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Acute Disseminated Encephalomyelitis (ADEM) in Adult Women, Is it Unpreceded by Infection History?: A Case Report

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is a demielination disease of the central nervous system (CNS) in response to previous infection or immunizations that occur acute, monofasic. ADEM generally occurs in children and young adults, rarely in middle-aged or elderly.
Case report: We present a woman 46 years old with chief complaint of headache since 7 months ago, weakness of both legs, sudden loss of vision in both eyes since 3 days after weakness of both legs. There was no history of infection or previous vaccination. Brain and whole spine MRI were performed. Initial therapy methylprednisolone does not show improvement, then continued with administration of intravenous immunoglobulin. After 6 months, clinical improvements were obtained and no new lesions of the imaging.
Conclusion: In this case report it is presented a case of ADEM in adult without a history of infection who recovered after intravenous immunoglobulin. Then that is still the current question, whether ADEM in the adult can be occur without preceded infection history?

Key words: ADEM, adult woman, history of infection.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease characterized by monophasic acute inflammation and demyelination of the central nervous system (CNS) of the brain and spinal cord (sometimes the optic nerve). Inflammation that occurs in response to infection or previous vaccine history. ADEM is encephalomyelitis that occurs after an infection, acute, rapid progression, autoimmune process that occurs in the CNS.[1,2]

ADEM generally occurs after a viral infection, bacterial infection, or vaccination. Clinical characteristics include focal neurologic deficits, accompanied by encephalopathy that develops one to three weeks after viral infection. ADEM can be characterized by rapid neurologic deficits, but a single symptom of spastic paresis alone is rare. ADEM common occurs in children and young adults, rarely in middle-aged or elderly. Symptoms of ADEM may be fulminant, but usually recover in 50–75% of cases and may progress to multiple sclerosis (MS) in 20% of cases. Atypical cases of ADEM have been reported in middle-aged.[1]

ADEM is a rare disease, but there are approximately 1:125.000-250.000 individuals who suffer from ADEM each year. Although the majority of cases occur in children (the majority are under the age of ten years, and the rest are between the ages of 10 to 20 years), it is also found in adults with an age range 18 to 82 years. The disease is more common in men than

women (male to female ratio 1.3:1), and is more common in winter and spring.[3]

In this case report, we will present a case of a middle-aged woman with ADEM who had no previous history of infection and experienced clinical improvement after administration of intravenous immunoglobulin.

CASE REPORT

A woman 46 years old was brought to our hospital with chief complaint of headache since 7 months ago, weakness of both legs, sudden loss of vision in both eyes since 3 days after weakness of both legs. There was no history of infection or previous vaccination.

She was evaluated with vital signs normal. On neurological examination, her GCS was 456, no meningeal sign was present. She was decreased of visual acuity in the right eye and left eye (visus 1/~ both eyes), while the examination of the other cranial nerves was normal. Motor weakness was found in both legs with motor strength 1. She altered in sensorium with hypesthesia at the level of the thoracal myelum segment 4. Tone was increased in lower limb with brisk deep tendon reflexes. Plantars were upgowing. Autonomic system and vertebral column was normal.

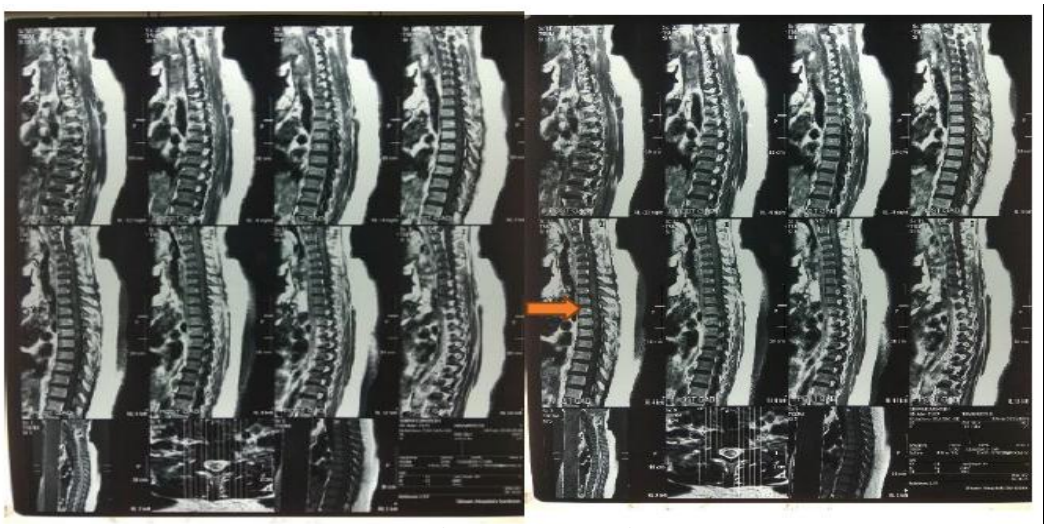

Figure 1: MRI T1 weighted with and without contrast before administration of intravenous immunoglobulin showing multiple patchy enhancing lesions of intra spinal cord & periventricular white matter according to multiple sclerosis.

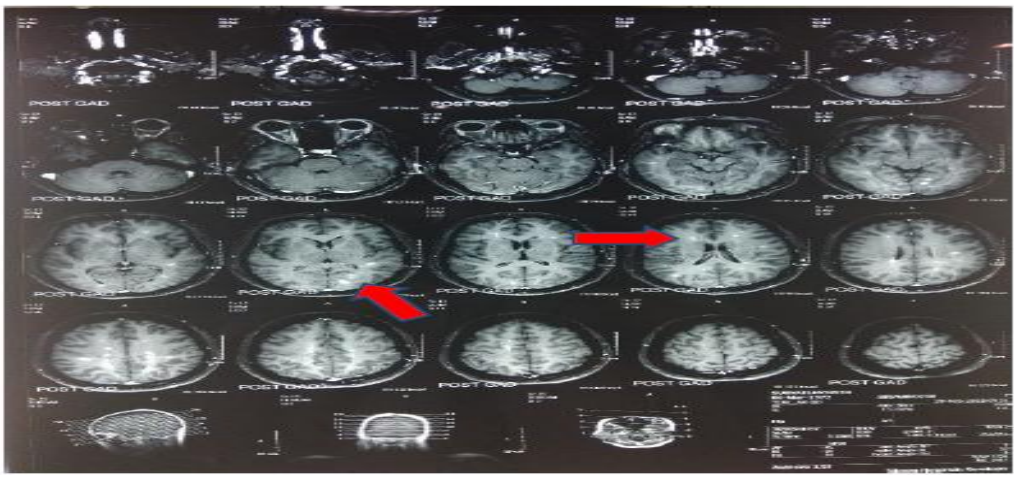

Figure 2: T1 Weighted Brain MRI before administration of intravenous immunoglobulin showing multiple enhancing lesions in the juxtacortical parietal both sides (left >), on the left and right lateral periventricle with Dawson's finger (+) in accordance with Multiple Sclerosis, bilateral optic neuritis.

Initial investigations revealed an increase of white blood cells ($15{,}870 \times 10^3/\mu L$) and erythrocyte sedimentation rate (ESR) (30mm/h). Lymphocytes was decrease (4.9%). Chest x-ray examination was normal. Cerebrospinal

fluid examination was not performed because the patient refused to perform a lumbar puncture. MRI whole spine was done which showed multiple patchy enhancing lesions in T1 weighted intra spinal cord & periventricular white matter supporting multiple sclerosis. Brain MRI showed multiple enhancing lesions in the juxtacortical parietal both sides (left >), lateral periventricular both sides with dawson finger (+) supporting Multiple sclerosis, bilateral optic neuritis (Figure 1 and 2).

Initial therapy was given intravenous methylprednisolone 250 mg, every 4 hours, for 5 days, then gradually decreased the dose and continued with oral methylprednisolone. The patient did not show any improvement after giving methylprednisolone, so she continued with intravenous immunoglobulin 0.4 mg/kg body weight/day (BB: 70 kg) for 5 days. After first administration of intravenous immunoglobulin, visual acuity was improved in both eyes, which was > 2/60, but there was no improvement in motor strength. The patient then discharged and monitored regularly. The patient was given a second intravenous immunoglobulin at the same dose for 5 days and the intravenous immunoglobulin was given 6 times every 28 days at the same dose every month. After giving intravenous immunoglobulin 6 times, there was a full improvement in the motor strength of both lower limbs. In addition, brain and whole spine MRI were improved, which performed 6 months later.

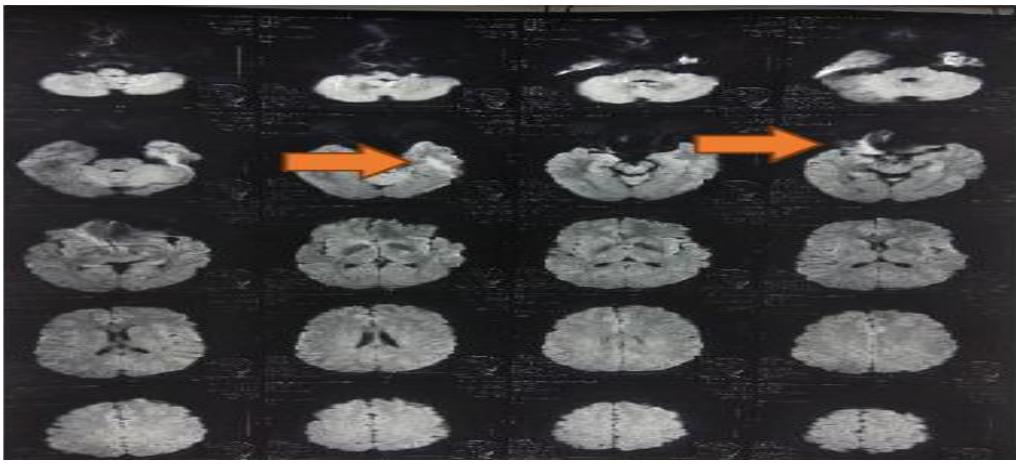

Figure 3: After administration of intravenous immunoglobulin. Brain MRI with and without contrast showing currently multiple hyperintense lesions on T2W1/Flair in centrum semiovale, corona radiata, and periventricular both sides, no patchy enhancement on contrast administration, there was improvement in radiollogical impression.

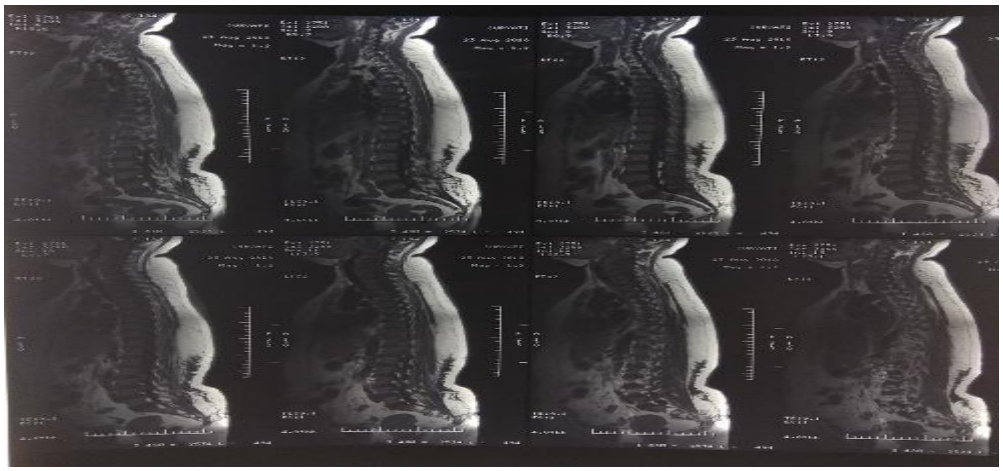

Figure 4: After administration of intravenous immunoglobulin. Whole spine T1 weighted MRI with and without contrast showing no abnormal hypo/hyperintense lesion in spinal cord, which on contrast enhancement did not appear. Multilevel buldging disc causing mild to moderate compression of the anterior dural sac, severe at levels VL 4-5, VL5-VS1, thickening of the ligamentum flavum, hypertrophy and facet joint effusion, causing mild to moderate narrowing of the right and left lateral recess (severe at level VL 4-5, VL5-VS1) and mild foraminal neural stenosis at VL 4-5, VL5-VS1 levels.

DISCUSSION

According to a study conducted in China, the incidence of ADEM was highest in aged 0-9 years (0.77/100,000/year), and the incidence decreased with age (among people younger than 50 years). However, the incidence increased at the age of 50-59 years (0.45/100,000/year), followed by individuals 60-69 years (0.43/100000/year). Senile ADEM, rarely reported.[4]

Risk factors for ADEM include genetics, exposure to infectious organisms, vaccination, and people with lighter skin pigmentation. All ethnic groups are susceptible to ADEM, and this condition occurs worldwide. ADEM is associated with infection or previous vaccination in 50%-75% of cases. The majority of cases follow a previous viral or bacterial infection (although the causative pathogen is not always identified).[3]

The exact mechanism of ADEM is not fully understood, but it can be result from inflammation triggered by environmental stimuli (eg, vaccination or infectious disease) in genetically susceptible individuals. The organisms most commonly associated with ADEM are Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpes-virus-6, influenza virus, hepatitis A, human immunodeficiency virus, and Mycoplasma pneumonia. In addition, it can also be caused by infection with Leptospira bacteria, beta-hemolytic streptococci, and Borrelia burgdorferi.[5,6,7]

Cell-mediated responses or antibodies produced in response to environmental triggers that cross-react with myelin autoantigens (e.g., myelin basic protein, oligodendrocyte myelin, proteolipid protein in the CNS resulting in demyelination that typically seen in ADEM.[5]

Symptoms in ADEM varied, depend on the area of the CNS that are demyelinated, and usually polysymptomatic. Common symptoms are encephalopathy, hemiparesis, optic neuritis, myelitis, brain stem syndrome, cerebellar ataxia. Rarely myeloradiculopathy and extrapyramidal disorders. In the consensus of the international pediatric multiple sclerosis study group, encephalopathy is one of the diagnostic criteria for ADEM. Encephalopathy is often found in children aged less than 3 years. However, in the middle-aged group, encephalopathy is not always present.[9,10] Until now, there are still no appropriate criteria for the diagnosis of ADEM in adults and the effectiveness of high-dose corticosteroid therapy, intravenous immunoglobulin, and plasmapheresis.[11]

In this case, we found a middle-aged woman with complaints of chronic cephalgia, generalized paraplegia, hypesthesia at the level of the 4th thoracal myelum segment, and bilateral optic neuritis. Compared to multiple sclerosis, patients with ADEM often complain of headaches. Bilateral optic neuritis is present in 23-40% of ADEM. In multiple sclerosis, unilateral optic neuritis is found. Bilateral optic neuritis is rare in multiple sclerosis, but is common in neuromyelitis optic (NMO). In the early phase of NMO, there were no lesions in the white matter area, but recent studies have shown lesions similar to ADEM and multiple sclerosis.[10]

The diagnosis of ADEM in this case was supported by the presence of leukocytosis, lymphopenia, and an increase in the erythrocyte sedimentation rate. Patients with ADEM have increased inflammatory markers (leukocytosis and increased erythrocyte sedimentation rate) and decreased levels of lymphocytes in the blood (lymphophenia), whereas patients with multiple sclerosis are often normal.[10]

MRI is an important part of establishing the diagnosis of ADEM and multiple sclerosis. Both of these diseases show disseminated inflammatory lesions in the CNS (especially lesions in the white matter area). T2/FLAIR MRI lesions in ADEM are diffuse, symmetrical, irregular, and usually have homogeneous patchy hyperintense areas of gray and white matter. More than half of cases involve

infratentorial structures and more than one third of cases involve the spinal cord. Multifocal hyperintense lesions in the subcortical white matter area are difficult to distinguish from lesions caused by inflammation, infection, and rheumatic disease that have clinical and radiological features that similar to ADEM.[1,10]

Brain MRI examination in this patient obtained multiple enhanced lesions in juxtacortical parietal both sides (left >), lateral periventricle both sides with Dawson finger (+) in accordance with Multiple Sclerosis, and also found bilateral optic neuritis. Brain lesions in ADEM are not well-defined, in contrast with well-defined lesion in multiple sclerosis. In 78% patients with ADEM there were no periventricular lesions. However, at 22% of ADEM obtained periventricular similar to multiple sclerosis. The presence of additional lesions, infratentorial lesions, periventricular lesions have a high potential to develop into multiple sclerosis. In addition, the presence of lesions in the corpus callosum, well-defined lesions were specific predictors of recurrence and multiple sclerosis with mean of recurrency was 4.9 years[12]

In multiple sclerosis, there are focal neurologic deficits with different time episodes, confluent demyelinating lesions with an ovoid shape which appropriate with age, and predominantly lesions in white matter area. In addition, oligoclonal bands in cerebrospinal fluid examination were more often found than in ADEM. The lesions in ADEM with gadolinium contrast mimic those of multiple sclerosis, but their incidence varies with the time of imaging is performed. Nearly a quarter of ADEM patients will develop multiple sclerosis so it is highly recommended to repeat imaging after 3 and 6 months for new lesions screening.[13,14,15]

Patients with ADEM may experience spontaneous improvement. However, in patients who do not receive immune-modulating therapy, there is often an incomplete recovery. There is no established standard therapy based on controlled trials. The use of high-dose steroids, plasma exchange, and intravenous immunoglobulin is based on analogy of the pathogenesis of ADEM with multiple sclerosis.[9]

ADEM therapy includes supportive therapy, specific therapy, physical therapy, and rehabilitative therapy. Most ADEM therapies are based on empirical data. Specific therapy includes high-dose intravenous methylprednisolone, intravenous immunoglobulin (IVIg), and plasmapheresis. Intravenous methylprednisolone is the first-line therapy in ADEM. The therapeutic dose is 10-30 mg/kg/day, up to a maximum of 1 g/day, for 3-5 days (class IV). Full recovery has been reported in 50%-80% of patients. Methlprednisolone therapy had a much better outcome than dexamethasone with respect to disability status. Intravenous corticosteroid administration is continued orally with gradual dose reductions over 6 weeks to reduce the risk of recurrence. However, this administration of oral corticosteroids is not based on randomized controlled trials. Vaccination should be avoided in the first 6 months after the recovery phase.[9]

Plasma exchange (PE) therapy or plasmapheresis is given when high-dose corticosteroid therapy fails (level of evidence 1b). Plasma exchange therapy as much as 4-6 times show moderate to continuous clinical improvement. Another therapy is intravenous immunoglobulin (IVIG) (0.4 gram/kg/day for 5 days), but it requires high costs (class IV therapy modality). Improvements are visible in 2-3 days. Second-line therapy with plasmapheresis or intravenous immunoglobulin has minimal clinical trial studies. Consideration of second-line therapy depends on the severity of the disease, complications, and comorbidities.[9]

In middle age with ADEM showed that there was clinically and radiologically improvement after steroid administration. Several case reports obtained that combination of steroid therapy with

intravenous immunoglobulin or plasmapheresis in older patients showed good results. This indicates that the pathophysiology of ADEM is similar in both children and young adults. In addition, complete improvement after 1-6 months is found in 50-75%.[1]

Furthermore, follow-up of brain and whole spine MRI performed at 6 months did not reveal any new contrast enhance lesions. There was resolution of monophasic demyelinating lesions with clinical neurologic resolution. Based on research conducted by Jordan et al. showed that 10 of 11 patients with post infectious encephalomyelitis would have resolution on MRI after 3 months, but this was not seen in multiple sclerosis.[1]

CONCLUSION

ADEM is rare in middle age and elderly. The prognosis is unknown due to the lack of cases reported in the literature. This case report presents a case of ADEM in middle age without a history of infection or previous vaccination with very good response to intravenous immunoglobulin treatment. Therefore, it is highly recommended to give aggressive therapy in adult patients with ADEM so that it is expected to get a good clinical outcome. Then the question at this time is whether ADEM in adulthood can be done without a history of infection?

Table 1: Differential diagnosis of ADEM [9,10]

No		ADEM	Multiplesclerosis
1.	Epidemiology - Age - Gender	 - < 10 years - No preferences	 - 10 years - Especially women
2.	Precipitation factor	History of infection, vaccinations	Not known history of infection, vaccination
3.	Signs & symptoms - Progressive - Encephalopathy - Optic neuritis	Polysymptomatic - Not progressive, monophasic - Yes - Bilateral	Monosymptomatic - Remitting and/or progressive relapse - There is not any - Unilateral
4.	Imaging - MRI Lesions - MRI follow-up	 - Cortical & inner gray matter lesions (more common) - Diffuse, bilaterally symmetrical - No new lesions	 - Periventricular lesions, corpus callosum - Periventricular There's a new lesson
5.	Cerebrospinal fluid	Lymphocytosis	Intrathecal oligoclonal IgG (40-95%)
6.	Basic laboratory	Leukocytosis, increased erythrocyte sedimentation rate, lymphopenia	Normal
7.	Prognosis	Recovery is fast and usually complete	Recovery varies

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