Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Cytomegalovirus encephalitis in an immunocompetent child: a sceptic diagnosis

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Summary

The authors present the case of an apparently immunocompetent 9-year-old child with probable cytomegalovirus encephalitis. The clinical picture was characterised by fever, frontal headache and behavioural changes, associated with visual and auditory hallucinations. Cerebrospinal fluid (CSF) biochemistry and brain CT were normal. Electroencephalography showed left temporal paroxysmal activity. Diagnosis was based on cytomegalovirus (CMV) DNA detection on the CSF by PCR. Acyclovir and ceftriaxone were given until herpes simplex virus (HSV) and bacterial encephalitis were ruled out. Rapid resolution of fever and complete clinical recovery was observed. Remarkably, anti-CMV serum antibodies were not detected on admission or until 6 months later. This discrepancy led us to question the presence of an impaired specific host humoral response, immune evasion by the virus or a false-positive result for CMV DNA in CSF.

BACKGROUND

Human cytomegalovirus (CMV) is a ubiquitous pathogen with a worldwide seroprevalence that may range from 60 to 100%.¹ The morbidity and mortality of this infection is well documented among immunocompromised patients. On the other hand, primary infection in the immunocompetent host is usually asymptomatic or has a benign and self-limited course, presenting as an undifferentiated viral infection or a mononucleosis-like syndrome. Occasionally, CMV infection may cause severe disease in the immunocompetent host, the gastrointestinal tract and the central nervous system being the most frequently involved organs.^{1 2}

In the medical literature, CMV encephalitis in the immunocompetent is limited to a minority of case reports. The clinical presentation usually consists of fever, headache, altered level of consciousness, significant change in personality or behaviour, seizures or focal neurological signs.³ The aetiological diagnosis should be based on virus isolation from cerebrospinal fluid (CSF) by PCR or through detection of specific intrathecal antibody production.⁴ PCR techniques allow nucleic acid amplification, making it possible for rapid detection of as few as 1–10 copies of a target DNA from the original sample. As a result this is an extremely effective method for diagnosis, with a high sensitivity and a specificity of 86–100%.⁵ Serology is less useful for diagnosis as there is a 2–4 week delay in obtaining a rise in antibody titres.^{4 5}

CASE PRESENTATION

A 9-year-old girl presented to the emergency department with behavioural changes associated with repeated visual and auditory hallucinations. Low-grade fever (38.3°C) and a bilateral frontal headache were reported beginning 2 days earlier. There was no history of substance abuse, head trauma or recent travel. Immunisations were up to

date according to the national vaccination calendar, diphtheria, tetanus, and pertussis/polio (DTaP/IPV) and measles, mumps, and rubella (MMR) being the last vaccines administered in 2007. She had a medical history of development dysplasia of the hip and uncomplicated chickenpox at the age of three. Family history was irrelevant. On admission she was conscious, oriented and speech was adequate, but she was anxious and agitated. Her tympanic temperature was 37.3°C and her vital signs were stable. Her pupils reacted normally to light and ocular movements were normal. No facial asymmetry or motor weakness was noted. There were no abnormal movements or postures. Reflexes were normal and Babinski was negative. Nuchal rigidity, Kernig and Brudzinski signs were absent. The rest of her physical examination was normal, with the exception of an inflamed pharynx.

INVESTIGATIONS

On the day of admission, laboratory investigation included a white blood cell count of 5800/μl (5–13 000/μl) with monocytosis (13%), haemoglobin and platelets on the normal range and C reactive protein of 18 mg/dl (<5 mg/dl). The urine was negative for benzodiazepines. CSF at presentation revealed leucocytes 9/mm³ (<19/mm³), some erythrocytes, protein 30 mg/dl (15–45 mg/dl) and glucose 71 mg/dl (40–70 mg/dl). Gram stain and cultural exam of CSF were negative. PCR for detection of viral nucleic acid in the CSF was positive for CMV DNA. PCR was negative for herpes simplex virus (HSV) 1 and 2, human herpes virus 6 and 7 and enterovirus RNA in CSF. Blood serology for CMV at presentation and after 4 weeks failed to demonstrate the presence of either IgG or IgM antibodies directed against the virus. Serology was also negative for *Mycoplasma pneumoniae* and Epstein-Barr (EBV) virus on

admission. Blood culture was negative. Neuroimaging revealed a normal brain CT scan and electroencephalography showed posterior left temporal paroxysmal activity.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included encephalitis caused by other infecting agents, autoimmune encephalitis, systemic infections, toxin ingestion or epilepsy.

TREATMENT

Empiric therapy with intravenous acyclovir and ceftriaxone was started on admission. Both were stopped on day 7 based on a negative result for HSV viral nucleic acid in the CSF by PCR and negative blood and CSF cultures.

OUTCOME AND FOLLOW-UP

Outcome was favourable with resolution of fever on the day after admission and no further hallucinations were reported.

On follow-up at 4 weeks, she was doing well, with no behavioural disturbances and a normal neurological examination.

At 3 and 6 months, repeat serology for CMV remained negative. Serology for EBV remained negative at 6 months.

Serum immunoglobulins (IgG, IgM and IgA) and IgG subclasses (IgG1, IgG2, IgG3 and IgG4) were normal. Antibody levels to diphtheria and tetanus were above 0.1 UI/ml indicating an adequate response to immunisation.

DISCUSSION

We present the case of an immunocompetent 9-year-old child with probable CMV encephalitis. The diagnosis of CMV encephalitis is based on the clinical presentation of fever, headache and hallucinations and the detection of CMV DNA on the CSF by PCR. A concomitant search of CMV in serum, urine or throat swab would have supported this aetiological diagnosis. Interestingly, anti CMV serum antibodies could not be detected at presentation of symptoms or until 6 months later, casting doubt on the diagnosis. Seroconversion as late as 5 months after the beginning of illness has been previously reported in the literature.⁶ Primary or acquired immunodeficiency could explain the lack of specific antibodies, but absence of recurrent infections, a favourable clinical outcome and normal serum immunoglobulins and IgG subclasses, makes this an unlikely option. A normal specific IgG response to the diphtheria and tetanus immunization also speaks against immunoglobulin deficiencies. Nonetheless, the pathogenesis of most infectious diseases remains unknown in the vast majority of patients. Environmental microbial or non-microbial factors and genetic or non-genetic host factors contribute in various ways to this complex process. Single-gene predisposition to more common pathogens in otherwise resistant children has been documented, as illustrated by HSV encephalitis in patients with UNC-93B, TRAF3, and TLR3 deficiency.⁷ Through the years, herpes viruses have evolved mechanisms to modulate the host immune response, either by immune evasion or by induction of specific immune

responses modification to allow viral survival. Among these virus, CMV encodes the greatest number of genes committed to changing both innate and adaptive immune responses.⁸ In the case presented, lack of antibodies directed against the virus could represent a specific humoral response evasion in isolation, or in combination with a single-gene inborn error of immunity. A false-positive result should also be considered. Cross-reaction between CMV and EBV has been described, but in the case presented a negative EBV serology on admission and at 6 months makes this an unlikely alternative. In this case scenario, a wider search for other aetiological agents including adenovirus, influenza, mumps and *Borrelia burgdorferi* may have been useful.

Learning points

- Cytomegalovirus should be considered in the aetiological investigation of acute encephalitis in an immunocompetent patient.
- A positive cytomegalovirus PCR result from the cerebrospinal fluid in an immunocompetent patient requires careful interpretation with regard to the individual clinical context and should be followed up by a peripheral blood PCR.
- Lack of seroconversion should raise the possibility of an immune defect, which may not always be explained.
- Extensive aetiological investigation should be undertaken to include the most likely infective agents, and in the presence of negative results autoimmune encephalitis may also be considered.

Competing interests None.

Patient consent Obtained.

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