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Biomarker Value of Neurofilaments and Glial Fibrillary Acidic Protein in Central Nervous System Lymphoma and Tumors

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Brain malignancies are among the most important causes of morbidity and mortality among central nervous system (CNS) disorders. These malignancies can be mainly divided into two groups as those formed within the CNS and invasion of metastatic cells from other parts of the body to the CNS (1). Those originating from the CNS are known as gliomas. Gliomas are the most common primary brain tumors (2). Astrocytomas constitute 60–70% of gliomas, and glioblastoma multiforme (GBM) is the most common, aggressive, and malignant form of astrocytoma in adults (1,2). A patient with GBM diagnosis can live an average of 12 months (1). Traditionally, the diagnosis of gliomas is accomplished by imaging methods and histopathological analysis which may often result in misdiagnosis (3). As in many types of cancer, radiotherapy and chemotherapy treatments damage healthy tissue in glioma treatment, and the tumor tissue cannot be directly targeted in current clinical applications (3). Similarly, in the case of brain metastases, failure to routinely perform imaging methods before the appearance of clinical symptoms causes delays in diagnosis (1). Considering the rapid spread of gliomas and increasing incidence of brain metastasis (1), identification of new biomarkers is needed for an early diagnosis, follow-up of the disease course, and targeted treatment options. In this respect, cerebrospinal fluid (CSF) and blood-based biomarkers are of utmost importance for being less invasive and practical. Two of these biomarkers have come to the fore most recently: neurofilaments and glial fibrillary acidic protein (GFAP).

Neurofilaments are intracellular neuronal cytoskeleton proteins. The extracellular expression of these proteins increase following an axonal damage (4). In recent years, neurofilaments have been identified as prominent biomarkers for many CNS diseases such as Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) (4,5). Especially the neurofilament heavy chain (NfH)/phosphorylated NfH (pNfH) ratio has gained importance in the prognosis of neurodegeneration (6). These proteins are also highly sensitive for neuronal damage which might be caused by metastatic cell infiltration into the CNS, the compression resulted from the brain tumors, or the glial scar tissue formations after tumor resections (7). According to a few recent studies examining lung cancer patients with and without brain metastases, serum neurofilament light chain (NfL) levels were significantly increased in patients with metastases, and high NfL levels were associated with a lower chance of survival (8,9). Moreover, the measurability of NfL in serum before the appearance of symptoms related to metastasis reflects the importance of NfL in early diagnosis (8). Another study found that CSF pNfH levels were significantly increased in patients with spinal cord injury, meaning that pNfH may be an important biomarker in the follow-up of glial scar tissue and neurodegenerative process that may occur after CNS tumor resection (7). Thus, neurofilaments have substantial qualifications as a biomarker for brain metastases and tumors.

GFAP is a cytoskeletal protein belonging to the intermediate filament (IF) family. As one of the most basic cell markers, GFAP is mainly involved in cell signaling, blood-brain barrier functioning, and CNS repair mechanisms (3,10). GFAP, which is also an important marker for traumatic brain injury, dementia, and MS, is additionally considered as a new biomarker candidate for glioma malignancy (10). Although it was reported in 1986 that CSF GFAP levels increased in the presence of glioblastoma and after tumor resection (11), the biomarker value of GFAP was ignored for many years. Recent mass spectrometry-based protein analyzes highlight GFAP as a potential biomarker for glioblastoma (3). In a meta-analysis of 2022, it was reported that cell death/proliferation ratio and blood-

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brain barrier permeability increase as the level of GFAP released from high-grade CNS tumors elevate (10). It has also been mentioned that the presence of serum GFAP (sGFAP) is a grade-IV glioma indicator and the sGFAP level is correlated with tumor volume (10). Furthermore, as for NfL, increased GFAP levels have been reported to be associated with glial scar formation (7), risk of brain metastasis, lesion damage, and poor survival (9) indicating its biomarker value in CNS tumors and metastasis.

Little is known about the diagnostic and prognostic biomarkers of CNS lymphoma. Most of the proposed biomarkers are immunological factors related with acquired and innate immunity including IL-10, CCL2, IL-6 and IL-2 receptor (12,13). Nevertheless, proteomic studies suggest that cytoskeletal proteins including GFAP and neurofilaments may also be used as biomarkers in lymphoma (3). Our personal unpublished observations also indicate that CSF levels of NfL and GFAP are closely correlated with the clinical severity of CNS lymphoma.

In summary, neurofilaments and GFAP appear to be highly critical biomarkers for brain malignancies. In the future, routine evaluation of these markers in blood and CSF with high-sensitivity methods will facilitate early diagnosis, progression monitoring and the treatment response.

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