REVIEW ARTICLE

The research status of pathogenesis of rasmussen encephalitis

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Rasmussen Encephalitis (RE) is a rare, chronic inflammatory disease that starts in children and often affects one hemisphere of the brain. The main clinical manifestation is focal epileptic seizure, progressive hemiplegia, cognitive decline and unihemispheric brain atrophy. Over the past half century, researches on this disease have achieved great progress, but the etiology of this disease is still not clear. Hemispherectomy still remains the only cure for the disease. In this paper, the research status of the pathogenesis of RE is reviewed for peer reference.

Key Words: *Rasmussen encephalitis; Pathogenesis; Virus infection; Autoimmunity.*

INTRODUCTION

In 1958, Theodore Rasmussen and his colleagues at the Montreal Neurological Institute firstly reported three cases of focal epilepsy patients with chronic focal inflammation in the brain tissue named Rasmussen encephalitis (RE) [1]. According to pathology examination, the feature of the brain tissue in RE patients include microglial and lymphocytic nodules and perivascular cuffing, neuronal death and neuronophagia, which were similar to viral encephalitis. Therefore, Rasmussen inferred that the etiology of this disease may be caused by viral infection [2]. But, subsequent studies have not found viral inclusion bodies and some scholars infer that it may be a neuro-immunology disease [3,4]. At present, the pathogenesis of RE mainly focuses on two aspects: one theory is the virus infection and the other is the neuro-immunology. This review summarized the research status as of RE as follows.

INTRODUCTION

Viral infection theory

The correlation between virus infection and RE has always been the focus of neurologists. Due to the clinical manifestations and pathological characteristics, many researchers believe that viral infection induces the inflammatory response in RE brain tissue. In recent decades, many studies at home and abroad have found some evidence to support this theory. Walter et al. used Polymerase Chain Reaction (PCR) to amplify the DNA in two RE patients' brain tissues and detected the amplified fragments of Epstein-Barr (EB) virus DNA nucleic acid suggesting that the occurrence of RE may be related to EB virus infection [5]. Power et al. detected HCMV antigens in neurons, astrocytes and endothelial cells in RE brain tissues inferring that the occurrence of RE may be related to HCMV infection [6]. Jay et al. found HCMV-specific DNA amplified fragments were detected in 6 patients and Herpes Simplex Virus 1 (HSV-1) specific DNA amplified fragments were detected in 2 patients from 10 patients [7]. Lachlan et al. treated 4 early stage of RE patients with ganciclovir, and 3 patients' clinical symptoms were relieved in varying degrees [8]. Merkler et al. found virus-specific Cytotoxic T Lymphocyte (CTL) can eliminate Lymphocytic Choriomeningitis Virus (LCMV) in most cells except neuron in young mice, and the virus can exist in the neuron and cannot be cleared by CTL. However, LCMV can re-infect in adult mice and the inflammatory changes are similar to the pathological manifestations of RE [9]. Based on this, Merkler proposed the "Deja Vu hypothesis" suggesting that this infection-reactivation pattern may be related to the onset of RE. Takahashi et al. found that nearly half of RE patients had a history of viral infection and vaccination prior to the seizure [10]. Chen et al. detected Human Papillomavirus (HPV) antigen in the brain tissue of 4 RE patients and 3 patients had been detected HPV DNA amplified fragments by in situ Hybridization (ISH) in the brain tissue, thus speculated that HPV infection may be also associated with RE [11]. Liu et al. detected EBV and HHV6 in RE brain tissues and the above virus can both infect neuron and astrocyte [12]. In summary, although all of the above studies detected viral components from the brain tissues of RE patients, none of the research group detected virus particles. In addition, there are also a few negative researches about viral infection in RE patients. Therefore, the relationship between virus infection and RE still needs to be clarified by large samples of RE patients.

Neuro-immunology theory

Evidence for an immune-pathological evidence of RE is growing. The theory about neuro-immunology mainly includes antibody-mediated against GluR3 and T-cell cytotoxicity.

Antibody-mediated against GluR3: In recent years, the theory of Glutamate Receptors (GluRs) has been particularly prominent in the pathogenesis research progress of RE. As we all known, GluRs can be divided into ionotropic GluRs (iGluRs) and metabotropic GluRs (mGluRs) and both of them have important functions in central nervous system. Furthermore, there are three types of iGluRs such as N-methyl-D-aspartate Receptor (NMDAR), Kainic Acid Receptor (KAR) and □-amino-3-hydroxy-5-methyl-4-isox-azolepropionic acid receptor (AMPAR). The role of GluRs in CNS autoimmunity, and especially the formation of autoantibodies to NMDAR subunits GluN1 and GluN2 has recently been focused on various forms of encephalitis, including paraneoplastic encephalitis and RE [13,14]. In 1993, Rogers found glutamate receptor-3 (GluR3) antibody in RE patients and using plasmapheresis removaling GluR3 can help a few patients alleviate symptoms of seizure. So, RE was considered an autoimmune disease mediated by GluR3 antibodies from that time [15,16]. Recently studies found that excessive GluR3 can produce excitotoxicity lead to apoptosis of neurons and astrocytes [16]. Takahashi et al. found anti-GluN2B antibodies inducing synaptic plasticity and development were detected in serum and cerebrospinal fluid of RE patients. With the deepening of research on GluRs, many antibodies activating GluRs to excite neurons and glial cells have been found in RE children, such as the alpha-7 nicotinic acetylcholine receptor or Munc-18-1 [17,18]. However, there are also some opposite research results. Levite et al. found that the pathological changes in brain tissues of BALB/c, C3H/HeJ and SJL/J mice immunized with GluR3 peptide may account for the neuronal death and the brain pathology were similar to RE, but may not be sufficient to underly epilepsy. Even the induction into the brain and the destruction of the blood-brain barrier cannot produce the pathological state of epilepsy [19]. Other authors found that GluRs antibodies are not specific to RE and can also be seen in other types of epilepsy, especially in drug refractory epilepsy [20]. Therefore, the theory of humoral immunity mediated by GluRs antibodies also has certain limitations and cannot fully reveal the pathogenesis of RE.

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T lymphocytes mediated cellular immune injury: Cytotoxic T lymphocytes (CTL) seem to play a major part in the pathogenesis of RE. Previous studies have found that the immune response mediated by T lymphocytes is also an important mechanism leading to the inflammatory response in the brain tissues of RE patients. The activation of T lymphocyte-mediated immune response mechanism in RE patients may be caused by specific antigens. In 1999, Levite et al. found anti-GluR3b T cells in RE animal models and believed that CTL played an important role in the pathogenesis of RE. Tilman et al. showed that the apoptosis of astrocytes and neurons are characteristic pathological manifestations of RE and astrocytes and neurons in these tissues showed upregulated expression of type I major histocompatibility complex (MHC)-I. Therefore, it is infered that the specific attack of CTL may lead to the loss of neurons and astrocytes in RE patients, lead to seizure finally [21]. Gahring et al. found that CTL releases of granzyme B (GB) onto neurons suggesting neuronal apoptosis were related to CTL [22]. In 2002, Bien et al. found that most of the GB-positive T cells attached to MHC-I molecule-positive neurons suggesting that the pathogenesis of RE might be caused by CTL-mediated neuronal injury [23,24]. In 2005, Tekgul et al. supported the pathogenesis of RE as an immune response mediated by CD8+ T lymphocytes and the content of interleukin (IL)-6 showed the severity of inflammation in RE brain tissue [25]. In 2007, Bauer et al. found that astrocyte apoptosis and subsequent neuronal loss are characteristic manifestations of RE, which can be found both in cortex and white matter [26]. In 2009, Takahashi analyzed the cerebrospinal fluid of RE patients and found that the proportion of CD34, CD44 and CD84 T lymphocytes increased throughout the course of the disease with a gradual increase of CD4+ T cells and a gradual decrease of CD84 T cells. The content of CD3+ T cell increased in the early stage, decreased in the middle stage and increased again in the late stage, suggesting that T cells were involved in neuronal injury. Takahashi et al. detected the 2 subunit antibody and its antigenic determinants of NMDA-GluR in serum and cerebrospinal fluid of 20 RE patients suggesting that anti-GluR 2 antibody may be a diagnostic marker of RE with/without EPC. It is speculated that cellular immunity and subsequent humoral immunity against GluR 2 contribute to the pathophysiological process of RE [27]. The detection NMDAR antibodies in the cerebrospinal fluid of 18 patients showed that the antibody levels of GluN2B and GluN1 receptors were significantly higher than those in the control group, and the higher the seizure frequency, the higher the antibody titer [28]. Mirones et al. found that CXCR3 was expressed by CTL in RE brain tissue, while CXCL10 was expressed by neurons and astrocytes in the same area. Activation of lymphocytes stimulating CTL via the CXCR3-CXCL10 axis leads to pathological changes in RE patients and this chemotactic phenomenon may be used as a potential target for drug therapy [29]. By immunohistochemical staining of brain tissues of 7 patients, Khojah et al. found that most of them were permanent CD8 positive T lymphocytes expressing CD103 and CD 69, which run through the whole process of inflammatory response. Early clinical use of monoclonal antibodies such as natazumab can effectively prevent T lymphocytes from passing through the blood-brain barrier, thereby inhibiting the immune inflammatory response and delaying the progression of the disease [30].

In conclusion, viral infection and neuro-immunology theory such as antibody-mediated against GluR3 and T lymphocytes mediated cellular immune injury can be more or less supported by some evidence, but no single theory can fully explain the pathogenesis of RE. And, according to these theories, clinical antiretroviral, plasmapheresis and immunosuppressive therapy can improve the early stage of clinical symptoms of RE patients [31-34]. So, we can infer viral infection, autoimmune circulating antibodies and T cell immunity are involved in the development of RE. In addition, with low incidence of RE, the clinical sample size is small in most of the epilepsy center, which has become a key factor restricting the study on the pathogenesis of RE. For this reason, the International Brain Tissue organization Transfer Plan was founded in 2011 by John Hopkins and David geffen school of medicine, university of California, Los Angeles aiming to shared brain tissue specimen and set up international research cooperation and promote the pathogenesis research of RE [35]. In our country, Professor Guoming Luan from Sanbo Brain Hospital of Capital Medical University initiated and established the RE research alliance to promote the research on the pathogenesis research of RE in china. It is believed that with research cooperation established at home and abroad, the mystery of the pathogenesis of RE will be uncovered in the near future.

In conclusion, a large number of studies have been conducted on the pathogenesis of RE at home and abroad in recent decades, and a series of research achievements have been made in the aspect of the pathogenesis. However, the exact pathogenesis of RE is still not clear and needs to be further studied.

CONFLICT OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

ETHICAL APPROVAL

For this type of study formal consent is not required.

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