Case report (1301 Words)

Full title

Echovirus 18 Fatal Leukoencephalitis in a Child

Running title

EV-Related Leukoencephalitis

Delphine Brunel¹,³, Jérôme Jacques¹,², Jacques Motte⁴, Laurent Andréoletti¹,²*

¹ Laboratoire de Virologie, Centre Hospitalier Universitaire;
² IFR 53/EA-3798 (DAT/PPCIDH), Faculté de Médecine;
³ Service de Pédiatrie A, American Memorial Hospital, Centre Hospitalier Universitaire;
⁴ INSERM Unité 666 Strasbourg; France.

None of the authors of the present manuscript have a commercial or other association that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy). This work was supported in part by grant for Clinical and Virological research (EA-3798: DAT/PPCIDH) from the Medical University and School of Medicine of Reims, France.

*Corresponding author: Laurent Andréoletti (MD, PhD), Laboratoire de Virologie, Service de Microbiologie, Hôpital Robert Debré, Avenue du Général Koenig, 51092 REIMS Cedex, France. Tel: (33) 3 26 78 39 93; Fax: (33) 3 26 78 41 34; Electronic address: landreoletti@chu-reims.fr
Abstract (50 words):

Rare cases of leukoencephalitis have been reported in infants with documented enterovirus (EV) central nervous system (CNS) infections. A case of fatal encephalitis with white matter lesions caused by an Echovirus 18 is described and it highlights the role of EV CNS infection as potential cause of leukoencephalitis in infants.

Key-words: Encephalitis, Enterovirus, leukoencephalitis, central nervous system infection.
Case report:

The patient described herein, was a healthy 18-month-old male infant who was the first of a three children family without any particular medical history. Twelve hours before his hospital admission, his parents reported fever, vomiting and a general tonic and clonic seizure. On hospital admission, he was afebrile (36.5°C), conscious, feverish and without any particular symptoms on physical and neurological examination. Lumbar puncture revealed the presence of 184 white cells per microliter of cerebrospinal fluid (CSF) with 98% of lymphocytes. CSF protein and glucose concentrations were 2.08 g/L and 3.77 mmol/L respectively, and the blood was 5.74 mmol/L. No bacterial counts were observed after classical staining of CSF.

Moreover, electroencephalogram findings revealed diffuse and excessive slow-wave activity. Initial treatment included ceftriaxone (100mg/kg/day), amoxicillin (100mg/kg/day) and acyclovir (250 mg/m²). Following a new episode of febrile general seizure, this young infant was transferred to paediatric department of the regional university hospital (Champagne Ardenne, France). On admission, he presented a child modified Glasgow score evaluated to 13/15, eyes opening to voice and consolable crying; he was afebrile, tachycardic and normotensive. A second lumbar puncture revealed the presence of 81 white cells per microliter of CSF with 100% of mononuclear cells. CSF protein and glucose concentrations were 3.2 g/L and 3.1 mmol/L respectively and associated with an interferon-alpha value of 12 IU/ml (INF-alpha value was <2 IU/ml of plasma blood). Three days after the beginning of febrile illness, Glasgow score remains the same (13/15) and it was not associated with high levels of C reactive proteins (CRP<3 mg/L). Classical biochemical parameters reflecting metabolic disorders were examined and found to be normal, indicating absence of inborn metabolic disorder.

Two days after the admission of this infant to the university hospital, brain magnetic resonance imaging (MRI) studies with and without gadolinium revealed diffuse hyper signal
The MRI T2 that signals modifications involved symmetrically the white matter of the both cerebral hemispheres those were predominantly located in peri-ventricular and sub-cortical white matter (Figure 1, panels A and C). Seven days after his initial admission to the university hospital, second brain MRI studies revealed extensive and diffuse hyper signal in the sub-cortical and deep white matter of both cerebral hemispheres (Figure 1, panels B and D). At this time, several images evidenced extension of hyper signal in cortical gray matter (not shown).

CSF, peripheral blood, throat and urine samples were tested by classical bacterial culture assays demonstrating an absence of pathogens. These serum samples demonstrated an absence of specific IgM and IgG antibodies directed against Mycoplasma and Chlamydia pneumoniae by ELISA detection assays. The presence of protective post-vaccination IgG levels against mumps, measles, rubella associated with an absence of anti-HBV and anti HIV-1 and 2, influenza types A and B, adenovirus, varicella zoster virus, human cytomegalovirus and coxsackievirus B4 specific antibodies was demonstrated in the same serum samples tested by ELISA detection assays, whereas the presence of anti-Epstein-Barr virus antibodies was assessed by western-blot assay demonstrating a profile compatible with an old infection (not shown). An EV strain was isolated from a throat sample by classical viral cell culture techniques, and it was then identified by micro-seroneutralisation technique as a non-typable echovirus strain (not shown).

PCR analysis for Herpes viruses did not show any amplification and thus excluded the possibility of herpesvirus encephalitis. The use of a standardized EV RT-PCR assay followed by micro-well hybridization assessed the presence of EV genomic RNA in throat and CSF samples (1). Genotyping of these EV strains by partial amplification and sequencing of VP1 gene, revealed 100% sequence homology both in throat and CSF samples of this infant.
The phylogenetic analysis placed them closest to Echovirus-18, which was circulating during the same epidemic season (Figure 2) (2).

Four days after the beginning of febrile illness, high IV solumedrol bolus-dose of 1 gr/1.73m2/day was delivered during three days with no improvement of clinical symptoms and neurological signs. Within the two days after the initiation of this corticosteroid therapy, this infant developed generalized seizures that were successively treated by intravenous clonazepam (0.2 mg/kg/day) and oral valproic acid (24 mg/kg/day). The appearance of dysautonomic troubles associated with a Glasgow score to 8/15 implies a rapid admission of this infant in a paediatric intensive care unit. This patient died 8 days after the beginning of the infectious syndrome by major cerebral oedema inducing a bilateral cerebellar tonsils herniation. No autopsy was carried out.

Enteroviruses (EV) (Picornaviridae), specifically echoviruses and cosackieviruses A or B, are usually responsible for aseptic meningitis occurring in summer and falls in young infants (3). Moreover, EV can induce acute cerebral lesions and could account for 11 % of the total number of viral encephalitis cases in the general population (4). In contrast to aseptic meningitis, encephalitis due to EV can cause focal grey matter lesions in infants and may be responsible for neurological impairment (1,4). Rare cases of encephalitis with white matter lesions have been reported in infants with documented EV central nervous system (CNS) infections (5-8). EV-related leukoencephalitis has been previously reported by David et al. who described a potential case of acute disseminated encephalomyelitis (ADEM) after coxsackie B infection, and more recently by Mariotti et al. and Saitoh et al. who described positive EV PCR detection in the CSF of children with radiological features of ADEM (5-7). In the present case report, radiological findings of the patient and detection of EV genomic RNA are highly suggestive of infective...
meningoencephalitis (6). MRI brain findings showing symmetrical diffuse hyper intense signals on T2-weighted studies located predominantly in periventricular and subcortical white matter, are not suggestive of an ADEM (Figure 1) (7). Moreover, serological results and vaccine management do not favor for recent post-infectious or post-vaccinal events that may have potentially induced immune-mediated mechanisms responsible for ADEM in this infant (8).

The use of a standardized EV-RNA PCR followed by hybridization assay allowed us to determine the presence of EV genomic RNA in the CSF sample of the study infant (1). This positive EV molecular detection associated with high levels of IFNα was compatible with a viral CSF in this study (1,3). Moreover, RT-PCR amplification of the VP1 gene and amplicon sequencing has been used to identify genetically identical echovirus-18 strains in paired CSF and throat samples (figure 2) (2). This documented echovirus-18 CNS infection appeared as the only evident cause responsible for the development of the neurological syndrome, therefore demonstrating that EV infection can cause meningoencephalitis with diffuse and extensive white matter lesions in infants aged more than 12 months. EVs are neurotropic agents, which are also capable to infect in vitro cultured glial cells (9). Moreover in mice models, it has been demonstrated that Theiler’s virus (picornaviridae) could not only replicate in glial cells but also induce viral immune mediated mechanisms responsible for the destruction of non-infected white matter cells producing myelin-specific mRNAs (10). Therefore in the present case, we hypothesized that an active EV CNS infection may have initiated an infective meningoencephalitis with white matter involvement.

PCR based assays had been demonstrated to have distinct advantages over cultures methods for diagnosis of encephalitis due to EV, therefore, these techniques should help to define more precisely the significance of these viruses in infants with encephalitis (3). However, it is likely that the frequency of acute encephalitis with EV infection is underestimated, because
of it is not usual to perform cranial MRI scans associated with EV PCR detection assay in CSF of all infants with acute or sub-acute onset of general or multifocal neurological symptoms (6).

Along with, this report highlights the role of EV central nervous system infections as potential cause of leukoencephalitis in infants. Moreover, our findings suggest that the use of RT-PCR techniques for the detection of viral infection in the CSF may be valuable for the medical management of infants with leukoencephalitis.

Acknowledgements:

This work was supported in part by grant for Clinical and Virological research (EA-3798: DAT/PPCIDH) from the Medical University and School of Medicine of Reims, France.
References:


Footnotes of the Figure 1:

(A,C): Axial T2-weighted diffuse hyper intense signals, with a particular predominance in periventricular and subcortical white matter of the both cerebral hemispheres at the second day after the symptoms onset (see the arrows).

(B, D): Seven days after symptoms onset, the axial T2-weightened study revealed an extension of diffuse cerebral hyper signals in the sub cortical and deep white matter of both cerebral hemispheres (see the arrows).
Figure 1. MRI brain studies (Axial T2-weightened):
Figure 2. Comparison of the VP1 gene sequences of the two echovirus-18 strains isolated from samples of the case report, with those obtained from other co-circulating EV strains isolated in the throat of some infants with classical aseptic meningitis during the same epidemic season.

A

B