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Aquaporin-4 Gene Polymorphisms in Relapsing Inflammatory Optic Neuropathy and RANKL in Glioblastoma: Research and Progress on Biomarkers

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Neurology is one of the disciplines where prognostic and diagnostic biomarkers have recently become an important part of clinical practice. In the last decade or so, there has been a tremendous rise in discovery and innovation of novel prognostic and predictive blood and cerebrospinal fluid biomarkers in neurology. This progress is even more pronounced in the fields of neuro-immunology (particularly autoimmune demyelinating diseases such as multiple sclerosis) and primary brain tumors including glioblastoma and oligodendroglioma. As editors and neuroscience researchers, we have recognized a similar trend in article submissions, which has reflected itself in increasing number of biomarker articles in the recent, present and imminently forthcoming issues of our journal.

Although genetic features of multiple sclerosis (MS) have been meticulously scrutinized, polymorphisms associated with other demyelinating disorders have only recently been brought under spotlight. Recurrent optic neuritis (RON) is one of these disorders, which has been scarcely investigated at molecular level. RON is an intriguing disease, which may be encountered in a diverse set of demyelinating disorders such as multiple sclerosis and neuromyelitis optica spectrum disorders (NMOSD). Alternatively, RON may also manifest as an isolated entity, which may also be referred to as relapsing inflammatory optic neuropathy (RION), without fulfilling the diagnostic criteria of any well-characterized neurological disease. RON manifesting alone or in combination with other demyelinating disorders may or may not exhibit aquaporin-4 (Aqp-4) antibodies (1). Aqp-4 is involved in astrocyte functions, water homeostasis in the brain and inflammation (2). Congruently, Aqp-4 gene single nucleotide polymorphisms (SNPs) have been identified in autoimmune disorders including NMOSD and systemic lupus erythematosus (3). In a recent study, a novel intronic Aqp-4 gene SNP (rs26856556) was identified in 40% of RION patients (with normal neuroimaging and no well-known serum autoantibodies) as opposed to around 6% of typical NMOSD patients and healthy controls (4). Whether this finding is an omen of a distinct form of neuroinflammation or Aqp-4 gene variants can potentially be used as diagnostic tools need to be further studied.

A contemporary article in our journal has put forward and compared features of isolated RION, MS with RON and NMOSD. In this article, RION patients were reported to exhibit a lower number of relapses, higher duration between relapses, lower prevalence of accompanying autoimmune disorders and non-inflammatory cerebrospinal fluid findings (5). These findings suggest that isolated RION is a different entity than MS and NMOSD manifesting with presumably distinct features of inflammation/autoimmunity.

Soluble receptor activator of nuclear factor-κB ligand (sRANKL) is another promising biomarker for neurological diseases that stands out with its critical role in microglial inflammation by stripping away from its known primary function as bone remodeling. sRANKL has a double effect by increasing the immune response by activation of pro-inflammatory pathways or on the contrary, activating anti-inflammatory pathways by stimulating regulatory T (Treg) cells or by its effect on microglia (6). An article published in our journal states that increased serum levels of soluble RANKL in patients with glioblastoma multiforme (GBM) indicate a decreased total life span and poor prognosis of the disease and may have both prognostic and therapeutic value (7). Consistent with this, another study demonstrated that gliomas with increased RANKL expression have a more invasive phenotype (8). Apart from its contribution to tumorigenesis, RANKL is recommended as a biomarker for brain ischemia and MS (6). Studies in MS subtypes have shown elevated

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serum levels of sRANKL in all subgroups (9). Besides, RANKL inhibition has been reported to reduce the increased activity of Th17 cell group via sRANKL secreted from T lymphocytes (10). By contrast, studies of ischemic brain injury have revealed that increased RANKL activation has a neuroprotective effect on neural damage (11).

The role of biomarkers and personalized medicine is becoming increasingly important not only in neuro-oncology and neuro-immunology but also in cerebrovascular diseases and neurodegenerative disorders. Novel biomarkers will certainly be most useful in precise diagnostics, determination of prognosis, prediction of treatment response and improved treatment decisions.

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