1261 INCREASED CONCENTRATIONS OF S100B AND NEUROFILAMENT LIGHT CHAIN IN SERUM INDICATE CHECKPOINT INHIBITOR-INDUCED CNS INFLAMMATION

[1]Sara Bjursten*, [1]Ankur Pandita, [1]Zhiyuan Zhao, [2]Joel Simrén, [2]Henrik Zetterberg, [3]Anna Rudin, [1]Lars Ny, [1]Max Levin. [1]*Sahlgrenska University Hospital, Gothenburg, Sweden*; [2]*Institute of Neuroscience and Physiology, Gothenburg, Sweden*; [3]*Institute of Medicine, Sahlgrenska, Gothenburg, Sweden*

Background Checkpoint inhibitor (CPI)-induced CNS inflammation is a severe neurological adverse event.[1, 2] CPI-induced CNS inflammation can be difficult to diagnose because symptoms indicate more common conditions such as tumor progression or infection.[3-5] There is a clinical need for blood tests to facilitate diagnosis of CPI-induced CNS inflammation.

Our objective was to evaluate if increased concentrations of brain damage markers S-calcium-binding protein B (S100B) and neurofilament light chain (NfL) in serum indicate CPI-induced CNS inflammation.

Methods Medical records and laboratory data were examined in patients with metastatic melanoma or metastatic renal cell carcinoma. The patients were treated with double checkpoint inhibition (nivolumab and ipilimumab) between March 2018 and April 2022 (n=197) at Sahlgrenska University Hospital, Sweden. In patients with suspected CNS-inflammation, brain MRI and analysis of cerebrospinal fluid were performed and brain damage markers S100B and NfL in serum were analyzed repeatedly. S-100B has a dual function as it is secreted by some melanoma metastases as well as damaged astrocytes.[6, 7] S-100B concentrations in patients with melanoma metastases that do not secrete S-100B (n=29) and renal cell carcinoma patients (n=10) were used as double checkpoint inhibitor treated controls. As controls for NfL, we analyzed frozen plasma from melanoma patients treated with double checkpoint inhibition (ipilimumab + nivolumab) or monotherapy nivolumab (n=49).

Results Nine out of 197 patients had a verified CPI-induced CNS inflammation (4.6%) within 200 days from the first double checkpoint inhibitor treatment (table 1). S100B and NfL in serum increased during CNS inflammation (figure 1A-D and F) and normalized when patients were treated with immunosuppression (figure 1A-C, E and G). S100B concentration in serum increased early in patients with CPI-induced CNS inflammation (figure 1A-C), whereas NfL increased later (figure 1A-C). The sensitivity of an increased S100B and NfL to detect a CPI-induced CNS inflammation was 100% for S100B and 79% for NfL and the specificity was 89% for S100B and 74% for NfL (figure 2).

Conclusions The combined analysis of S100B and NfL in serum is a tool for early detection and monitoring of CPI-induced CNS inflammation. Early diagnosis of CPI-induced CNS inflammation may save lives, prevent long-term hospitalization, and reduce neurological complications.

REFERENCES

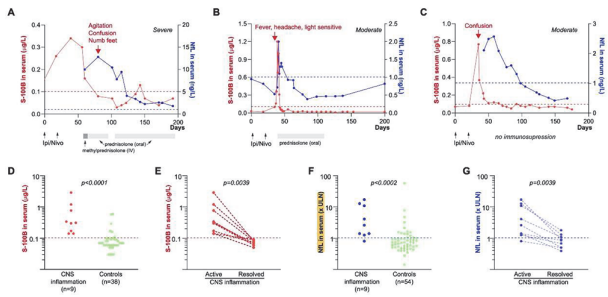
1. D Dubey *et al.* Severe Neurological Toxicity of Immune Checkpoint Inhibitors: Growing Spectrum. *Ann Neurol.* 2020;**87**(5):659–669. doi: 10.1002/ana.25708.
2. S Bjursten *et al.* Early rise in brain damage markers and high ICOS expression in CD4+ and CD8+ T cells during checkpoint inhibitor-induced encephalomyelitis. *J Immunother Cancer.* 2021;**9**(7). doi: 10.1136/jitc-2021-002732.
3. JR Brahmer *et al*. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2018;36(17):1714–1768. doi: 10.1200/JCO.2017.77.6385.
4. J Haanen *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;**29** (Suppl 4):iv264–iv266. doi: 10.1093/annonc/mdy162.
5. I Puzanov *et al.* Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer.* 2017;**5**(1)95. doi: 10.1186/s40425-017-0300-z.
6. HD Abraha, LC Fuller, AWPDU Vivier, EM Higgins, and RA Sherwood. Serum S100 protein: a potentially useful prognostic marker in cutaneous melanoma. *British Journal of Dermatology*. 1997;**137**:381-385.
7. R Gerlach *et al.* Active secretion of S100B from astrocytes during metabolic stress. *Neuroscience*. 2006;**141**(4):1697–701. doi: 10.1016/j.neuroscience.2006.05.008.

Ethics Approval The study was approved by the Regional Ethics Board (151-16, 477-18, 2021-04093)

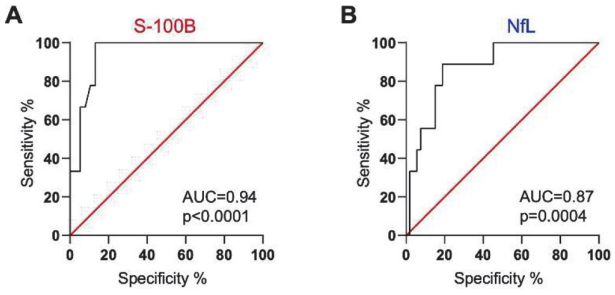
Abstract 1261 Table 1 Checkpoint inhibitor-induced CNS inflammation

	Case #1*	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7	Case #8	Case #9	Case #10
Severity	Severe	Severe	Severe	Severe	Severe	Moderate	Moderate	Moderate	Moderate	Moderate
Days in hospital	71	83	5	9	7+5	4	12	14	5	12
Symptoms and signs	Peak Loss of consciousness Central respiratory depression requiring mechanical ventilation Total paresis in lower body and sphincter Recovery Walks with support	Peak Headache Disorientation Leg parapareisis Loss of reflexes in lower extremities Recovery Walks short distances Lightly disrupted balance	Peak Disorientation, agitation Sense of cold/discomfort in both feet Lightly disturbed balance Recovery Lightly disturbed balance	Peak Severely reduced leg strength Loss of sensation in legs Moderately disturbed balance Recovery Lightly disturbed balance	Peak Headache Fever Photosensitivity Spasm right leg Recovery Spasm right leg	Peak Disorientation Disturbed balance Memory loss Recovery Fatigue Tactlessness	Peak Headache Fever Photosensitivity Stiff neck Myalgia Recovery Mild headache	Peak Fever Fatigue Confusion Recovery Full recovery	Peak Disorientation Confusion Unsteady gait Recovery Full recovery	Peak Headache Fever Fatigue Impaired motor function right leg Nausea Tunnel vision Recovery Full recovery
Brain MRI/CT	Peak diffuse lesions brain + spinal cord Recovery Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal	Peak Normal
CSF	Brain damage markers GFAp: 74 x ULN NFL: 94 x ULN Tau: 3.5 x ULN Inflammation CXCL13: not analysed Protein: 6.9 x ULN Lymphocytes: Slightly elevated Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp: 28 x ULN NFL: 4 x ULN Tau: 3.5 x ULN Inflammation CXCL13: 215 x ULN Protein:3.4 x ULN Lymphocytes: Slightly elevated Infection Virus: Negative Bacteria: Negative	Not analyzed (declined by patient)	Brain damage markers GFAp: 1.1 x ULN NFL: 2.9 x ULN Tau: 1.1 xULN Inflammation CXCL13: 9.2 x ULN Protein: 1.1 x ULN Lymphocytes: Normal Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp: 1.3x ULN NFL:17.8 x ULN Tau: 1.7xULN Inflammation CXCL13: 6.8 x ULN Protein: 1.1x ULN Lymphocytes: 4xULN Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp: 1.2 x ULN NFL: 5.6 x ULN Tau: 1.1 xULN Inflammation CXCL13: 38 x ULN Protein: 5.8 x ULN Lymphocytes: 6.25xULN Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp: Normal NFL: Normal Tau: Normal Inflammation CXCL13: Normal Protein: Normal Lymphocytes:3.5 xULN CXCL10:5.8xULN Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp:Normal NfL: Normal Tau:1.5 x ULN Inflammation CXCL13: 10,8 x ULN Protein: 1.4 x ULN Lymphocytes: Not analyzed Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp:Normal NfL: Normal Tau:Normal Inflammation CXCL13: 1,7 x ULN Protein: Normal Lymphocytes:2.3 x ULN Infection Virus: Negative Bacteria: Negative	Brain damage markers GFAp:Normal NfL: 6xULN Tau: Normal Inflammation CXCL13: 3,2x ULN Protein: 1,3XULN Lymphocytes:5.3 x ULN Infection Virus: Negative Bacteria: Negative
Serum	Brain damage markers S-100B peak: 3,1 x ULN Recovery: normal NFL:17,2 x ULN Recovery: normal GFAp: 58 x ULN Recovery normal	Brain damage markers S-100B peak: 3,0 x ULN S-100B recovery: normal NFL peak: 4,1 x ULN Recovery: normal	Brain damage markers S-100B peak: 3,4 x ULN Recovery: normal NFL peak:12,8 x ULN Recovery: Normal	Brain damage markers S-100B peak: 2,1 x ULN S-100B recovery: normal NFL: not analyzed	Brain damage markers S-100B peak: 59 x ULN Recovery: Normal NFL: 10.9 x ULN	Brain damage markers S-100B peak: 7,7 x ULN Recovery: Normal NFL: 2,6xULN	Brain damage markers S-100B peak:12 x ULN Recovery: Normal NFL:1,4xULN	Brain Damage markers S-100 peak: 1,4 x ULN Recovery: Normal NFL peak: Not analyzed	Brain Damage markers S-100 peak: 1,7 x ULN Recovery:Normal NFL peak: normal	Brain Damage markers S-100 peak: 2,5 x ULN Recovery: Normal NFL peak: normal

*Patient described in detail in reference 5; PMID: 34215689.
MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; ULN, upper limit of normal; GFAp, glial fibrillary acidic protein; NFL, neurofilament light; Tau, Tau protein; CXCL13, Chemokine (C-X-C motif) ligand 13; S100B, S100 calcium-binding protein B



Abstract 1261 Figure 1 Neurological Symptoms and Serum Concentrations of Brain Damage Marker S100B and NfL in Patients with or without CPI-induced CNS inflammation



Abstract 1261 Figure 2 Receiver-Operating Characteristic (ROC) Curves

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1261