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REVIEW

Usefulness of serum neurofilament light in the assessment of neurologic outcome in the pediatric population: a systematic literature review

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Abstract

Children undergoing general anesthesia and surgery in the early years of life are exposed to the possible neurotoxicity of anesthetic agents. Prospective studies have shown deficits in behavior, executive function, social communication, and motor function in children undergoing anesthesia and surgery. Different biomarkers of neuronal injury have been evaluated neuronal injury in the pediatric population, among which neurofilaments represent a significant advantage as they are proteins exclusively expressed in neuronal tissue. Our aim was to evaluate the utility of serum neurofilament light (NfL) as a prognostic biomarker of neuronal injury in the pediatric population. A literature search was performed on PubMed, Embase, and Cochrane Databases in November 2022 for studies concerning serum NfL in the pediatric population in addition to a neurological assessment. Inclusion criteria were as follows: (1) prospective or retrospective studies, (2) studies including pediatric population until the age of 18 years, (3) serum NfL sampling, and (4) evaluation of neurological outcome. Data collection regarding study design, pediatric age, serum NfL levels, and results for neurological assessment were extracted from each study. Four manuscripts met the inclusion criteria and evaluated the prognostic utility of serum NfL in neonatal encephalopathy in correlation with the neurodevelopmental outcome that was assessed by the Bayley Scales of Infant Development until the age of 2 years. Children with neonatal encephalopathy showed significantly higher serum NfL vs. healthy controls and high serum NfL levels predicted an adverse neurological outcome. The decrease of serum NfL to a nadir point between 10 and 15 years old reflects the brain growth in healthy controls. No studies were available in the perioperative period.

Conclusions: Serum NfL is a valuable biomarker in evaluating neuronal injury in the pediatric population. Further studies with perioperative serial sampling of serum NfL combined with standardized neurodevelopmental tests should be conducted to evaluate the neurotoxicity of anesthetic agents and monitor the effectiveness of specific neuroprotective strategies in pediatric patients undergoing anesthesia and surgery.

What is Known:
- *Preclinical animal data have shown neurotoxicity of the anesthetic agents in the developing brain.*
- *Data regarding anesthetic neurotoxicity in humans show limitations and no objective tools are available.*

What is New:
- *This systematic review showed that serum NfL is a valuable biomarker of neuronal injury in the pediatric population.*
- *Perioperative use of serum NfL may be considered in future trials evaluating anesthetic neurotoxicity in the pediatric population and in monitoring neuroprotective strategies.*

Keywords Perioperative · Neurofilament light · Neurotoxicity · Anesthesia · Pediatric · Neurodevelopment

Abbreviations

GABA	Gamma-aminobutyric acid
NMDA	N-Methyl-D-Aspartate
NfL	Neurofilament light
TH	Therapeutic hypothermia
HIE	Hypoxic-ischemic encephalopathy
IQR	Interquartile range

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BSID	Bayley Scales of Infant Development
GFAP	Glial fibrillary acidic protein
UCH-L1	Ubiquitin C-terminal hydrolase-L1
Simoa	Single-molecule array

Introduction

Much concern exists regarding the exposure of young children to anesthesia and its eventual detrimental effects on the developing brain [1]. Indeed, routinely used anesthetic agents targeting gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors have an inhibitory effect on neurotransmission that can lead to neuroapoptosis [2–4]. To date, 10 prospective studies have tried to address specific aspects of the potential neurotoxicity of anesthetic agents in children exposed to general anesthesia and surgery in the early years of life [5–16] (Table 1). Although the results of these studies do not consistently associate general anesthesia exposure with deficits in intelligence or memory and language, associations have been reported with deficits in behavior, executive function, social communication, and motor function [5, 9, 16]. In most of these studies, various neurocognitive tests have been used to test the neurotoxicity of anesthetic agents, but the significant latency between the conduction of these studies and the neurodevelopmental assessment remains a major issue. In contrast, the use of biomarkers of neuronal injury within the frame of the perioperative period could be extremely valuable as an objective tool to evaluate anesthetic neurotoxicity [17]. Different biomarkers of neuronal injury have been evaluated in the pediatric population. However, none of the currently evaluated neurobiomarkers has emerged as a reliable diagnostic and/or prognostic tool for assessing postoperative neurological complications, as the release of such proteins (e.g., Neuron Specific Enolase, S100 calcium-binding protein B) can arise from extracranial sources [18, 19]. In contrast, neurofilaments are exclusively expressed in neuronal tissue as they are a group of proteins involved in the scaffolding of axons [20]. Additionally, the perioperative analysis of neurofilament light (NfL) has been facilitated considering the possibility of sampling from serum [21].

The aim of this systematic review was to evaluate the utility of serum NfL as a prognostic biomarker for neuronal injury in the pediatric population. If serum NfL shows to be a valuable biomarker of neuronal injury in the pediatric population, it will enable the monitoring of the effect of specific neuroprotective strategies in pediatric patients undergoing anesthesia and surgery.

Materials and methods

The literature search and data extraction were performed by AJS on PubMed, Embase, and Cochrane databases in November 2022 using the terms "serum" AND "neurofilament light" AND "pediatric" AND "outcome", "neurofilament light" AND "pediatric" AND "neurologic outcome" AND "plasma" AND "neurofilament light" AND "newborns" AND "outcome". Inclusion criteria were as follows: (1) prospective or retrospective studies, (2) studies including pediatric population until the age of 18 years, (3) serum NfL sampling, and (4) evaluation of neurological outcome. Studies not fulfilling these criteria were excluded. No restriction on language or on the year of publication was applied. To identify studies based on the inclusion criteria, titles and abstracts of articles were screened. There were no discrepancies concerning excluded articles among the authors. The final eligible studies were examined by AJS and MM and were selected based on the methods and the results for neurological assessment. Data extraction included authors' details, publication year, patient characteristics, serum NfL with sampling time, and neurodevelopmental outcome in neonatal encephalopathy and in healthy controls. The methodology checklist for cohort studies as described in the National Institute for Health and Care Excellence (NICE) guidelines was used for quality assessment.

Results

The search resulted in 20 articles (Fig. 1), of which 6 were duplicates. Among the remaining 14 manuscripts, 6 were rejected as they were unrelated to our search (concerning non-pediatric populations). Eight studies remained eligible for detailed analysis, but only 4 mentioned a standardized neurological assessment as a secondary endpoint and were thus included in our current review (Table 2).

Interestingly, two discarded articles described elevated serum NfL in children with acquired demyelinating syndrome and provided evidence that serum NfL is associated with disease severity and may guide treatment decisions in pediatric multiple sclerosis [22, 23]. A third discarded article showed a significantly higher serum NfL in children with cardiac arrest vs. healthy controls, but no follow-up neurological assessment was performed [24]. Another discarded article was a pilot study published in 2018 by Shah et al. [25]. The authors demonstrated that serum NfL levels were raised in newborns undergoing therapeutic hypothermia (TH) for hypoxic-ischemic encephalopathy (HIE) who concomitantly had a cerebral MRI predictive of unfavorable neurodevelopmental outcome. A few years later, the same authors completed a neurodevelopmental

Table 1 Summary of studies that used neurocognitive tests in children exposed to general anesthesia in the early years of life

Author	Design	Age	Primary endpoint	Secondary endpoints	GA (*n*)	Comparator (*n*)	Time to follow-up	Results
Warner et al. (2018) [5]	Prospective analysis of patients previously anesthetized	< 3 y	FSIQ standard score of the Wechsler abbreviated scale of intelligence	Individual domains from a comprehensive neuropsychological assessment and parent reports	*n* = 380 (singly exposed) *n* = 206 (multiply exposed)	411 (no GA)	At 8–12 y or 15–20 y	GA < 3 y = no deficit in general intelligence Multiple exposures = behavioral and learning difficulties
Davidson et al. (2016) [6]	RCT	< 60 W postmenstrual age	Wechsler preschool and FSIQ at 5 y	Bayley III at 2 y of age	359	363 (RA)	At 2 y	< 1-h GA = no increase in adverse neurodevelopmental outcome
McCann et al. (2019) [7]	RCT	< 60 W postmenstrual age	Wechsler preschool and FSIQ at 5 y	Bayley III at 2 y of age	242	205 (RA)	At 5 y	< 1-h GA = no alteration in neurodevelopmental outcome
Sun et al. (2016) [8]	Prospective analysis of patients previously anesthetized	< 36 months	IQ (global cognitive function)	Domain-specific neurocognitive function and behavior	105	105 (no GA)	At 8–15 y	Single GA < 36 months = no differences in IQ scores
Stratmann et al. (2014) [10]	Prospective analysis of patients previously anesthetized	< 1 y	Recognition memory testing Wechsler abbreviated scale of intelligence	NA	28	28 (matched children with no GA)	At 6–11 y	GA impairs recollection
Taghon et al. (2015) [11]	Prospective analysis of patients previously anesthetized	< 24 months	Functional MRI analysis of prefrontal cortex and caudate nucleus	NA	15	15 (matched children with no GA)	At 10–17 y	Early GA = no difference in accuracy or response time, but intergroup brain patter activation differences
Bakri et al. (2015) [12]	Prospective study	1.5–5 y	Child behavior checklist	NA	35	35 (matched children with no GA)	No long-term follow-up	Repeated GA = risk for behavioral and emotional disturbances
Kochfe et al. (2019) [13]	Prospective analysis of patients previously anesthetized	< 2 y	Behavioral changes analyzed by Eyberg child behavior inventory questionnaire	NA	168	226 (RA)	At 9–12 y	GA, early GA, and long GA exposure = increased behavioral disorder
Chemaly et al. (2014) [14]	Prospective analysis of patients previously anesthetized	< 4 y	Behavioral changes analyzed by Eyberg child behavior inventory questionnaire	NA	292	300 (no GA)	At 10–12 y	GA, early GA, long GA exposure, and multiple anesthetics = increased behavioral disorder
Zhang et al. (2017) [15]	Prospective study	6–12 y	Intelligence quotient	NA	*n* = 179 stratified by duration of GA	30 (no GA)	At 1 month postoperatively	> 3-h GA and early exposure = reduced IQ
Walkden et al. (2020) [16]	Prospective analysis of patients previously anesthetized	< 4 y	Neurodevelopmental outcome	NA	*n* = 1110 (singly exposed) *N* = 212 (multiply exposed)	*n* = 12,111 (no GA)	At 7–16 y	Early GA = no neurodegenerative effects, but lower motor and social linguistic performance

RCT randomized controlled trial, *y* years, *GA* general anesthesia, *FSIQ* full-scale intelligence quotient, *RA* regional anesthesia, *MRI* magnetic resonance imaging

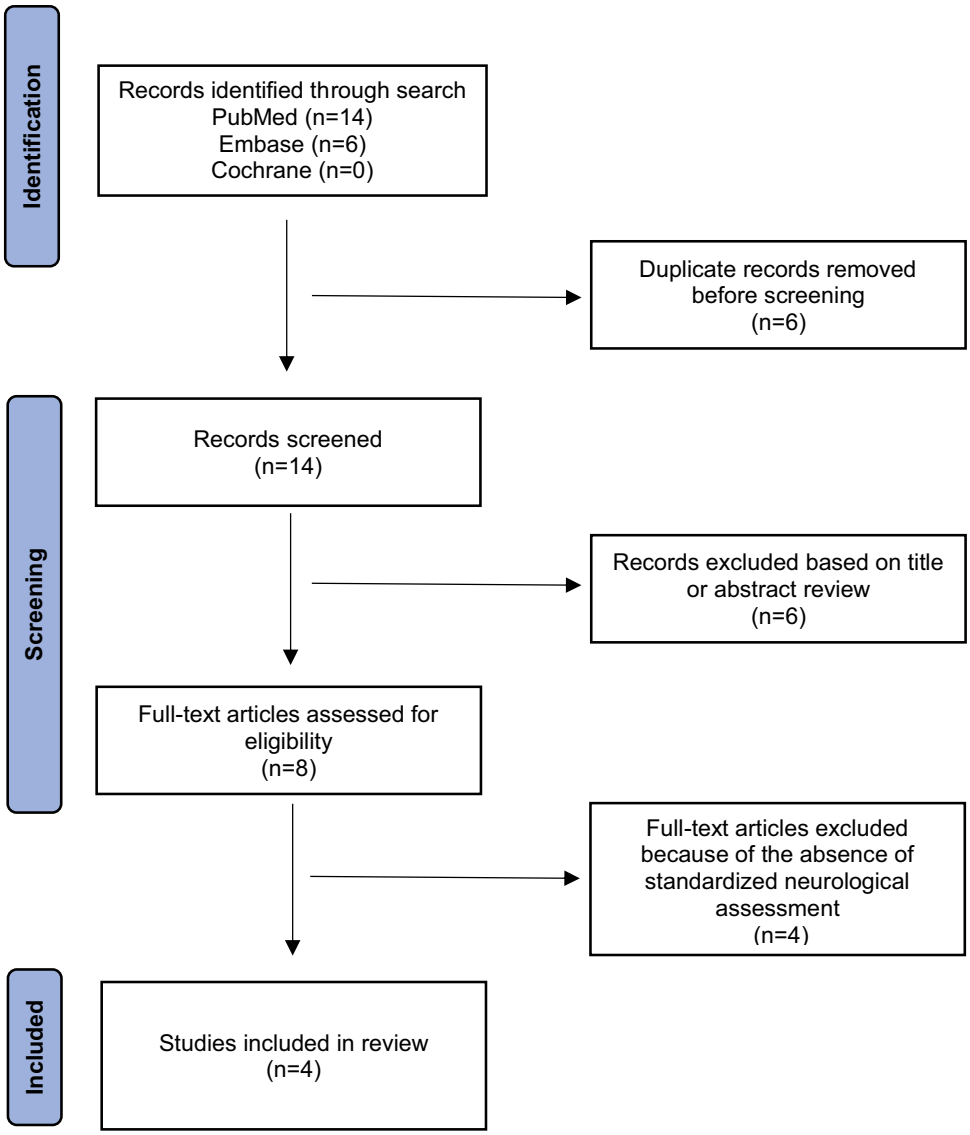

Fig. 1 PRISMA 2020 flow diagram of studies included in this systematic review

test in 33 out of these 37 included children at a median age of 2.7 years [26]. The latter study met the inclusion criteria and was included in our results.

The 4 fully analyzed manuscripts investigated serum NfL in neonatal encephalopathy (Table 2). In these studies, neurodevelopmental outcome was assessed by Bayley Scales of Infant Development (BSID) until the age of 2 years. Serum NfL sampled at 3 time points in the pilot study of Shah et al. rose during TH and was the highest at postrewarming [26]. They demonstrated that in newborns (median age of 98 h) with HIE who had undergone therapeutic hypothermia, persistently raised serum NfL levels (with a cut-off level of > 436 pg/mL) after rewarming strongly predicted adverse outcomes ($p = 0.009$). Goeral et al. measured serial serum NfL from initial peri-/intraventricular hemorrhage diagnosis in the first days of life through term equivalent age [27]. They showed that serum NfL was on average 113-fold higher [IQR 40–211 pg/mL] in cases of peri-/intraventricular hemorrhage compared to controls. They also found that high serum NfL level was an independent predictor of poor motor outcome or death at 1 and 2 years old. Sjöborn et al. evaluated preterm newborns in a cohort study and found that high serum NfL levels during the first weeks of life correlated with poor neurodevelopmental outcomes at 2 years of age, as determined by an unfavorable BSID [28]. They also reported that preterm newborns with serum NfL of more than 33.5 pg/mL at the postnatal age of 2–4 weeks were at risk of developing retinopathy of prematurity. Yang et al. retrospectively compared neonates with neonatal encephalopathy to healthy neonates and also found that serum NfL increased during hypothermia [29]. They showed that early serum NfL at 0–6 h of life is higher in the neonatal encephalopathy cohort (85 pg/mL) compared to controls (10 pg/mL) and differentiated a poor vs. good

Table 2 Summary of studies with serum neurofilament light levels predicting neurodevelopmental outcomes in children

Author	Design	Population	Age	sNfL sampling	Neurodevelopmental tests
Shah et al. (2020) [26]	Retrospective cohort study ($n=40$)	Mild HIE with no TH ($n=11$) vs. moderate-severe HIE with TH ($n=26$)	Term newborns > 39-week postmenstrual age	sNfL ($n=33$) -In the first week for Mild HIE -In the first week at 33–34 °C, prior to rewarming and when rewarming completed for HIE TH	Neurocognitive test at median age of 2.7 years -Bayley III ($n=23$) -ASQ-3 ($n=4$) -Follow-up information by team ($n=6$)
Goeral et al. (2021) [27]	Prospective observational study ($n=48$)	Severe PIVH grade 3 ($n=20$) and grade 4 ($n=25$) vs. PIVH grade 2 ($n=3$)	Preterm newborns < 32 gestational age	sNfL at visits -At diagnosis, confirmation and TEA visits for all infants -At EVD, EVD-plus, CSF-3, and CSF4 for infants needing CSF drainage	Bayley III at 2 years Bayley III at 1 year
Sjöborn et al. (2021) [28]	Retrospective cohort study ($n=221$)	3 clinical studies combined	Preterm newborns < 32 gestational age	sNfL ($n=209$) simultaneously on all patients	Bayley II and III at 2 years ($n=81$)
Yang et al. (2022) [29]	Retrospective cohort study ($n=77$)	Neonatal encephalopathy ($n=40$) vs. healthy neonates ($n=37$)	Neonates	sNfL at 5 time points (0–6, 12, 24, 48, and 96 h of life) in both cohorts	Death or Bayley III at 17–24 months

sNfL serum neurofilament light, *HIE* hypoxic-ischemic encephalopathy, *TH* therapeutic hypothermia, *ASQ-3* ages and stages questionnaire-3, *ARDS* acute respiratory distress syndrome, *PIVH* peri-/intraventricular hemorrhage, *TEA* term equivalent age, *EVD* extraventricular drainage, *CSF* cerebrospinal fluid

Table 3 Proposed pediatric reference values for serum neurofilament light at different ages

Age	10 m	20 m	30 m	40 m	50 m	60 m	70 m	80 m	7–12 y	12–14 y
sNfL level	27 pg/mL	24 pg/mL	22 pg/mL	20 pg/mL	18 pg/mL	16 pg/mL	15 pg/mL	14 pg/mL	7 pg/mL	3 pg/mL

sNfL serum neurofilament light, *m* months, *y* years

long-term neurological outcome with the use of BSID testing until 24 months of age.

Risk-of-bias assessment revealed that selection bias was present in the study of Shah et al., Goeral et al., and Yang et al. due to the method of allocation to intervention groups [26, 27, 29]. Detection bias (with an unclear risk of bias) was present in the study of Shah et al. and Goeral et al. due to non-blinding of the investigators [26, 27]. None of the studies had a risk of performance bias or attrition bias [26–29].

Discussion

Anesthesia-related neurotoxicity in the developing brain is still a concern although evidence in humans is still scarce. Moreover, it is unclear whether repeated and/or prolonged exposures are harmful and whether their effects are more pronounced in newborns and infants with brains more vulnerable to injury.

The neurodevelopmental assessment evaluating the potential neurotoxicity of anesthetic agents is laborious and shows substantial variability as neurocognitive tests must be age-adapted. In addition, there often exists an important issue of latency between anesthesia/surgery and the neurologic evaluation. The use of biomarkers of neuronal injury in the perioperative period could be extremely valuable as an objective tool to evaluate anesthetic neurotoxicity.

Neurofilaments as biomarkers for neuronal cell damage represent a significant advantage compared to other biomarkers previously tested as they are proteins exclusively expressed in neuronal tissue [20, 30]. Serum NfL has shown to be a better diagnostic and prognostic biomarker than glial fibrillary acidic protein (GFAP), tau, and ubiquitin C-terminal hydrolase-L1 (UCH-L1) for assessing neuronal damage, due to the biphasic release of GFAP and the variable levels of tau and UCH-L1 [31].

In adults, abnormally high levels of NfL have been correlated with neuronal cell damage in the context of neuroinflammatory diseases such as multiple sclerosis, neurodegenerative disorders, traumatic brain injury, and stroke [20, 32–34]. Although very few studies have evaluated the prognostic utility of serum NfL in the pediatric population, its use seems promising as it has been shown to correlate with neurologic outcomes in various pathologies [22, 25–29, 35, 36]. However, little is known about the kinetics of serum NfL in healthy newborns, infants, and children. Based on healthy control cohorts, we propose reference values of serum NfL for the healthy pediatric population [22, 31, 35–38] (Table 3). Data are unavailable for serum NfL levels in terms of newborns under 10 months of age. Serum NfL concentrations significantly decrease with age and reach a nadir point between 10 and 15 years [22, 35, 37, 38]. This decrease could reflect the turnover of neuronal growth until adolescence (brain growth) [35]. The serum NfL values from healthy pediatric population could thus provide a theoretical reference to guide the diagnosis, treatment, and prognosis of neurological diseases in pediatric patients, providing confirmation in larger prospective cohorts [38].

Recently the highly sensitive single-molecule array (Simoa) immunoassays have enabled serum NfL detection [39]. Considering the latter point and based on the available literature on the pediatric population, serum NfL should be investigated as a possible tool to evaluate the neurotoxicity of anesthetic agents in pediatric patients [39]. This requires further studies in larger cohorts with a serial sampling of serum NfL, combined with standardized neurodevelopmental tests to correlate clinical neurological outcomes with serum NfL levels [24, 25]. As of today, 1 trial is registered at ClinicalTrials.gov evaluating this issue (NCT05369949). The investigators hypothesize that a potentially less neurotoxic anesthesia regimen compared to the current standard of care results in a smaller release of serum NfL. This RCT will start in 2023 and will include patients between 0 and 3 years, and neurodevelopmental outcomes of both groups will be compared in addition to postoperative values of serum NfL.

This review article shows some limitations. First, the included studies were mixed in nature (prospective and retrospective cohorts). Second, none of the studies examined serum NfL in the perioperative period. Third, including patients until 18 years old in our search strategy might have added heterogeneity to the results. However, the pediatric population of the eligible studies ranged from preterm newborns to neonates, resulting in less heterogeneity. Our work nevertheless shows some strengths. It is the first systematic review associating serum NfL and neuronal injury in the pediatric population. We moreover propose pediatric reference values for serum NfL at different ages.

In summary, based on the available literature, serum NfL seems to be a valuable biomarker of neuronal injury in the pediatric population. Few studies have reported serum NfL levels in healthy children, and there is currently no data on its diagnostic or prognostic value in the perioperative period.

Perioperative use of biomarkers such as serum NfL is at the center of our attention as they could become an objective tool to evaluate possible anesthetic neurotoxicity and help in the development of neuroprotective strategies in the future.

Authors' contribution Independent literature search, extraction of data, and interpretation of data were performed by Aurélie Jacobs Sariyar (AJS) and Mona Momeni (MM). The first draft of the manuscript was written by Aurélie Jacobs Sariyar (AJS) and Mona Momeni (MM). All authors critically reviewed the manuscript for intellectual content and commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval Not required as the article is a systematic review.

Consent to participate Not applicable. There was no involvement of a patient as the paper is a systematic review.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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