peripheral nervous system diseases；Neurofilament proteins；Neurofilament light protein；Markers，clinical；Central nervous system；Nervous system

Neurofilaments (Nfs) are highly specific for neuronal cell damage and death, and neurofilament light chain (NfL) has been identified as a biomarker of axonal damage in many central nervous system (CNS) diseases，which is the pathological basis of many acute and chronic neurological diseases leading to permanent disability[1-3]. The diagnostic value of the cerebrospinal fluid NfL (cNfL) and/or serum NfL (sNfL) levels has been convinced in neurodegenerative diseases[3-6]，demyelinating lesions of the central nervous system[7-11],traumatic brain injury[12], infectious diseases such as Creutzfeldt-Jakob disease[13], hereditary diseases such as Huntington disease[14], and other nerves / mental diseases[15].Moreover, it can be also used to assess disease activity, monitor treatment response, and predict prognosis. Furthermore, the evidence for cNfL and sNfL as very potential biomarkers for CNS disease is increasing.

In recent years, more attention was attracted to the application of NfL in peripheral neuropathy, which is reviewed as follows.

1 Structure and function of Nfs

Cytoskeletal proteins can be classified according to their diameter into 6 nm actin filaments, 10 nm intermediate filaments (including Nfs and glial filaments), and 15 nm myosin filaments composed of motor proteins. Nfs is a highly specific major cytoskeletal component in central and peripheral neurons, which is expressed by large-diameter myelinated axons that maintains axonal stability structurally, provides tensile strength for dendrites and axons, and enables radial growth of axons[1,16].Functionally, Nfs assembles each other and provides cross-bridging with actin filaments and metallothionein.The dynamic cytoskeleton is essential in the intracellular transport to the axon to improve the axonal impulse conduction velocity and in the process of post-translational modifications that regulate neurite outgrowth[17]. Nfs are composed of NfL, neurofilament medium chain, neurofilament heavy chain and α-interconnect protein, all of which have a conserved α-helical rod domain with variable amino termini and carboxyl groups. In the terminal region, the different lengths of the variable region give the subunits different molecular weights, 61.5, 102.5, 112.5, 55.4 kilodaltons (kDa), respectively.NfL is considered to be the most important part of Nfs and the only Nfs that can self-assemble into functional fibers. Furthermore, it is the most abundant and soluble subunit in Nfs, which maks NfL the most reliable Nfs subunit that can be measured.

2 Detection methods, reference ranges and physiological influences of NfL

Many studies have used enzyme-linked immunosorbent assay (ELISA) and/or commercial kits to detect NfL.Two highly specific non-competitive monoclonal antibodies (mAB47:3 and mAB2:1) were used to quantify soluble NfL by ELISA assay, which are considered reliable in the detection of cNfL[18-19].However, ELISA assay kits is in short of the capacity of detecting the ultra-low abundance protein in blood, as its sensitivity could only reach pg/ml level generally[20]. Whereas, the assay based on electrochemiluminescence (ECL) has high sensitivity and wide dynamic range when detecting small sample size. But neither of the techniques could detect subtle changes associated with the dynamics of the diseases.

Single molecule array (Simoa) is a newly developed single-molecule protein technology based on the sandwich ELISA method of paramagnetic beads with ultra-high sensitivity. It could reach 1000 times sensitivity than ELISA assay kits , and the lower limit of detection fg/ml. This method detect proteins in a variety of different matrices (serum, plasma, cerebrospinal fluid, urine, cell extracts, etc.).Several studies have confirmed that Simoa technology can reliably detect NfL in blood samples (over the full range of concentrations), including

NfL in healthy individuals[20-23], thereby providing a different way for evaluating the brain injuries and neurodegenerative diseases.

In a physiological state, NfL is continually released from axons at a low levelinan age-dependent manner. The cNfL level increased by 3.30% per year in healthy, with higher cNfL level in male[3]. VAGBERG et al.[24] showed that the average cNfL level in healthy adults under 30 years was about 187 ng/L, 274 ng/L for 30 to 40 years , 466 ng/L for 40 to 60 years. However, a higher level of cNfL was released in those 60 years and older, which reached 693 ng/L.A study of 335 healthy aged 38.5 to 85.6 years showed the median sNfL level was 32.30(23.15, 43.95) pg/ml[25], which is not consistent with the results in other studies[17].The possible reason might be the lack of globally standardization of the detection and the cut-off values, which are necessary for the NfL before it can be reliably used in clinical practice[26].

3 NfL and peripheral neuropathy

3.1 NfL and Guillain-Barre syndrome (GBS) GBS is an immune-mediated acute peripheral neuropathy characterized by flaccid paralysis, which leads to a high risk of severe disability and death[27]. It is essential to seek out some reliable biomarkers either in the serum or cerebrospinal fluid that can predict prognosis in the early stage of GBS. Previous studies have found that the level of sNfL and cNfL significantly increased in patients with GBS[28-29].ALTMANN et al.[21]observed the correlation between clinical outcomes and sNfL in 27 GBS patients, and found that the average sNfL level was 85.5 pg/ml in GBS patients while 9.1 pg/ml in controls. And the increased sNfL level on admission was associated with bad outcomes, such as longer hospital stay, admission to the intensive care unit (ICU), and poor short-term outcomes at discharge. KÖRTVELYESSY et al.[30]also found in their recent study that the level of sNfL and cNfL in GBS patients was higher than control. And in those GBS patients admitted to ICU, sNfL increased prominently which was also significantly correlated with the disability function score. MARTIN-AGUILAR et al. [22] evaluated the long-term prognosis of GBS patients by detecting the NfL in 98 serum samples and 24 cerebrospinal fluid samples by Simoa technology, showing that the levels of sNfL and cNfL were significantly higher than those of controls. Further multivariate regression analysis revealed sNfL level was associated with the disability of one year later in GBS patients, suggesting that sNfL could also be a biomarker for evaluating the long-term prognosis of GBS.AXELSSON et al.[19] found that high cNfL level at the disease onset could predict long-term disability and worse quality of life in 18 GBS patients by ELISA assay kits. All the above studies showed that elevated sNfL and cNfL at

early stageis associated with the disease severity in GBS patients, and sNfL and cNfL could be independent predictive indicators for short-term and long-term prognosis of GBS patients. The early detection of NfL in GBS patients is helpful for individualized disease risk stratification and prognosis judgment.

MARTIN-AGUILAR et al.[22] reported that the sNfL level in patients with acute motor sensory axonal neuropathy (AMAN) were higher than other subtypes (199.53 pg/ml vs 46.77 pg/ml, P=0.006).The sNfL levels of acute motor sensory axonal neuropathy(AMSAN) and other uncertain electrophysiological subtypes were higher than those of acute inflammatory demyelinative polyradiculoneuropathy (AIDP) (107.15 pg/ml, 104.7 pg/ml, 33.88 pg/ml, respectively).The sNfL levels in pure motor variant and Miller Fisher syndrome were higher than those of sensorimotor subtype (162.18, 95.5 and 38.02 pg/ml, respectively). KÖRTVELYESSY et al.[30]observed that, the cNfL/sNfL ratio of the mixed neuropathy subtype or pure axonal injury subtype, classified by electrophysiology, was lower than that of control. However, the cNfL/sNfL ratio of 3 patients with demyelinating subtype was similar to that of control. Conclusively, the NfL varies in patients with different subtypes of GBS. The increased sNfL level and decreased cNfL/sNfL ratio are more indicative of axonal injury-dominated subtypes, implying NfL could be a potential biomarker of axonal injury.

The correlation between sNfL and axonal injury has been recently verified by sural nerve biopsy[31]. In axonal neuropathy, sNfL levels were associated with sural nerve axonal loss, and with an inverse relationship with fiber density. However, ALTMANN et al.[21] reported that there was no significant difference in sNfL levels between AIDP and AMAN in a cohort of 27 GBS patients including 17 AIDP, 5 AMAN and 5 unidentified subtypes, the researches explained that even in the demyelinated peripheral neuropathy confirmed by electrophysiology, the axonal damage has already existed below the threshold that can be detected by electrophysiology, and Nfs were released persistently from the damage nerve fibers. Therefore, the electrophysiological pattern of GBS is not representative of the actual pathological process occurring. In addition, sNfL can be used as a sensitive serum biomarker in GBS for early assessment of axonal damage before definitive electrophysiological damage occurs.

3.2 NfL and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) CIDP is a rare acquired immune-mediated demyelinating neuropathy with strong heterogeneity in clinical manifestations,

prognosis and treatment responses[32-33].There are no reliable blood biomarkers in CIDP so far, which could be helpful in diagnosing , monitoring the progression and predicting the prognosis of the diseases Futhermore, objective disease activity parameters are also urgently needed to guide treatment in patient receiving maintenance therapy.

It is reported recently that significant increases of sNfL levels were observed in CIDP patients with high disease activity. And sNfL was associated with age and gender, but not correlated with disease duration as there was no significant difference between newly diagnosed patients and relapsed patients[34-36].VAN LIEVERLOO et al.[36] made the nerve conduction test (NCS) in CIDP patients before treatment, and found that higher sNfL level was associated with lower negative peak area and total negative peak area of compound muscle action potential (CMAP) in median nerve, suggesting a correlation between sNfL level and axonal injury. FUKAMI et al.[35] further confirmed this speculation by both NCS and pathological studies, showing that sNfL level was negatively correlated with the CMAP changes in tibial nerve, and positively correlated with the degree of active axonal degeneration in pathology. Therefore, combined with NCS, sNfL could be a reliable biomarker for evaluating axonal injury and responding dynamically to persistent axonal injury in CIDP. Moreover, sNfL has an advantage over NCS because of non-invasion.

HAYASHI et al.[37] observed the dynamic changes of sNfL in different stages of CIDP, and found that the sNfL level increased significantly in 11 patients before treatment with gamma globulin, and decreased significantly after treatment and in remission. VAN LIEVERLOO et al.[36] reported a significant decrease and normalization of sNfL levels in 5 patients who responded to treatment during follow-up, while sNfL levels were higher when the disease is active, suggesting that sNfL can be used as a biomarker to evaluate the disease activity in CIDP. GODELAINE et al.[38] found that sNfL, detected by ECL method, was associated with 1-year disease progression (reduced MRC total score) in CIDP, and patients with high sNfL levels had an increased poor response to the treatment during follow-up. These evidence further suggested that sNfL could be used as a biomarker to evaluate the disease activity and prognosis in peripheral neuropathies. In addition, sNfL may be valuable in clinical decision by identifying patients who ultimately need to switch therapy or who should immediately start more intensive therapy, such as combination therapy.

It has been elucidated recently that the mechanism of neuropathies in patients with IgG4 autoantibodies targeting para-junctional components of the node of Ranvier, such as Neurofasciu-

155 (NF155), is different from that in CIDP patients with macrophage-induced demyelination[39]. The CIDP cohort study (FUKAMI et al.)[35] including 13 patients with positive anti-NF155 antibody Found that compared with patients with antibody negative, sNfL level of patients with positive anti-NF155 antibody was significantly increased. Both the sNfL level and the antibody titer in 8 patients were significantly decreased after treatment, and the changes of sNfL level were positively correlated with the antibody titers. This study supported the hypothesis that autoantibodies might act on axon-Schwann cells, leading to extensive neuronal damage, which in turn resulting in elevated sNfL levels. FUKAMI et al.[35] found that there was no significant difference in sNfL levels between typical and variant types of CIDP. No studies have focused on cNfL levels in CIDP patients

3.3 NfL and other immune-mediated/inflammatory peripheral neuropathy A recent cohort studied by MARIOTTO et al.[28], including 12 CIDP, 5 GBS, and 3 multifocal motor neuropathy (MMN), 3 myelin associated glycoprotein (MAG) antibody positive peripheral neuropathy and 1 non-systemic vasculitis neuropathy, showed that the NfL level was significantly increased totally, and the cNfL level was higher than that of sNfL. Moreover, sNfL is associated with disease activity and could predict subsequent disability progression. Unfortunately, the researchers did not further discuss the differences of NfL among different kinds of peripheral neuropathies. Interestingly, STASCHEIT et al.[34] found that there was no difference among MMN, classic and variant types of CIDP. The sNfL levels were significantly increased in 63 CIDP patients, indirectly suggesting a possible role of sNfL levels in assessing MMN disease activity. However, the author did not mention the differences between MMN and the controls in the study. Nevertheless, the latest prospective study focused on the anti-MAG peripheral neuropathy of 24 patients who had not received therapy, and found that no correlation between sNfL and disease activity[40]. Therefore, further studies are needed to convince the relationship between sNfL and disease activity of other immune-mediated peripheral neuropathies .

The diagnosis of vasculitic neuropathies (VN) is relied on the peripheral nerve biopsy, but the feasibility of its clinical application is limited due to the invasive nature and other reasons. In a retrospective observation, BISCHOF et al.[41] analyzed the clinical data of 11 VN and found sNfL could be a biomarker of vasculitis injury and/or disease activity, with the evidence that the sNfL level was significantly higher at the time-point of making diagnosis than the period of remission. Therefore, the relationship of sNfL with disease activity in other immune-mediated peripheral neuropathy should be determined by futher studies.

3.4 NfL and hereditary peripheral neuropathy In two cohort studies with Charcot-Marie-Tooth disease (CMT) (including CMT1A, CMTX1 and SPTLC1) reported by SANDELIUS et al.[42] and MILLERE et al.[26] respectively, the sNfL levels were significantly increased and consistent with disease severity, prominently higher in CMTX1 than in CMT1A and other CMT disease types. Moreover, there is not distinction between the axonal or demyelinated subtypes in CMT patients. The two authors pointed out that it is reasonable in view of the importance of the interaction between Schwann cells and axons in the maintenance of neuronal function, and the degree of disability in CMT1A (mainly demyelination) determined by the degree of axonal injury rather than the decrease of conduction velocity in the previous observation. After 1-year follow-up, the variability of sNfL level in 9 CMT patients was 16.4%, which was in line with the expectation of slow and constant progression of hereditary diseases, indicating that it could be used as a marker of disease progression. MAIA et al.[43] studied untreated hereditary transthyretin amyloidosis (ATTR) peripheral neuropathy at different stages of the diseases. It is found that sNfL could be used as a marker to distinguish asymptomatic mutation carried from early symptomatic patients, as well as sensory neuropathy from motor neuropathy, and even an indicator of the efficacy of disease-oriented treatments in clinical and preclinical trials. The finding was also verified by the subsequent study[44-45], which showed that sNfL levels were increased in amyloid light chain degeneration peripheral neuropathy and ATTR peripheral neuropathy and were also associated with the severity of ATTR peripheral neuropathy, and that sNfL can be used to assess the severity of ATTR peripheral neuropathy and monitor its progress. LUIGETTI et al.[45] have recently further verified the previous conclusion that sNfL can be used to evaluate the severity of ATTR peripheral neuropathy and monitor its progress.

Based on the available evidence, sNfL can be used as a possible biomarker in hereditary peripheral neuropathies by monitoring the disease activity and evaluating the therapeutic efficacy.

3.5 NfL and chemotherapy drug-related peripheral neuropathy (CIPN) A growing studies on CIPN and NfL have been reported recently. In an animal model of CIPN induced by vincristine chemotherapy, sNfL levels increase continuously during the period of vincristine administration, and increased nearly 4-fold when axonal signs and intraepidermal nerve loss occurred[46].The similar phenomenon was also observed in CIPN animal models induced by cisplatin and paclitaxel chemotherapy, as well as in patients with CIPN induced by oxaliplatin[47]. The level of sNfL was related to the severity of morphological and functional changes of axonal structures[48].HUEHNCHEN et al.[49]observed the

changes of NfL in breast cancer and ovarian cancer patients receiving paclitaxel chemotherapy, and found that sNfL was associated with the development and severity of CIPN, which was further verified by exposingthe sensory neuronsto paclitaxelin vivo, which derived from pluripotent stem cell. It is useful to monitor the changes of sNfL during chemotherapy to provide information for ongoing axonal injury and the severity of CIPN.

3.6 NfL and diabetic peripheral neuropathy (DPN) Less attention paid to the correlation between DPN and NfL. CELIKBILEK et al.[50] proposed firstly that sNfL-mRNA could be used as an alternative marker for early prediction of prediabetic peripheral neuropathy. MORGENSTERN et al.[51] found recently that the increased sNfL in DPN may be related to the development of hyperalgesia phenotype.

4 Different origin and diagnostic value of cNfL and sNfL in central and peripheral nervous system(PNS)

MILLERE et al.[26] pointed out that several issues still need to be addressed regarding the future use of NfL as a biomarker: the overlapping area of NfL level between patients and controls, the standardization of detection methods and cut-off values, the low-specificity of NfL, and the general moderate correlation with disease severity.

In CNS diseases, the axonal cytoskeletal protein family Nfs were released into the cerebrospinal fluid when cell destruction, and then into the blood circulation via arachnoid granulosa. So cNfL is considered to be of CNS origin, and in this situation there is a certain correlation between cNfL and sNfL. A recent systematic review on cNfL showed that high levels of cNfL have been observed in cognitively impaired HIV patients, amyotrophic lateral sclerosis, frontotemporal dementia, and Huntington's disease[18].Moreover, the level of cNfL in men was higher than that in women, and increased with age. The cNfL is helpful in the differential diagnosis of frontotemporal dementia and Alzheimer's disease, or Parkinson's disease and atypical Parkinson's syndrome[18], although sometimes it is indiscernible in most of the similar types of CNS diseases.

While in PNS diseases such as GBS/CIDP, both the intrathecal and extrthecalportions could be damaged. A significant correlation between cNfL and sNfL in GBS has also been observed in relevant studies[22,34].Elevated sNfL levels reflect damage to nerve roots and/or peripheral nerves, and it is hypothesized that sNfL in most acute active GBS originates from damage to the peripheral nervous system. The cNfL/sNfL ratio can be used to roughly assess the peripheral or central origin of NfL[30]. The average cNfL/sNfL ratio in the healthy control was 26.7[30], indicating the CNS origin of NfL was

dominant under normal physiological state. However, when inpathological conditions, such as in GBS with axonal or mixed axonal-demyelinated damage, the cNfL/sNfL ratio was significantly lower, as the blood-nerve barrier (BNB) and blood-cerebrospinal fluid barrier (BCB) are disrupted and then NfL was released into the cerebrospinal fluid. But when BNB/BCB deteriorates extensively, the NfL in peripheral blood can also enter the cerebrospinal fluid system[19]. Whereas in other peripheral neuropathies, any changes in sNfL levels reflect only neuropathic changes. Therefore, sNfL might be more sensitive than cNfL in monitoring disease activity and axonal damage in PNS.

In conclusion, the comprehensive evidence suggests that sNfL could be a potential biomarker for monitoringdynamic axonal injury and disease activity, and even could be an indicator for evaluating the responses or efficacy of the treatment of future clinical trials.

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Reference

1. KHALIL M, TEUNISSEN C E, OTTO M,et al. Neurofilaments as biomarkers in neurological disorders[J]. Nat Rev Neurol. 2018 Oct;14(10):577-589. DOI: 10.1038/s41582-018-0058-z.

2. GAETANI L, BLENNOW K, CALABRESIP,et al. Neurofilament light chain as a biomarker in neurological disorders [J]. J Neurol Neurosurg Psychiatry. 2019 Aug;90(8):870-881. DOI: 10.1136/jnnp-2018-320106.

3. BRIDEL C, WIERINGEN W N, ZETTERBERG H, et al. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology A Systematic Review and Meta-analysis [J] . JAMA Neurol. 2019 Sep 1;76(9):1035-1048. DOI: 10.1001/jamaneurol.2019.1534.

4. ZETTERBERG H. Neurofilament Light: A Dynamic Cross-Disease Fluid Biomarker for Neurodegeneration [J]. Neuron. 2016 Jul 6;91(1):1-3. DOI: 10.1016/j.neuron. 2016.06.030.

5. PREISCHE O, SCHULTZ S A, APEL A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease[J]. Nat Med. 2019 Feb;25(2):277-283. DOI: 10.1038/s41591-018-0304-3.

6. ASHTON N J, LEUZY A, LIM Y M, et al.Increased plasma neurofilament light chain concentration

correlates with severity of post-mortem neurofibrillary tangle pathology and neurodegeneration[J]. Acta NeuropatholCommun. 2019 Jan 9;7(1):5. DOI: 10.1186/s40478-018-0649-3.

7.HÅKANSSON I, TISELL A, CASSEL P, et al .Neurofilament levels, disease activity and brain volume during follow-up in multiple sclerosis [J] . J Neuroinflammation. 2018 Jul 18;15(1):209. DOI: 10.1186/s12974-018-1249-7.

8. DEISENHAMMER F, ZETTERBERG H, FITZNER B, et al. The Cerebrospinal Fluid in Multiple Sclerosis [J] . Front. Immunol, 2019 Apr 12;10:726. DOI: 10.3389/fimmu.2019.00726.

9.KAPOOR R, SMITH K E, ALLEGRETTAM, et al. Serum neurofilament light as a biomarker in progressive multiple sclerosis [J] .Neurology. 2020 Sep 8;95(10):436-444. DOI: 10.1212/WNL.0000000000010346.

10.MOMTAZMANESH S, SHOBEIRI P, SAGHAZADEH A, et al. Neuronal and glial CSF biomarkers in multiple sclerosis: a systematic review and meta-analysis[J] . Rev Neurosci. 2021 Feb 17;32(6):573-595. DOI: 10.1515/revneuro-2020-0145. Print 2021 Aug 26.

11. FERREIRA-ATUESTA C, REYES S, GIOVANONNI G, et al.The Evolution of Neurofilament Light Chain in Multiple Sclerosis [J] . Front Neurosci. 2021 Apr 6;15:642384. DOI: 10.3389/fnins.2021.642384.

12. SHAHIM P, TEGNER Y, MARKLUND N, et al.Neurofilament light and tau as blood biomarkers for sports-related concussion[J] .Neurology. 2018 May 15;90(20):e1780-e1788. DOI: 10.1212/WNL.0000000000005518.

13. THOMPSON A G B, LUK C, HESLEGRAVE A J, et al.Neurofilament light chain and tau concentrations are markedly increased in the serum of patients with sporadic Creutzfeldt-Jakob disease, and tau correlates with rate of disease progression[J] . J Neurol Neurosurg Psychiatry. 2018 Sep;89(9):955-961. DOI: 10.1136/jnnp-2017-317793.

14. JOHNSON E B, BYRNE L M, GREGORY S, et al.Neurofilament light protein in blood predicts regional atrophy in Huntington disease[J] .Neurology. 2018 Feb 20;90(8):e717-e723. DOI: 10.1212/WNL.0000000000005005.

15. EVERS K S, ATKINSON A, BARRO C, et al.Neurofilament as Neuronal Injury Blood Marker in Preeclampsia[J].Hypertension.2018 Jun;71(6):1178-1184. DOI: 10.1161/HYPERTENSIONAHA.117.10314.

16. GAETANI L, BLENNOW K, CALABRESI P, et al.Neurofilament light chain as a biomarker in

neurological disorders[J].J Neurol Neurosurg Psychiatry. 2019 Aug;90(8):870-881. DOI: 10.1136/jnnp-2018-320106.

17. LEE Y, LEE B H, YIP W, et al. Neurofilament Proteins as Prognostic Biomarkers in Neurological Disorders[J] . Curr Pharm Des. 2020;25(43):4560-4569. DOI: 10.2174/1381612825666191210154535.

18. BRIDEL C, WIERINGEN W N, ZETTERBERG H, et al.Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis[J] . JAMA Neurol. 2019 Sep 1;76(9):1035-1048. DOI: 10.1001/jamaneurol.2019.1534.

19. AXELSSONM, SJÖGRENM, ANDERSENO, et al.Neurofilament light protein levels in cerebrospinal fluid predict long-term disability of Guillain-Barré syndrome: A pilot study[J] . Acta Neurol Scand. 2018 Aug;138(2):143-150. DOI: 10.1111/ane.12927.

20. KUHLE J, BARRO C, ANDREASSON U, et al.Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa[J] . Clin Chem Lab Med. 2016 Oct 1;54(10):1655-61. DOI: 10.1515/cclm-2015-1195.

21.ALTMANN P, SIMONI D, KAIDER A, et al.Increased serum neurofilament light chain concentration indicates poor outcome in Guillain-Barré syndrome[J] . J Neuroinflammation. 2020 Mar 17;17(1):86. DOI: 10.1186/s12974-020-01737-0.

22. MARTÍN-AGUILAR L, CAMPS-RENOM P, LLEIXÀ C, et al.Serum neurofilament light chain predicts long-term prognosis in Guillain-Barré syndrome patients[J] .J Neurol Neurosurg Psychiatry. 2020 Nov 5;jnnp-2020-323899. DOI: 10.1136/jnnp-2020-323899. Online ahead of print.

23. MATTSSON N, CULLEN N C, ANDREASSON U, et al.Association Between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients With Alzheimer Disease[J] . JAMA Neurol. 2019 Jul 1;76(7):791-799. DOI: 10.1001/jamaneurol.2019.0765.

24. VAGBERG M, NORGREN N, DRING A, et al.Levels and Age Dependency of Neurofilament Light and Glial Fibrillary Acidic Protein in Healthy Individuals and Their Relation to the Brain Parenchymal Fraction[J] . PLoS One. 2015 Aug 28;10(8):e0135886. DOI: 10.1371/journal.pone.0135886. eCollection 2015.

25. KHALIL M, PIRPAMER L, HOFER E, et al.Serum neurofilament light levels in normal aging and their association with morphologic brain changes[J] . Nat Commun. 2020 Feb 10;11(1):812. DOI: 10.1038/s41467-020-14612-6.

26. MILLERE E, ROTS D, SIMRÉN J, et al.Plasma neurofilament light chain as a potential biomarker in Charcot-Marie-Tooth disease[J] . Eur J Neurol. 2021 Mar;28(3):974-981. DOI: 10.1111/ene.14689.

27. WILLISON H J, JACOBS B C, VAN DOORN P A.Guillain-Barré syndrome[J] . Lancet. 2016 Aug 13;388(10045):717-27. DOI: 10.1016/S0140-6736(16)00339-1.

28. MARIOTTO S, FARINAZZO A, MAGLIOZZI R, et al.Serum and cerebrospinal neurofilament light chain levels in patients with acquired peripheral neuropathies[J] . J PeripherNerv Syst. 2018 Sep;23(3):174-177. DOI: 10.1111/jns.12279.

29. GAIOTTINO J, NORGREN N, DOBSON R, et al.Increased neurofilament light chain blood levels in neurodegenerative neurological diseases[J] . PLoS One. 2013 Sep 20;8(9):e75091. DOI: 10.1371/journal.pone.0075091. eCollection 2013.

30. KÖRTVELYESSY P, KUHLE J, DÜZEL E, et al.Ratio and index of Neurofilament light chain indicate its origin in Guillain-Barré Syndrome[J] . Ann Clin Transl Neurol. 2020 Nov;7(11):2213-2220. DOI: 10.1002/acn3.51207.

31. MARIOTTO S, CARTA S, BOZZETTI S, et al.Sural nerve biopsy: current role and comparison with serum neurofilament light chain levels[J] . J Neurol. 2020 Oct;267(10):2881-2887. DOI: 10.1007/s00415-020-09949-3.

32. LEHMANN H C, BURKE D, KUWABARA S.Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment[J] . J Neurol Neurosurg Psychiatry. 2019 Sep;90(9):981-987. DOI: 10.1136/jnnp-2019-320314.

33. VAN DEN BERGH P Y K, VAN DOORN P A, HADDEN R D M, et al.European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision[J] . Eur J Neurol. 2021 Nov;28(11):3556-3583. DOI: 10.1111/ene.14959.

34. STASCHEIT F, HOTTER B, KLOSE S, et al. Calprotectin in Chronic Inflammatory Demyelinating Polyneuropathy and Variants-A Potential Novel Biomarker of Disease Activity [J] . Front Neurol. 2021 Sep 13;12:723009. DOI: 10.3389/fneur.2021.723009. eCollection 2021.

35. FUKAMI Y, IIJIMA M, KOIKE H, et al.Association of serum neurofilament light chain levels with clinicopathology of chronic inflammatory demyelinating polyneuropathy, including NF155 reactive patients[J] . J Neurol. 2021 Oct;268(10):3835-3844. DOI: 10.1007/s00415-021-10537-2.

36. VAN LIEVERLOO G G A, WIESKE L, VERHAMME C, et al.Serum neurofilament light chain in

chronic inflammatory demyelinating polyneuropathy[J] . J PeripherNerv Syst. 2019 Jun;24(2):187-194. DOI: 10.1111/jns.12319.

37. HAYASHI T, NUKUI T, PIAO J L, et al.Serum neurofilament light chain in chronic inflammatory demyelinating polyneuropathy [J] . Brain Behav. 2021 May;11(5):e02084. DOI: 10.1002/brb3.2084.

38. GODELAINE J, DE SCHAEPDRYVER M, BOSSUYT X, et al.Prognostic value of neurofilament light chain in chronic inflammatory demyelinating polyneuropathy [J] . Brain Commun. 2021 Mar 9;3(1):fcab018. DOI: 10.1093/braincomms/fcab018. eCollection 2021.

39. KOIKE H, KATSUNO M.Pathophysiology of Chronic Inflammatory Demyelinating Polyneuropathy: Insights into Classification and Therapeutic Strategy[J] . Neurol Ther. 2020 Dec;9(2):213-227. DOI: 10.1007/s40120-020-00190-8.

40. AMAADOR K, WIESKE L, KOEL-SIMMELINK M J A, et al.Serum neurofilament light chain, contactin-1 and complement activation in anti-MAG IgM paraprotein-related peripheral neuropathy[J] . J Neurol. 2022 Feb 14. DOI: 10.1007/s00415-022-10993-4. Online ahead of print.

41. BISCHOF A, MANIGOLD T, BARRO C, et al. Serum neurofilament light chain: a biomarker of neuronal injury in vasculitic neuropathy[J] . Ann Rheum Dis. 2018 Jul;77(7):1093-1094. DOI: 10.1136/annrheumdis-2017-212045.

42. SANDELIUS A, ZETTERBERG H, BLENNOW K, et al.Plasma neurofilament light chain concentration in the inherited peripheral neuropathies[J] . Neurology. 2018 Feb 6;90(6):e518-e524. DOI: 10.1212/WNL.0000000000004932.

43. MAIA L F, MACESKI A, CONCEIÇAO I, et al.Plasma neurofilament light chain: an early biomarker for hereditary ATTR amyloid polyneuropathy[J] . Amyloid. 2020 Jun;27(2):97-102. DOI: 10.1080/13506129.2019.1708716.

44. LOUWSMA J, BRUNGER A F, BIJZET J, et al.Neurofilament light chain, a biomarker for polyneuropathy in systemic amyloidosis[J] . Amyloid. 2021 Mar;28(1):50-55. DOI: 10.1080/13506129.2020.1815696.

45. LUIGETTI M, PAOLANTONIO A D, GUGLIELMINO V, et al.Neurofilament light chain as a disease severity biomarker in ATTRv: data from a single-centre experience[J] . Neurol Sci. 2022 Apr;43(4):2845-2848. DOI: 10.1007/s10072-021-05850-7.

46. MEREGALLI C, FUMAGALLI G, ALBERTI P, et al.Neurofilament light chain as disease biomarker in a rodent model of chemotherapy induced peripheral neuropathy[J] . Exp Neurol. 2018

Sep;307:129-132. DOI: 10.1016/j.expneurol.2018.06.005.

47. MEREGALLI C, FUMAGALLI G, ALBERTI P, et al.Neurofilament light chain: a specific serum biomarker of axonal damage severity in rat models of Chemotherapy-Induced Peripheral Neurotoxicity[J] . Arch Toxicol. 2020 Jul;94(7):2517-2522. DOI: 10.1007/s00204-020-02755-w.

48. KIM SH, CHOI MK, PARK NY, et al.Serum neurofilament light chain levels as a biomarker of neuroaxonal injury and severity of oxaliplatin-induced peripheral neuropathy[J] . Sci Rep. 2020 May 14;10(1):7995. DOI: 10.1038/s41598-020-64511-5.

49. HUEHNCHEN P, SCHINKE C, BANGEMANN N, et al.Neurofilament proteins as a potential biomarker in chemotherapy-induced polyneuropathy[J] . JCI Insight. 2022 Mar 22;7(6):e154395. DOI: 10.1172/jci.insight.154395.

50. CELIKBILEK A, TANIK N, SABAH S, et al.Elevated neurofilament light chain (NFL) mRNA levels in prediabetic peripheral neuropathy[J] . Mol Biol Rep. 2014 Jun;41(6):4017-22. DOI: 10.1007/s11033-014-3270-y.

51. MORGENSTERN J, GROENER J B, JENDE J M E, et al.Neuron-specific biomarkers predict hypo- and hyperalgesia in individuals with diabetic peripheral neuropathy[J] . Diabetologia. 2021 Dec;64(12):2843-2855. DOI: 10.1007/s00125-021-05557-6.