Case report

Child with cytomegalovirus associated acute demyelinating encephalomyelitis: a case report

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Abstract:

Cytomegalovirus (CMV) is a common virus that causes mild, self-limiting illness in immunocompetent individuals. However, CMV is also frequently associated with acute demyelinating encephalomyelitis (ADEM), which is an uncommon monophasic idiopathic inflammatory demyelinating disease. It affects both children and adults. This is a case of unfortunate boy with CMV infection which was complicated with ADEM. Prompt diagnosis and aggressive treatment had provided a good outcome in this patient.

Keywords: CMV; ADEM;immunocompetent; children.

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Introduction:

Acute disseminated encephalomyelitis (ADEM) is an autoimmune disease that affects the central nervous system particularly the white matter by causing acute demyelinating disease and rarely affecting grey matter and spinal cord. Children under 10 years are affected by ADEM, with male predominance[1, 2]. It mostly arises 2 to 40 days after an infection but seldom after vaccination[2]. Some rare cases have been reported after a snake's envenomation or following antivenom administration[3]. But most of the time no infectious or causative agents are identified. One of the common organisms that are associated with ADEM is Cytomegalovirus. It is well known that CMV causes central nervous system (CNS) infections in immunocompromised patients but CMV infection in healthy individuals is mostly subclinical even though there was reports describing CMV encephalomyelitis in immunocompetent individuals as well [4]. The prognosis for the patients with isolated CMV encephalitis was excellent in contrast to those with multiorgan or non-CNS infection [5]. Fatal death following CMV infection has also been reported due to fulminant variant, acute hemorrhagic leucoencephalitis (AHLE)[6]. Recently we encountered a case of CMV-associated ADEM after an interval of 3 weeks following acute tonsillopharyngitis with non-residual sequelae in a previously healthy child.

Case report:

An 11-year-old boy presented to general practitioner with ataxia and altered behavior, described as slow responder, frequent blank stare and always sleepy for three weeks. Otherwise, there is no documented fever, fitting episodes, preceding head trauma, nor symptoms of respiratory or urinary tract infection. Three weeks prior the onset symptoms, the patient was admitted to a district hospital for 11 days. He was initially treated as acute tonsillopharyngitis but noted to have an unresolved fever for 2 weeks thus was investigated and treated for prolonged fever during that admission. Fortunately, he responded to antibiotics. The investigations for blood for malaria parasites as well as urine and blood cultures were negatives. He was discharged home well. He has been well for 3 weeks before the mother noticed the changes. Pre-morbidly he was an average kid who was actively involved in sport at school. His birth history was uneventful. His immunization was up to age. He is the youngest in the family and none of the family members has any neurological disorders.

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He was then referred for admission for further evaluation.

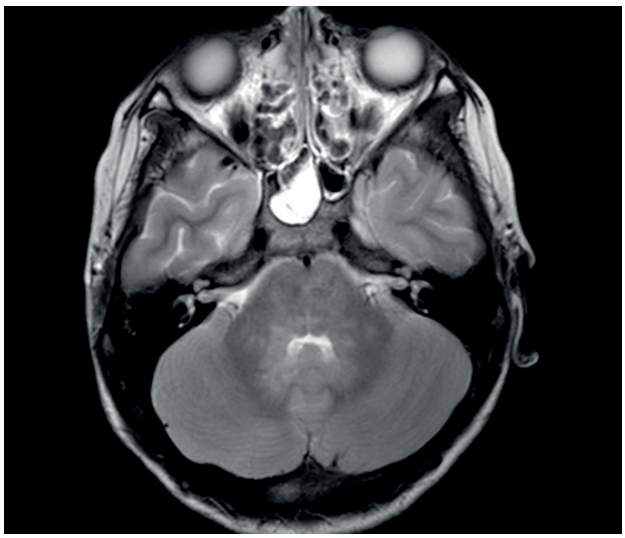
Examination revealed a sleepy child,with normal vital signs. There were positive cerebellar signs and vertical nystagmus. No signs of meningism were noted. Neurological examination noted increased tone and reduced power over both upper and lower limbs with hyperreflexia over left limbs and clonus was seen over right side.Sensory examination was intact. Other examinations were unremarkable.At first, meningoencephalitis, X-linked leukodystrophy, spinal cerebellar atrophy and anti-N-methyl-D-aspartate (NMDA) receptor encephalitis were considered as differential diagnoses.

Initial investigations revealed no leukocytosis. Electrolytes and liver function tests were normal. CRP was 22 mg/L. ASOT was negative. Mycoplasma IgM, toxoplasma-IgM and IgG, CMV-IgM and HSV2 IgM were negative, but this patient has positive serology of CMV IgG (291.9 U/ml) and HSV1 IgG positive. However, cultures for HSV 1&2 were negative for both as well as blood cultures were negative for any organism. No paired CMV-IgG and PCR were done for this patient. Immunological parameters were positive for ANA (1:160, speckled type), C3/C4 were within normal limits. Cerebrospinal fluid (CSF) analysis showed cell count was 15 cells (100% lymphocytes), protein 0.46 g/L and glucose was 3.3 mmol/L (random blood glucose was 5.2mmol/L). CSF latex test was negative for all bacterial pathogens and cultures showed no growth.

Contrasted CT brain done on admission showed normal brain study. MRI of the brain was done subsequently which showed symmetrical bilateral abnormal signal intensities seen involving bilateral corona radiate, internal capsule, basal ganglia, thalami, midbrain, pons, periaqueductal and periventricular at 4th ventricle region. It shows ill define heterogeneous hypointense signal intensity on T1, hypointense on T2, not suppressed in FLAIR. Some area in the basal ganglia shows restriction on DWI. Some areas on thalamic shows minimal patchy enhancement post-contrast which may represent ADEM and differential diagnosis of Multiple Sclerosis (MS). This patient was referred to an ophthalmologist for possible optic neuritis, however, the eye assessment was normal. EEG was also done, revealed no epileptic or any changes to suggest viral encephalitis. There is some slowing of the background of acute encephalopathic changes (no alpha activity posteriorly). The diagnosis of ADEM was considered because of clinical presentation and the positive serological findings of CMV infection and MRI findings.

The child was started on IV methylprednisolone 900mg od for 5 days followed by oral prednisolone for 2 weeks following tapering regime. Intravenous acyclovir 550mg TDS and Rocephin 1.6mg OD were given in keeping with possible meningoencephalitis. He remained afebrile throughout the admission and neurologically improved by resolution of ataxia and absence of cerebellar signs within 2 weeks.

Figure 1: *T2 weighted MRI image at posterior fossa.*



Abnormal high signal intensity surrounding the fourth ventricle.

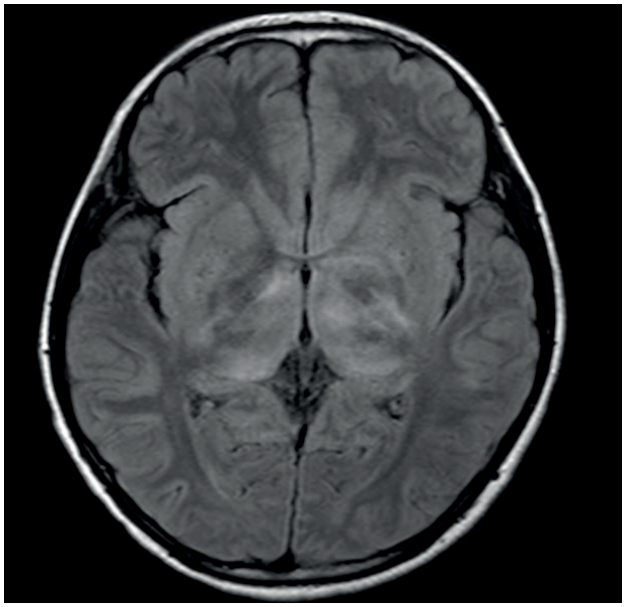


Figure 2: *Axial MRI in FLAIR sequence shows abnormal hyperintense signal within bilateral basal ganglia and internal capsule.*

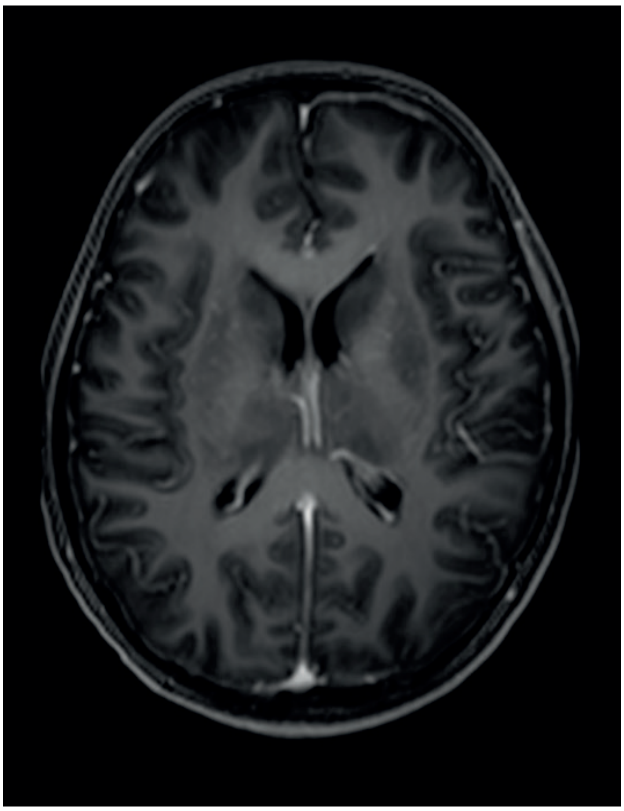


Figure 3: *Axial slice contrasted T1 image show the abnormal signals are not enhanced.*

Discussion

In the 60-70s Malaysia was highly endemic for cytomegalovirus infection. CMV is the most known cause of congenital infections and 10.4% causes of CNS infection[7]. Cytomegalovirus is one of herpes viruses, and it infects only humans. Primary infection in immunocompetent persons is usually minimal and self-limiting, characterize by malaise, protracted fever, mild hepatitis, and lymphocytosis with atypical lymphocytes occurring inapproximately 10% of cases, but infrequently patients may develop a fulminant infection that manifests as multiple organ involvement and marked constitutional symptoms[5].

CMV complicated with ADEM is not rare but it is not commonly found especially in primary care. This case highlights the importance ofconsidering CMV infection in previously healthy child with severe viral infection especially when there is multiple organs involvement. The exact pathophysiology on how CMV causes ADEM in immunocompetent individuals is still unclear. It has been postulated that T cell-mediated cross-activation and response against myelin proteins, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein (MOG), through a mechanism of molecular mimicry cause ADEM. Another pathogenic possibility is a non-specific self-sensitization of reactive T cells against myelin proteins secondary to infections localized in the CNS[2]. The autoimmune hypothesis is supported by the presence of anti-MOG antibodies in the cerebrospinal fluid (CSF) and the reduction to undetectable levels in follow-up samples of children with the monophasic disease[8].

In most cases, ADEM follows a trivial infection, mainly upper respiratory tract infection, whereas only less than 5% of cases are vaccination related. In this case, the presentation is prominent 3 weeks after his admission for acute tonsillopharyngitis, longer than the usual latent period of 7-14 days [9]. The presentation may vary among individuals from a mild headache to seizures, loss of consciousness, vision loss, dysarthria, aphasia, facial palsy, quadriplegia and ataxia [10]. The prominent clinical features are a change in behavior and/or in consciousness and it is accompanied by encephalopathy with a monophasic course, often resolving after treatment within three months of its onset. The relapses might occur in 20–30% of cases[2].In childhood ADEM, prolonged fever and headaches occur more frequently, but in adult cases, motor and sensory deficits are more prominent[9]. In our case, this child presented with ataxia and excessive sleepiness for 3 weeks after an episode of prolonged fever and tonsillopharyngitis.

The diagnosis is considered straightforward when ADEM occurs after an exanthem or immunization. A clear-cut latent period between systemic symptoms such as fever, malaise, myalgias, headache, nausea, and vomiting and neurological illness favors ADEM along with the typical pattern of diffuse and multifocal involvement of both the central nervous system and peripheral nervous system and the characteristic MRI appearance. However, the challenges begin when there are no apparent prodromal symptoms which might be confused with the first onset of multiple sclerosis or other immune-mediated encephalitides that could occur in the pediatric age namely Hashimoto's encephalopathy, Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, Limbic encephalitis and Rasmussen encephalitis[2].

The initial management was to treat as CNS infection even though blood parameters and the initial CT brain were normal. Furthermore, the diagnosis of the case was delayed by parental refusal for lumbar puncture (LP) due to misconceptions about the procedure. After through explanation about the procedure, we managed to convince the mother

to agree with LP. Lumbar puncture has excluded active meningoencephalitis. In ADEM, CSF can be normal or show lymphocytic pleocytosis and/or increased level of proteins which was seen in this case. The most important CSF finding is the absence of oligoclonal bands, which are typical of MS. Cell culture and molecular biology techniques for bacteria and viruses in CSF are commonly used, but their diagnostic value is uncertain because they are often negative and does not contribute to the diagnosis[10].

Diagnosis of ADEM could be unfocused because of uncertainties on etiopathogenesis, can lead to delay in establishing appropriate therapy. In this case, lack of knowledge and awareness about the disease and the perception of mild symptoms by the caretaker which was probably one of the causes for the delay in seeking health care for this patient. It took three weeks after the onset of symptoms for the parents to bring the child for medical attention. In addition, a common misconception about the clinical procedure such as lumbar puncture has slightly delayed the treatment. It is very crucial to diagnose the illness early and provide adequate therapeutic support in order to have a favorable outcome with full recovery. However, in the case of diagnostic delay or the case of inappropriate treatment, some children might develop neurological sequelae or persistent deficits and progress to MS[10]. As for this case, despite delayed presentation, the diagnosis of ADEM was considered in view of high clinical suspicioun supported by initial investigations that don't fit into infective causes, thus has led the pediatrician to do MRI to support the diagnosis.

MRI is the most useful technique to confirm the diagnosis of ADEM. The lesions are more often identified in T2-weighted and fluid-attenuated inversion recovery images as multifocal, irregular, poorly marginated areas with diameters between 5 mm and 5 cm.They usually involve the subcortical and central white matter of the entire CNS, particularly frontal and temporal lobes, including also spinal cord and brainstem. Even gray matter of thalamus and basal ganglia can be involved, but lesions are mainly in the cortical gray-white junction. Five patterns have been proposed to describe CNS lesions which includes ADEMwith small lesions (<5 mm), ADEM with large confluent white matter asymmetric lesions, ADEM with symmetric bithalamic involvement, ADEMwith a leukodystrophy pattern with diffuse bilateral and usually non-enhanced white matter-sited lesions, and ADEM with acute hemorrhagic encephalomyelitis. However, these patterns seem unrelated to the overall clinical course [2].

There is no standardized therapy for ADEM.Currently, the most widely used treatment is immunosuppression because of the presumed autoimmune etiopathogenesis of this encephalomyelitis [2]. As most children present with meningism, fever, and acute encephalopathy, with evidence of inflammation in blood and CSF, they should be covered initially with appropriate antibiotic and acyclovir until a diagnosis can be established. Once the diagnosis of ADEM is established, treatment usually commences with 3–5 days of intravenous methylprednisolone (20–30 mg/kg/day), with or without the following course of oral prednisolone commencing at 2 mg/kg/day and tapering over 4–6 weeks, depending on resolution of clinical signs. In children who have early relapses or in whom there has been a delay in diagnosis, intravenous methylprednisolone is used for longer duration, depending on the clinical responses [10]. Other alternative options include dexamethasone, intravenous immunoglobulins, and plasmapheresis[9].

Conclusion

In view of our previous high prevalence rate of CMV infection in Malaysia, our case has highlighted an important spectrum of CMV infection with ADEM. The challenges occur in term of delayed onset of the symptoms, the recognition and awareness of more sinister complication of CMV infection and the absence of diagnostic tools or markers for the confirmation of ADEM. The mainstay of diagnosis is based on MRI findings. This could be a nightmare for managing team in places where MRI facilities is not available which may lead to delayed commencement of immunosuppressive therapy. Fortunately for this case, prompt diagnosis and treatment has prevented the development of more serious complications.

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Authors contribution: All authors contributed equally to this work.

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