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Research Article

Neurofilament light protein as a cerebrospinal fluid marker after whiplash trauma

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Abstract

The purpose was to investigate if a whiplash trauma may cause an increased concentration of the Neurofilament Light (NFL) protein, and if so; is this related to the injury severity and the radiological findings?

Adult car occupants, with neck problems after rear-end collisions, were investigated in a study on Whiplash-Associated Disorders (WAD) in 1997-2001. The study protocol included a neurological examination, plain radiography and MRT of the cervical spine, and a lumbar puncture for Cerebrospinal Fluid (CSF) within six weeks after the accident. Similar CSF samples were also taken three and twelve months later. All CSF samples were analyzed for NFL. Of 52 subjects who entered the study, 43 completed it. The WAD grade was I in two of the 43 cases, II in 13, and III in 28. No one had radiological signs, indicating injuries to the cervical spine or spinal cord.

Six subjects showed an increased NFL concentration at the primary examination. This was judged to be caused by whiplash trauma in three of them (7%). There was no relation between an increased NFL concentration and the number of pathological changes on plain radiographs or MRT. Neither was there a relation between the NFL concentration and the WAD grade.

An increased NFL concentration can be found in some WAD patients. It might be difficult to relate such an increase to clinical or radiological findings. Further studies should investigate NFL as a marker for injuries to the central nervous system in whiplash trauma, including minimal traumatic brain injuries.

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Abbreviations

ALS: Amyotrophic Lateral Sclerosis; NFL: Neurofilament Light; MRT: Magnetic Resonance Tomography; MS: Multiple Sclerosis; mTBI: mild Traumatic Brain Injury; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; WAD: Whiplash-Associated Disorders.

Introduction

Whiplash-Associated Disorders (WAD) have caused frustrating problems for inflicted individuals and large costs for the society for decades [1-3].

The car industry has managed to handle some of these problems. Improvements in whiplash protection systems have reduced the risk of long-term WAD by about 50% in some brands [4]. However, the medical society has not succeeded to improve the diagnostics and treatment of WAD to the same degree.

Besides musculoskeletal problems, like neck/shoulder pain and reduced cervical mobility, WAD also includes neurological symptoms and signs like headache, dizziness, unsteadiness, visual disturbances, altered head and eye movement control, fatigue, and cognitive problems [5-10].

Many of these neurological problems can occur also after minor head trauma, and during the last years, evidence has emerged that the significance of so-called mild Traumatic Brain Injury (mTBI) has been underestimated [11-14].

A whiplash trauma may also influence the brain, because of inertia effects that cause strains of the brain tissue during a head acceleration. The occurrence of cerebral injury symptoms after whiplash trauma is well described in the literature and in clinical praxis [9,15,16,17].

Cervical spine involvement should also be suspected in mTBI, although there is a lack of data about the association between mTBI and posttraumatic cervical problems [18].

There are established methods for the diagnosis of mTBI, including diffuse axonal injuries [19-20]. However, so far, such methods are seldom used routinely for mTBI after whiplash trauma in humans. Thus, brain injuries are probably underestimated after whiplash trauma.

Traumatic brain injury and degenerative brain diseases may cause a release of molecules from nerve cells into the spinal fluid. One of these molecules is Neurofilament Light Protein (NFL), which reflects axonal damage in a wide variety of neurological disorders and trauma [21-23]. Increased levels of NFL have also been shown after whiplash trauma [24].

Long-term effects of whiplash trauma are related to degenerative changes in the cervical spine [25-27]. Degenerative changes of the spine include narrowing of the intervertebral foramina (foraminal stenosis) caused by degenerative changes of the zygapophyseal (facet) joints and/or the uncovertebral joints (von Luschka´s joints). Neurological deficits after whiplash trauma were noted more often in subjects with foraminal stenosis than in those without [28]. Foraminal stenosis will increase the possibility that nerve roots emerging through the foraminal canal will be pinched. Other spinal changes, which could influence the nervous system, include disk protrusions and herniated disks. Also, a narrow spinal canal is unfavorable in whiplash patients [29]. Thus, certain radiological findings may influence the outcome of whiplash trauma.

The purpose of this study was to measure the NFL concentration in CSF in adults after whiplash trauma in rear-end impacts, indicating an involvement of the CNS, and to investigate if such an increase was related to the WAD grade and the radiological findings in the cervical spine.

Material and methods

The study was approved by the Ethics Committee of Gothenburg University (ID: L-388-97). All participants in this analysis have previously accepted sample storage for further determinations and formerly signed an informed consent form in the main study (WAD patients 1997 to 2001).

Study population

This study is based on data from a main study on WAD patients between 1997 and 2001 [28] That study was accomplished by the former Traffic Injury Register at Sahlgrenska University Hospital, together with the Accident Investigation Team at Volvo Car Cooperation, Sweden. The overall purpose of that study was to identify differences in symptom patterns and clinical findings in car occupants injured in frontal and rear-end collisions, which could indicate vulnerable anatomical structures, mechanisms of injury, and methods for protection in car crashes.

In that main study, male and female car occupants, at least 16 years old, with neck problems after car impacts were recruited prospectively from the Accident & Emergency departments of the two main hospitals in Gothenburg and from the accident investigation team at Volvo CC. In total, 152 subjects were enrolled for the main study. Clinical examinations were made by physiotherapists, specialized in WAD patients, as soon as possible after the accident and after three and twelve months. Plain radiographs of the cervical spine were obtained in all cases.

Of the total 152 subjects in the main study, 108 had been injured in rear-end impacts (77 in Volvo cars), and they were offered to enter a neurological study. The inclusion and exclusion criteria for the neurological study are shown in Table 1. Of 52 subjects, who fulfilled the criteria for the neurological study, seven could not finish the study for various reasons, most often due to unwillingness or fear to implement all parts of the study design. The remaining 45 subjects underwent a detailed clinical neurological examination by one of the authors (GSC). These 45 subjects were also investigated with MRT of the cervical spine, and an analysis of the NFL concentration in the CSF obtained from a lumbar puncture. In two cases, the NFL sample at the first examination was unmarked, why these cases could not be included in the analyses. Thus, the present study finally comprised 43 subjects.

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Table 1: Criteria for the neurological study.

Inclusion criteria
Injured in a rear-end car impact.
Age 18 or older.
Neck problems (pain, stiffness, tenderness; WAD I, II, III) after the accident.
Exclusion criteria
Structural cervical spine injury on plain radiographs.
Head impact at the accident with loss of consciousness or memory.
Known neurological disease.
Experience of at least one of the following during the last year before the accident:
Concussion
Spinal injury (including neck).
Acute low back pain.
Disk hernia.
Oppressive neck pain.
Ongoing medication with anticoagulants.
Having a pacemaker.
Having a metal object in the body.
Claustrophobia.
Pregnancy.
Weight over 150 kg.

Study methods

Medical evaluation: The initial medical condition was evaluated regarding the symptoms and signs found at the first clinical examination and the radiological findings. The neck problems were graded according to the WAD classification shown in Table 2.

Radiological evaluation: The plain radiographs and the MRT images were investigated by a specialized radiologist, regarding skeletal post-traumatic changes, degenerative changes, misalignment of the spinal curvature, disk protrusion or disk hernia, stenosis of the spinal canal, foraminal stenosis, impingement of the spinal cord, and signal changes of the spinal cord. The occurrence of each of these findings was related to the NFL concentration for each case.

Procedure for the measurement of the NFL concentration: CSF NFL concentration was measured with enzyme-linked immunosorbent assay (ELISA) technique [30]. The samples were stored at -70 ºC, and the first analyses were made in direct connection to the study period (1997 – 2001). The ELISA technique has been successively refined since then, why we found it of interest to re-analyze the old samples, and in this study, we used the samples with the technique that has existed since 2018 [31]. The reference values for the NFL concentration for different ages are shown in Table 3 [32].

The first NFL samples were obtained within 15-40 days (median 24 days) after the accident. Follow-up samples were obtained three to four months after the accident in cases with an initial increase and after one year.

The NFL concentration usually increases during the first days after a trauma. The elevation decreases over time but can persist for several months [33].

Statistical methods

The Chi-square test was used for all statistical analyses.

Results

The NFL concentration among the 43 subjects who fulfilled the study, and for whom complete data were obtained, was increased in six cases as shown in Table 4, which also shows the WAD grade and the occurrence of the seven types of radiological findings at the primary investigation.

In three of the six cases with increased NFL concentration, the increase was considered to possibly have other causes

Table 2: WAD-grades.

Grade	Meaning
0	No complaint about the neck. No physical signs.
I	Complaint of neck pain, stiffness, or tenderness only. No physical sign(s).
II	Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of movement and point of tenderness.
III	Neck complaint AND neurological sign(s). Neurological signs include decreased or absent tendon reflexes, weakness, and sensory deficits.
IV	Neck complaint AND fracture or dislocation.

Table 3: NFL reference values.

According to Aylin, et al. 2017. [32]	
Age (years)	**NFL concentration (ng/l)**
< 30	< 380
30-40	< 560
40-60	< 890
60+	< 1850

Table 4: Cases with increased NFL values at the first examination.

Case	Age	Gender	WAD	NFL_Prim	NFL_3Months	NFL_1Year	Radiological findings
5	62	F	2	1350	999		a, b, c, e
13	53	F	2	1089	3607		a, e, f
31	**47**	**F**	**2**	**1657**	**653**	**559**	**a, e**
38	32	M	2	968	1316		a, c, e
45	**50**	**F**	**3**	**1396**	**1207**		**a, b, e**
46	**38**	**F**	**3**	**4782**	**384**	**-**	**-**

Bold characters indicate cases, where the NFL increase had no other explanation than the accident

a: Degenerative changes
b: Misalignment of the spinal curvature
c: Disk protrusion/-hernia
d: Stenosis of the spinal canal
e: Foraminal stenosis
f: Impingement of the spinal cord
g: Signal changes in the spinal cord

Note: The NFL concentration at three months was not measured in four of these six cases, because of unwillingness to undergo a lumbar puncture at that time. However, they accepted a lumbar puncture at the one-year follow-up.

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than the accident. Case 5 turned out to have a progressive neurological disease. Case 13 had sustained a concussion one month before the one-year follow-up. Case 38 suffered from psoriasis and had heavy medication.

For the remaining three cases, indicated with bold characters in Table 4, the accident was judged to have caused the primary NFL increase.

Radiological findings in the cervical spine and NFL

There were no radiological changes in the cervical spine, which could be attributed to the whiplash trauma *per se*. Degenerative cervical spine changes of any degree were noted in about two-thirds of the cases, irrespective of the NFL concentration. Misalignment of the spinal curvature was noted in about one-third of the cases, irrespective of the NFL concentration. Disk protrusion or disk hernia was not noted in any case with increased NFL concentration but in almost one-third of the other cases. Foraminal stenosis was more frequently seen in cases with elevated NFL concentration (17%) than in those with normal NFL concentration (4%), but this difference was not statistically significant. Stenosis of the spinal canal was noted in five cases without elevated NFL concentration and in no one of those with elevated NFL concentration. Altogether, there was no correlation between the number of radiological findings of any kind and an increased NFL concentration at the first examination (Table 4).

WAD-grade and NFL

Two of the three cases with increased NFL concentration at the first examination, likely due to the accident, were graded as WAD III. Thirteen of the 37 cases without increased NFL concentration at the first examination were graded as WAD III. This difference was not statistically significant.

Discussion

The main purpose of the study was to investigate NFL as an indicator for injuries to the CNS in WAD patients. There are several injury markers in the spinal fluid, but NFL was chosen as it can remain increased for weeks up to several months after trauma before it reduces [34]. If the NFL does not decrease over time after trauma, other causes should be suspected. Persistent, moderately elevated NFL concentrations can be seen in chronic conditions like ALS, MS, and vascular dementias. In cases with acute or rapidly progressive degradation of myelinated axons, the NFL levels can increase very sharply, e.g., after a stroke, trauma, neonatal asphyxia, cardiac arrest, herpes simplex encephalitis, inflammatory polyradiculitis, or Creutzfeldt-Jakob's disease [35].

The use of biomarkers for CNS dysfunction has increased dramatically during the last decades. The diagnostics of brain pathology in Alzheimer's disease and of mTBI in certain sports like football and amateur boxing both have improved considerably using NFL measurement. Lately, the possibility to measure the NFL concentration in blood samples has been shown for various conditions [36-39]. This makes it possible to use blood samples instead of spinal fluid samples for monitoring CNS injuries, which should considerably simplify further studies on WAD and mTBI.

In our material, the NFL concentration was measured in CSF, as blood measurements were not available. The reason why the results from the actual study were not published earlier was the limitations of the analysis methods at that time. With somewhat improved NFL analysis methods, a study was made on 23 road traffic casualties with spinal cord injury, including 17 cases with WAD III injuries in 2003 [24]. CSF NFL concentration was elevated in three of the WAD III cases during the first three weeks in that study. In two of these, the NFL concentration was normalized after 18 months. The third case was not re-examined. In 2018, the analysis method had been further improved, which was our reason to re-analyze our material from the 1990-ies.

Of the six cases in the present study with increased NFL concentration (Table 4), cases 5 and 38 were excluded from further analyses, because the increase might have other causes than the whiplash trauma. Case 5 turned out to have a progressive neurological disease, and case 38 had psoriasis and heavy medication. In both cases, the NFL concentration remained increased at the one-year follow-up, which indicates other causes than the whiplash trauma. Case 13 had an increased NFL concentration at the first examination, which was interpreted as due to the whiplash trauma. As depicted in Table 4, the NFL concentration in case 13 was even more increased at the one-year follow-up. This further increase might depend on a brain concussion some weeks before the follow-up.

The increased NFL concentrations in the remaining three cases (31, 45, 46) were considered to be due to the accident as the concentration had decreased at follow-up. However, in case 45, an increase was still seen after one year compared to the reference value. But, related to the initial value, the decrease itself, and that the subject did not have other diseases, speaks against causes other than the accident.

Spinal changes may affect the CNS. In this study, the occurrence of seven types of radiological changes on plain radiographs and MRIs were documented. Of these, all may influence the spinal cord and/or the nerve roots. Of the three cases with increased NFL concentration, probably due to the accident, one had no radiological changes, and the other two had two and three types of changes, respectively. The number of radiological changes in those with normal NFL values, however, was greater, why degenerative changes do not seem to influence the CNS in whiplash trauma. One exception might be stenosis of the foramina canal, which might increase the risk of injury to spinal nerve roots.

Although brain injuries probably are very seldom diagnosed after whiplash trauma, the possibility of brain injury should be considered in whiplash cases with disturbances of the central nervous system. A brain injury can be caused in at least three ways: 1) the head being struck; 2) the head striking an object; and 3) the brain undergoing an acceleration/deceleration movement (i.e., whiplash) without direct external trauma

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[40]. The risk of brain injury also depends on the type of acceleration; rotational acceleration being more detrimental than linear acceleration [41-43]. Clinically, in the acute phase, trauma patients commonly are asked about head impact, but the risk of an acceleration/deceleration injury without a head impact is often overlooked when it comes to CNS injuries [44].

Similar symptoms are often noted in patients with mTBI and in whiplash patients. This is especially true for headaches and cognitive deficits [18,45-47].

mTBIs usually are not visualized during the acute phase using DT or MRI. mTBI is, above all, a clinical diagnosis. There are many studies, however, which may show axonal injuries in these cases by use of Diffusion Tensor Imaging [20,48-52] but this type of investigation is not used in ordinary clinical settings.

It seems possible that a whiplash trauma may cause injuries to the spinal cord or its meningeal covers, as a flexion-extension movement of the cervical spine will induce a several cm relative movement of the cord with respect to the surrounding spinal elements [53]. During a whiplash movement, great transient pressure changes in the venous plexus embedded in the spinal canal also seem to affect the spinal ganglia during a whiplash trauma [54]. Both mechanisms may influence the CNS.

As an acceleration-deceleration trauma, except from influencing the risk of injury to the cervical spine, also may cause a brain injury, one can imagine that the increased NFL concentration registered in the three cases in the actual study can indicate a brain injury. Case 13, who had a high NFL concentration at the one-year follow-up, and who had sustained a concussion short for the one-year follow-up, de facto indicates that a brain injury is an explanation for this increase.

The increased NFL levels in the study by Guéz, et al. 2003 were obtained from patients with a whiplash trauma probably more severe than in our study, as all their patients were classified as WADIII [24]. The NFL concentration was increased in three of their 17 cases. This increase indicated axonal damage corresponding to earlier reports in the literature about the possible impact on CNS in whiplash trauma. Their three cases belonged to those patients with persisting symptoms. In our study, the patients with increased NFL represented both WAD II and III.

An increased NFL concentration in spinal fluid could not be related to any specific radiological finding in the cervical spine in this study. Such an increase, however, might be related to a cerebral injury. In fact, a cerebral injury might be suspected in one of the three cases with increased NFL concentrations, which was excluded due to a still high follow-up value.

Our study is too small to draw any conclusions about the importance of increased NFL concentration in WAD and its relation to the severity of the symptoms. The NFL concentration was measured in the cerebrospinal fluid, taken from a puncture of the lumbar spine. Using punctures of the spinal canal limits the possibility to make large studies on how the CNS reacts to whiplash trauma, as this method has several disadvantages including the risk of harm and injury to the subject. During the last decades, the possibility to measure the NFL concentration in blood samples has evolved [55] and this makes it easier and safer to collect data for more comprehensive studies on NFL and WAD.

Conclusion

Acceleration – deceleration trauma may cause injuries to the central nervous system.

It is important to examine the possibility of a brain injury after whiplash trauma.

Further studies are recommended to evaluate relationships between serum NFL and the severity of WAD symptoms and pathologic radiological findings.

Such studies should be made to validate if an increased NFL concentration could be used as a prognostic tool.

Transparency, rigor and reproducibility summary

The study was not formally registered because, at the start of the study, the authors were not aware of this demand. The analysis plan was not formally registered for the same reason. There was no need for choosing a statistical power value or sample size as the study was mainly explorative. At the start, 52 subjects fulfilled the inclusion criteria. Seven of these did not fulfill the study. Primary NFL samples were collected for the remaining 45 subjects, but in two of them, the identifications were unclear, which gave 43 cases with complete primary and follow-up data. Data analyses were performed by investigators blinded to the relevant characteristics of the participants. Data were acquired between 1997 and 2001. The NFL concentration was measured with the ELISA technique that has existed since 2018. Specificity in the presence of other relevant clinical conditions, anatomical variants, and comorbidities was assessed by one of the authors (GSC). Equipment and software used to perform the acquisition and analysis of the NFL samples may be available upon request from the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. The key inclusion criteria are established standards in the field. Statistical tests for comparing mutual groups used the chi-square method. Correction for multiple comparisons was not necessary. No replication or external validation studies have been performed or are planned/ongoing at this time to our knowledge. De-identified data from this study will be made available (as allowable according to institutional IRB standards) by emailing the corresponding author as of 2023-07-19. There is no analytic code associated with this study. The authors agree or have agreed to publish the manuscript using the Mary Ann Liebert Inc. "Open Access" option under the appropriate license.

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OB was head of the Traffic Injury Register (TSR) at the Department of Orthopaedics, Sahlgrenska University Hospital in Gothenburg at the time of the study. TSR conducted the study in cooperation with the Safety Centre at Volvo Car Corporation (VCC), Gothenburg. VCC also financed essential parts of the study.

Conflicts of interest

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, 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).

References

1. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining «whiplash» and its management. Spine (Phila Pa 1976). 1995 Apr 15;20(8 Suppl):1S-73S. Erratum in: Spine 1995 Nov 1;20(21):2372. PMID: 7604354.

2. Nordin M, Carragee EJ, Hogg-Johnson S, Weiner SS, Hurwitz EL, Peloso PM, Guzman J, van der Velde G, Carroll LJ, Holm LW, Côté P, Cassidy JD, Haldeman S; Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Assessment of neck pain and its associated disorders: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S101-22. doi: 10.1097/BRS.0b013e3181644ae8. Erratum in: Spine (Phila Pa 1976). 2009 Mar;18(3):435-6. Erratum in: Spine. 2009 Mar 15;34(6):640. PMID: 18204385.

3. Sterling M, Carroll LJ, Kasch H, Kamper SJ, Stemper B. Prognosis after whiplash injury: where to from here? Discussion paper 4. Spine (Phila Pa 1976). 2011 Dec 1;36(25 Suppl):S330-4. doi: 10.1097/BRS.0b013e3182388523. PMID: 22020603.

4. Kullgren A, Krafft M. Gender analysis on whiplash seat effectiveness: results from real-world crashes. IRCOBI Conference. 2010; 17–28. www.ircobi.org/wordpress/downloads/irc0111/2010/Session1/1-1.pdf.

5. Radanov BP, Sturzenegger M, Di Stefano G. Long-term outcome after whiplash injury. A 2-year follow-up considering features of injury mechanism and somatic, radiologic, and psychosocial findings. Medicine (Baltimore). 1995 Sep;74(5):281-97. doi: 10.1097/00005792-199509000-00005. PMID: 7565068.

6. Karlsborg M, Smed A, Jespersen H, Stephensen S, Cortsen M, Jennum P, Herning M, Korfitsen E, Werdelin L. A prospective study of 39 patients with whiplash injury. Acta Neurol Scand. 1997 Feb;95(2):65-72. doi: 10.1111/j.1600-0404.1997.tb00071.x. PMID: 9059723.

7. Kasch H, Bach FW, Stengaard-Pedersen K, Jensen TS. Development in pain and neurologic complaints after whiplash: a 1-year prospective study. Neurology. 2003 Mar 11;60(5):743-9. doi: 10.1212/01.wnl.0000046661.82212.04. PMID: 12629227.

8. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. J Orthop Sports Phys Ther. 2009 May;39(5):364-77. doi: 10.2519/jospt.2009.2834. PMID: 19411769.

9. Treleaven J. Dizziness, unsteadiness, visual disturbances, and postural control: implications for the transition to chronic symptoms after a whiplash trauma. Spine (Phila Pa 1976). 2011 Dec 1;36(25 Suppl):S211-7. doi: 10.1097/BRS.0b013e3182387f78. PMID: 22020615.

10. Seroussi R, Singh V, Fry A. Chronic whiplash pain. Phys Med Rehabil Clin N Am. 2015 May;26(2):359-73. doi: 10.1016/j.pmr.2015.01.003. Epub 2015 Mar 7. PMID: 25952070.

11. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, Kraus J, Coronado VG; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004 Feb;(43 Suppl):28-60. doi: 10.1080/16501960410023732. PMID: 15083870.

12. Numminen HJ. The incidence of traumatic brain injury in an adult population--how to classify mild cases? Eur J Neurol. 2011 Mar;18(3):460-4. doi: 10.1111/j.1468-1331.2010.03179.x. Epub 2010 Aug 16. PMID: 20722703.

13. Vos PE, Alekseenko Y, Battistin L, Ehler E, Gerstenbrand F, Muresanu DF, Potapov A, Stepan CA, Traubner P, Vecsei L, von Wild K; European Federation of Neurological Societies. Mild traumatic brain injury. Eur J Neurol. 2012 Feb;19(2):191-8. doi: 10.1111/j.1468-1331.2011.03581.x. PMID: 22260187.

14. Skandsen T, Nilsen TL, Einarsen C, Normann I, McDonagh D, Haberg AK, Vik A. Incidence of Mild Traumatic Brain Injury: A Prospective Hospital, Emergency Room and General Practitioner-Based Study. Front Neurol. 2019 Jun 18;10:638. doi: 10.3389/fneur.2019.00638. PMID: 31275229; PMCID: PMC6591366.

15. Ettlin TM, Kischka U, Reichmann S, Radii EW, Heim S, Wengen D, Benson DF. Cerebral symptoms after whiplash injury of the neck: a prospective clinical and neuropsychological study of whiplash injury. J Neurol Neurosurg Psychiatry. 1992 Oct;55(10):943-8. doi: 10.1136/jnnp.55.10.943. PMID: 1431958; PMCID: PMC1015197.

16. Taylor AE, Cox CA, Mailis A. Persistent neuropsychological deficits following whiplash: evidence for chronic mild traumatic brain injury? Arch Phys Med Rehabil. 1996 Jun;77(6):529-35. doi: 10.1016/s0003-9993(96)90290-7. PMID: 8831467.

17. Beeckmans K, Crunelle C, Van Ingelgom S, Michiels K, Dierckx E, Vancoillie P, Hauman H, Sabbe B. Persistent cognitive deficits after whiplash injury: a comparative study with mild traumatic brain injury patients and healthy volunteers. Acta Neurol Belg. 2017 Jun;117(2):493-500. doi: 10.1007/s13760-017-0745-3. Epub 2017 Jan 19. PMID: 28102492.

18. Morin M, Langevin P, Fait P. Cervical Spine Involvement in Mild Traumatic Brain Injury: A Review. J Sports Med (Hindawi Publ Corp). 2016;2016:1590161. doi: 10.1155/2016/1590161. Epub 2016 Jul 26. PMID: 27529079; PMCID: PMC4977400.

Citation: Bunketorp O, Lindh M, Pujol-Calderón F, Rosengren L, Carlsson GS, et al. (2023) Neurofilament light protein as a cerebrospinal fluid marker after whiplash trauma. Open J Trauma 7(1): 004-011. DOI: https://dx.doi.org/10.17352/ojt.000041

19. Khong E, Odenwald N, Hashim E, Cusimano MD. Diffusion Tensor Imaging Findings in Post-Concussion Syndrome Patients after Mild Traumatic Brain Injury: A Systematic Review. Front Neurol. 2016 Sep 19;7:156. doi: 10.3389/fneur.2016.00156. PMID: 27698651; PMCID: PMC5027207.

20. Jang SH, Kwon YH. A Review of Traumatic Axonal Injury following Whiplash Injury As Demonstrated by Diffusion Tensor Tractography. Front Neurol. 2018 Feb 8;9:57. doi: 10.3389/fneur.2018.00057. PMID: 29472891; PMCID: PMC5809420.

21. Zetterberg H, Jacobsson J, Rosengren L. P4-127: CSF neurofilament light as a diagnostic and prognostic biomarker for amyotrophic lateral sclerosis. Alzheimer's & dementia, 2006: 2:S553-S553. https://alz-journals-onlinelibrary-wiley-com.ezproxy.ub.gu.se/doi/pdf/10.1016/j.jalz.2006.05.1866

22. Christiansson M, Källen Å, Zetterberg H. Monitoring the biochemical aftermath of boxing by cerebrospinal fluid analyses. Alzheimer's & Dementia 2006; 2: S206-S206. https://doi-org.ezproxy.ub.gu.se/10.1016/j.jalz.2006.05.748

23. Constantinescu R, Zetterberg H, Holmberg B, Rosengren L. Levels of brain related proteins in cerebrospinal fluid: an aid in the differential diagnosis of parkinsonian disorders. Parkinsonism Relat Disord. 2009 Mar;15(3):205-12. doi: 10.1016/j.parkreldis.2008.05.001. Epub 2008 Jun 17. PMID: 18562238.

24. Guéz M, Hildingsson C, Rosengren L, Karlsson K, Toolanen G. Nervous tissue damage markers in cerebrospinal fluid after cervical spine injuries and whiplash trauma. J Neurotrauma. 2003 Sep;20(9):853-8. doi: 10.1089/089771503322385782. PMID: 14577863.

25. Radanov BP, Sturzenegger M, De Stefano G, Schnidrig A. Relationship between early somatic, radiological, cognitive and psychosocial findings and outcome during a one-year follow-up in 117 patients suffering from common whiplash. Br J Rheumatol. 1994 May;33(5):442-8. doi: 10.1093/rheumatology/33.5.442. PMID: 8173848.

26. Rydman E, Kasina P, Ponzer S, Järnbert-Pettersson H. Association between cervical degeneration and self-perceived nonrecovery after whiplash injury. Spine J. 2019 Dec;19(12):1986-1994. doi: 10.1016/j.spinee.2019.07.017. Epub 2019 Aug 5. PMID: 31394280.

27. Watanabe K, Daimon K, Fujiwara H, Nishiwaki Y, Okada E, Nojiri K, Watanabe M, Katoh H, Shimizu K, Ishihama H, Fujita N, Ichihara D, Tsuji T, Nakamura M, Matsumoto M. The Long-term Impact of Whiplash Injuries on Patient Symptoms and the Associated Degenerative Changes Detected Using MRI: A Prospective 20-year Follow-up Study Comparing Patients with Whiplash-associated Disorders with Asymptomatic Subjects. Spine (Phila Pa 1976). 2021 Jun 1;46(11):710-716. doi: 10.1097/BRS.0000000000003901. PMID: 33394988.

28. Bunketorp O Jakobsson L, Norin H. Comparison of frontal and rear-end impacts for car occupants with whiplash-associated disorders - Symptoms and clinical findings. 2004. Int IRCOBI Conf 245-56. www. ircobi.org/wordpress/downloads/irc0111/2004/Session5/5.3.pdf

29. Pettersson K, Kärrholm J, Toolanen G, Hildingsson C. Decreased width of the spinal canal in patients with chronic symptoms after whiplash injury. Spine (Phila Pa 1976). 1995 Aug 1;20(15):1664-7. doi: 10.1097/00007632-199508000-00003. PMID: 7482014.

30. Rosengren LE, Wikkelsø C, Hagberg L. A sensitive ELISA for glial fibrillary acidic protein: application in CSF of adults. J Neurosci Methods. 1994 Mar;51(2):197-204. doi: 10.1016/0165-0270(94)90011-6. PMID: 8051950.

31. Gaetani L, Höglund K, Parnetti L, Pujol-Calderon F, Becker B, Eusebi P, Sarchielli P, Calabresi P, Di Filippo M, Zetterberg H, Blennow K. A new enzyme-linked immunosorbent assay for neurofilament light in cerebrospinal fluid: analytical validation and clinical evaluation. Alzheimers Res Ther. 2018 Jan 23;10(1):8. doi: 10.1186/s13195-018-0339-1. PMID: 29370869; PMCID: PMC6389166.

32. Yilmaz A, Blennow K, Hagberg L, Nilsson S, Price RW, Schouten J, Spudich S, Underwood J, Zetterberg H, Gisslén M. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV-negative controls. Expert Rev Mol Diagn. 2017 Aug;17(8):761-770. doi: 10.1080/14737159.2017.1341313. Epub 2017 Jun 14. PMID: 28598205.

33. Zetterberg H, Hietala MA, Jonsson M, Andreasen N, Styrud E, Karlsson I, Edman A, Popa C, Rasulzada A, Wahlund LO, Mehta PD, Rosengren L, Blennow K, Wallin A. Neurochemical aftermath of amateur boxing. Arch Neurol. 2006 Sep;63(9):1277-80. doi: 10.1001/archneur.63.9.1277. PMID: 16966505.

34. Bergman J, Dring A, Zetterberg H, Blennow K, Norgren N, Gilthorpe J, Bergenheim T, Svenningsson A. Neurofilament light in CSF and serum is a sensitive marker for axonal white matter injury in MS. Neurol Neuroimmunol Neuroinflamm. 2016 Aug 2;3(5):e271. doi: 10.1212/NXI.0000000000000271. PMID: 27536708; PMCID: PMC4972001.

35. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019 Aug;90(8):870-881. doi: 10.1136/jnnp-2018-320106. Epub 2019 Apr 9. PMID: 30967444.

36. Hier DB, Obafemi-Ajayi T, Thimgan MS, Olbricht GR, Azizi S, Allen B, Hadi BA, Wunsch DC 2nd. Blood biomarkers for mild traumatic brain injury: a selective review of unresolved issues. Biomark Res. 2021 Sep 16;9(1):70. doi: 10.1186/s40364-021-00325-5. PMID: 34530937; PMCID: PMC8447604.

37. Shahim P, Tegner Y, Adiutori R. Serum Neurofilament Light Protein and Visin-like Protein-1 in Concussed Professional Ice Hockey Players. Alzheimer's & dementia. 2014; 10:P655-P655.

38. Shahim P, Gren M, Liman V, Andreasson U, Norgren N, Tegner Y, Mattsson N, Andreasen N, Öst M, Zetterberg H, Nellgård B, Blennow K. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. Sci Rep. 2016 Nov 7;6:36791. doi: 10.1038/srep36791. PMID: 27819296; PMCID: PMC5098187.

39. Ljungqvist J, Zetterberg H, Mitsis M, Blennow K, Skoglund T. Serum Neurofilament Light Protein as a Marker for Diffuse Axonal Injury: Results from a Case Series Study. J Neurotrauma. 2017 Mar 1;34(5):1124-1127. doi: 10.1089/neu.2016.4496. Epub 2016 Oct 13. PMID: 27539721.

40. Mild Traumatic Brain Injury Committee. J Head Trauma Rehabil. 1993; 8:86-7.

41. Holbourn AHS. Mechanics of head injuries. The Lancet 1943; 242:438-41.

42. Genarelli TA, Ommaya AK, Thibault LE. Comparison of Translational and Rotational Head Motions in Experimental Cerebral Concussion. Proc of Fifteenth Stapp Car Crash Conference NY., Soc. Automotive Engineers. 1971; 797-803.

43. Gennarelli TA, Thibault LE, Ommaya AK. Pathophysiologic Response to Rotational and Translational Accelerations of the Head. Proc. of Sixteenth Stapp Car Crash Conference N.Y., Soc. Automotive Engineers, 1972; 296-308.

44. Peixoto C, Buchanan DM, Nahas R. Missed Emergency Department Diagnosis of Mild Traumatic Brain Injury in Patients with Chronic Pain After Motor Vehicle Collision. Pain Physician. 2023 Jan;26(1):101-110. PMID: 36791299.

45. Stålnacke BM. Postconcussion symptoms in patients with injury-related chronic pain. Rehabil Res Pract. 2012;2012:528265. doi: 10.1155/2012/528265. Epub 2012 May 22. PMID: 22685666; PMCID: PMC3364720.

46. Kischka U, Ettlin T, Heim S, Schmid G. Cerebral symptoms following whiplash injury. Eur Neurol. 1991;31(3):136-40. doi: 10.1159/000116663. PMID: 2044626.

47. Gil C, Decq P. How similar are whiplash and mild traumatic brain injury? A systematic review. Neurochirurgie. 2021 May;67(3):238-243. doi: 10.1016/j.neuchi.2021.01.016. Epub 2021 Jan 30. PMID: 33529694.

48. Kwon HG, Jang SH. Delayed gait disturbance due to injury of the corticoreticular pathway in a patient with mild traumatic brain injury. Brain Inj. 2014;28(4):511-4. doi: 10.3109/02699052.2014.887228. Epub 2014 Feb 24. PMID: 24564187.

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49. Seo JP, Jang SH. Traumatic axonal injury of the corticospinal tract in the subcortical white matter in patients with mild traumatic brain injury. Brain Inj. 2015;29(1):110-4. doi: 10.3109/02699052.2014.973447. Epub 2014 Oct 30. PMID: 25356741.

50. Jang SH, Kwon HG. Injury of the dentato-rubro-thalamic tract in a patient with mild traumatic brain injury. Brain Inj. 2015;29(13-14):1725-8. doi: 10.3109/02699052.2015.1075170. Epub 2015 Oct 19. PMID: 26479208.

51. Jang SH, Yi JH, Kwon HG. Injury of the inferior cerebellar peduncle in patients with mild traumatic brain injury: A diffusion tensor tractography study. Brain Inj. 2016;30(10):1271-5. doi: 10.1080/02699052.2016.1178805. Epub 2016 Jun 13. PMID: 27294795.

52. Jang SH, Lee HD. Severe and extensive traumatic axonal injury following minor and indirect head trauma. Brain Inj. 2017;31(3):416-419. doi: 10.1080/02699052.2016.1239274. Epub 2017 Jan 17. PMID: 28095027.

53. O'Connell JEA. The Clinical Signs of Meningeal Irritation. Brain 1946; 69:9-21.

54. Svensson M, Aldman B, Hansson H-A, Lövsund P, Seeman T, Suneson A, Örtengren T. Pressure Effects in the Spinal Canal During Whiplash Extension Motion - A Possible Cause of Injury to the Cervical Spinal Ganglia. Proceedings of the IRCOBI Conference, Eindhoven, Netherlands 1993; 189-200. www.ircobi.org/wordpress/downloads/irc1993/pdf_files/1993_13.pdf

55. Zetterberg H. Neurofilament Light: A Dynamic Cross-Disease Fluid Biomarker for Neurodegeneration. Neuron. 2016 Jul 6;91(1):1-3. doi: 10.1016/j.neuron.2016.06.030. PMID: 27387643.

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