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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - OTHER

Increased cerebrospinal fluid S100B protein levels in patients with trigeminal neuralgia and hemifacial spasm

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Abstract

Background The pathophysiology of neurovascular compression syndrome has not been fully elucidated, and cerebrospinal fluid levels of nerve tissue-related markers involved in this disorder have not yet been reported.

Methods We measured cerebrospinal fluid levels of S100B protein, neuron-specific enolase, and myelin basic protein in 21 patients with trigeminal neuralgia, 9 patients with hemifacial spasms, and 10 patients with non-ruptured intracranial aneurysms (control). Cerebrospinal fluid levels of these markers were determined using commercially available assay kits.

Results Both trigeminal neuralgia and hemifacial spasm groups showed significantly increased cerebrospinal fluid levels of S100B compared with the control group (1120 [IQR 391–1420], 766 [IQR 583–1500], and 255 [IQR 190–285] pg/mL, respectively; $p = 0.001$). There were no statistically significant differences in cerebrospinal fluid levels of neuron-specific enolase or myelin basic protein among the groups.

Conclusion Cerebrospinal fluid S100B levels were significantly higher in patients with trigeminal neuralgia and hemifacial spasm than in controls, which suggests the involvement of S100B in the underlying pathophysiology of neurovascular compression syndrome.

Keywords Cerebrospinal fluid · Hemifacial spasm · Nerve compression · Trigeminal neuralgia · S100B

Introduction

Neurovascular compression syndrome (NVCS) in conditions such as trigeminal neuralgia (TN) and hemifacial spasm (HFS) is thought to be caused by vascular compression of the responsible cranial nerve root, which results in focal demyelination and excitability of the involved nerve fibers [16, 18]. However, the underlying pathophysiology of NVCS has not been fully elucidated, and cerebrospinal fluid (CSF) levels of nerve tissue-related markers associated with this disorder have not yet been reported.

To enable the pathological analysis of this condition, attempts have been made to create rodent models that mimic human TN. These include the cobra venom suborbital nerve injection [1], trigeminal root compression [21], and chronic constriction injury of the rat's infraorbital nerve (ION-CCI) models [39]. In the ION-CCI model, an increase in the CSF and serum level of S100B protein has been observed in the surgical group. The S100B protein is expressed specifically in the nervous system and is involved in pain and cognitive functions [19]. To gain insight into the molecular events involved in NVCS, we measured CSF levels of S100B protein, neuron-specific enolase (NSE), and myelin basic protein (MBP) in patients with TN and HFS and compared the levels with those in patients with non-ruptured intracranial aneurysms.

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Methods and materials

Patient population and clinical data

Twenty-one patients with TN and 9 patients with HFS were treated surgically. Ten patients who received clipping for asymptomatic non-ruptured intracranial aneurysms were included in the control group. No patient had a history of any central nervous system disease. Patients with TN and HFS, respectively, were prescribed carbamazepine and were injected with Botox. Informed consent was obtained from all patients. All procedures were conducted in accordance with the policies of the ethics committees of Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital (IRB No. 20110628–3).

We reviewed the patients' clinical and surgical records. During microvascular decompression surgery, the vessel most likely to be the source of the associated symptoms was identified in each case (hereafter referred to as the "culprit vessel"). The site of neurovascular compression was classified as proximal (medial third), midpoint (middle third), or distal (lateral third) of the cisternal portion segments for the trigeminal nerve; and at the root exit zone (RExZ), attached segment (AS), root detachment point (RDP), or cisternal portion (CP) for the facial nerve [4]. Compression severity was defined as follows: mild, contact without nerve indentation; moderate, nerve indentation without course deviation; and severe, with nerve course deviation.

CSF sampling

Approximately 2 ml of CSF samples was collected from cerebellomedullary or cerebellopontine cisterns for infratentorial lesions, and from Sylvian fissure for supratentorial lesions, and meticulous attention was paid to avoid contamination of blood or saline which was used in operative fields. CSF samples were centrifuged at 10,000 × g for 10 min at 4 °C. The supernatant was stored in aliquots and frozen (− 35 °C) until analyzed. The samples were divided into small portions, frozen, and thawed once for measurement. The frozen CSF samples were thawed at the time of measurement. The amount of S100B was compared before and after freezing, and similar values were obtained, confirming the samples' stability during storage.

Measurement of CSF S100B protein, MBP, and NSE levels

CSF S100B levels were determined with an enzyme-linked immunosorbent assay kit (BioVendor, Modrice, Czech Republic), MBP levels with an enzyme immunoassay kit (T994ZB31; Cosmic Corporation, Tokyo, Japan), and NSE concentrations with an electrochemiluminescence assay kit (ECLIA; Roche Diagnostics, Indianapolis, USA). All assays were performed in duplicate and according to the manufacturer's protocols. The lower detection limits of the assays for S100B, MBP, and NSE were 15 pg/mL, 31.3 pg/mL, and 0.05 ng/mL, respectively.

Statistical analysis

All descriptive results are expressed as mean ± standard deviation. Mann–Whitney U test was used to compare the duration of symptoms between the TN and HFS groups. Kruskal–Wallis and Steel–Dwass tests were used for multiple comparisons of the TN and HFS groups with the control group. Sex, neurovascular compression site, vascular compression severity, and culprit vessel were tested as categorical variables. To detect factors that independently affected CSF S100B level in the TN and HFS groups, univariate and multivariate analyses were performed using the linear regression model. Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Table 1 lists the characteristics of the patients in each group. The sex and age at the time of surgery were not significantly different (TN: 64 years [IQR 56–73], HFS: 57 years [IQR 41–63], and control: 59.5 years [IQR 51.3–64]) among the three groups. The duration of symptoms was 46 months (IQR 36–98) in the TN group and 48 months (IQR 21–72) in the HFS group, and no significant difference between the groups were found. The culprit vessel was identified during surgery in all patients with TN or HFS. The most common site of compression was the proximal segment, followed by the midpoint segment in the TN group; in the HFS group, the most common site of compression was the AS, followed by the RExZ. The culprit vessel was mobilized and then fixed away from the trigeminal or facial nerve. All patients were completely free of symptoms after the surgery. In the control group, all aneurysms were less than 10 mm in diameter and were located in the anterior circulation: the internal carotid artery in 5 cases, the middle cerebral artery in 4 cases, and the anterior communicating artery in 1 case.

CSF S100B protein, NSE, and MBP levels

Both the TN and HFS groups had significantly increased CSF S100B levels (1120 pg/mL [IQR 391–1420] and 776 pg/mL [IQR 583–1500], respectively) compared with

Table 1 Patient characteristics

	Control group			TN group			HFS group			*p* value
	(Non-ruptured AN)									
Number of patients	10			21			9			
Sex (male/female)	6/4			4/17			4/5			0.172
Age at surgery (years) *	59.5 (51.3–64)			64 (56–73)			57 (41–63)			0.190
Duration of symptoms (months) *	ND			46 (36–98)			48 (21–72)			0.571
Disease characteristics	AN location			Culprit vessel			Culprit vessel			
		ICA	5		SCA	16		PICA	5	
		MCA	4		petrosal vein	2		AICA	3	
		A-com. A	1		AICA	2		VA	1	
	AN size				VA	1				
		< 10 mm	10	Compression severity			Compression severity			
		> 10 mm	0		Severe	11		Severe	3	
					Moderate	7		Moderate	6	
					Mild	3		Mild	0	
				Location of neurovascular compression			Location of neurovascular compression			
					Proximal	14		RExP	5	
					Midpoint	7		AS	4	
					Distal	0		RDP	0	
								CP	0	

A-com A, anterior communicating artery; *AICA*, anterior inferior cerebellar artery; *AN*, aneurysm; *AS*, attached segment; *CP*, cisternal portion; *HFS*, hemifacial spasm; *ICA*, internal carotid artery; *MCA*, middle cerebral artery; *ND*, not determined; *PICA*, posterior inferior cerebellar artery; *RDP*, root detachment point; *RExP*, root exit point; *SCA*, superior petrosal artery; *TN*, trigeminal neuralgia; *VA*, vertebral artery; * median (interquartile range)

that in the control group (225 pg/mL [IQR 190–285]; control vs. TN, $p < 0.01$; control vs. HFS, $p < 0.01$) (Fig. 1 and Table 2). The CSF S100B level in the TN group was not significantly different from that of the HFS group (TN vs. HFS, $p = 0.908$). A trend indicated higher CSF NSE levels ($p = 0.098$, non-significant) in both the TN and HFS groups (4.6 ng/mL [IQR 3.5–12.1] and 6.2 ng/mL [IQR 4.4–11], respectively) compared with those in the control group (2.8 ng/mL [IQR 2.4–4.4]). CSF MBP levels were below the detection limit of 31.3 pg/mL in all except for 2 patients in the TN group (31.6 pg/mL and 33.4 pg/mL). CSF MBP levels did not differ significantly among the groups ($p = 0.901$).

Discussion

To the best of our knowledge, this is the first study to demonstrate significantly increased CSF S100B levels in patients with TN and in patients with HFS. We also observed that the mean CSF S100B levels did not differ significantly between the TN and HFS groups. These results may be valuable in understanding the pathophysiology of TN and HFS.

The first clinical observation suggests that excitation and/or demyelination of the trigeminal or facial nerves due to neurovascular compression may have resulted in elevation of CSF S100B levels. NVCS, which is associated with TN and HFS, is thought to result from local excitation and/

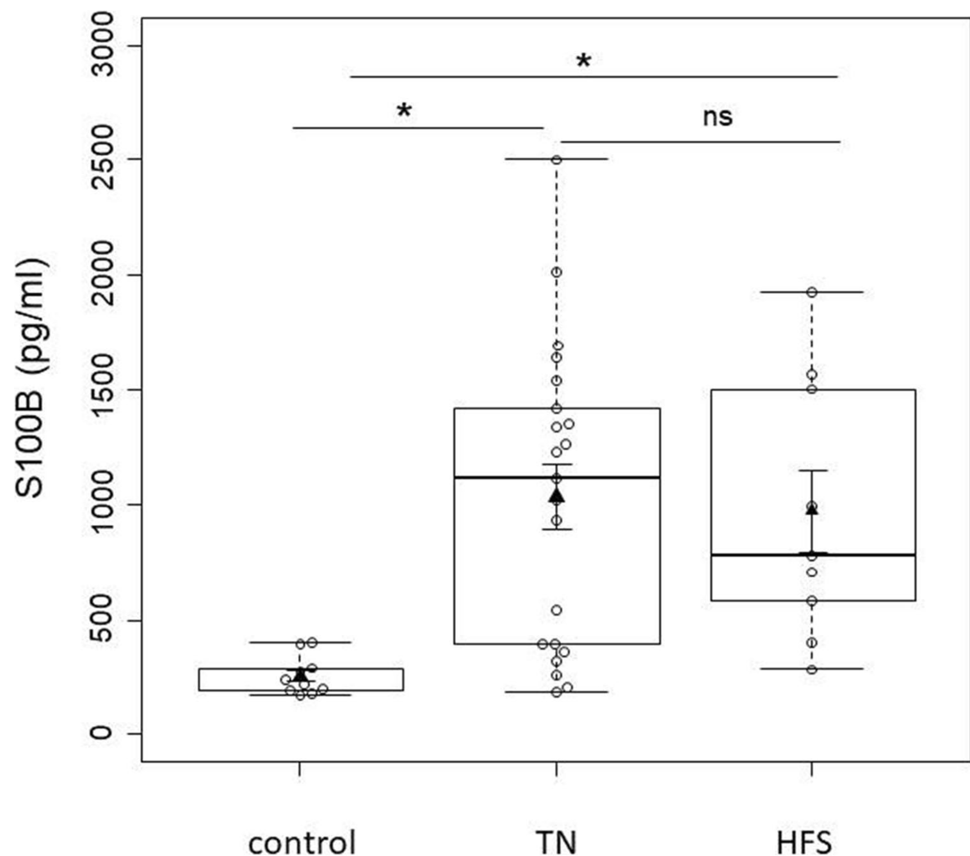

Fig. 1 Comparison of S100B concentrations in the cerebrospinal fluid of TN, HFS, and control groups. Data are expressed as means ± standard errors of the mean (▲, mean). The Mann–Whitney *U* test was used to compare pairs of results (*: $p < 0.01$, ns: not significant). TN: trigeminal neuralgia, HFS; hemifacial spasm

Table 2 Cerebrospinal fluid concentrations of S100B, NSE, and MBP

	Control group ($n = 10$)	TN group ($n = 21$)	HFS group ($n = 9$)	*p* value
S100B (pg/mL) *	225 (190–285)	1120 (391–1420) **	776 (583–1500) **	0.001
NSE (ng/mL) *	2.8 (2.4–4.4)	4.6 (3.5–12.1)	6.2 (4.4–11)	0.098
MBP (n)				
< 31.3 pg/mL	10	19	9	0.901
> 31.3 pg/mL	0	2	0	

HFS, hemifacial spasm; *MBP*, myelin basic protein; *NSE*, neuron-specific enolase; *TN*, trigeminal neuralgia
* median (interquartile range), ** $p < 0.01$ vs. control by Kruskal–Wallis and Steel–Dwass test

or demyelination of the nerve fibers due to vascular compression of the responsible cranial nerves [16, 18]. S100B belongs to a family of calcium-binding proteins implicated in intracellular and extracellular regulatory activities, which is localized mainly in the cytoplasm of astrocytes, oligodendrocytes, and Schwann cells [6, 37]. Therefore, it may be assumed that the excitation and/or demyelination of nerve fibers acts on the localized site of S100B expression, resulting in an increase in the CSF S100B levels. Based on the location of S100B expression, three possible mechanisms for elevation of CSF S100B levels may be considered: 1) secretion from astrocytes and/or oligodendrocytes, 2) secretion from Schwann cells, and 3) leakage from Schwann cells. In this study, S100B present in the central nervous system was evaluated as CSF samples were collected.

The first possible mechanism is that S100B may be secreted from astrocytes and/or oligodendrocytes as a result of hyperexcitation of the trigeminal or facial nerves due to neurovascular compression. Astrocytes and oligodendrocytes are known to secrete vesicles containing S100B into the extracellular space [31, 38, 8]. It has been also reported that astrocytes secrete S100B in a neural activity-dependent manner that is critically dependent on the presynaptic release of neurotransmitters and activation of metabotropic glutamate receptor 3 [29]. In temporal lobe epilepsy, for instance, the selective upregulation of S100B expression in astrocytes as well as increased tissue levels of S100B is also noted in surgically resected temporal lobe neocortex, suggesting the involvement of S100B in the pathophysiology of epilepsy [10]. Notably, in TN and HFS, the hyperexcitation of the trigeminal or facial nerves by neurovascular compression results in electrical action potentials, which are conducted not only to the peripheral side but also to the central side. As a result, astrocytes and/or oligodendrocytes in the brain parenchyma may secrete S100B into the cerebrospinal fluid space in a neural activity-dependent manner in response to the nerve hyperexcitation.

The second possible mechanism underlying the observed increase in CSF S100B levels is the active secretion of S100B from Schwann cells at the site of neurovascular compression. Schwann cells have secretory vesicles in which S100B is stored [27, 13]. S100B is known to act as a ligand for receptor for advanced glycation end products (RAGE), which is expressed mainly in neurons, immune cells, activated endothelial cells and vascular smooth muscle cells, bone-forming cells, and various cancer cells [10, 27]. Activation of RAGE by S100B leads to neural outgrowth [15], neuroprotection [14], and neuromodulation [8]. Notably, RAGE has been found to play an important role in peripheral nerve regeneration after acute injury to sciatic nerve cells [26, 28]. Similarly, in NVCS, the nerves are physically stressed, as evidenced by pathology. For example, affected nerve samples in patients with TN showed evidence of morphological and histological changes such as axonal loss, axonal injury, demyelination, and collagen deposition [35]. Thus, it is presumed that chronic physical stress on the cranial nerves may promote the secretion of S100B from Schwann cells to aid nerve regeneration.

However, it is unlikely that S100B is secreted by Schwann cells at the site of neurovascular compression caused by physical stress. This is because the increase in CSF S100B did not differ between the TN and HFS groups in the present study. Notably, the trigeminal and facial nerves differ in thickness; therefore, we speculate that if S100B is secreted from Schwann cells, there would also be a difference in the amount of secreted S100B observed in the TN and HFS groups.

Most patients with HFS reportedly have vascular compression in the root entry/exit zone (REZ) [32, 33] and the myelin sheath of the REZ is composed of oligodendrocytes, instead of Schwann cells [11]. S100B is unlikely to be actively secreted from Schwann cells at the site of neurovascular compression.

The third possible mechanism for increased CSF S100B levels is leakage of S100B into the CSF from damaged Schwann cells at the site of neurovascular compression. In patients with disc herniation and sciatica, the CSF levels of both S100B and neurofilament protein are elevated [3]. A similar mechanism has been found in ischemic or traumatic brain injury [23]. After an acute ischemic stroke, for example, plasma levels of S100B protein are known to increase transiently and correlate well with infarct volume and clinical outcome; this phenomenon is thought to be caused by leakage of S100B from damaged astrocytes [24].

The CSF levels of NSE, a highly specific marker of axonal injury [5], neuronal loss, and degeneration [12], showed no statistically significant increase in the NVCS groups. There was no significant molecular leakage of MBP, a non-secretory protein, from the Schwann cells, because its CSF levels were less than the lower detection limit of the assay in most of the present cases. For a more detailed analysis, it is necessary to create and evaluate a system for MBP quantification with higher sensitivity using techniques like gas chromatography-mass spectrometry, and liquid chromatography-mass spectrometry, which are used in CSF metabolomics [25]. These suggest that this mechanism of passive leakage of S100B from damaged Schwann cells is unlikely.

In summary, S100B may be secreted from astrocytes and oligodendrocytes as a result of hyperexcitation of the trigeminal and facial nerves due to neurovascular compression.

The second clinical observation was that CSF S100B levels did not differ significantly between the TN and HFS groups despite the difference in clinical symptoms. Although carbamazepine is prescribed to patients with TN, S100B levels in the serum reportedly decrease when carbamazepine is administered to patients with focal seizures [22]. In the

present study, the amount of S100B in the CSF was significantly elevated in patients with TN; therefore, the increase in S100B was probably unrelated to the prescription.

One possible reason for this is that the increase in S100B may play a neuroprotective role. The action of S100B is concentration-dependent [7, 9], with nanomolar concentrations exhibiting neuroprotective and astrocyte-proliferating effects [17, 30], whereas micromolar concentrations are neurotoxic in cell culture assays [23, 36]. In the present study, the mean CSF S100B levels (approximately 1000 pg/mL) in the TN and HFS groups were as low as nanomolar concentration (molecular weight of S100B: 10.7–21 kDa), which suggests the neuroprotective role of S100B in these disorders. In other words, we can presume that S100B performs a neuroprotective role against the hyperexcitation and/or demyelination of the trigeminal and facial nerves caused by neurovascular compression. Thus, given that the concentration of increased CSF S100B was low and independent of clinical factors, the increase in S100B in TN and HFS may serve a neuroprotective function, leading to no difference in its concentration between the TN and HFS groups.

The present study is a cross-sectional analysis focusing on the expression of several nerve tissue-related markers in a small number of patients. Therefore, the general findings are limited. However, further studies that evaluate the signaling events of S100B may contribute to the elucidation of the underlying pathophysiology of NVCS. The functional diversity of extracellular S100 proteins has been demonstrated in previous reports. For instance, S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE immunoglobulin domains [20]. To gain a better understanding of the pathophysiology of NVCS, including signaling events, changes in not only S100B but also in other S100 proteins in the CSF need to be elucidated.

Alterations in gene expression of the S100B have been associated with several pathologies, including Down syndrome, Alzheimer's disease, chronic inflammation, and epilepsy [2]. Therefore, for the specific diagnosis and prognosis of TN and HFS, a search for more specific biomarkers is required, considering the increased expression of S100B. The pain level of TN patients depends on the degree of NVC [34]. In the future, when more promising candidate biomarkers are identified, their relationship with age at surgery, sex, symptom duration, degree of compression, and location of neurovascular compression should be investigated.

Conclusions

S100B concentrations in CSF were significantly higher in patients with trigeminal neuralgia and hemifacial spasm compared with those of controls, suggesting S100B involvement in the underlying pathophysiology of neurovascular compression syndrome.

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Author contribution Study design: Eiji Ito, Yukio Seki; data collection: Eiji Ito, Yukio Seki, Kiyoshi Saito; statistical analyses: Eiji Ito, Yukio Seki; manuscript writing and editing: Eiji Ito, Yukio Seki, Ryuta Saito.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval All procedures were conducted in accordance with the policies of the ethics committees of Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital (IRB No. 20110628–3).

Conflict of interest The authors declare no competing interests.

References

1. An JX et al (2011) A new animal model of trigeminal neuralgia produced by administration of cobra venom to the infraorbital nerve in the rat. Anesth Analg 113:652–656
2. Arrais AC et al (2022) S100B protein: general characteristics and pathophysiological implications in the Central Nervous System. Int J Neurosci 132:313–321
3. Brisby H, Olmarker K, Rosengren L, Cederlund CG, Rydevik B (1999) Markers of nerve tissue injury in the cerebrospinal fluid in patients with lumbar disc herniation and sciatica. Spine (Phila. Pa) 24:742–746
4. Campos-Benitez M, Kaufmann AM (2008) Neurovascular compression findings in hemifacial spasm. J Neurosurg 109:416–420
5. Chabok SY et al (2012) Neuron-specific enolase and S100BB as outcome predictors in severe diffuse axonal injury. J Trauma Acute Care Surg 72:1654–1657
6. Donato R (2003) Intracellular and extracellular roles of S100 proteins. Microsc Res Tech 60:540–551
7. Donato R et al (2012) Functions of S100 Proteins. Curr Mol Med 13:24–57
8. Gerlach R et al (2006) Active secretion of S100B from astrocytes during metabolic stress. Neuroscience 141:1697–1701
9. Gonzalez LL, Garrie K, Turner MD (2020) Role of S100 proteins in health and disease. Biochim Biophys Acta Mol. Cell Res 1867:32057918
10. Griffin WST et al (1995) Overexpression of the neurotrophic cytokine S100β in human temporal lobe epilepsy. J Neurochem 65:228–233
11. Guclu B et al (2011) Cranial nerve vascular compression syndromes of the trigeminal, facial and vago-glossopharyngeal nerves: Comparative anatomical study of the central myelin portion and transitional zone; Correlations with incidences of corresponding hyperactive dysfunctio. Acta Neurochir (Wien) 153:2365–2375

12. Haque A, Polcyn R, Matzelle D, Banik NL (2018) New insights into the role of neuron-specific enolase in neuro-inflammation, neurodegeneration, and neuroprotection. Brain Sci 8:1–2
13. Hofmann MA et al (1999) RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 97:889–901
14. Huttunen HJ et al (2000) Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through receptor for advanced glycation end products (RAGE) activation. J Biol Chem 275:40096–40105
15. Huttunen HJ, Fages C, Rauvala H (1999) Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-κB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem 274:19919–19924
16. Jannetta PJ (1967) Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 26:159–162
17. Kligman D, Marshak DR (1985) Purification and characterization of a neurite extension factor from bovine brain. Proc Natl Acad Sci USA 82:7136–7139
18. Kuroki A, Møller AR (1994) Facial nerve demyelination and vascular compression are both needed to induce facial hyperactivity: a study in rats. Acta Neurochir (Wien) 126:149–157
19. Langeh U, Singh S (2020) Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders. Curr Neuropharmacol 19:265–277
20. Leclerc E, Fritz G, Weibel M, Heizmann CW, Galichet A (2007) S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE (receptor for advanced glycation end products) immunoglobulin domains. J Biol Chem 282:31317–31331
21. Leung Brain K et al (2012) Basic Science An Animal Model for Trigeminal Neuralgia by Compression of the Trigeminal Nerve Root. Pain Physician 15:187–196
22. Maiti R et al (2018) Effect of anti-seizure drugs on serum S100B in patients with focal seizure: a randomized controlled trial. J Neurol 265:2594–2601
23. Michetti F et al (2019) The S100B story: from biomarker to active factor in neural injury. J Neurochem 148:168–187
24. Missler U, Wiesmann M, Friedrich C, Kaps M (1997) S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 28:1956–1960
25. Noga MJ et al (2012) Metabolomics of cerebrospinal fluid reveals changes in the central nervous system metabolism in a rat model of multiple sclerosis. Metabolomics 8:253–263
26. Perrone L, Peluso G, Melone MAB (2008) RAGE recycles at the plasma membrane in S100B secretory vesicles and promotes Schwann cells morphological changes. J Cell Physiol 217:60–71
27. Riehl A, Németh J, Angel P, Hess J (2009) The receptor RAGE: bridging inflammation and cancer. Cell Commun Signal 7:8–9
28. Rong LL et al (2004) Antagonism of RAGE suppresses peripheral nerve regeneration. FASEB J 18:1812–1817
29. Sakatani S et al (2008) Neural-activity-dependent release of S100B from astrocytes enhances kainate-induced gmma oscillations in vivo. J Neurosci 28:10928–10936
30. Selinfreund RH, Barger SW, Pledger WJ, Van Eldik LJ (1991) Neurotrophic protein S100β stimulates glial cell proliferation. Proc Natl Acad Sci U S A 88:3554–3558
31. Shashoua VE, Hesse GW, Moore BW (1984) Proteins of the brain extracellular fluid: evidence for release of S-100 protein. J Neurochem 42:1536–1541
32. Sindou MP (2005) Microvascular decompression for primary hemifacial spasm. Importance of intraoperative neurophysiological monitoring. Acta Neurochir (Wien) 147:1019–1026
33. Sindou M, Keravel Y (2009) Traitement neurochirurgical du spasme hémifacial primaire par décompression vasculaire microchirurgicale. Neurochirurgie 55:236–247
34. Sindou M, Leston J, Decullier E, Chapuis F (2007) Microvascular decompression for primary trigeminal neuralgia: Long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. J Neurosurg 107:1144–1153
35. Sindou M, Howeidycevedo T, GAcevedo G (2022) Anatomical observations during microvascular decompression for idiopathic trigeminal neuralgia (with correlations between topography of pain and site of the neurovascular conflict). Prospect Stud Ser Patients 579 144:1–2
36. Sorci G, Riuzzi F, Agneletti AL, Marchetti C, Donato R (2004) S100B Causes apoptosis in a myoblast cell line in a RAGE-independent manner. J Cell Physiol 199:274–283
37. Steiner J et al (2008) S100B is expressed in, and released from, OLN-93 oligodendrocytes: Influence of serum and glucose deprivation. Neuroscience 154:496–503
38. Van Eldik LJ, Zimmer DB (1987) Secretion of S-100 from rat C6 glioma cells. Brain Res 436:367–370
39. Wang L et al (2020) Trigeminal neuralgia causes neurodegeneration in rats associated with upregulation of the CD95/CD95L pathway. Mol Pain 16:1–14

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