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The Characteristics of Acute Disseminated Encephalomyelitis Can Slightly Vary Based on the Geographical Region

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Abstract

Background: Acute Disseminated Encephalomyelitis (ADEM) is an inflammatory disease of the central nervous system which affects white matter and leads to a polysymptomatic disease with clinical signs and symptoms.

Aim: The present study was initiated to report on the various modes of presentation and raises the awareness of the diagnosis of ADEM.

Methods: In this retrospective study, we assessed the characteristics of the disease in an Iranian population during a period of 10 years (2005-2015) whit at least 2 years follow up. All patients presenting to Alzahra Hospital, Isfahan, Iran, with a high probability of diagnosis of ADEM. Their demographic, clinical, laboratory, and imaging data were collated and analyzed by performing the t-test and chi-square test using SPSS25 software.

Results: Forty-seven patients with a mean age of 14.7 ± 10.04 years and a female predominance participated in this study. Most patients had a recent history of infectious disease (37 cases) or vaccination (5 cases). Seasonality in incidence with predominance in spring (31.9%) and winter (29.7%) was also noted. CSF analysis was normal in 14.8% cases and 27 patients were found to have pleocytosis. MRI data revealed that most lesions were in the cortical, periventricular, and basal ganglia areas. Re-imaging showed complete (34 patients) or partial (13 patients) resolution of previous lesions with no new lesions in next follow up MRI.

Conclusion: We found some disagreement with previous epidemiologic and imaging studies that could be of significance in the detection and understanding of ADEM.

Keywords: ADEM; Epidemiologic study; Infection; Iranian population; MRI; MS; CSF

Introduction

Pathologies of the white matter of the Central Nervous System (CNS) generally occur due to demyelination and inflammation, and the term Acute Disseminated Encephalomyelitis (ADEM) is used when there is a single episode of disseminated demyelination. Monophasic ADEM is a one-time episode that can develop over as long a period as 3 months. Any new or changing symptoms developing within this 3 month period are considered a single event. Symptoms that might occur during an oral steroid taper, or within 1 month of completion of the taper, are also classified as one single episode. ADEM episodes must occur more than 3 months after the initial event and more than 1 month after the completion of steroid therapy to be considered recurrent. The symptoms and Magnetic Resonance Imaging (MRI) findings in recurrent ADEM are similar to that of the initial episode [1]. Children aged 3 to 10 years are more susceptible to ADEM than the general population [2-4]. Although ADEM mostly involves the pediatric group, adults may also experience an episode of the disease.

An epidemiologic study of ADEM's occurrence in people aged less than 20 years revealed an estimated prevalence of 0.4 per 100,000 individuals in the United States of America [5]. Another study on a Japanese population aged less than 15 years showed a prevalence of 0.64 per 100,000 disease presentations with a male predominance [6]. As suggested by previous studies, post-infection and post-vaccination processes are possible mechanisms that can trigger the disease. Among microorganisms, mycoplasma, varicella, Epstein-Barr virus and group A *streptococci* may trigger the immunologic processes that could lead to ADEM [7,8]. Although several criteria and definitions are available for the disease, there are no clear criteria for definite diagnosis of ADEM [9]. Hence, ADEM should be considered as a differential diagnosis in patients who present the following signs and symptoms: cerebellar ataxia, seizure, meningoencephalopathy, optic neuritis (especially bilateral pattern) and evidence of CNS involvement in MRI with disseminated white matter lesions and pleocytosis of the cerebrospinal fluid without oligoclonal bands which is not typically seen in Multiple sclerosis [9,10].

Different diseases cause CNS white matter injury; their complications and prognosis are of great significance to physicians during the process of getting to the final diagnosis. MS, the main differential diagnosis of ADEM, can lead to severe disability and needs special attention to ensure early intervention, whereas there is no similar prognostic feature in ADEM [8]. In order to establish definitive criteria for the diagnosis of the disease, complete knowledge of its symptoms, signs, and laboratory and imaging features are needed. In this study, we examined the characteristics of this disease in a local Iranian population.

Method and Materials

This was a retrospective study. Patients presenting to Alzahra medical hospital, a referral center for CNS demyelinating disorders

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in Isfahan, Iran, between 2005 and 2015 were included in the study. The inclusion criteria were as follows: Radiologic reports containing the terms "Acute Disseminated Encephalomyelitis" or "ADEM", codes applied to patients with this diagnosis by the department of information services and a database held in the department of neurology, patient's informed consent for participation in the study, and patient's willingness for further assessment of signs and symptoms and follow up MRI to ensure diagnosis of ADEM.

We excluded patients with: Acute isolated mono-symptomatic syndromes such as optic neuritis or transverse myelitis, undetermined clinical histories, features pathognomonic for alternative diagnoses, and patients who did not have any previous MRI [1,3]. Patients that were diagnosed with Multiple Sclerosis after 1 year of follow up, were also excluded (25 cases).

After obtaining the written consent of the patients, two neurologist experts on MS confirmed patient's diagnosis based on ADEM diagnostic guideline provided by international pediatric MS study group [11], then a medical student collected data from the department of Neurology's archives using medical software, as well as hard copies of their records. The following information was collected: Demographic data; clinical signs and symptoms at first presentation; history of vaccination, drug administration, or infectious disease in the weeks preceding the onset of ADEM, positive familial history of ADEM or MS, season of the onset of the disease; laboratory findings including erythrocyte sedimentation rate (ESR), imaging data including rapid MRI and enhancement following administration of gadolinium, and information on the course of treatment followed. Imaging investigations were performed in all patients who had undergone MRI previously. The MRI records were re-evaluated by an expert neuroradiologist who was blinded to the objective of the study and the interpretation of the existing MRI reports. The patients were then followed-up for at least 2 years (Range: 0.7, Median: 2.2) to detect any new signs or lesions in the MRI with gadolinium enhancement which were conducted every 6 months.

Finally, all the gathered data were analyzed by performing the chi-square test and t-test using SPSS25 software (SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered statistically significant.

Results

Demographic information

Table 1 summarize the demographic features of the study. Initially, fifty-one patients who were known cases of ADEM between 2005 and 2015 participated in this study, but four patients left the study during follow up. The study sample had a mean age of 21.9 (SD=12.1, range=1-37) in men and 19 (SD=8.7, range=3-41) in females. The study population included 18 (38.2%) males and 29 (61.7%) females. Most patients were in the age group of 0-10 years and the incidence of the disease was predominantly seen in winter and spring. Analysis using t-test revealed no significant difference between the mean age of male and female patients (P=0.37). Only 1 patient had a positive familial history of MS (Table 1).

Parameter		Frequency	Percentage
Age	0-10 years	18	38.2
	10-19 years	14	29.7
	20-29 years	12	25.5
	≥ 30 years	3	6.3
Season of incidence	Spring	15	31.9
	Summer	7	14.8
	Autumn	11	23.4
	Winter	14	29.7
History of recent infectious disease	Positive	37	78.7
History of recent vaccination	Positive	5	10.6

Table 1: Age, season of incidence of ADEM and history of recent infectious disease and vaccination.

Clinical information

Prodromal illnesses reported in 37 cases (78.7%), whit the majority of these being upper respiratory tract infections 27 patients (57.4%). Other Patients had varicella (4 patients), gastroenteritis (4 patients), brucellosis (1 patient) and pneumonia (1 patient). Ten patients (21.3%) had no identifiable prodromal illness. History of vaccination prior to the onset of the disease was noted in 5 patients (10.6%), they had received measles (2 patient), meningococcal conjugate vaccine (2 patients) and DPT (1 patient) vaccines.

Assessment of neurological signs revealed a polysymptomatic presentation in 42 patients (89.3%) with a mixture of following signs: alteration in level of consciousness in 27 patients (57.4%), pyramidal motor signs in 19 patients (40.4%) [plegia in 4 (8.5%) patients], cranial neuropathies in 14 patients (29.7%), optic neuritis in 12 patients (25.5%, bilateral in all), sensory disturbance in 5 patients (10.6%), true vertigo in 11 patients (23.4%), brain stem and cerebellar syndromes in 27 (57.4%) [Seventh Nerve palsy in 3 and ocular motor dysfunction in 11 patients] and 7 patients (14.8%) respectively, myelitis in 1 patient (2.1%) and urinary incontinence in 6 patients (12.7%).

Laboratory information

Mean value of ESR was 17.07 ± 17.33 mm/h, 27 patients (57.4%) had elevated ESR (Calculated for each individual's age). CSF examination was performed in 45 patients (95.7%) and was normal in seven of them (14.8%). CSF analysis showed pleocytosis (27 patients), increased protein (21 patients) and 12 patients had both pleocytosis and increased protein. No patient showed oligoclonal bands in CSF.

As a part of our differentiation process between ADEM and Neuromyelitis optica, Anti-AQP4 antibody of serum in all patients with bilateral optic neuritis measured via indirect immunofluorescence. As to our expectations all test results were negative.

MRI finding

Although ADEM typically presents bilaterally and asymmetrically, sites of involvements and number of lesions were highly variable. The MRI findings are summarized in Table 2. All patients underwent repeat MRI with gadolinium enhancement every six months for two years (Range: 0.7, Median: 2.1), as a part of the follow-up. The findings were normal in 34 (72.3%) patients and the lesions had decreased in number and size in 13 patients (27.6%). Re-imaging showed complete or partial resolution of previous lesions. During the two year follow up, none of the patients had new lesions suggesting multiple sclerosis as a possible diagnosis (Figure 1; Table 2).

Descriptor		Frequency (Percentage)
Location	Periventricular/ Corpus callosum	28(8.5)
	Cortical/Subcortical	36(76.5)
	Basal Ganglia/Thalamic	22(48)
	Brainstem/cerebellum	19(40.4)
	Spinal cord	6(12.7)
Gadolinium	Enhancement	40(85.1)

Table 2: First MRI finding.

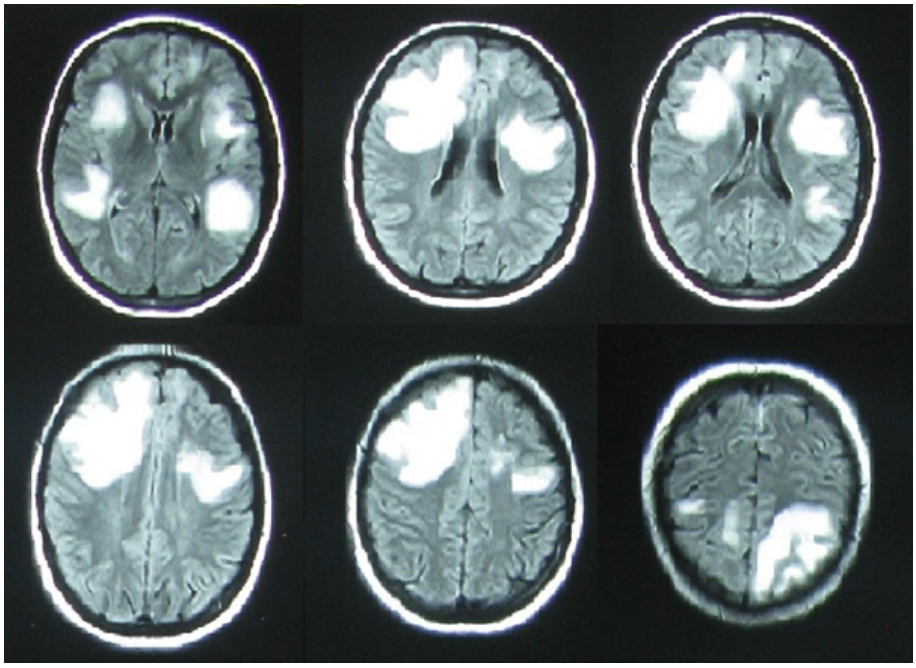

Figure 1: A 13-year-old female presents with Encephalopathy. Axial flare MRI shows tumefactive lesion in cortical and subcortical areas

Management and outcome

All patients underwent treatment and follow-up for two years by neurologists. Steroids (intravenous methylprednisolone, followed by tapering with oral prednisolone) was used in 100% patients. Eight patients (17%) were treated with plasmapheresis and 1 patient (2.1%) was treated with intravenous immunoglobulin and a combination of steroids. Longitudinal follow-up of patients showed no new clinical findings and a 100% survival rate with complete recovery in 31 patients (65.9%). It also showed complications following one episode of the disease in 16 patients (34%) during two years of follow up. The complications included visual loss (1 patient), mild ataxia (9 patients), dysarthria (2 patient), paraparesis (1 patient), hemiparesis (1 patient) and mild amnesia (2 patients). Recurrence was seen in 10 patients (21.2%). [All patients showed recurrence less than one month after the end of therapy] (Range: 0.73, Median: 0.56).

Discussion

ADEM is a disorder caused by immunologic processes in the CNS which are characteristically acute, with mono-phasic and polysymptomatic features including encephalopathy and other inflammatory processes such as optic neuritis or myelitis [9,10]. ADEM's neurologic signs might be variable depending on the site of CNS involvement, but alteration in the mental state and level of consciousness is commonly reported in most cases (21-74%) [2-5,12-18].

Our study corroborates these findings with 57.4% of the cases presenting with alteration in mental status. Bilateral optic neuritis was seen in 25.5% of the cases, whereas unilateral optic neuritis was less common in our study. While unilateral optic neuritis is commonly seen in MS rather than in ADEM, there are three important differential diagnoses for bilateral optic neuritis: Neuromyelitis optica (NMO), ADEM, and Myelin Oligodendrocyte Glycoprotein (MOG) antibody syndrome. As stated previously, We also measured serum AQP4 antibody level via indirect immunofluorescence in patients with bilateral optic neuritis to help Differentiate these two diseases which is highly essential as early intervention would reduce the risk of severe disability and future relapse [10,19,20].

We included all cases of ADEM in our local area over a period of 10 years in this study. Out of 47 cases of ADEM in our study, the highest rate of disease incidence was seen in the age group of 0-10 years. 61.7% of the cases were female, which is in disagreement with previous studies that suggested either no gender predilection or a slight male predominance [2,13,15]. Previous studies suggested a seasonality in the incidence of ADEM, especially in spring and winter [4,5,13]. A similar pattern of incidence was found in our study, with most of the ADEM presentations occurring in spring (31.9%) and winter (29.7%). Some studies explored the possibility of a relationship between onset of ADEM and recent vaccination; small pox, influenza and rabies vaccines were suspected to be potential triggers for ADEM [21,22]. However, post-vaccination ADEM is a rare phenomenon and only 10.6% of our cases had a recent history of vaccination [13]. As mentioned earlier, some infectious microorganisms could also trigger the disease and we found that 78.7% of our cases had a positive history of a recent infectious disease such as common cold, varicella, gastroenteritis, etc.

Neuroimaging studies, especially MRI, play a significant role in distinguishing between ADEM and other CNS inflammatory diseases such as MS. ADEM lesions, as seen in MRI, are generally poorly marginated, whereas the lesions in MS have more accurately defined margins [23]. In a study by Callen et al., distribution of ADEM lesions in different anatomic sites was determined, and lesions were mostly seen in deep white matter and juxtacortical sites. They also found that periventricular lesions are more frequent in children with MS than inpatients with ADEM [24]. Other studies have also reported that ADEM lesions were more frequently seen in deeper white matter and that 29-60% of lesions were periventricular [3,4,13]. In contrary to previous studies, we found that 76.5% of the cases had cortical/subcortical

lesions. Periventricular, basal ganglia, and brainstem were other sites of disease involvement. All patients in our study underwent repeat MRI with gadolinium enhancement for follow-up and most of them (34 patients) revealed complete recovery with no sequel or pathological signs. However, there were 13 patients (27.6%) with persistent lesions, all of which were decreased in size and located at the same site. Findings of earlier studies show that although some symptomatic new lesions may be found on repeat MRI in children with MS, ADEM lesions are generally completely or partially resolved [25-27].

Studies in the scope of disease prognosis have reported that ADEM is a disorder with no significant complications in most cases and a full recovery in 70-90% of patients in the months following the disease episode [2-5,9,12-17]. Our findings suggest a similar recovery pattern since most of the cases (65.9%) showed complete recovery. However, others had different sequels including mild ataxia, mild amnesia, visual loss, etc. Studies have reported that the recurrence rate of ADEM ranges between 9% and 28% [2,13,14]. Our study showed a recurrence rate of 21.2%.

Conclusion

In conclusion, we evaluated the demographic, clinical, laboratory, imaging, and prognostic features of ADEM in 47 cases over a period of 10 years in an Iranian population. The disease was polysymptomatic with a seasonal pattern of distribution but contrary to others there was a female predominance in our study. According to our data, which is consistent with other previous studies, ADEM may also be present in adults and we must consider the fact that some ADEM patients can be misdiagnosed with multiple sclerosis based on McDonald Criteria. There were elevated inflammatory markers in the blood and increased cell count and protein in the CSF. Correspondent to previous studies, cortical, periventricular and basal ganglia lesions were more commonly seen in our patients. Future studies investigating the characteristics of ADEM can help further for our understanding of this disease and assist physicians in making more accurate diagnoses.

Acknowledgment

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