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Review Article

The immunogenetics of subacute sclerosing panencephalitis: A comprehensive review

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ABSTRACT

Background: Subacute sclerosing panencephalitis (SSPE) is a rare devastating complication of measles virus (MV) involving the central nervous system (CNS). SSPE occurs 4–11/100,000 cases of the measles.

Main Body: A poor cellular immune response seems to predispose individuals to the development of SSPE. The presence of mutations that may lead to MV persistence has also been demonstrated in samples obtained from SSPE patients. However, no study to date has definitively revealed the pathogenesis of SSPE caused by persistent infection in the CNS of MV.

Conclusion: In this review, we provide a brief overview of SSPE from both an immunological and genetic perspective. We will try to focus on the mechanisms underlying the pathogenesis of SSPE that results in MV persistence. Clarifying the pathogenesis of SSPE will enable both the expansion of therapeutic options and the prediction of disease prognosis.

Keywords: Measles virus, Innate immunity, Immunogenetics, Subacute sclerosing panencephalitis, Polymorphisms

BACKGROUND

Measles virus (MV) is a myelotropic, lymphotropic and epitheliotropic negative-strand RNA virus belonging to the Paramyxoviridae family.[1] Subacute sclerosing panencephalitis (SSPE) is a progressive fatal demyelinating disease caused by infection of a mutant strain of the MV.[2] SSPE develops approximately 2–10 years measles infection, but the latency period ranges from 1 month to 27 years. The incidence of SSPE can vary depending on the country and it is approximately 4–11 cases per million population per year.[3-5] The diagnosis of SSPE is made clinically by the presence of neurological findings and the analysis of laboratory findings such as blood, cerebrospinal fluid (CSF), electroencephalogram and imaging tests.[6] The pathogenesis of SSPE is still unclear. The possible underlying mechanism is mutant MV with an altered M protein, leading to a persistent viral infection. The M gene of SSPEV is limited in expression and highly susceptible to mutations.[7,8] In addition to mutations of M gene, immaturity of the cellular immune mechanism, host cell modifications and immunopathology are also believed to be involved in the pathogenesis of SSPE. The review aims to highlight the role of innate and adaptive immune responses and genetic risk factors that are linked with the increased susceptibility to SSPE.

VIROLOGICAL CHARACTERISTICS OF SSPE

The MV is a single-stranded RNA of 15,894 nucleotides and belongs to the Paramyxoviridae family.[9] The genome is encoding six structural proteins including nucleocapsid (N) protein, phosphorylated (P) protein, matrix (M) protein, fusion (F) protein, haemagglutinin (H) protein and polymerase (large, L) protein.[10] The M protein coats the internal surface of the envelope.[11] Once the MV enters the brain, it undergoes genetic mutations and begins to multiply in the brain parenchyma.[12] A variety of genetic differences have been noted in the isolates recovered from the brain tissues of SSPE patients. Defects in the M protein result in the failure to form virus particle facilitating persistence of MV in neuronal cells.[13] In an isolated Canadian D6 strain, several mutations were observed throughout the viral genome. The most of the nucleotide variability in the entire viral genome (17.6%) was present in the M gene.[14]

HOST IMMUNE RESPONSE TO SSPE

Clearance of the MV requires a coordinated innate and adaptive humoral and cell-mediated immune response. Many previous studies have shown that some changes in the host's immune response contribute to the pathogenesis of persistent MV infections such as SSPE.[15] Most patients with SSPE exhibit a decreased MV-specific T helper (Th) 1 cytokine and preserved Th2 cytokine synthesis.[16] As a result of suppression of Th1 cytokine production, it was determined that peripheral blood mononuclear cells of SSPE patients showed defective interferon-gamma (IFN-γ) response to MV.[17] Higher serum interleukin-2 (IL-2) concentrations and suppressed Th2 cytokines (IL-4, IL-6 and IL-10) were also shown in patients compared to the control group.[18] In brain samples taken from SSPE patients, besides cluster of differentiation (CD)4+ T- and B-cell activation, the presence of IL-1β, IL-2, IL-6, tumour necrosis factor-α (TNF-α), lymphotoxin and IFN-γ cytokines was also demonstrated.[19,20] Detection of higher IL-10 levels in both CSF and serum of SSPE patients supported that there is a suppressive environment in this disease.[21,22] In another study, it was found that IL-4 and IL-6 concentrations were lower, while the serum IL-2 concentration was higher in the CSF samples of SSPE patients. Therefore, it was emphasised that Th1 is more dominant than Th2 type cytokines in the early inflammatory response of SSPE.[18] Another study demonstrated that increased concentration of Th1 and Th17 cells and production of cytokines IL-12, IL-23, IL-17 and IL-22 in response to MV peptide stimulation in SSPE patients.[23]

GENETIC SUSCEPTIBILITY OF SSPE

The gene polymorphisms are thought to cause patients with SSPE to exhibit an altered cellular response to common antigens and different cytokine levels. The first study for genetic susceptibility of SSPE was done by Kusuhara *et al.* in 2000. In this study, the relationship between the CD46 genes, which functions as a cellular receptor for MV, and SSPE was investigated, but CD46 gene was not a risk factor in the development of SSPE.[24] Related gene polymorphisms have been investigated in many studies to determine the genetic background of Th1/Th2 cytokine responses in patients with SSPE. In a study with Japanese population, IL-4–589T allele was demonstrated significantly associated with SSPE.[25] The myxovirus resistance A (MxA) protein is a protein whose production is stimulated by type I IFNs. In another group consisting of Japanese subjects, the frequency of T allele and TT genotype of MxA-88G/T polymorphism were found to be significantly higher in SSPE patients than in controls.[26] Taşdemir *et al.* demonstrated that the frequency of DD genotype and D allele was significantly higher in SSPE children.[27] Three candidate genes, MxA, IL-4 and IFN regulatory factor 1 genes, were studied in Japanese patients with SSPE. The TT genotype of MxA and CT genotype of IL-4 were found to relate SSPE susceptibility.[28] Yılmaz *et al.* evaluated the relationship between IL-2, IL-12 and IFN-γ gene polymorphisms and SSPE. In their study, IL-12 gene rs3213113 and IL-2 gene rs2069762 polymorphisms were found to be significantly higher in SSPE patients compared to controls.[29] Ishizaki *et al.* investigated the effect of toll-like receptor 3 (TLR), retinoic acid-inducible gene I and melanoma differentiation-associated protein 5 gene polymorphisms in the pathogenesis of SSPE. They found that the haplotype frequency of TLR3 gene was significantly increased in SSPE patients.[30] In a study conducted with Turkish SSPE patients by Piskin *et al.*, it was showed that the rs1946518 (G/C) and rs187238 (C/A) IL-18 gene polymorphisms might be a protective factor.[31] Programmed death 1 (PD-1) is a coinhibitory molecule and is involved in the suppression of T lymphocytes. A statistically significant difference in PD-1 gene polymorphisms has been found in patients with SSPE in a study from Turkey.[32] Sodium voltage-gated channel alpha subunit 1 gene mutations, which have been associated with epilepsy, have been shown to increase cerebral neuron susceptibility to measles infection.[33] Celik *et al.* evaluated associations of TLR and IL17 gene polymorphisms with SSPE. They found that TLR4 Asp299Gly was associated with the development of SSPE.[34] In another study, G allele and GG genotype of rs8192917 polymorphism in granzyme B gene were found to be a protective factor for SSPE.[35] Dundar *et al.* showed that AA genotype or A allele of IL-12 (-1188) A/C polymorphism was decreased the risk of SSPE by 2.06- and 1.65-fold, respectively.[36] In a recent study from Turkey demonstrated that the G allele of IL28B rs8099917 was found to increase 2.183-fold risk of SSPE. They also found higher expression levels of miR-548b-5p,

miR-548c-5p and miR-548i in the SSPE patients compared to controls.[37]

CONCLUSION

Although SSPE is rare, it is still an important source of morbidity and mortality in many parts of the developing world. The pathogenesis of SSPE remains unclear and there is no defined treatment. Many reported studies have demonstrated that host cell modifications and gene polymorphisms contribute to the pathogenesis of persistent MV infections. The role of T cells, B cells, cytokines, the type of MV and the role of host genetic background should be considered together to explain the underlying pathophysiology of SSPE. Genome association studies, well-designed researches involving gene-gene interactions and functional gene analyses may reveal the genetic basis of SSPE. In this review, we summarised the cellular and molecular mechanisms underlying of SSPE. We also highlighted gene polymorphisms that were studied in SSPE until date. The future studies integrating genetics are expected to result in increased knowledge of the cellular and humoral mechanisms of SSPE. Revealing the pathophysiology of the disease may help future targeted therapies and provide information that can be translated to the clinical.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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