Neurological symptoms and blood neurofilament light levels

Running head: Neurological symptoms and blood NfL

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Abstract

Neurofilament light chain (NfL) is an incredibly specific marker of neuronal injury that is not specific for cause or location of the neuronal damage. NfL is increasingly considered as possible biomarker of disease activity in neurological conditions. Several works reviewed the utility of NfL in the different diseases. Nonetheless, NfL is a universal marker of neuronal damage, which interpretation spaces beyond the single disease. Because of this the interpretation of NfL may benefit by also considering how neurological symptoms relate to its blood concentration. Here we review how different neurological symptoms can be associated with blood NfL levels with a practical interpretation of it.

Introduction

Neurofilament light chain (NfL), a component of the neuronal cytoskeleton, is increasingly recognized as promising biomarker in the clinical evaluation of neurological patients.[1,2] NfL is released from the neurons to the cerebrospinal fluid (CSF) and blood upon damage. Damage of the peripheral nervous system will also result in a release of NfL primarily into the blood.[3] The concentration in blood is approximately 50 times lower than in CSF, due to the proximity of CSF to the neuronal tissue.[4]

Lately highly sensitive assays enabled a reliable quantification of NfL in blood.[5] In our experience, the sensitivity and automation implemented with this technology enable the prospective and reliable evaluation of NfL levels in the blood of patients.[1] There is a high correlation between NfL levels measured in plasma and serum[6,7] and the evidence collected by plasma or serum measurements resulted to be consistent; thus we refer in this review to blood NfL. Of note, the absolute NfL concentration is about 15% lower in EDTA plasma than serum, therefore longitudinal comparisons of absolute values or with a reference range should be done within the same source fluid and same collection method such as EDTA, heparin or citrate (pre-analytical variability was further discussed in [1]). An increased NfL level is not specific for one disease, but the prospective monitoring of NfL can be helpful in already diagnosed conditions (reviewed in [1]). Moreover, NfL is a universal marker of neuronal damage, which interpretation can space beyond the single disease. Hence, we reasoned that it could be useful to review the knowledge on NfL without categorizing it on diseases but focusing on the symptoms associated with those neurological diseases with available knowledge on NfL levels. We structured this with the same order used during a neurological examination. We also emphasized the use of the time course of NfL change rather than the absolute NfL levels, **Figure 1**.

1. Cognition and speech (Table 1)

Cognition. Impaired cognition can be a consequence of metabolic, respiratory dysfunction or intoxication[8] that are usually treated by internal medicine specialists or be a symptom of an underlying neurological disease. Acute neurological conditions, such as stroke, traumatic brain injury (TBI) and epilepsy, as well as chronic neurodegenerative conditions, can result in different grades of cognitive alterations.[8] Importantly, by an acute event the increase in NfL is not immediate but becomes clearly detectable a few days following neuronal damage – in the subacute phase.[9,10] Therefore, acute cognitive decline due to acute neuronal damage is reflected by a normal level of blood NfL at symptom onset followed by an increase in the following days peaking weeks to months after the event.[9–11] Notably, for individuals younger than 60 years of age the normal NfL level could be extrapolated by population based reference ranges, but the high interindividual variability that appears at older ages and in patients with comorbidities[1,12] suggests that the normal NfL level should be the baseline level of that individual. In this context, the normal level of an elderly patient would be the level measured at/near symptom onset. Thus, a second sample few days later would disclose the presence or absence of neuronal damage as respectively indicated by the presence or absence of an increase in NfL levels from the normal level of the patient. Chronic conditions of cognitive decline as neurodegenerative forms of dementia are characterized by slow accrual in neuronal damage and slow increase in NfL levels over years.[13,14] Thus, the second sample taken few days after the event will not show a change in NfL levels if the cognition was altered for example because of Alzheimer disease (AD), Parkinson disease (PD) or vascular dementia.[11,13–16] Of note, there are few studies that also looked at NfL in epilepsy and partial or generalized epileptic seizures were not associated with an increase in NfL levels but status epilepticus resulted in increased NfL.[17,18] Avoiding the increase in blood neurofilaments or decreasing their levels could be a relevant aspect for assessing the efficacy of forthcoming treatments - as shown in multiple sclerosis (MS).[19]

Speech. *Aphasia*. Acute speech impairments, as aphasia, are commonly seen in epileptic attacks[20], primary progressive aphasia (PPA) or strokes.[21] The change in NfL levels

differs between the latter two conditions: the days following an ischemic or hemorrhagic neuronal damage are characterized by a progressive increase in blood NfL levels[9], whereas patients with an aphasia related to a chronic neurodegenerative condition as PPA present only a minimal and slow increase in blood NfL[22]. The quantification of NfL at symptom onset could be an ancillary tool in the differential diagnosis of an acute manifestation of aphasia vs. chronic neurodegenerative condition. In this context, increased NfL levels after the event (in the subacute phase) can indicate an underlying stroke, even if not detected in the CT scan, and therefore the need for a more accurate imaging as brain MRI. In contrast, normal NfL levels could support a different origin of the symptoms as for example a focal epileptic episode and thus the need for an EEG. Of note, the presence of a status epilepticus was associated with increased NfL levels.[17]

Dysarthria. The inability to correctly articulate words is often associated with a paralysis of the facial nerve and part of the umbrella of symptoms seen in stroke.[23] In this case, dysarthria will be associated with increasing NfL levels starting from a few days after symptom onset.[9] Dysarthria can also be one initial symptom in patients with bulbar-onset amyotrophic lateral sclerosis (ALS).[24] In ALS, the NfL levels are increased already a few months prior to symptom onset[25]; thus low NfL levels at the onset of dysarthria could indicate a stroke rather than an initial ALS manifestation. Of note, the symptom onset may not always be clear to the patient or the family. In such cases, NfL could be of further use: low NfL levels without sign of increase over few days would be indicative of a pre-existing condition rather than an acute pathology causing the dysarthria, i.e., differentiating these conditions from stroke and ALS.

2. Cranial nerves (Table 1)

N. olfactorius (N. I). Impaired olfactory function can be present in chronic neurodegenerative conditions, such as PD, MS or AD, or acute conditions, such as TBI,[26] and it recently manifested in patients affected by coronavirus disease 2019 (COVID-19).[27] In all these conditions, except PD, NfL levels appear increased.[13,15,28,29]

N. opticus (N. II). One of the more common conditions affecting the optical nerve is *optic neuritis* and has been associated with increased NfL levels in the CSF[30] and in 25-50% of cases it is the first symptom of MS[31] where disease activity is responsible for further spikes ("relapses") in NfL concentration.[4] Another important cause of damage of the optical nerve is stroke. Stroke can cause a sudden loss of vision that depending on the location of the lesion can affect the entire or a part of the visual field and affect one or both eyes.[32] This condition can be accompanied by further stroke symptoms and be therefore associated with an important increase in NfL levels over the days following symptom onset.[9]

N. oculomotorius (N. III), N. trochlearis (N. IV) and N. abducens (N. VI). A damage to these cranial nerves results in an impairment of the eye movement. This can be caused by acute conditions as stroke[33] or chronic as MS[34]. Here, NfL could help discriminate between a pre-existing dysfunction - congenital (normal NfL levels) or acutely occurred - stroke (increasing over few days)[9] or slowly progressing chronic condition - MS (slightly increased NfL levels).[4]

N. trigeminus (N. V). This nerve is responsible for conveying sensory and part of the motor information from/to the face.[35] One of the more recurrent pathologies affecting this nerve is trigeminal neuralgia, a chronic disease that manifests as repetitive sharp facial pain.[36] Stroke, TBI, MS or compression due to a tumor or blood vessel can all be causing this condition.[35] Some of these etiologies are associated with neuronal damage, such as TBI[10] and MS,[4] although other etiologies, such as vascular compression, are not known to cause neuronal damage. In this context, NfL could help to discriminate between etiologies that are causing and etiologies that are not causing neuronal damage.

N. facialis (N. VII). In paralysis of the *N. facialis*, a first important step is to discriminate a central from a peripheral damage of the nerve. A central paralysis is often consequence of an ischemic insult of the central nervous system (CNS) and part of a wider umbrella of stroke related symptoms and therefore characterized by a rise in NfL.[9] On the other hand, determining the cause of a peripheral paralysis is a recurrent query for neurologists. In most of the cases the etiology of a peripheral paralysis is classified as idiopathic, *i.e.*, spontaneous with unknown

cause.[37] In a few cases, the clinical symptoms alone are not clear enough to discriminate between the central and the peripheral form, and here a low NfL level can be supportive of a peripheral rather than a central cause of paralysis.

N. vestibulocochlearis (N.VIII). An altered function of this nerve often manifests with nystagmus and vertigo.[38] These symptoms can be provoked by a peripheral[38] or a central[39] affection of the nerve. A central etiology is defined in the presence of CNS damage as a stroke and is therefore a medical emergency.[39] Peripheral etiologies are for example canalithiasis, vestibular neuritis or Ménière's disease and are not known to cause neuronal damage[38] and therefore the NfL levels should remain unaltered. Hence, if the anamnesis, clinical examination and MRI cannot find an indication of a stroke, low NfL could further support the hypothesis of a peripheral rather than a central origin for the symptoms. Of note, the presence of vertigo alone could have further differential diagnosis as hypotension as in PD[40] or hampered proprioception due to peripheral neuropathy that at advanced stages can also present increased NfL levels.[14,15,41,42]

N. glossopharyngeus (N. IX), N. vagus (N. X), N. accessorius (N. XI), N. hypoglossus (N. XII). Damage of these nerves are in most cases consequence of TBI or stroke that are associated with increase in NfL.[9,10]

3. Upper and lower extremities (Table 2)

a. Muscular tone. Muscles have a physiological level of contraction that allow their optimal function. An increased muscular tone can be the manifestation of a damaged upper motor neuron as seen in subacute stroke or MS, or alteration of regulatory centers as in PD. Of these conditions, PD presents only a slight increase in NfL[15], therefore increased NfL associated with increased tone can be indicative of a recent stroke or active MS rather than PD. Atypical parkinsonian disorders should also be considered as they are associated with a higher NfL than in PD patients.[15] On the other hand, a decreased muscular tone can be a symptom of a damaged lower motor neuron or a primarily muscular pathology. It is unclear whether NfL

increases in initially purely muscular diseases as myopathies, but it can rise even importantly in diseases of the peripheral nervous system as Guillain-Barré syndrome[42], Charcot-Marie-Tooth disease[41]. ALS can initially affect the upper or lower motor neuron and therefore manifest with either an increased or decreased muscular tone.[24] The early clinical presentation of ALS can be similar to other motor neuron diseases.[24] Nevertheless, ALS patients present a much higher increase in NfL levels than other motor neuron diseases.[43] Therefore, NfL can help in supporting a correct and rapid diagnosis of ALS.

b. Movement disorders. *Ataxic movement.* Movements of our body are precisely coordinated by specialized centers in the cerebellum and the extra-pyramidal system. These structures regulate efferent stimuli (from the motor cortex to the periphery) based on the afferent signal received from the periphery. A damage to one of these centers as well as a lack of feedback from the periphery manifests with poorly coordinated movements defined as ataxic.[44] There are more than 50 forms of ataxia with a genetic or non-genetic etiology.[44] NfL was explored in few of them. Multiple system atrophy, an adult-onset neurodegenerative ataxia was associated with increased NfL levels and NfL showed a good sensitivity and specificity in identifying this condition from ataxia of sporadic onset.[45] NfL was also increased in forms of ataxia with a genetic background as Friedreich's ataxia[46] and spinocerebellar ataxias.[47] Cerebellar stroke can also manifest with ataxia and is associated with increased NfL levels.[9] It is not the absolute level of NfL that can differentiate the different underlying pathologies but the change in NfL over time. In fact, a stroke is characterized by increasing NfL levels in the days after symptom onset[9] that is not present in neurodegenerative conditions. Moreover, a peculiarity of Friedreich's ataxia is the decreasing NfL level over age[46], thus potentially discriminating this pathology from other conditions where NfL levels increase with disease progression.

Tremor is a repetitive involuntary movement that can be classified as physiological or pathological based on the underlying mechanisms inducing it. The loss of dopaminergic neurons in the substantia nigra in PD manifests amongst other symptoms with low frequency resting tremor.[48] Other common pathological causes of tremor are essential tremor, stroke, MS

or drug intoxication.[48] The elevation of NfL in PD is mild when compared to other neurological diseases.[15] Therefore, tremor associated with low or slightly increased NfL levels would for example indicate a physiological tremor or an underlying PD rather than a cerebellar stroke or MS. The NfL levels in essential tremor are not investigated yet.

Chorea is a motor symptom characterized by flinging random movements and inability to exercise a voluntary movement for a prolonged time. Several conditions can be associated to this symptom and NfL was investigated in one of them, Huntington disease. In Huntington disease, NfL is increased and particularly in the manifest stage of the disease[49] where motor impairments are more evident. Thus, NfL could be used to monitor disease progression and stratify patients for prospective clinical trials.

Fasciculations are involuntary muscular contractions that can have a benign origin or be a manifestation of a pathology of the lower motor neuron, as for example in ALS.[24] In this context, low levels of NfL can suggest a benign etiology with fasciculations caused by neuronal hyperexcitability rather than a disease involving neuronal damage as for instance ALS[43] or Charcot-Marie-Tooth disease.[41]

c. Sensory and strength. Neuronal damage in the central or peripheral nervous system can manifest as altered sensation and/or strength. MS, TBI or stroke are frequent causes of neuronal damage in the CNS, and damage of the peripheral neurons is often caused peripheral polyneuropathies, radicular compression. The pathological process in motor neuron diseases is associated with damage of both peripheral and central nervous system.[24] Blood NfL increases with neuronal damage of both central and peripheral nervous system, therefore it cannot discriminate a central vs. peripheral location of the lesion. Although, a lesion of the peripheral nervous system does not cause an important increase of NfL in the CSF[3]; thus, increased blood NfL levels with normal CSF NfL levels can be indicative of a peripheral lesion. Of particular interest is the case of polyneuropathies caused (or possibly caused) by chemotherapeutical agents. In a recent work NfL detected drug induced neurotoxicity and decreased following cessation of treatment.[50] Of note, epileptic seizures can cause a

temporary paralysis of one side of the body that mimics the clinical presentation of a stroke, so-called Todd's paralysis.[51] A Todd's paralysis usually resolves within few days and NfL could help in excluding a stroke as etiology of such a paralysis, *i.e.*, low NfL could support a different etiology than stroke. A similar concept can be applied to MS patients presenting an acute worsening of symptoms. Precisely, NfL could help to discriminate an acute neuronal damage of a disease relapse – usually interpreted as a treatment failure - from a temporary neuronal dysfunction caused by an increase in body temperature and known as Uhthoff's phenomenon.[52] Thus, the patient would not need to change treatment.

Conclusion

Symptoms caused by an acute neuronal damage are reflected by an increase in neurofilament levels over the following days, whereas chronic conditions present minimal or no change in neurofilament levels. The clinical utility of NfL for the individual patient is currently explorative but it is increasingly investigated in the centers that possess the capacity for measuring it. Of note, despite the limited possibility of repeated sampling, CSF NfL is in general more sensitive than blood NfL for example a 10% change in CSF NfL led to a change of 7.4% and 5.8% in blood NfL of multiple sclerosis patients.[4,53] Therefore, CSF analysis could be a useful sensitive tool when neuronal damage is suspected despite a normal blood NfL. This particularly when the clinician plans to analyze other CSF biomarkers such as Aβ or oligoclonal bands. To summarize, in both acute and chronic neurological conditions NfL can detect the presence of neuronal damage, thus it has the potential to support the neurologist when the clinical assessment is not conclusive. Blood NfL presents the potential of being an ancillary tool in the hand of neurologists in a multitude of clinical cases.

Contributions

CB, HZ did literature search, reviewed the manuscript, drafted the manuscript, prepared the figures and tables. All authors read and approved the final version of the manuscript.

Conflict of interests

CB has nothing to disclose. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

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Table 1. Symptoms of altered cognition, speech and cranial nerves functions and their association with changes in NfL levels.

Symptoms	**Increased NfL**	**Neurological disease**	**NfL dynamics**	**References**
Altered cognition	Yes	Stroke	Increase days following the event	[9]
		Traumatic brain injury		[10]
		Alzheimer's disease	Increase over years	[13]
		Parkinson's disease		[14]
	No/Yes	Epilepsy	Not increased by focal or generalized seizure. Increased in status epilepticus.	[17,18]
	Unknown	Transient global amnesia	Unknown	-
Aphasia	Yes	Stroke	Increase days following the event	[9]
		Primary progressive aphasia	Increase over years	[22]
	No/Yes	Epilepsy	Not increased by focal or generalized seizure. Increased in status epilepticus.	[17,18]
Dysarthria	Yes	Stroke	Increase days following the event	[9]
		Amyotrophic lateral sclerosis	Increased months prior to symptom onset	[25]
Hyposmia / Anosmia	Yes	Stroke	Increase days following the event	[9]
		Multiple Sclerosis	Increase over years	[4]

		Traumatic brain injury	Increase days following the event	[10]
		Parkinson's disease	Increase over years	[14]
		COVID-19	Unknown	[28]
Vision loss	Yes	Stroke	Increase days following the event	[9]
		Opticus neuritis	Unknown / 50% cases as in MS	[30]
Impaired eye movement	Yes	Stroke	Increase days following the event	[9]
		Multiple sclerosis	Increase over years	[4]
	No	Congenital	-	-
Trigeminal neuralgia	Yes	Stroke	Increase days following the event	[9]
		Traumatic brain injury	Increase days following the event	[10]
		Multiple sclerosis	Increase over years	[4]
	No	Tumor or vascular compression	-	-
Dizziness	Yes	Stroke	Increase days following the event	[9]
		Hypotension in Parkinson's disease	Increase over years	[14]
		Peripheral neuropathies	Unknown	[41,42]
	No	Peripheral etiologies (Ménière's disease, vestibular neuritis, canalithiasis)	-	-

Table 2. Symptoms of neurological deficits of upper and lower extremities and their association with changes in NfL levels.

Symptoms	**Increased NfL**	**Neurological disease**	**NfL dynamics**	**References**
Increased muscular tone	Yes	Stroke	Increase days following the event	[9]
		Multiple sclerosis	Increase over years	[4]
		Parkinson's disease	Increase over years	[14]
		Amyotrophic lateral sclerosis	Increased months prior to symptom onset	[25]
Decreased muscular tone	Yes	Guillain-Barré syndrome	Unknown	[42]
		Charcot-Marie-Tooth disease	Unknown	[41]
		Peripheral neuropathies	Unknown	[41,42]
		Amyotrophic lateral sclerosis	Increased months prior to symptom onset	[25]
Ataxic movement	Yes	Multiple system atrophy	Unknown	[45]
		Friedreich's ataxia	Decreases over years	[46]
		Spinocerebellar ataxias	Increase over years	[45]
		Cerebellar stroke	Increase days following the event	[9]
	No	Sporadic adult onset ataxia	-	[45]
Tremor	Yes	Parkinson's disease	Increase over years	[14]
		Multiple sclerosis	Increase over years	[4]

		Stroke	Increase days following the event	[9]
	Unknown	Physiological tremor	Unknown	-
		Essential tremor		
Chorea	Yes	Huntington disease	Increase over years	[49]
Fasciculations	Yes	Amyotrophic lateral sclerosis	Increased months prior to symptom onset	[25]
		Charcot-Marie-Tooth disease	Unknown	[41]
	Unknown	Benign fasciculations	Unknown	-
Altered sensation or/and strength	Yes	Multiple sclerosis	Increase over years	[4]
		Traumatic brain injury	Increase days following the event	[10]
		Stroke	Increase days following the event	[9]
		Peripheral neuropathies	Unknown	[41,42]
	No/Yes	Epilepsy	Not increased by focal or generalized seizure. Increased in status epilepticus.	[17,18]
	Unknown	Radicular compression	Unknown	-
	No	Uhthoff's phenomenon	-	-