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Delirium pathophysiology in cancer: neurofilament light chain biomarker – narrative review

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ABSTRACT

Background Delirium is a debilitating disorder with high prevalence near the end of life, impacting quality of life of patients and their relatives. Timely recognition of delirium can lead to prevention and/or better treatment of delirium. According to current hypotheses delirium is thought to result from aberrant inflammation and neurotransmission, with a possible role for neuronal damage. Neurofilament light chain (NfL) is a protein biomarker in body fluids that is unique to neurons, with elevated levels when neurons are damaged, making NfL a viable biomarker for early detection of delirium. This narrative review summarises current research regarding the pathophysiology of delirium and the potential of NfL as a susceptibility biomarker for delirium and places this in the context of care for patients with advanced cancer.

Results Six studies were conducted exclusively on NfL in patients with delirium. Three of these studies demonstrated that high plasma NfL levels preoperatively predict delirium in older adult patients postoperatively. Two studies demonstrated that high levels of NfL in intensive care unit (ICU) patients are correlated with delirium duration and severity. One study found that incident delirium in older adult patients was associated with increased median NfL levels during hospitalisation.

Conclusions Targeted studies are required to understand if NfL is a susceptibility biomarker for delirium in patients with advanced cancer. In this palliative care context, better accessible matrices, such as saliva or urine, would be helpful for repetitive testing. Improvement of biological measures for delirium can lead to improved early recognition and lay the groundwork for novel therapeutic strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neurofilament light chain (NfL): biomarker of neuronal damage.
⇒ NfL seems a predictor of delirium in older adults patients.

WHAT THIS STUDY ADDS

⇒ NfL is a potential susceptibility biomarker for delirium in patients with advanced cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ NfL could help in early detection of delirium and finding novel therapeutic strategies.
⇒ Exploring the role of NfL in the pathophysiology of delirium.

INTRODUCTION AND RATIONALE

Delirium is a highly disruptive neuropsychiatric syndrome occurring in the late phase of advanced cancer developing over a short period of time (hours to days), in which consciousness is disturbed and the patient is often confused.[1] In patients with cancer, delirium may occur in 26%–44% of patients on admission to the hospital or hospice and up to 88% of patients in the last 24–48 hours of life, when it is often irreversible (terminal delirium).[2–4] Delirium can be subdivided into three clinical subtypes based on psychomotor behaviour and level of arousal: hyperactive, hypoactive and mixed. The hypoactive subtype, characterised by psychomotor retardation, lethargy and reduced awareness of surroundings, is the most common type of delirium in the advanced cancer and palliative care setting (median (range) 39% (22%–86%))[4 5] compared with hyperactive delirium (14% (0%–33%)).[4] Hypoactive delirium is difficult to recognise and commonly misrecognised and undertreated.[5 6] Rates of delirium misdiagnosis, mostly as depression, range from 42% to 64%.[7] Following a delirium,

patients report the experience of having felt powerless and abandoned, distant from relatives, threatened by healthcare professionals, they present as aggressive and they refuse care leading to feelings of guilt, shame and regret after a delirium episode.[8] Also, relatives and healthcare professional are affected by the burden of a delirium. Delirium interferes with the patients' needs in the final phase of life, where contact and the peace to say goodbye are essential.[9]

Susceptibility to developing delirium is difficult to ascertain. Yet, detection of early signs of delirium allows healthcare professional to be more alert and timely communicate with patients and their relatives. This could adequately prepare them and prevent further (clinical) deterioration when possible, ensuring patients to maintain their best possible quality of life, even in the last phase of their disease.[10 11] The Delirium Observation Screening (DOS) scale, a 13-point screening for delirium, designed to be completed by nurses, is meant to detect delirium in an early stage.[12] Although the DOS is considered a validated, user-friendly, sensitive and specific instrument to screen for delirium, it is also time-consuming as it has to be completed for a minimum of three times a day. Therefore, the DOS is not consistently applied in clinical settings. An easily accessibly biomarker could support the clinicians in predicting which patients may be particularly vulnerable to develop a delirium, thereby selecting the patients in whom the DOS should be performed. In addition, the clinical delirium screenings tools are not as suitable for detecting a hypoactive delirium.[13 14] A biomarker could support healthcare professionals by creating awareness, which could be of specific clinical significance in case of a hypoactive delirium.

Neuronal damage is the pathological substrate of many neurological disorders.[15] Emerging evidence suggests that neuronal damage may also play a role in the pathophysiology of delirium. Neurofilaments, especially neurofilament light (NfL), have gained increasing attention as candidate biomarkers of neuronal damage. Neurofilaments are abundant cytoskeletal proteins exclusively expressed in neurons and highly specific and therefore potent indicators for axonal damage and eventual neuronal cell death. As a result of axonal damage in neurodegenerative, inflammatory, vascular and traumatic brain diseases, they reach abnormal levels in extracellular fluid, cerebrospinal fluid (CSF) and peripheral blood, depending on the extent of the damage.[15 16] Importantly, for practical implementations, NfL can adequately be measured in the CSF, as well as blood plasma and serum.[15 16] We present a narrative review summarising the current knowledge on the pathophysiology of delirium and the role of NfL in delirium to explore the potential of NfL as a susceptibility biomarker for delirium in patients with advanced cancer.

Pathophysiology of delirium

The pathophysiology underlying delirium is not precisely known. Current hypotheses state that delirium is a multidimensional syndrome and the result of dysregulation of inflammation and impairment in neurotransmission: a failure of the vulnerable brain to react to an acute stressor. This vulnerability can originate from a multitude of processes that are not exclusive. Key processes include changes in (1) brain connectivity, (2) neuroinflammation and (3) vascular changes. First, brain connectivity declines with ageing and neurodegeneration, both of which have consequences for brain network function and cognitive function in response to acute stressors.[17] Second, both microglia and astrocytes are 'primed' by existing neurodegeneration to produce exaggerated proinflammatory responses to secondary inflammatory stimuli (such as infection and trauma or ischaemia), thereby aggravating inflammation specifically in areas already made vulnerable by neurodegeneration.[18 19] Previous studies have shown that while elevation of the proinflammatory cytokines IL-6 and IL-8 is correlated with occurrence of delirium in acute admissions of older adult patients to hospital, the existence of prior cognitive impairment was a stronger predictor of delirium.[20 21] Thus, the interaction of systemic inflammation with ongoing degenerative changes is key to many episodes of delirium. Third, ageing and neurodegeneration also trigger vascular and neurodegenerative pathological changes in the brain,[22] which lead to impaired brain perfusion and reactivity, disruption of transport of important plasma proteins into the brain and leakiness of the blood–brain barrier, potentially making the brain more vulnerable to the effects of circulating inflammatory molecules and thereby increasing delirium risk.[23]

It is necessary to investigate neuronal activity in order to better understand the pathophysiology of delirium. Functional MRI has demonstrated decreased neuronal activity and brain connectivity in a number of brain regions related to delirium.[24] Delirium was accompanied by reversible impairment in the functional connectivity of the subcortical areas and a breakdown in the exchange of the dorsolateral prefrontal cortex with the posterior cingulate cortex.[24] The subcortical areas provide regulation of memory, emotions, pleasure and hormone production. Ineffective reversible signalling in these areas lead to typical delirious symptoms, such as loss of memory and uncontrolled emotions. The impairments between the dorsolateral prefrontal cortex and the posterior cingulate cortex leads to disinhibition of arousal, focus, attention, planning and working memory.[24]

Recent studies have found a connection between delirium and long-term neuronal dysfunction or neuronal damage.[5 25] Mechanisms underlying the vulnerability of the brain for delirium by neuronal damage and neuronal dysfunction can be classified into

two major categories. First, direct neuronal damage caused by hypoxia, drugs (eg, opioids), hypotension, trauma, infarcts and strokes. Second, aberrations in the normally adaptive systemic and central nervous system (CNS responses to stressors such as infection and surgery.[5 25] In patients with cancer, both mechanisms seem to play a role. Specifically, in patients with cancer, neuronal damage can happen by direct effects of cancer on the CNS (eg, metastatic brain lesions), by indirect effects of cancer or treatments for cancer (eg, electrolyte imbalances due to chemotherapy, metabolic changes or infection) or as the result of symptom treatment (eg, the use of opioids as pain management).[3 26 27]

Axonal damage and loss are the pathological substrate of NfL in acute and chronic neurological disorders, such as Alzheimer's disease and multiple sclerosis. In those chronic neurological disorders, the reliability of NfL as a biomarker for predicting and demonstrating neurodegeneration has been established.[28 29] In addition, NfL is also established as a marker for neuronal damage in acute diseases such as ischaemic stroke.[16 30] Therefore, we hypothesise that NfL could also be elevated in delirium.

NfL chain as biomarker of neuronal damage

Neurofilaments are members of the family of intermediate filaments and consist of three chains that differ in size: NfL chain (NfL; 68 kDa), neurofilament medium chain (150 kDa) and neurofilament heavy chain (190–210 kDa), which together with an associated protein form four subunits. After correct assembling of the four subunits, the neurofilament of 10 nm diameter is formed[29] (figure 1).

Neurofilaments are components of the neuronal cytoskeleton and are particularly abundant in the axons of neurons. The stability of the cytoskeleton is established by neurofilaments through cross-bridging and connecting with other components of the cytoskeleton.[31] For the axons, neurofilaments provide structural support by maintaining their size, shape and capacity.[32] Neurofilaments form a dynamic structure involved in neuronal differentiation, axon outgrowth and regeneration.[33] Under normal circumstances, low levels of neurofilaments are continuously released in body fluids such as the CSF and blood. This may be an age-dependent process since it increases in older adults.[34]

Neurofilaments are prime candidate biomarkers of neuronal damage because they can be well measured in CSF and blood. In addition, they are exclusively expressed in neurons and have a relationship with diseases and disease severity. In neurodegenerative, inflammatory, vascular and traumatic diseases, abnormal levels of NfL are found as a result of neuronal damage not only in the CSF but also in serum (40-fold lower than in the CSF[34]). Neurofilament's utility has been highlighted not only for diagnostic but also for prognostic purposes, and for evaluation of treatment efficacy in some neurological conditions.[15] Moreover, NfL levels increase before any clinical manifestations, and therefore, could potentially be used as susceptibility

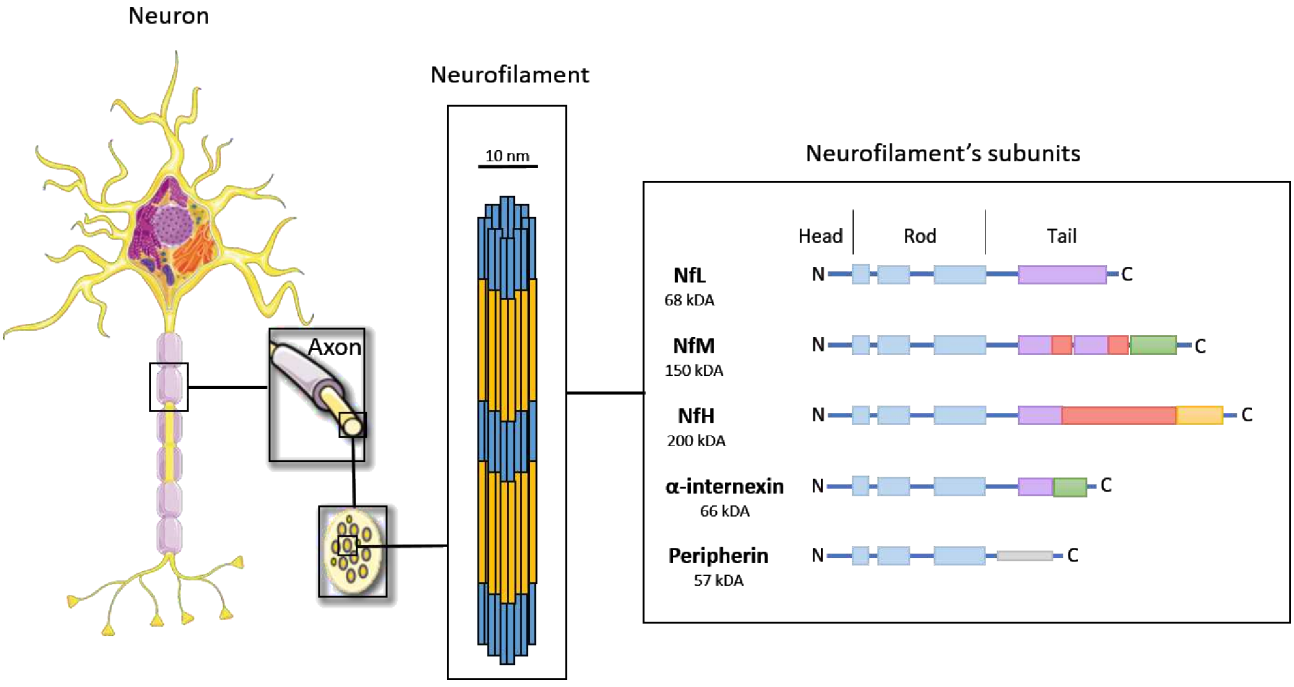

Figure 1 **Structure of neurofilament subunits.** All neurofilament subunits share a common structure composed of a globular amino-terminal head domain, a double stranded and central conserved α-helical rod domain (comprising several coiled coils), and a carboxy-terminal tail of variable length. NFM and NFH are characterized by long C-terminal tail domains. NfH, neurofilament heavy chain; NfL, neurofilament light chain; NfM, neurofilament medium chain.

biomarker.[28] As neuronal damage occurs by direct and indirect effects of cancer and its treatment, NfL could be a potential susceptibility biomarker for delirium in patients with advanced cancer.

Measuring/detecting NfL

Since NfL is the most abundant and soluble of the three chains of neurofilaments, it is the most accurate and reliable subunit to measure in bodily fluids and as such the most logical target for a potential biomarker.[34] The first assay to measure NfL was an ELISA assay based on polyclonal antisera,[35] which was later upgraded to a highly specific assay based on monoclonal antibodies against NfL epitopes.[36] More recently, two novel monoclonal antibodies (NfL21 and NfL23) and a new ELISA assay were generated.[37] NfL ELISA, (NF-light ELISA kit; UmanDiagnostics AB, Umeå, Sweden) allows for quantification of CSF NfL with a low sample volume and it shows good stability after handling and storage.[36] The main disadvantage is its low sensitivity for quantifying blood NfL. Quantification of blood NfL (and CSF NfL) has become optimised with the development of the ultrasensitive Simoa (Quanterix).[34 38] Simoa is 125-fold and 25-fold more sensitive than conventional ELISA and ECL-based assays, respectively. Notably, it can detect a concentration as low as 0.1 pg/mL of protein.[39] Currently, the Simoa assay is also validated with a dried blood spot obtained by fingerprick, which is even less invasive.[40 41] As there is now a realistic option for less invasive screening methods, samples can be taken in distant settings, such as at patients' homes and in general practices and nursing homes. In addition, the flexibility of sample collection improves the ability to execute large population studies, which are required to unravel the clinical course of diseases. This is especially relevant when studying delirium occurring in patients with advanced cancer since patients are frequently not well enough to undergo invasive procedures or are admitted to nursing homes and hospices.

The application of NfL biomarker in delirium in previous studies

As stated above, neuronal damage may play a role in the pathophysiology of delirium. This could indicate a possible role for NfL as a biomarker for delirium in cancer. However, no such studies in this specific setting have been performed so far.

Two recent studies showed that high blood levels of NfL predict the occurrence of delirium in postoperative older adult patients and found a correlation with elevated NfL-levels prior to operation.[42 43] In one study, higher serum NfL levels were present in patients with hip fractures who developed delirium both before and after operation, compared with patients who did not develop delirium.[42] Another study found that patients undergoing major elective surgery with postoperative delirium had significant higher plasma NfL levels after operation compared with patients without delirium.[43] Furthermore, this study also found that the patients with elevated levels of plasma NfL preoperatively were at increased risk for incident delirium, suggesting that patients with pre-existing levels of neuronal damage may be more likely to develop delirium during an acute event.[43]

Recent studies investigating the association between plasma NfL levels and delirium severity found that patients with elevated levels of plasma NfL preoperatively experienced more severe delirium.[43] Another study found that plasma NfL rose more sharply in postoperative delirium patients compared with patients without delirium, and that this relationship showed dose-dependency as plasma NfL rose proportionately to delirium severity.[44]

One study investigated the effects of delirium on both cognitive trajectories and any neuronal injury, measured via NfL in participants aged 65 years.[45] During hospitalisation, incident delirium was associated with increased median NfL levels. They found delirium to precipitate a decline in cognition and an increase in NfL, most evidently in people with better cognitive function at the previous 6-month assessment.[45]

NfL as biomarker for delirium was also investigated in two studies among critically ill patients admitted to the ICU.[46 47] One study found that the majority of critically ill patients already had a high NfL level on admission. Patients with higher plasma NfL levels on days 1 and 3 after admission spent significantly more days in delirium or deep sedation.[46] The other study found that peak NfL levels did not predict which patients developed delirium directly after extubation, nor 5 days later.[47] However, they did found a correlation between peak NfL levels and total duration of delirium.[47]

The six studies presented in this narrative review reflect the potential role of NfL as a biomarker in the prediction of delirium occurrence, duration and severity. The association between elevated NfL and delirium in these studies underline the hypothesis that delirium may be directly connected to (ongoing) neuronal damage. Underlying mechanisms of the neuronal damage in these patients could be damage to peripheral nerves during surgery, toxic effects of anaesthesia and systemic physiological reactions.[42]

DISCUSSION

In this narrative review, the current knowledge on delirium pathophysiology and the potential role of NfL as a susceptibility biomarker of delirium were discussed. The combined evidence (N=6 studies) provided in this review demonstrates a connection between delirium, long-term neuronal dysfunction and/or neuronal damage. Studies have both incorporated and focused on NfL for diagnostic and prognostic purposes showing the potential of NfL beyond

neurodegenerative disease with regard to surgery and postoperative cognitive dysfunction and delirium. Higher levels of NfL correlate with delirium occurrence, duration and severity.

The studies as presented in this narrative review have several important limitations. Studies were often small in terms of sample size and mismatched controls, which is especially important because increased NfL levels are also associated with older age, dementia and brain metastases. In addition, the studies cannot reliably ascertain relationships between NfL levels, delirium and clinical outcomes.

Researching NfL as susceptibility biomarker in patients with advanced cancer, therefore, requires a robust study controlling for confounding variables, such as age and neurodegenerative diseases. Especially in patients with advanced cancer, it is important to either include a disease-specific control group with brain cancer and brain metastases or to exclude this group as a whole.

Overall, similar results are expected researching NfL in patients with advanced cancer with(out) delirium as the studies in surgical patients and ICU patients. The studies in surgical patients show that patients with pre-existing levels of neuronal damage may be more vulnerable to developing delirium, where damage to peripheral nerves during surgery, noxious effects of anaesthesia and systemic physiological reactions could then be the possible trigger that leads to delirium.[42–44] It is conceivable that high NfL levels can early detect a delirium or represent the susceptibility to develop a delirium also in patients with advanced cancer as neuronal damage in these patients can occur by direct effects of cancer on the CNS (eg, metastatic brain lesions), by indirect effects of cancer or treatments for cancer (eg, electrolyte imbalance, metabolic changes, infection, surgery) or as the result of symptom treatment (eg, opioids). Any of these effects can in addition also trigger the delirium itself.[3 26 27]

Measuring NfL

NfL is a biomarker that may currently be detected in CSF and blood. Patients with advanced cancer are mostly frail and the high invasiveness and inconvenience of CSF lumbar puncture are well recognised. Since blood serum collection is also cumbersome for many patients with cancer, a validated alternative could be a finger prick and dried blood spot analysis, which is less painful for the patient.[40 41] Despite punction being less inconvenient, it is still invasive. Waste material (eg, urine and saliva) would be a better alternative, especially for future clinical application, as it can be collected in every setting (eg, hospices, general practices, at home) and at any time. Urine, as a promising biomarker source, has been largely understudied in the brain disease field compared with other body fluids. Nonetheless, limited studies on urinary-based biomarkers of brain diseases provide some evidence that urine could be used as brain disease biomarker source.[48] These studies show that levels of some molecules in the urine are different between brain disease groups and control groups.[48] One study found urine was unsuitable as a matrix for NfL analysis in frontotemporal dementia patients where serum NfL levels are high.[49] However, another study demonstrated that NfL could be non-invasively detected in urine from healthy volunteers and patients with acute neuronal and glial damage. NfL showed in this study robust association between serum and urine concentrations and a strong effect size for discriminating between target and control groups.[50] Future research is needed to see if a urine is a suitable matrix for NfL analysis for delirium in patients with advanced cancer. Urine sample usage would also be more accessible for large-scale population research on delirium.

CONCLUSIONS

Overall, empirical data summarised in this narrative review suggest that patients with pre-existing neuronal damage may be more likely to develop delirium in acute biological stress situations and that this neuronal damage could be determined by measuring NfL levels in plasma or CSF. NfL could be a potential biomarker for susceptibility to develop a delirium or early detection of delirium in patients with advanced cancer in whom the cancer and its treatment cause neuronal damage. However, further prospective research with matched controls is needed to better understand the pathophysiology and to see if NfL is also a susceptibility biomarker for delirium in patients with advanced cancer. In addition, investigating whether NfL can be measured in urine makes an NfL test more suitable for future clinical application in frail patients. The risk could then be accurately estimated through blood (spot) analysis, after which non-invasive monitoring via urine can be employed to observe whether an individual is at risk of developing delirium in the short term. More research can potentially lead to early detection, novel therapeutic strategies and improvements in quality of life of patients faced with delirium as well as their relatives.

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