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Biomarkers of Encephalitis

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1. Introduction

The development of encephalitis presents a dilemma to the clinician as during the early stages, when treatment would be most effective, the symptoms can be nonspecific with a broad differential. Imaging tests (e.g. magnetic resonance imaging and computed axial tomography scan), blood and urine tests as well as lumbar puncture are used to isolate and identify viruses, and together with careful and continuous neurological assessment provide data that may be suggestive of viral encephalitis. In the case of post-infectious or autoimmune encephalitis, a more intense investigation is needed to generate an accurate diagnosis. In addition to imaging tests and electroencephalography, blood and cerebrospinal fluid (CSF) need to be analyzed for evidence of inflammation and the presence of antibodies against cellular antigens. In recent years clinicians and investigators have pursued biomarkers that can aid in the diagnosis as well as prognosis and monitoring of patients with encephalitis. These biomarkers are increasingly important in the recognition and treatment of inflammatory and autoimmune central nervous system (CNS) disorders. This chapter will review the current literature of emerging biomarkers in the different types of encephalitis.

2. Infectious encephalitis

2.1 HIV encephalitis

HIV encephalitis (HIVE) is characterized by the presence of microglial nodules, multinucleated giant cells, glial activation and neuronal loss (Budka 1991). About 25% of immunosuppressed patients infected with HIV develop neurological deficits ranging from cognitive impairments, motor abnormalities, behavioral symptoms to HIV-associated dementia (HAD) (Dore et al 1999; Nath & Sacktor 2006). In HIVE macrophages/microglia are productively infected with HIV and are hypothesized to play a pivotal role in the neurodegenerative process leading to HAD (Ellis et al 2007; Navia et al 1986). The need to diagnose the pathogenic process of HIVE and HAD led to the pursuit for plasma and CSF biomarkers that might provide insight into pathogenesis and also facilitate the diagnosis and disease staging in addition to clinical signs and symptoms.

Historically, HIV-1 RNA load was measured in the brain and CSF of HIV-infected patients to verify whether it could be a marker of HIV-induced neuropathology (Achim et al 1994; Cinque et al 1998). Cinque et al. examined HIV-infected patients with neurological symptoms for the presence of HIV-1 p24 antigen by immunohistochemistry as well as CSF HIV-1 RNA by quantitative polymerase chain reaction (PCR). Their results showed that CSF

HIV-1 RNA copy numbers were significantly higher in patients with HIV encephalitis than in patients without encephalitis. From this study they concluded that CSF HIV-1 RNA levels were associated with HIVE and the associated neuropathology (Cinque et al 1998). Although there were studies that did not show significant difference in CSF levels of HIV-1 RNA between patients with or without HIVE (Bossi et al 1998) many studies in non-human primates infected with simian immunodeficiency virus (SIV) confirmed a correlation between SIV viral load and encephalitis (Bissel et al 2008; Bonneh-Barkay et al 2008; Zink et al 1999; Zink et al 2005).

Because macrophages are the predominant immune cell and the predominant infected cell in the brains of patients with HIVE, it was assumed that immune activation-associated factors in the CSF could serve as a surrogate biomarker for the disease. One of those factors is neopterin, an intermediate of pteridine metabolism, that is produced by activated macrophages in response to cytokines (Anderson et al 2002; Williams & Hickey 2002) that was also found to predict systemic disease progression (Fuchs et al 1989b). Several studies showed that neopterin was elevated in the CSF of HIV-infected patients, particularly patients with HAD (Brew et al 1990; Fuchs et al 1989a; Sonnerborg et al 1989). However Wiley et al. did not find a strong correlation between CSF neopterin and severity of encephalitis in autopsied patients with HIVE (Wiley et al 1992). A recent study by Hagberg et al. showed that in untreated HIV-infected patients CSF neopterin concentrations were almost always elevated and increased progressively as immunosuppression worsens and blood CD4 cell counts fell. Patients with HAD exhibit particularly high CSF neopterin concentrations, above those of patients without neurological disease suggesting that this might be a useful CNS disease marker (Hagberg et al 2010).

Additional factors that suggest immune activation are of course cytokines and chemokines. Previous studies showed that some HIV patients exhibited elevated CSF levels of interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) but no tumor necrosis factor- α (TNF α) or interleukin-2 (IL-2) were detected (Gallo et al 1989). In contrast other studies reported high levels of CSF TNF α in HIV-1 sero-positive patients who had neurologic involvement (Sharief et al 1992). The profile of cytokines may differ according to the level of macrophage/microglia infection or activation or the presence of opportunistic infections. Previous studies have also tried to establish correlations between CSF chemokines and CSF HIV viral load. Increased CSF levels of chemokines like CCL2 (also known as MCP-1), were reported in patients with HIVE and HAD (Kelder et al 1998). Moreover, recent reports showed a possible association between CSF CCL2 levels and the development of HAD, suggesting that this chemokine could be used as a biomarker of disease progression (Cinque et al 2005; Sevigny et al 2004; Sevigny et al 2007). Furthermore Almeida et al. obtained similar results and also suggested that CCL2 expression was associated with leukocyte transmigration into the CNS (Monteiro de Almeida et al 2006; Monteiro de Almeida et al 2005). In addition, CXCL10 was found to be positively correlated with CSF HIV viral load (Christo et al 2009; Gisolf et al 2000) and CSF pleocytosis (Cinque et al 2005; Kolb et al 1999) suggesting that this chemokine may contribute to HAD pathogenesis (Christo et al 2005).

Activation of the plasminogen system has been reported in different neurological disorders such as stroke and other forms of acute brain injury (Bonneh-Barkay & Wiley 2008). Expression of the urokinase plasminogen activator (uPA) and its receptor (uPAR) was also found in HIV-1-associated CNS disease (Sidenius et al 2004). CSF soluble uPAR levels were significantly higher in HIV-infected patients than in HIV-negative controls. Moreover CSF

soluble uPAR levels correlated with CSF HIV-1 RNA, but not with plasma soluble uPAR concentrations. In addition, highly active antiretroviral therapy (HAART) was associated with a significant decrease of CSF soluble uPAR in parallel to reduction in viral load (Cinque et al 2004).

A recently identified biomarker for HIVE is YKL-40 (chitinase 3-like protein 1, HC-gp39). YKL-40 is up-regulated in inflammatory conditions (e.g. Crohn's disease and rheumatoid arthritis) as well as in cancers (e.g. melanoma, glioblastoma, and myeloid leukemia) (Kirkpatrick et al 1997; Rehli et al 2003). In addition it was found to be induced in astrocytes in acute and chronic neurological conditions (Bonneh-Barkay et al 2010a).

Unbiased proteomics approach was used to identify proteins that are differentially expressed in the CSF of SIV-infected macaques that develop encephalitis. Among the proteins that showed differential up-regulation was YKL-40. Longitudinal analysis of CSF from SIV-infected pigtailed macaques showed an increase in YKL-40 concentration 2 to 8 weeks before death from encephalitis. This increase in YKL-40 correlated with an increase in CSF viral load (Bonneh-Barkay et al 2008). Similar results were obtained in CSF from HIV patients. YKL-40 was higher in patients with HIV viral load higher than 10,000 copies/ml (Figure 1A) and there was a significant elevation in CSF YKL-40 in HIV patients with HIVE

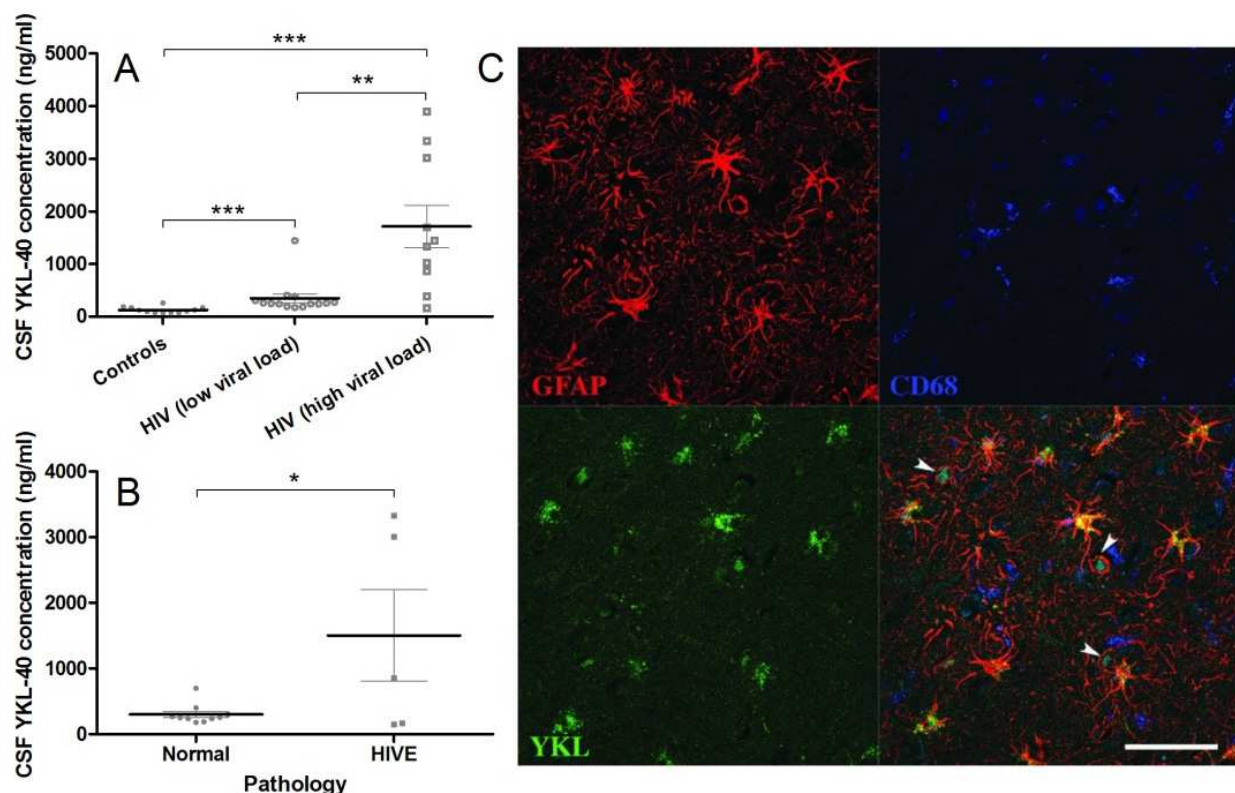


Fig. 1. (A) CSF from HIV-infected patients categorized on the basis of CSF HIV RNA copies (Low viral load= $\leq 10,000$ HIV copies; High viral load= $\geq 10,000$ HIV copies) was analyzed for YKL-40. (B) CSF YKL-40 correlation with HIVE pathology. (C) YKL-40 localized in astrocytes and occasional CNS activated macrophage/microglia in HIVE. Triple-label immunofluorescence for YKL-40 (green) and CD68 (blue) or glial fibrillary acidic protein (GFAP) (red). Co-localization of YKL-40 and astrocytes appears as yellow and co-localization of YKL-40 and CD68 positive macrophages is evident as aqua signal (arrowheads); scale bar= $50\mu\text{m}$ (Bonneh-Barkay et al 2008).

versus patients without encephalitis (Figure 1B). Previous studies have shown that high viral load in the CSF correlates with the severity of SIV encephalitis (SIVE) (Bissel et al 2006; Zink et al 1999) and HIVE (Cinque et al 1998; Wiley et al 1998). The correlation between YKL-40 levels and CSF viral load in SIVE and HIVE further support its potential use as a biomarker of HIVE. Immunohistochemistry showed that YKL-40 is expressed in astrocytes in the vicinity of microglial nodules in HIVE (Figure 1C).

It seems that YKL-40 can serve as a biomarker for Neuroinflammation in general as our recent study also showed that CSF YKL-40 levels are elevated in patients with severe traumatic brain injury (TBI), and that they correspond to levels of inflammatory cytokines (Bonneh-Barkay et al 2010b). In addition our previous study showed more pronounced YKL-40 expression in patients with acute infarcts and diminished expression in subacute or older infarcts (Bonneh-Barkay et al 2010a). In that previous study, combined ISH and GFAP staining showed induced YKL-40 expression in astrocytes that was restricted to the penumbra of the infarct. While the precise biological functions of YKL-40 are speculative, its expression is related to inflammation in a variety of disease states. Further work is required to further evaluate the utility of YKL-40 as a biomarker and its role in Neuroinflammation.

2.2 Herpes simplex encephalitis

Herpes simplex encephalitis (HSE) is an acute or subacute illness, causing both general and focal signs of cerebral dysfunction induced by Herpes simplex virus type 1 (HSV-1) (Kennard & Swash 1981; Koskiniemi et al 1996; Miller & Ross 1968; Sivertsen & Christensen 1996; Whitley et al 1989). HSV invades the CNS and is capable of replicating in neurons and glial cells which produce acute focal, necrotizing encephalitis localized in the temporal and subfrontal regions of the brain, often with a progressive course (Booss & Kim 1984). Early treatment with acyclovir is important to decrease mortality and limit CNS injury in HSE (Skoldenberg 1991). In addition corticosteroids may be given as therapy during the acute phase of HSE in order to reduce inflammation and edema in the CNS (Skoldenberg et al 1984). Despite adequate treatment almost all surviving patients suffer from neurological sequelae. The most common long-term symptoms after HSE are memory impairment, personality and behavioral abnormalities and epilepsy (McGrath et al 1997).

Confirmation of the diagnosis depends on the identification of HSV in the CSF by means of PCR although in some cases the PCR can be negative. In these cases detection of intrathecal synthesis of specific immunoglobulins could be useful (Denes et al 2010; Felgenhauer et al 1982; Felgenhauer & Reiber 1992; Reiber & Lange 1991). Widespread viral replication has not generally been found beyond the acute stage of HSE. Histopathologic studies of autopsy specimens showed that HSV antigen was detected in the brains of 21 out of 29 who died within 3 weeks after the onset of neurologic disease but not in the 8 who died thereafter (Booss & Kim 1984). HSV DNA seems to be cleared from the CSF in about the same period (Aurelius et al 1991), but PCR has shown HSV DNA at autopsy in a few cases of late-stage HSE. Despite lack of firm evidence, it seems that a low-grade continuous or recurrent viral replication may occur in certain foci resulting in continued antigen stimulation. Thus in general PCR is more useful in diagnosing acute HSE.

In HSE there is evidence of a vigorous intrathecal immune response during the acute phase, as shown by increased levels of β 2-microglobulin and neopterin in CSF, followed by a chronic phase of low-grade intrathecal inflammation (Aurelius et al 1993). In addition the

levels of a variety of CSF cytokines and their receptors are elevated like IL-6, IFN γ , soluble IL-2 receptor (sIL-2R) and soluble CD8 (Asaoka et al 2004; Aurelius et al 1994; Ichiyama et al 2008; Linde et al 1992; Rosler et al 1998). IFN γ and IL-6 levels increased during the first week of HSE while TNF α , IL-2, and soluble CD8 became elevated at 2–6 weeks (Aurelius et al 1994). A more recent study tried to assess whether there is a correlation between cytokines levels and outcomes. Kamei et al. showed that initial IFN γ and maximum IL-6 levels in patients with a poor outcome were higher than those with a good outcome and thus could serve as prognostic biomarkers in HSE (Kamei et al 2009).

Patients with viral CNS infections have previously been studied with regard to neuronal and astroglial markers in CSF (Rosengren et al 1994; Sindic et al 1985). The concentrations and kinetics of these markers in HSE imply that they may be used as brain damage markers to follow individual patients longitudinally or to evaluate therapeutics. Studahl et al. followed neuronal and astroglial marker proteins for up to 6 months in patients with HSE and found markedly higher CSF levels of neuron specific enolase (NSE), neurofilament protein, GFAP and S100 in the acute stage of HSE that was decreased within 45 days after acute infection (Studahl et al 2000). Although high levels of these markers were associated with neurological damage in other acute CNS damaging disorders, such as cerebral infarction (S100 and GFAP) (Aurell et al 1991), neonatal asphyxia (Blennow et al 1995), and after cardiac arrest (NSE) (Karkela et al 1993) Studahl et al. were not able to evaluate the prognostic use of these CSF markers in HSE. It seems that other factors (e.g. duration of disease before start of treatment, age, localization of the infected area and size of hemorrhagic necrosis) can influence the clinical outcome. Bigger cohorts may be needed to determine whether concentrations are correlated with clinical outcome (Studahl et al 2000). Additional biomarker that might indicate the severity and progression of cerebral injury in HSE is soluble Fas (sFas) which is involved in apoptosis through the Fas/Fas Ligand pathway (Sabri et al 2006). Elevated levels of sFas have been reported in a variety of neurological diseases like HIV, TBI and multiple sclerosis (De Milito et al 2000; Felderhoff-Mueser et al 2001; Lenzlinger et al 2002; Mogi et al 1996; Sabri et al 2001; Towfighi et al 2004; Zipp et al 1998). Sabri et al. found high levels of sFas in CSF samples collected after neurological onset in 84% of HSE patients. In addition they observed that HSE patients with severe neurological sequelae had an increase in changes of CSF sFas as compared to patients with mild or moderate neurological outcome.

In summary, markers of immune activation (e.g. IL-6, IFN γ , neopterin and β 2-microglobulin) are found early during the course of HSE and high levels are found to correlate with severe clinical outcome as well as with mortality (Aurelius et al 1993). Additionally there are markers that are indicative of persistent immune activation like soluble IL-2R and CD68 (Aurelius et al 1994).

2.3 Influenza-associated encephalopathy

Influenza-associated encephalopathy (IAE) is a CNS complication with high mortality and neurological sequelae with estimated mortality rate of 27% to 44% (Morishima et al 2002). The clinical symptoms of IAE include symptoms of both flu and CNS dysfunction. CNS neurological manifestations including seizure, altered or loss of consciousness, decreased cognitive performance, motor paralysis or sensory loss, abnormal or delirious behavior, and change in mental status. The neurological complications usually appear within several days of the first symptoms of flu (Wang et al 2010).

The influenza-virus usually can not be detected in the CNS of IAE patients and thus the pathophysiology of IAE remains unclear. The early studies reported that thrombocytopenia and severely elevated serum aspartate aminotransaminase levels were associated with a poor prognosis (Morishima et al 2002). High concentration levels of various cytokine such as IL-6 and TNF α have been reported (Aiba et al 2001; Hosoya et al 2005; Ichiyama et al 1998; Togashi et al 2004). Ichiyama et al. reported significantly higher levels of serum and CSF IL-6 in the IAE group with a poor prognosis relative to the group without sequelae. In addition serum levels of soluble TNFR1 and IL-10 levels were higher (Hasegawa et al 2011; Ichiyama et al 2004). Hosoya et al. reported significantly elevated levels of TNF α and cytochrome c concentrations in patients with poor prognosis as compared to good outcome (Hosoya et al 2005). The authors suggested that apoptosis of the CNS parenchyma contributes to the cerebral atrophy observed in patients with sequelae.

Recently, a new test for the evaluation of oxidative status, the Diacron-Reactive Oxygen Metabolites (d-ROM) test, has become available (Cesarone et al 1999). Yamanaka et al. assessed the prognostic value of serum and CSF d-ROM levels of patients with IAE in the initial stage (Yamanaka et al 2008; Yamanaka et al 2006). CSF d-ROM levels showed that the oxidative trend status corresponds to the therapeutic response and thus oxidative stress may be related to the pathogenesis of IAE. Similar results by Kawashima et al. showed high concentrations of NO $_x$ levels in the serum and CSF of the patients with IAE during the initial stage (Kawashima et al 2002; Kawashima et al 2003).

Another approach to discovering specific biomarkers of patients with IAE was to analyze all metabolites in CSF by using metabolome analysis. Two metabolites (molecular weights: 246.0092 and 204.0611) were significantly higher than those in other diseases including influenza without convulsion. These results indicate that the metabolites detected in CSF could serve as primary markers for the diagnosis of IAE (Kawashima et al 2006).

2.4 West Nile Virus encephalitis

West Nile virus (WNV) is a mosquito-borne, neurotropic, single-stranded sense RNA flavivirus (Brehin et al 2008). The classical symptoms of WNV infection range from fever (Hayes & Gubler 2006; Leis & Stokic 2005; Leis et al 2002; Leis et al 2003; Nash et al 2001; Sejvar et al 2003; Tilley et al 2007) to CNS disease of severe meningoencephalitis (Petersen & Marfin 2002). Clinical symptoms of CNS disease include persistent weakness, flaccid paralysis, myelitis, ataxia, seizures, or change in mental status. Neurological signs in WNV infection have been reported in about 42% of the cases.

One of the main diagnostic criteria for neurologic involvement in WNV infection is the presence of WNV IgM in CSF though it can be detected in the CSF for more than 6 months (Kapoor et al 2004). Therefore a more specific marker is necessary in order to distinguish WNV from other infections with neurological symptoms. Nixon et al. evaluated CSF WNV IgA as a marker of WNV neuroinvasive infection but found that it had equivalent value to IgM (Nixon & Prince 2006).

In addition to specific antibodies, protein biomarkers are an attractive tool for assessing neuronal death and glial pathology. Petzold et al. showed a significant elevation of those CSF proteins like GFAP, S100B, and neurofilament-SMI35 in patients suffering from WNV CNS disease (Petzold et al 2010). However, CSF GFAP and S100B were also increased in all of patients with WNV fever only thus decreasing their usefulness as a biomarker for CNS disease. Interestingly, in patients that died from the disease high CSF S100B levels were related to a shorter time to death.

In summary, most of the studies aiming to discover biomarkers of viral encephalitides were targeted towards studying known pathways believed to be involved in immune activation or cell damage. These studies, however, have achieved limited success. Over the last few years, unbiased proteomic techniques have been utilized to discover novel biomarkers in different diseases without the a priori selection of specific proteins (Romeo et al 2005). In recent years there are more and more studies using those techniques to discover biomarkers in neurological conditions and neurodegenerative diseases (e.g. multiple sclerosis and Alzheimer's disease) (Craig-Schapiro et al 2010; Ottervald et al 2010; Perrin et al 2011). Unbiased proteomics profiling is very complex and requires a multi-discipline approach from sample preparation and protein identification to data processing and validation. These analyses most likely will result a combination of candidate biomarkers that will need to be tested in larger cohorts.

3. Autoimmune encephalitis

Autoimmune encephalitis encompasses a variety of disorders resulting from an immune reaction against antigens expressed in neurons. As a result there is rapidly progressive cognitive decline and behavioral abnormalities. The antibodies against those antigens are important markers for these disorders (Vitaliani et al 2008).

3.1 Limbic encephalitis

Paraneoplastic neurologic disorders are immunologic complications induced by malignancies that express proteins that are usually restricted to the CNS (Vernino et al 2007). They are characterized by memory impairment, temporal lobe seizures and psychiatric symptoms. The most common tumors associated with paraneoplastic neurological disorders are small-cell lung carcinoma (SCLC), testicular cancer, thymoma and breast cancer (Ahern et al 1994; Gultekin et al 2000; Vernino & Lennon 2004).

A variety of autoantibody markers are associated with limbic encephalitis like anti-Hu and anti-CV2/CRMP5 (Gultekin et al 2000; Voltz 2002). In recent years different subtypes of this disorder have been discovered as well as new antigens. Anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis was identified as a subtype of limbic encephalitis. This disease usually starts with an episode of fever, headache, or malaise, followed by mood and behavioral changes, psychiatric symptoms and decline of consciousness that could deteriorate to death. It usually affects young women and is associated with ovarian teratoma. These patients demonstrate serum and CSF presence of antibodies against NMDA receptor subunit 1 (NR1) and NMDA receptor subunit 2 (NR2) (Iizuka et al 2008). Additional subtype of limbic encephalitis is characterized by antibodies against voltage gated potassium channels (VGKC) (Buckley et al 2001; Thieben et al 2004; Vincent et al 2004). VGKC limbic encephalitis is mostly non-paraneoplastic, although VGKC antibodies have been found in a small number of patients with tumors (Pozo-Rosich et al 2003). Jarius et al. showed that even patients without CSF pathological findings or inflammatory changes can be positive for VGKC antibodies (Jarius et al 2008).

Non-herpetic acute limbic encephalitis (NHALE) has been identified as a new subgroup of limbic encephalitis with a clinical presentation which is similar to HSE (Asaoka et al 2004; Ichiyama et al 2009; Kusuhara et al 1994; Shoji et al 2004). Autopsy cases showed neuronal loss and severe gliosis with inflammatory cell infiltrations in the hippocampus and amygdala. Examination of the CSF revealed occasional mild pleocytosis, and increased IL-6

levels (Ichiyama et al 2008; Shoji 2010). Recent reports associate the disease with the presence of anti-glutamate receptor epsilon 2 antibodies (Shoji 2010). Takahashi et al. reported the presence of those antibodies in the serum and CSF of patients in acute and chronic stages (Takahashi et al 2010).

3.2 Hashimoto's encephalopathy

Hashimoto's encephalopathy (HE) is a rare autoimmune disease affecting mostly women that is associated with elevated titers of antithyroid antibodies in serum and CSF (Brain et al 1966; Chong et al 2003). HE is characterized by various neuropsychological symptoms, including personality changes, cognition deterioration, seizures, myoclonus and loss consciousness (Ghika-Schmid et al 1996; Henchey et al 1995; Kothbauer-Margreiter et al 1996; Mijajlovic et al 2010; Peschen-Rosin et al 1999; Shaw et al 1991). HE patients show high CSF protein levels (oligoclonal bands or an increased total protein concentration) without pleocytosis and high titer of antithyroid antibodies (Archambeaud et al 2001; Ferracci & Carnevale 2006; Hartmann et al 2000; Shaw et al 1991). The etiology of the disease is not entirely clear but there are some reports claiming an inflammatory response to antineuronal antibodies (Oide et al 2004; Takahashi et al 1994).

3.3 Rasmussen's encephalitis

Rasmussen's encephalitis is an acquired progressive inflammatory encephalopathy characterized by seizures and cognitive deterioration resulting from an atrophy of a single brain hemisphere. Rasmussen's encephalitis is divided into two clinical subtypes by the existence of *epilepsia partialis continua* (EPC). EPC is characterized by continuous myoclonic jerks of the extremities and/or the face, usually without impairment of consciousness (Takahashi et al 1997). The etiology of the disease has been hypothesized to be associated with an autoimmune process mediated through antibodies against the glutamate receptor subunit 3, (Mastrangelo et al 2010). Takahashi et al. reported that antibodies against NMDA type GluR ϵ 2 were detected in Rasmussen's encephalitis patients with and without EPC (Pleasure 2008; Takahashi et al 2003; Takahashi et al 2005). This suggests that autoantibodies against GluR ϵ 2 are important for the diagnosis of both subtypes of Rasmussen's encephalitis, independent of EPC.

4. Conclusion

Viral and autoimmune disorders of the CNS are a heterogeneous group of disorders. Many viruses are known to cause acute viral encephalitis in humans which can cause a variable degree of meningeal as well as parenchymal inflammation. CSF abnormalities typically consists lymphocytic pleocytosis and protein elevation. Identification of viral antigens, viral nucleic acid or antibody analysis may provide an important diagnostic help in addition to imaging (e.g. CT scan and MRI) (Debiasi & Tyler 2004). The clinical and laboratory findings in many of those viral and autoimmune disorders are largely similar and thus more specific biomarkers for diagnostic and prognostic purposes are warranted. These biomarkers are increasingly important in the recognition and treatment of viral and autoimmune CNS disorders (Dale & Brilot 2010).

Many of the viral encephalitides are accompanied by CSF markers for immune activation like β_2 microglobulin and neopterin or elevated levels of cytokines and chemokines in

addition to the presence of the virus or viral antigens. Many studies also tried to predict the progression of the disease and response to therapeutics base on those biomarkers. Despite the plethora of surrogate markers of immune activation and neuronal and glial destruction, their clinical use is still obscure in that there are no clinical trials that showed a correlation with clinical status and that they respond to a therapeutic intervention. There is a great need for validation of these studies in larger trials before surrogate marker measurements would be accepted universally as clinical end-points. In conclusion, although more and more studies were aimed to identify specific biomarkers for each type of encephalitis there is still need for more studies to validate their use in larger trials.

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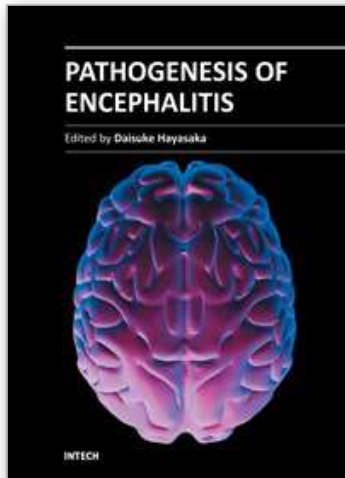
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Pathogenesis of Encephalitis

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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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