ACUTE DISSEMINATED ENCEPHALOMYELITIS FOLLOWING A DIPHTHERIA-PERTUSSIS-TETANUS VACCINATION: A CASE REPORT

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ABSTRACT

Introduction: *Acute disseminated encephalomyelitis (ADEM) is a rare, acute progressive autoimmune disease that occurs in the brain and spinal cord, in response to infection or immunization. Myelin autoantigens could share similar antigenic determinants with a pathogen and cross-react with a human's antibody, causing demyelination of the nerve sheath. Identifying ADEM is essential to treat the patient and reduce any sequelae.* ***Case description:*** *An 11-year-old male was brought to the ER with one day of weakness of the face and the left side of the body. Along with that, the patient vomited, complained of headache and fever. One day prior, the patient received a Diphtheria-Pertussis-Tetanus Vaccination at his elementary school. A head computer tomography (CT) scan with contrast was done and showed multiple hypodense lesions in the bilateral internal capsule, bilateral lateral periventricular, subcortex of the right frontal lobe, and right cerebellum, with suspicion of ADEM.* ***Discussion:*** *There were many clinical signs of patients with ADEM, depending on the lesion. Brain and cerebellar lesions can cause irritability, confusion, coma, incoordination, and gait problems. Spine lesions can cause numbness and paralysis of the limbs. Lesions in the cranial nerve can cause dysarthria, blurry vision, double vision, and facial weakness.* ***Conclusion:*** *The prognosis for ADEM is good and often has improvement within a month. However, some patients need to undergo supportive therapy as appropriate. Further follow-up needs to be done to evaluate the disease progression, as ADEM may be manifesting as Multiphasic ADEM or any other demyelinating disease.*

Keywords: ADEM, Children, DPT Vaccination.

ABSTRAK

Pendahuluan: Ensefalopati Diseminasi Akut (ADEM) adalah penyakit autoimun langka yang bersifat akut progresif, yang terjadi pada otak dan medulla spinalis sebagai akibat dari infeksi atau imunisasi. Myelin autoantigen dapat memiliki determinan antigen yang serupa dengan pathogen, sehingga terjadi reaksi silang dengan antibodi, yang menyebabkan adanya demyelinisasi. Penting untuk mengenali gejala dan karakteristik ADEM dalam kaitan pemberian terapi lanjutan untuk mengurangi risiko kecacatan. **Deskripsi Kasus:** Seorang anak laki-laki berusia 11 tahun dibawa ke IGD RS dengan keluhan lemas pada wajah dan sisi kiri tubuh sejak 1 hari yang lalu. Selain itu, pasien mengeluhkan muntah, nyeri kepala sisi kanan dan panas. Sehari sebelumnya, pasien diberikan imunisasi DPT di sekolah. Saat dilakukan CT Scan kepala dengan kontras pada pasien didapatkan adanya lesi hipodense multiple pada capsula interna kanan-kiri, periventrikel lateral kanan-kiri, subcortex lobus frontalis kanan dan cerebellum sisi kanan, suspek ADEM. **Diskusi**: Terdapat beberapa gambaran klinis pada pasien dengan ADEM, tergantung dari letak lesi. Lesi pada otak dan cerebellum dapat menimbulkan gejala iritabilitas, gangguan kesadaran, inkoordinasi dan gangguan gait. Gangguan pada medulla spinalis dapat menyebabkan rasa hipestesia dan paralisis pada anggota gerak. Lesi pada saraf pusat dapat menyebabkan disatria, pandangan kabur, pandangan dobel, dan kelemahan pada otot wajah. **Kesimpulan:** Prognosis ADEM pada umumnya baik dan sering kali mengalami perbaikan dalam 30 hari. Akan tetapi, beberapa pasien masih memerlukan terapi suportif sesuai kasusnya. Evaluasi lebih lanjut diperlukan untuk menilai perjalanan penyakit, karena ADEM dapat bermanifestasi sebagai ADEM Multifasik atau penyakit demyelinisasi lain.

Kata Kunci: ADEM, Anak, Vaksinasi DPT

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INTRODUCTION

Acute disseminated encephalo-myelitis (ADEM) or post-infectious encephalomyelitis, is an acute, rapid progressive autoimmune process that is characterized by demyelination in the brain and spinal cord as a result of inflammation that occurs in response to infection or immunization[1,2]. ADEM is more commonly associated with viral infections of the gastrointestinal or respiratory tracts[2].

Viral causes for ADEM are Coxsackie Virus, Hepatitis Virus, Influenza Virus, Varicella-Zoster Virus Epstein-Barr virus, Human Herpes Virus, Herpes Simplex Virus, Cytomegalovirus, and Human Immunodeficiency Virus. Bacterial causes are Mycoplasma, Chlamydia, Salmonella, Campylobacter, Leptospirosis, and group A β-hemolytic streptococcus [11,14]. Immunization such as Rabies, BCG, Diphtheria, Pertussis, Tetanus, Measles, Rubella, Meningitis, Influenza, Japanese B encephalitis, Varicella, HPV, Poliomyelitis, and Pneumococcus, have been reported to cause ADEM[1,9].

Primarily, ADEM affects children with the average onset around 4-8 years[3,9]. ADEM can be found in about 3-6 cases per million children a year. ADEM has a slightly male predominance and is genetically related[9,13]. In this study, we report a case of ADEM following a Diphtheria-Pertussis-Tetanus Vaccination. This study is made is to discuss the symptoms and signs, diagnostic workups, and the treatment for ADEM.

CASE DESCRIPTION

An 11 year old male was brought to the ER with one day of weakness of the face and the left side of the body. Along with that, the patient vomited and complained headache on the right side of the head. One day prior, the patient received a Diphtheria-Pertussis-Tetanus Vaccination at his elementary school. After the vaccination was given, the patient had a fever and headache. The patient didn't experience any Coryza-

like symptoms or any illness before. There was no decrease in consciousness, seizure, or trauma history. The patient had never experienced similar symptoms before. His developmental history was normal, but his growth history was below normal, based on the patient's Kartu Menuju Sehat (KMS) Chart. The patient's father had the same symptoms of weakness following vaccination when he was a child.

On admission, the patient was awake but slightly confused (Glasgow coma scale score of 13 to 15, fluctuative). He was afebrile nor distressed. Neurological examination revealed a left facial palsy, central type paralysis on the left 7th cranial nerve, and on the left and right 3rd cranial nerve. He also had a decreased motoric strength, both scored 2 and 3 each on the left upper extremity and left lower extremity, according to Muscle Grading System (ASIA), whilst the right side both scored 5. There was no rigidity on the neck, but a decreased physiological reflex on the affected side. He also had positive pathological reflexes on the left side of the body. Fundoscopic examination revealed no signs of abnormality. The patient's neurological deficits combined with the history of the disease suggested a primitive diagnosis of encephalitis.

Several laboratory tests were done, including a complete blood test, electrolyte serum (i.e. serum Na^+, K^+, Cl^-, and Ca^{2+}), albumin, blood urea nitrogen, and creatinine. Slight differences were found in the results of serum K^+ (3.19 mmol/l, normal: 3.50-5.10 mmol/l), serum Cl^- (102 mmol/l, normal: 97-100 mmol/l). However, the other results were within normal limits.

Due to limited facility, magnetic resonance imaging (MRI) scan on the brain and lumbar puncture weren't done. Instead, the head computer tomography (CT) scan with contrast was done and showed multiple hypodense lesions in the bilateral internal capsule, bilateral lateral periventricular, subcortex of the right frontal lobe, and right cerebellum, with suspicion of ADEM.

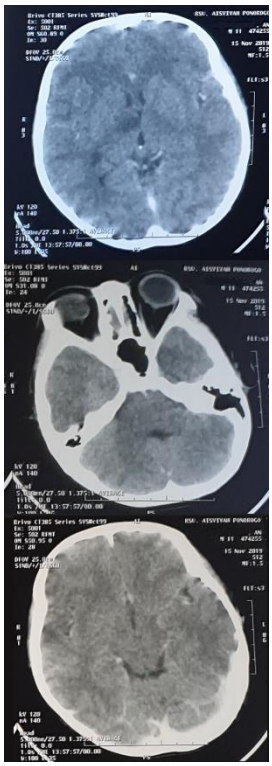

Figure 1. Brain CT Scan with Contrast

Initial broad-spectrum antibiotic (Ceftriaxone (40 mg/kg/dose; IV, q2 h)), a nootropic drug (Piracetam (10mg/kg/dose; IV, q3 h)), PPI agent (Lansoprazole (0.5-1mg/kg/dose; IV, once daily)), and symptomatic therapy of antipyretic and anti-emetic were applied. Methylprednisolone IV for 4 days (at 2.5 mg/kg/dose, q6 h) was also given, followed by oral steroid taper (using Prednisone (1mg/kg/dose, once daily) for 4 weeks. Over 5 days of therapy, there was a clinical improvement. The patient became fully conscious and there were increased physiological reflexes.

DISCUSSION

The initial symptoms of ADEM include fever, headache, malaise, nausea, and vomiting, which happened 1 to 2 weeks after an infection or, rarely, after a vaccination[3,14,15]. Encephalopathy is the characteristic feature of ADEM. It develops fast and manifests as an altered level of consciousness (ranging from sleepiness to coma), cognitive dysfunction, changes in behavior, and seizures. Other common signs of ADEM include cranial neuropathies (dysarthria, abnormalities in eye and face movement), acute hemiparesis, cerebellar ataxia (decreased coordination), and long tract pyramidal signs (decreased voluntary movement)[2,6,9].

In 2013, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) updated the definitions for Pediatric ADEM (Table 1). In this case, the patient had a fever, headache, and vomiting, followed by an altered level of consciousness, facial palsy, and

hemiparesis of the left extremity after being given a DPT Vaccine. An altered level of consciousness is evident in this patient as a sign of encephalopathy. In this case, the patient had his first polyfocal, neurological event following vaccination. However, the head MRI cannot be done and a head CT scan with contrast was done instead. There are multiple hypodense, indistinct margin, and non-enhancing lesions in the bilateral internal capsule, bilateral lateral periventricular, subcortex of the right frontal lobe, and right cerebellum.

Table 1. Diagnostic criteria for Pediatric ADEM (IPMSSG, 2013)[3,6,10,16]

A first polyfocal, clinical, CNS event with a presumed inflammatory demyelinating cause
A first polyfocal, clinical, CNS event with a presumed inflammatory demyelinating cause
Encephalopathy that is not explained by fever, systemic illness, or postictal symptoms
Abnormal Brain MRI during the acute (3 months) phase can show: - Diffuse, poorly demarcated, large (>1-2 cm lesions) - Involvement of cerebral white matter - Deep gray matter lesions in the thalamus or basal ganglia
No new clinical or MRI findings emerge 3 months or more after the onset

Diagnosis is best made by MRI and seen on T2 weighted or FLAIR images. It can show a single lesion (small to large, confluent, or solitary) or multiple lesions in white (ex: subcortical and periventricular) and grey (ex: cortex, basal ganglia, thalamus) matter of the brain[2,4,7]. It is mostly seen as multiple, widespread, bilaterally asymmetric lesions in the brain. There may be additional lesions in the brainstem, cerebellum, and spinal cord, but usually exist only with the presence of a brain lesion[1].

ADEM may also have a normal MRI result, even after multiple scans. Although most cases resolve within 18 months, the lesions may appear late after the onset of the disease. Several studies suggested repeated imaging as there may be fluctuations in lesions despite the patient potentially remaining asymptomatic[2,14]. ADEM also needed to be distinguished from another demyelinating disease, such as MS. Several differences can be seen in Table 2.

Table 2. Differences of ADEM and Pediatric MS[3,5,10]

Differences	ADEM	Pediatric MS
History of preceding infectious illness or immunization	Often associated with a prodromal bacterial/viral illness, or prior to immunization	Unusual
The course of the disease	A monophasic disease in young children	Chronic relapsing-remitting course in pre-pubertal children
	Slightly male predominance	Female predominance
Clinical Presentation	The prominence of cortical signs, polyfocal abnormality	Isolated neurologic deficit
MRI Lesions	Often at a higher lesion load, larger and bilateral, but asymmetrical white matter lesions	Usually smaller; lie in the deep white matter
	Lesions have the same age, often with indistinct margin	Lesions are in different ages (spread in time and space), typically have a clear-cut margins
Thalamic Involvement	Up to 40%	Rare
CSF result	Lymphocytic pleocytosis and protein elevation: Common Oligoclonal bands: Unlikely	Lymphocytic pleocytosis and protein elevation: Uncommon Oligoclonal bands: More likely

A study has shown that asymmetric lesions and lesions localized in the parietal, temporal, and occipital lobes on the 1st MRI seem to cause sequelae in children with ADEM. Lesions in the frontal and parietal lobes on the 2nd MRI may also play a role. However, clinical and biological elements do not seem to have a prognostic value[4].

In urgent settings, a CT scan may be done, instead of MRI. In the case of ADEM, a CT scan is most often normal. However, in later stages, there might be focal or multifocal regions of white matter damage[2,7].

In this patient, several laboratory tests were done and light differences were found in the results of serum K^+ and serum Cl^-. However, the other results were within normal limits. In ADEM, elevated white cell count, moreover the lymphocyte count, is common. C reactive protein and erythrocyte sedimentation rate may also increase[6,9].

Blood serum can be used to test for antibodies associated with CNS demyelination (Myelin oligodendrocyte glycoprotein/ MOG), test for infections, metabolic disturbances, and vitamin D levels[16]. MOG is a protein expressed on myelin and myelin-producing cells. Persistent MOG antibody production relates to relapse[14,16]. Higher levels of vitamin D are associated with a lower risk of relapse in MS[12]. Monitoring of Potassium is essential as patients with

ADEM will be receiving steroids and at risk of hypokalemia.

Additional studies that can be done include CSF examination, EEG, and brain biopsy. Cerebrospinal fluid can be normal or show an increase of WBC in 29-85% of cases, and elevated protein in 17-48% of cases[2,11]. The presence of oligoclonal bands in the CSF can be found, but less common than in MS[2,15].

EEG may show diffuse slowing (88%) or focal slowing and spikes (25%) consistent with the encephalopathy or encephalitic picture[2,14,16]. Immune cells (macrophage and lymphocytes) can be found gathering around veins in the white matter, along with injured myelin and myelin-producing cells (oligodendrocytes)[2]. However, due to limited facilities, these additional studies can't be done.

As most children present with evidence of inflammation, they should be given appropriate antibiotics and antiviral drugs[1]. Once the diagnosis is made, the patient is given intravenous methyl-prednisolone (10–30mg/kg/day) or dexa-methasone (1-2mg/kg/day) for 3-5 days, with the following course of oral prednisolone (1-2mg/kg/day) and tapered over 4–6 weeks[1,12].

Intravenous immunoglobulin G (IVIG) at 2 g/kg divided over 2 to 5 days is an option in cases of inadequate response or contraindications to corticosteroids[12,15]. Plasmapheresis should be considered early in severe cases of ADEM. It involves 7 exchanges over 14 days, and improvements are mostly seen after the first plasma exchange[15]. Decompressive craniectomy is also beneficial for ADEM patients with intracranial hypertension[12].

ADEM has up to 3% mortality. Around 25% of patients will require ICU level care as supportive care might be needed for aiding breathing, seizures, and cerebral edema. Most of the patients with ADEM have a good prognosis. The patient may spend 1-3 weeks in the hospital (either in the hospital setting or outpatient) and get rehabilitation[1,6,14,16].

The long-term prognosis of

ADEM is usually good, and most patients are fully recovered in about 1–6 months[15]. Sequelae may consist of motor difficulties, visual problems, and seizures. Some cases reported subtle deficits in attention, executive function, and behavior more than 3 years after ADEM[11,16].

Supporting recovery for ADEM includes comprehensive neurophysiological testing, school accommodations, cognitive and behavioral therapies, follow-up of neuropsychiatric symptoms, monitoring for relapses, and providing immunosuppressive therapy when appropriate. Follow-up MRI in 3-4 months can show complete or partial resolution of lesions[7,14]. Up to 1/3 patients will have recurrent attacks, often with positive MOG[9,14,16].

Mostly ADEM is found as Monophasic ADEM, a single ADEM episode with no further demyelinating events or new MRI lesions outside the acute three-month period after onset. However, recurrent attacks may manifest as Multiphasic ADEM, with only two episodes of ADEM, but in at least three months in time. The second ADEM can have new or the same symptoms or MRI lesions compared to the first event. If there are three or more episodes of similar symptoms, further diagnostic for MS, Neuromyelitis Optica (NMO), or other demyelinating disorders need to be ruled out[6,16].

CONCLUSION

The prognosis for ADEM is good and often has improvement within a month. However, some patients need to undergo supportive therapy as appropriate. Further follow-up needs to be done to evaluate the disease progression, as ADEM may be manifesting as Multiphasic ADEM or any other demyelinating disorders.

INFORMED CONSENT

The informed consent was acquired from the patient's parent for the publication of this case.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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