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General review

Epidemiology of viral encephalitis in 2011

Épidémiologie des encéphalites virales en 2011

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Abstract

Encephalitis is an inflammation of the brain structures: neurons, vessels or glial cells. However, a consensual definition of the syndrome is difficult to obtain, and it is even more difficult to define encephalitis due a specific agent. Most viruses can be responsible for infectious encephalitis, but the number of encephalitis cases is very limited with regards of the incidence of benign infections from these pathogens. Viruses responsible for encephalitis can be animal-borne, vector-borne or human-to-human transmitted, they can infect preferentially immunocompetent or immunosuppressed patients, and some of them have demonstrated their epidemic potential. Herpes simplex encephalitis is recognized worldwide as the most frequent infectious encephalitis, and the only one with a validated specific treatment. Encephalitis following some viral infections such as measles or rabies can be prevented by vaccination. Unfortunately, effective treatment currently lacks for most encephalitic viral agents identified so far.

Keywords: Encephalitis; Virus; Herpes simplex virus; Vector; Vaccine; Outbreak

Résumé

Les encéphalites sont des inflammations des structures cérébrales : neurones, vaisseaux et cellules gliales. Cependant, il est difficile d'obtenir une définition consensuelle du syndrome et plus encore pour une encéphalite liée à un agent infectieux spécifique. La plupart des virus peuvent être responsable d'une encéphalite mais le nombre de cas d'encéphalites reste très limité au regard de l'incidence élevée des infections, en particulier bénignes, dues à ces virus. Les virus responsables d'encéphalites peuvent être d'origine zoonotique, être transmis par des vecteurs ou acquis par transmission interhumaine, infecter préférentiellement des patients immunocompétents ou non, et certains possèdent un important potentiel épidémique. L'encéphalite herpétique est reconnue mondialement comme l'encéphalite infectieuse la plus fréquente, et la seule à disposer d'un traitement spécifique validé. Certaines encéphalites telles que l'encéphalite rougeoleuse ou rabique peuvent être prévenues par la vaccination. Cependant, il n'existe toujours pas de traitement efficace pour la plupart des encéphalites virales connues à ce jour.

Mots clés : Encéphalite ; Virus ; Virus herpes simplex ; Vecteur ; Vaccin ; Épidémie

1. Introduction

Encephalitis is defined as an inflammation of the brain but most commonly addresses infections of the central nervous system (CNS) with brain involvement.

The contrast is remarkable between the high number of infectious agents, especially viruses, which are able to cause it, and the fact that most of these pathogens usually does not cause severe clinical presentations. It is difficult to provide a consensual clinical or biological definition of the syndrome, and it is even more difficult to relate encephalitis to a specific agent.

Viral encephalitis can be considered from various points of view: viral transmission, viral taxonomy, epidemic potential, preferential occurrence in immunocompetent or

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immunosuppressed patients, availability of specific treatment, or vaccines. Some viruses are transmitted by animals while others by human-to-human transmission only. Some are vector-borne and therefore geographically limited, while air-borne transmitted viruses are distributed worldwide. Few of them are prevented by individual or mass vaccination, and even fewer can be treated with specific drugs. Some viral encephalitis feature very evocative symptoms (rabies) and others a wide range of symptoms (ex. West Nile Virus).

Beside viruses, bacteria can also induce encephalitis, with a high incidence in published cohorts [1,2]. More recently, several types of autoantibodies have been demonstrated as important causes of encephalitis, mimicking herpes virus encephalitis [3].

We describe most viruses, or groups of viruses that can cause encephalitis, highlighting their specific epidemiological and/or clinical features (Table 1). We review the available data on their prevalence and their involvement in encephalitis.

2. Viruses

2.1. Herpesviridae

2.1.1. Herpes simplex virus (HSV)

Herpes simplex encephalitis (HSE) is due to the HSV 1 or 2 cycle in the central nervous system. The infection is human-to-human transmitted, and there is no apparent seasonality. HSV is the most frequent cause of infectious encephalitis worldwide (see below part 2).

After the primary infection, the virus remains latent in the trigeminal ganglion and olfactory bulb. HSE is a rare complication, occurring both after primary or recurrent HSV infections, possibly in patients with specific deficiency in the innate immunity [4]. HSV1 is far more frequent than HSV 2, in adult and adolescent HSE. Most cases of HSV2 encephalitis are diagnosed in neonates after exposure to the virus in the genital tract during delivery. For these neonates, the infection presents as a systemic disease, or as skin, eye, and mouth syndrome, or as encephalitis with a case fatality rate of 50% [5].

The main pattern in HSE is the extensive cortex necrosis, affecting temporal lobes most frequently, and frontal or parietal cortex less frequently. Despite this typical pattern, clinical signs are of low specificity and consequences are important on the initiation of treatment. HSE case fatality rate was an average of 70% among patients before there was any specific treatment.

2.1.2. Varicella Zoster Virus (VZV)

Humans are the only reservoir of VZV. The virus is transmitted from human to human by droplets.

As HSE, VZV encephalitis can occur shortly after chickenpox or shingles, or later.

After chickenpox, neurological complications occur in one to two cases/10,000 and usually present as cerebellar ataxia or encephalitis/cerebritis. Neurological complications tend to be more frequent in adults. Various mechanisms are involved: (1) large vessel vasculopathy responsible for hemorrhage and ischemia, (2) small vessel vasculopathy causing demyelinating lesions, (3) ventriculitis [6].

Zoster patients can present with symptoms evocative of meningitis (photophobia, headache) without any CNS involvement. The diagnosis of VZV encephalitis is difficult due to the possible identification of viral DNA in the CSF of zoster patients with normal neurological findings, as well as with CSF showing abnormalities (elevated white blood cell count, elevated protein level) [7]. PCR is widely used for the diagnosis and has a high sensibility, close to 100%, but its specificity in case of zoster is questionable. VZV encephalitis is more frequent in immunocompromized adult patients.

The outcome is usually favorable but can be fatal in patients with severe immunosuppressive diseases such as cancer [2].

2.1.3. Epstein Barr Virus (EBV)

Encephalitis is a rare sporadic presentation of EBV infection. In immunocompetent patients, encephalitis mainly occurs as a short-term complication of mononucleosis and less frequently after a viral reactivation. The cerebellum is frequently involved and myelitis can be associated. EBV encephalitis can be difficult to diagnose in immunosuppressed patients, and it may mimic a tumor [8].

2.1.4. Cytomegalovirus (CMV)

CMV is highly prevalent in humans; most young adults are infected in developing countries and 50–80% of adults are CMV-seropositive in developed countries. CMV encephalitis is rare in immunocompetent individuals and mainly occurs in the course of the primary infection. CMV encephalitis is more frequent in immunosuppressed patients during viral reactivation.

CMV used to be a frequent cause of encephalitis in AIDS patients. Its incidence as a cause of encephalitis has dramatically decreased thanks to combined antiretroviral therapy (cART), but it can still be diagnosed in patients with severe underlying conditions. However, in patients infected by both HIV and CMV, CMV encephalitis is difficult to distinguish from acute HIV encephalitis or HIV dementia.

2.1.5. Human Herpes virus 6 (HHV6)

In 1988, HHV6 was identified as one of the pathogens causing *exanthem subitum*. The infection has been present worldwide as demonstrated by a high prevalence of antibodies; but this prevalence was proved to be lower in people over 40 years of age [9]. Most infected individuals present with no symptoms.

Encephalitis after *exanthem subitum* is rare. HHV6 encephalitis is associated with viral reactivation in transplanted patients. HHV6 is often described as a cause of post-transplant acute limbic encephalitis (PALE) syndrome among recipients of allogeneic stem cell transplantation.

HHV6 was recently demonstrated as able to integrate chromosomes, and consequently viral DNA is permanently present in various body fluids, especially serum, blood, or CSF. It is therefore quite difficult to consider that an isolated positive CSF PCR is a positive diagnosis for HHV6 encephalitis. Such a diagnosis requires quantitative PCR and/or RT PCR (to detect lytic viral mRNA) performed on serum, blood, and CSF to discriminate between acute neuroinvasive infection and chromosomal integration [10].