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PATHOLOGY OF ACUTE DISSEMINATED ENCEPHALOMYELITIS

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Abstract

Acute disseminated encephalomyelitis (ADEM) is an acute, monophasic neurologic syndrome that occurs after vaccination against various viruses and after many viral infections and rarely occurs again in the same patient. Weston Hurst disease or acute hemorrhagic encephalomyelitis (AHE) is a hyperacute ADEM variant that shares many pathological similarities with ADEM. ADEM clinically and neuropathologically faithfully reflects the animal model of experimental allergic encephalomyelitis (EAE), and animal studies have provided us with new insights into pathogenesis of this disorder. Although there is much controversy whether ADEM is a separate disease or just one of possible manifestations of multiple sclerosis, there are clear histopathological characteristics that support ADEM as a separate disease This mini review will focus on pathological characteristics of ADEM emphasizing differences from other types of idiopathic demyelinating diseases.

Keywords

• Acute disseminated encephalomyelitis • Acute hemorrhagic encephalomyelitis • Pathology • Multiple sclerosis

Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute, monophasic neurologic syndrome that occurs after vaccination against various viruses and after many viral infections and rarely occurs again in the same patients. Although ADEM is a well accepted clinical entity in the pediatric literature, there are many controversies around existence of ADEM in adults. Many authors believe that ADEM is just one of possible manifestations of multiple sclerosis (MS) spectrum, mainly based on recurrence of symptoms. In 1994 Poser has proposed that ADEM with multiple episodes may be classified into two types: recurrent and multiphasic disseminated encephalomyelitis [1]. In the first one an initial acute episode from which there is a complete recovery is followed by recurrences that are characteristically stereotyped bouts reproducing the original clinical syndrome completely or in part; and multiphasic he defined as ADEM followed by bouts of clinical syndromes different from original one.

There are neither widely accepted clinical criteria nor definitions of ADEM or its recurrent forms in adults [2]. There are several reviews on clinical, CSF and MRI findings in ADEM patients, but it needs to be emphasized that neither of these can with great certainty differentiate between ADEM and MS. The only reproducible difference between two diseases have been pathohistological findings, however biopsies are rarely done in patients with demyelinating diseases and biopsy results are only seldom available.

This mini review will focus on pathological characteristics of ADEM emphasizing differences from other types of idiopathic demyelinating diseases.

Pathology

The precise mechanisms implicated in ADEM immunopathogenesis are not well known. Relationship between ADEM and MS has long been and still remains a matter of controversy.

At autopsy, edema is often the most conspicuous finding or in contrast to MS, the lesions in ADEM may not be visible macroscopically [3,4]. The first, and maybe the most well characterized pathological difference between ADEM and MS is that MS lesions are characterized by a sharp–edged plaque, that has never been seen in ADEM which is characterized with margins that are rather indistinct [5]. Second characteristic of ADEM are 'sleeves' of demyelination (Figure 1) that surround venules and are associated with significant inflammatory infiltrates dominated by T lymphocytes and macrophages (Figure 2a) [3]. Rarely, granulocytes or plasma cells are seen [6]. These perivascular lesions typically retain the same shape and size throughout the disease, whereas MS lesions tend to grow centrifugally by extension of macrophages or confluence of lesions (Figure 2b) [7]. Thus, the distinctive pathological criterion distinguishing ADEM and MS is the presence, or not, of confluent versus perivenous demyelination [8]. In view with this Young et al. performed a study to investigate whether perivenous demyelination versus confluent demyelination distinguishes ADEM from MS [9]. The main

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result of this study is that the diagnostic criteria for ADEM defined by the International Pediatric Multiple Sclerosis Group matched the pathological diagnosis of ADEM with sensitivity of 80% and a specificity of 91%. The perivenous demyelination cohort was more likely than the confluent demyelination cohort to present with encephalopathy (P<0.001), depressed level of consciousness (P<0.001), headache (P<0.001), meningismus (P = 0.04), cerebrospinal fluid pleocytosis (P = 0.04) or multifocal enhancing magnetic resonance imaging lesions (P<0.001). A distinct pattern of cortical microglial activation and aggregation without associated cortical demyelination was found among six perivenous demyelination patients, all of whom had encephalopathyand four of whom had depressed level of consciousness. This pattern of cortical pathology was not observed in the confluent demyelination cohort, even in one patient with depressed level of consciousness. Perivenous demyelination is associated with meningoencephalopathic presentations and a monophasic course. Depressed level of consciousness is a more specific clinical criterion for pathologically confirmed ADEM than encephalopathy, which over-diagnosed ADEM among MS patients. A distinct pattern of cortical microglial activation without cortical demyelination may be the pathological correlate of depressed level of consciousness in ADEM. This study has once again showed that that the clinical criteria for differentiation of ADEM and MS are imperfect, and it reveals considerable overlap in the clinical presentation between these two disorders. However, the co-occurrence of perivenous and confluent demyelination in some individuals suggests pathogenic overlap between ADEM and MS and misclassification even with biopsy.

The third characteristic of ADEM is that pronounced inflammation is associated with only minor demyelination restricted to the vicinity of the perivascular inflammatory infiltrates in contrast to MS where demyelination is the predominant feature (Figure 3) [6,7].

The fourth characteristic is that all lesions must be of the same age. They can be found in optic nerves, supra and infratentorial white, but importantly gray matter as well (particularly basal ganglion, thalami and brainstem, while

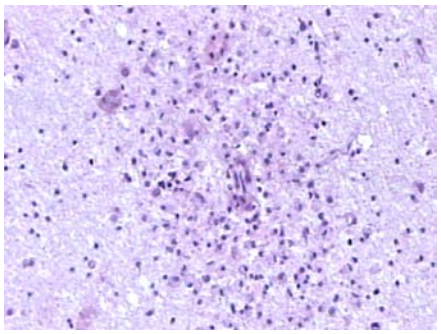

Figure 1. Venules in brain tissue are surrounded with mononuclear inflammatory cells (H&E, magnification 400 x).

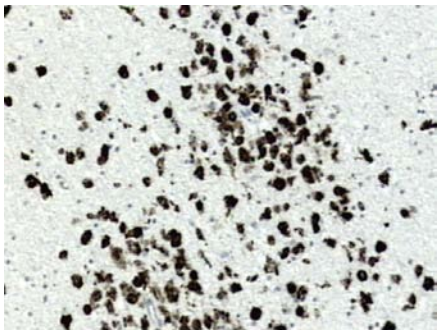

Figure 2a. Preivenular inflammatory infiltrate is predominantly composed of T lymphocytes and macrophages (immunohistochemistry to CD3, magnification 400x).

Figure 2b. Perivenular inflammatory infiltrate is multifocal predominantly composed of T lymphocytes and macrophages (immunohistochemistry to CD3, magnification 100x).

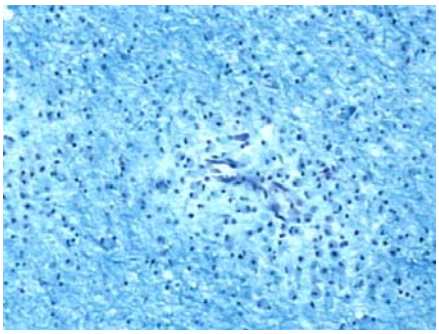

Figure 3. Perivenular inflammation is associated with only minor demyelination (Kluver-Barrera, magnification 400x) .

the corpus callosum is usually not involved), and in the spinal cord. [10] MRI studies have identified 4 typical patterns of lesion distribution: multifocal lesions of less than 5 cm, confluent multifocal lesions of more than 5 cm, multifocal lesions involving basal ganglia, and multifocal hemorrhagic and edematous lesions in the Weston Hurst disease [11]. Importantly the meninges (lymphocytes) and subpial regions (microglia) may also be inflamed [12].

One other important characteristic of ADEM is that it can be accompanied by lymphocytic meningitis. Peripheral nervous system involvement occurs in 40% of ADEM patients, shows mainly demyelinating pattern and if present is one of most convincing evidences supporting the diagnosis. However pathological studies of involved peripheral nerves are lacking [13].

Although most of pathological studies are done on monophasic courses of ADEM, there is one paper describing 5 well documented recurrent cases of ADEM with biopsy findings showing a mononuclear perivascular infiltration, demyelination, loosening of the white matter, and foamy macrophage compatible with ADEM [14]. In one study with a long term follow-up, in a cohort of 33 children with ADEM, 9 had relapses [15]. The risk of developing relapses was 27% but the risk of developing MS from ADEM was low at 6%. All relapsing cases had a benign course on prolonged follow-up, in spite of multiple relapses in the first 3 years. Three patients had biopsies done, 1 with prolonged encephalopathy, 1 with recurrent ADEM, 1 with multiphasic ADEM). In all patients, abundant parenchymal perivascular macrophages, activated microglia, and perivascular lymphocytes were noted. White matter was pale with nearly complete loss ofmyelin noted within the areas of pallor on Luxol fast blue/ periodic acid-Schiff stain. Neurofilament staining showed a relative preservation of axons compared to myelin loss with scattered axonal swellings consistent with some axonopathy.

As earlier mentioned, Weston Hurst disease or acute hemorrhagic encephalomyelitis (AHE) is a hyperacute ADEM variant. This disease similarly to ADEM shows perivenular inflammation and demyelination largely confined to the white matter. But contrary to ADEM where there is mostly lymphocytic infiltration, AHE produces a predominantly neutrophilic infiltrate, with pericapillary ball and ring hemorrhages and hematomas, and macroscopically focal haemorrhages may be present [16]. Perivascular necrosis, edema and inflammatory meningeal infiltrates are also frequently seen [17].

Animal models

The initiatory mechanisms in MS and ADEM are identical but propagative mechanism underlying MS is lacking in ADEM [18]. It was shown that ADEM clinically and neuropathologically faithfully reflects the animal model of experimental allergic encephalomyelitis (EAE) [7]. However EAE can present pathologically not only with perivenous but also with confluent demyelination, depending on the immunological mechanisms of disease [19]. EAE studies have suggested two possible mechanisms of ADEM: infectious mechanism and a secondary autoimmune response as contributing to CNS demyelination [14]. Maybe the best example is the infection of susceptible mice with Theiler's virus which cause a biphasic disease of the CNS [20]. The first phase is an acute encephalomyelitis when the virus infects mainly neurons in the gray matter of the brain and spinal cord, after which most animals survive and enter the second phase of the disease, during which the virus persists in the white matter of the spinal cord, mainly in macrophages and oligodendrocytes and this is associated with focal inflammatory lesions in which numerous demyelinated axons can be seen [20,21]. In this animal model the initial injury caused by an infectious agent may be followed by a secondary autoimmune response. Two possible mechanisms could explain recurrences; one is localization of ADEM to an area of selective vulnerability at the site of a previous injury of the CNS where impermeability of the blood brain barrier has been impaired. This was demonstrated in an experimental animal model, but also illustrated in clinical presentations [22-24].

Another possibility is via the phenomenon of molecular mimicry following a non-specific viral infection in an individual whose immune system has been previously primed by a viral protein with which it shares some epitope [25]. The molecular mimicry hypothesis suggests that structural similarities between the pathogen and the host are sufficient to induce T-cell activation but not sufficient to induce tolerance [12].

Another interesting study reported a murine model of AHE using a variation of the Theiler's Murine Encephalitis Virus (TMEV) MS model [26]. Authors have shown that during acute TMEV infection, C57BL/6 mice do not normally undergo demyelination. However, when 7 day TMEV infected C57BL/6 mice are intravenously administered the immunodominant CD8 T cell peptide, VP2121–130, animals develop characteristics of human AHLE based on pathologic, MRI and clinical features. These findings highlight two very important concepts. The first one is that a classically non-demyelinating strain can develop fulminant hemorrhagic demyelination by intravenous administration of an immunodominant peptide recognized by CD8 T cells, and second that this hyperacute model of hemorrhagic demyelination is the first TMEV-induced murine model of AHE.

Conclusions

ADEM is rare disease in adulthood, and by some authors it is considered as a MS spectrum disease. However there are clear histopathological characteristics that support ADEM as a separate disease. The strikingly different histopathological features of the two diseases have been long recognized, but in spite of that in many occasions it is difficult to differentiate between different demyelinating diseases based on biopsy samples alone. ADEM has many pathological and clinical expressions and is manifested in many different forms. It may affect single tract, or cause widespread demyelination of the brain and spinal cord, or severe edema mimicking a brain tumor, or localized hemorrhage. It is most often acute and monophasic, but may also recur or rarely become chronic and progressive.

ADEM is an autoimmune disorder and variations in its pathological and anatomical spectrum suggest that differences in

vulnerability to the hyperimmune challenge exist not only between CNS and PNS but also within CNS itself. The variations in response could be regarded as interplay between the individual's genetic endowment, past immunological history and the immunological challenge that determines the type and location of the response implying specific nature of the ADEM response [2].

Authors' contributions

Study concept and design: Habek. Acquisition of data: Habek and Zarkovic. Analysis and interpretation of data: Habek and Zarkovic. Drafting of the manuscript: Habek. Critical revision of the manuscript for important intellectual content: Habek and Zarkovic. Administrative, technical, and material support: Habek and Zarkovic.

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