

Viral Encephalitis through years A changing panorama, a review

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Encephalitis, an infectious or inflammatory process in the brain tissue, mainly caused by a virus, is a disease of children and young adults but may appear at any age. The picture has been changing along with vaccination and new emerging viruses, and along with therapeutic regimens, especially immunosuppression. Conventional childhood viruses, measles, mumps and rubella (MMR), are replaced by West Nile fever and by threat of new influenza strains. DNA detection, especially multiplex PCR, and new neuroradiological methods have improved diagnostic possibilities.

Keywords Encephalitis, central nervous system, virological, etiology, diagnosis

1. Introduction and various entities of encephalitis

Central nervous system (CNS) infections occur worldwide and are concentrated in young ages [1-6]. The term encephalitis is restricted to inflammatory disease in which the infectious agent has been identified. The identification may be difficult and the clinical turnover from encephalitis to encephalopathy may be obscure. Encephalitis is characterised by altered consciousness, focal or generalised seizures, pareses, ataxia, mental change, impaired speech, visual or sensory symptoms. Fever or other signs of infections may be present as well as neck stiffness, i.e. meningoencephalitis.

Encephalitis may be local in limbic, cingulate, and insular areas (a.o. Herpes simplex-1 encephalitis, HSVE), in deep or multifocal hemispheric areas (Rasmussen's encephalitis, syndrome), in mesencephalic and basal ganglia (encephalitis lethargica), in occipital lobe [7-10] or in any area, also in brain stem (Bickerstaff encephalitis) and cerebellum (cerebellitis). Brain stem encephalitis may be caused at least by enterovirus 71 and herpesviruses, VZV, HSV-1, HHV-6, enteroviruses and even *Tropheryma whipplei* may cause cerebellitis [11-14].

Subacute sclerosing panencephalitis (SSPE) is chronic encephalitis caused by measles virus years after childhood measles possibly due to dual viral hit [15]. After vaccination programs in Western countries it now is extremely rare. The same regards progressive rubella panencephalitis (PRP) [16]. In patients with stem cell transplantation measles inclusion body encephalitis (MIBE) has been reported without measles infection or vaccination presenting with afebrile focal seizures [17]. Even mumps may cause chronic CNS disease [18-20]. Progressive multifocal leukoencephalopathy (PML) is a chronic demyelinating disease caused by polyomaviruses [21-23]. Human herpesvirus 6 (HHV-6) is suggested as a cofactor in the development of PML and in HIV encephalopathy [24].

Acute disseminated encephalomyelitis (ADEM) is a severe disease, which seems to have some counterpart in childhood multiple sclerosis [25]. It affects large areas of CNS and localized neurological signs are poor. Motor, cognitive, cerebellar, cranial nerve palsies, seizures and meningeal symptoms may be present. At least enteroviruses, coronavirus and *Pasteurella multocida* have been reported in ADEM [26-29]. Rasmussen's syndrome may with time drop to the same category. Like ADEM, many CNS infections cover several regions of the CNS presenting as encephalomyelitis, meningoencephalomyelitis, myeloradiculitis or even polyradikuloencephalomyelitis [30].

An encephalopathic syndrome can be observed in acute MS or with HIV infection. In HIV dementia, bradykinesia and spasticity may be seen although HAART era has diminished their appearance [31-33]. Some infections progress insidiously to chronic infections, and some chronic diseases may be of

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infectious origin at least partly, MS, parkinsonian disease, amyotrophic lateral sclerosis (ALS) and some other conditions [34-41]. Even a part of mental retardation may represent viral encephalopathy [42,43], as well as psychiatric diseases [44, 45], not to talk of epilepsy [46-49]. Creutzfeldt-Jacob disease (CJD) and the variant CJD (vCJD), bovine spongiform encephalopathy transmitted from cows, known to be caused by prion and are not true viruses, present encephalopathic clinical disease with dementia, psychiatric and sensory symptoms [50]. 14-3-3 Antigen is referred to as a marker for CJD in the cerebrospinal fluid (CSF) [4]. To this series belongs paraneoplasia with encephalomyelitis, cerebellar ataxia or limbic encephalitis with or without microbial cause [10, 51, 52].

2. Viruses causing or associated with encephalitis

2.1. Herpesviruses

Herpesviruses are the best known and large group causing many kinds of CNS infections [11, 53-59]. HSV-1 causes sporadic hemorrhagic HSV-1 with odd but variable symptoms at any age [8, 54, 56]. HSV-1 affects any part of the CNS and diagnosis is always challenging [5, 32, 60]. HSV-2 is more prone to cause meningitis, even recurring Mollaret's meningitis [61]. VZV is now the most frequent single cause of different CNS infections [2, 62]. The probably most neurotropic is human herpesvirus 6 with predilection to several parts of the CNS [12, 63-65] and many chronic CNS problems [24, 66, 67]. CMV, EBV and HHV-8 occur preponderantly in immunocompromised patients. The role of HHV-7 and HHV-8 is thus far somewhat open in CNS infections [50, 68-70]. Double or triple infections have been anticipated with herpesviruses but in association with EBV that has been reported both in immunocompromised and in immunocompetent patients [71].

2.2. Enteroviruses

Enteroviruses, part of the large picornaviridae group, are common invaders of the CNS, mainly meningitides but also different types of encephalitis, cerebellitis and myelitis, which may have fatal course [13, 72, 73]. Coxsackie A and B viruses are most frequent and may be associated with severe organ involvement concomitantly with various CNS infections [74]. Rash may appear especially in Coxsackie A-infections which may present hand-foot-and-mouth disease. Cardiac disease, myocarditis or endocarditis, appears mostly in Coxsackie B infections, and the course may turn fatal [75]. Echovirus 22 can cause severe encephalitis [76]. Enterovirus 71 is known to cause brainstem encephalitis [77, 78]. Hepatitis A is a member of picornaviridae, enterovirus type 72 common in communities with low hygienic standard. Chronic enteroviral infections may occur in immunodeficient patients, especially caused by Echoviruses [79].

2.3 Influenza viruses

The first big influenza pandemic occurred in 1918 killing 40 million people, nearly 10% of victims [80]. Shortly before that epidemic encephalitis emerged as a fulminant encephalitis lethargica in 1916 continuing for years [81, 82]. It was considered influenzal but later on identified poststreptococcal [83]. Hongkong influenza was the first pandemic of Asian origin in 1957 [84]. Both influenza A and B cause various CNS infections in toddlers, in young adults and in elderly people [1, 2, 5, 85-87]. The viruses circulate all-around the year but in Western countries they accumulate in cold seasons. Influenza is of zoonotic origin and their genetic instability makes them unique as emerging threats [3].

2.4. Respiratory and respiratory like viruses

Respiratory viruses, adeno, corona, and respiratory syncytial virus (RSV) may cause encephalitis with acute onset and high fever, mainly in children [1]. Adenovirusinfection may present with delirious state and pulmonary infiltrate but with rapid recovery. Seroconversion, specific IgM and detection of specific nucleic acid or antigen are diagnostic.

Mycoplasma pneumoniae and *Chlamydia pneumoniae*, often called honour viruses, are indisputable causes of CNS infections, mainly encephalitis in hemispherical and even in other sites. Their diagnosis is challenging [47, 88-90]. PCR from CSF is seldom successful. Diagnosis is based on seroconversion or IgM finding in serum.

2.5. Childhood viruses MMR

Measles, mumps, rubella (MMR) group has nearby disappeared from Western countries [91-93]. Measles sometimes caused severe encephalitis. In the 70s mumps was the most common cause of meningitis in children and caused other CNS affections too, including hearing loss [1, 46]. Rubella seldom caused encephalitis, then very severe and sometimes chronic [1, 16].

2.6. Flaviviruses

Togaviruses Western equine encephalitis virus (WEEV) and North American Eastern equine encephalitis virus (EEEV) cause epizootics in appropriate conditions over wide geographic regions. Infected avian hosts may disperse the viruses and all of them may cause severe diseases in humans [94, 95]. Diagnosis is based on serology, virus identification in culture and by PCR. Outbreak of West Nile virus (WNV) appeared in USA in 1999 involving different parts of brain, meninges, brainstem, and spinal cord with focal neurological deficits, even flaccid paralysis [9, 96-102], diagnosed by detecting WNV specific IgM in CSF (and in blood). To the same group belong St. Louis encephalitis (SLE) virus, Powassan (POW) virus, tick borne encephalitis (TBE) virus in Scandinavia, around the Baltic and Central Europe as well as Dengue diagnosed by capture-linked EIA [103].

Californian encephalitis virus and La Crosse (LAC) virus are mosquito-borne and their incidence may be over 20/100,000 in endemic areas. LAC virus encephalitis mimics HSVE and should be considered in children living or travelling in endemic areas in summer and early fall [5, 103-105]. The diagnosis is based on RT-PCR and IgG and IgM antibody-capture EIAs.

2.7. Hantaviruses

Hantaviruses carried by rodents are known to cause haemorrhagic fevers [106]. The Puumala virus disease, nephropathia epidemica, is relatively benign with transient vision loss. It appears throughout Europe whereas Dobravavirus carried by yellow-necked mouse, only in Eastern and Central Europe. Detecting virus-specific IgM is diagnostic but for typing neutralisation antibody assay or RT-PCR is needed.

2.8. LCM and Lassa

Lymphocytic choriomeningitis (LCM) in CNS varies from meningitis to severe encephalitis with fever, chills, cortical paralysis and disorientation, even myelitis or ascending paralysis. It is house mouse mediated. The virus can be cultured from blood and CSF. Serology is possible too [107, 108]. Lassa virus appears mainly in Africa causing meningoencephalitis and sensorineural hearing loss.

2.9. Miscellaneous

In convenient circumstances any microbe may attack CNS. Parvovirus B19, the cause of the fifth disease, erythema infectiosum in childhood, is associated with encephalopathy in sickle cell patients at least [109]. Papovaviruses, JC and BK are persistent, stay in the kidney and may be detected from urine in immunosuppression. JC virus is the etiological agent of PML [21-23].

Human noroviruses, strains from animal caliciviruses, have considerable genetic diversity and transmissibility as well as long shedding in some individuals makes them an emerging threat even to CNS [110, 111].

The highly neurovirulent Borna disease virus (BDV) is associated with psychiatric symptoms in humans. Antibody positivity is evident but the virus is not with certainty isolated from human, possibly due to the short and transient viremia [112-114]. Virus may be identified in brain tissue using immunochemistry. BDV represents a new virus family and is a model to study viral persistence in the CNS [115].

Vaccinia employed as a vaccination for smallpox prevention may cause ADEM [116]. Human herpesvirus B (herpesvirus simiae, the ninth herpesvirus) causes self-limiting meningitis or fulminant encephalomyelitis after having contact with macaque monkeys [117]. Viral culturing, EIA serology, western blotting and MRI confirm the diagnosis.

HIV, visna virus and HTLV-1 belong to the retrovirus group and are associated with chronic debilitating diseases of which HIV forms now its own medical/social disease branch and has pandemic dimensions.

Hepatitis C virus (HCV) has been localised to CNS and it may replicate there [118]. Nucleic acid has been demonstrated both in brain tissue and from CSF. The symptoms may be neurological, cognitive, behavioural, and psychiatric although pathogenic mechanisms are unclear. It is related with WNV and other flaviviruses with significant neurotropism. It often accompanies HIV infection and may like HHV-6 contribute to the development of dementia in HIV patients [119].

Reoviruses and rotaviruses are common and may associate with encephalopathy [120-122]. Rabies is a result of diseased animal's bite with problematic premortem diagnosis [123, 124]. Ebola and Marburg are hemorrhagic fevers carried from endemic areas from Africa.

3. Diagnostic methods

3.1. Virus culture and antigen detection

Viral cultures from throat swab, stool, CSF, blood or tissue sample have been the golden standard in viral diagnostics, nowadays often replaced by tests detecting viral nucleic acid. Detection of viral antigen by immunofluorescence or viral particles in electron microscope suites well in acute conditions, but is seldom useful in CNS infections.

3.2. Polymerase chain reaction

Polymerase chain reaction (PCR) both for DNA and RNA -viruses appears now the method of choice for identification of the cause of CNS infection. Besides qualitative PCR-methods there are now quantitative and real time PCR and multiplex detection is possible for several groups of microbes as well as DNA microarrays [125-129]. PCR may be negative when performed 1-3 days after onset of symptoms, is then positive on days 4 to 7 and declines clearly after two weeks and is negative in nearly all cases after 30 days [62, 130, 131]. The PCR test is highly sensitive and specific [132]. In cases with HSVE, DNA can still be detected after onset of antiviral therapy and may even increase on days 5 to 6 [133]. Viral culture is now replaced by PCR in the major part of viral infections, although culture still is a valuable tool because it may detect unexpected agents.

3.3. Serological tests

Antibody measurement from serum and CSF by enzyme immune assay (EIA) or immunofluorescence (IF) antibody test is the core of diagnosis [2, 134] and immunoblotting in selected cases like AIDS and borreliosis. After tens of years' use serological tests hold out, just the technology is refined, and possibly microarray for antiviral antibodies will be available within a few years [135]. The methods are sensitive and specific, the CNS production of specific antibodies can be measured and at last, if all findings are negative, the test for oligoclonal bands (OCB) from the CSF sample may give clues of etiology [136-139]. Intrathecal antibody production may, although often useful, may be poor in severe herpes encephalitis and in children [62, 140]. The benefits measuring CSF antibodies and intrathecal antibody production are the possibility to identify chronic CNS infections, especially HSVE. After several months or even years antibodies can be detected from CSF and the IgG index is a good marker for that [141, 142]. Seroconversion is a definite diagnostic marker as well as 4-fold increase in IgG level and positive IgM. The two, however, may be positive in recurrences as well. Avidity of IgG antibodies may give diagnosis from one serum specimen and may differentiate primary infections from recurrences [143, 144]. PCR and antibody measurements are both needed in diagnosis of CNS infection [2, 69, 140].

3.4. Oligoclonal band test

OCB positivity indicates presence of specific antibodies in CSF originating from CNE, not from serum. They are regarded pathognomic for MS. The method has been known for 20 years. Just now the methodology is improved and can be applied to different inflammatory neurological diseases and with time the antigen specificity will probably be confirmed [136, 139]. The bands are characteristic to CNS infectious diseases, especially valuable in subacute and chronic CNS diseases.

4. Concluding remarks

The spectrum of CNS infections varies from time to time, outbreaks, even pandemics may occur, and new emerging microbes will rise [91-93, 145, 146]. Any microbe may turn neurotropic in convenient circumstances, especially in immunocompromised patients [147-149]. Choosing adequate diagnostic procedures and timing are important. Detecting one microbe does not exclude other possible agents. Every case with confirmed etiology of CNS diseases will benefit the patient.

Interest in CNS infections goes wavelike with emerging microbes, as examples polio in the 50s, HSVE in the 70s and West Nile virus encephalitis (emerging flaviviruses) in the late 90s as well as numerous rare encephalitides along the increasing numbers of immunosuppression. The WNV outbreak in USA brought an enormous interest in CNS infections, and has greatly stimulated the research.

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