ACUTE DISSEMINATED ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS AS UNUSUAL BRAIN STEM LESIONS IN CHILDREN

Faten Fawzy Mohammad, M.D.*, Doaa M.Youssef, M.D. , Ayman Ismaeel, M.D.*****
Diagnostic Radiology Department*, Pediatrics Department**, Neurosurgery Department***. Faculty of Medicine, Zagazig University.

Corresponding author:
Faten Fawzy
Tel:0122444497

ABSTRACT

Background: Brainstem could be the seat of an isolated lesion with clinical and imaging diagnostic overlap. **Patients and methods:** A retrospective study on 65 cases with acute neurologic deficit were presented for MRI diagnosis. **Results**:We found 8 patients with isolated brainstem lesion, 6 of them were diagnosed as glioma, one case was diagnosed as ADEM and one case as MS. Follow-up MRI in ADEM case proved dramatic response to steroid with complete clinical and radiological recovery while MS case revealed a progressive course. **Conclusion:** ADEM and MS should be considered in the differential diagnosis of isolated brainstem lesion in children.

Key words: ADEM, MS, DWI, brainstem

INTRODUCTION

Diagnostic uncertainty can occurs as a result of a broad spectrum of central nervous system disorders in children with considerable overlap in presenting symptoms and imaging characteristics. They include brain stem glioma, acquired demyelinating disorders (multiple sclerosis, acute disseminated encephalomyelitis, and neuromyelitisoptica), infectious brain stem encephalitis, CNS involvement of connective tissue disorders and other vasculitis disorders (systemic lupus erythematosus, Neuro-Behcet disease, and neurosarcoidosis), osmotic demyelination syndrome (CPM), brain stem ischemia, brain stem vascular anomalies, and, rarely, Alexander disease(1).

ADEM most commonly affects children, as it is a disease of young age, with an estimated incidence of 0.8/100,000/year. The median age of onset is 6.5 years. This is also the age group of brain stem glioma which is the most common neoplasm (2).

ADEM diagnosis is made on clinical grounds with the aid of MR imaging. If one is in doubt, the diagnosis has to be made by exclusion of a number of likely differential diagnoses. Sequential MR imaging during the follow-up period plays an important role in establishing the diagnosis of ADEM as it is a monophasic which is not associated with newly developed lesions (3).

Multiple sclerosis (MS) is a demyelinating disease characterized by multiple "plaques" in the white matter of the brain and the spinal cord. The primary lesions are found in the peri-vascular spaces along penetrating veins (4). Clinically, patients may present with virtually any neurologic deficits, most commonly muscle weakness, parasthesia and visual or urinary disturbance, ataxia and tremors. The clinical course of MS is variable as it may presents in acute, chronic or relapsing forms, but, the most common is the prolonged relapsingremitting disease (70% of cases). Symptomatic episodes can last from 24 hour to several weeks. As white matter lesions increases over time, the disease frequently becomes chronically progressive. Accumulating neurological deficits ultimately lead to permanent disability. Alternatively, MS can be chronically progressive from the beginning (5).

Multiple sclerosis can occur during childhood, even among children under 10 years of age, with difficult initial diagnosis. A first demyelinating event in children may be an episode of monophasic acute disseminated encephalomyelitis or a first episode of a macrophage activation syndrome, angiitis affecting the central nervous system. The risk of developing MS is lower if: the child is younger than 10 years old; onset is associated with severely altered consciousness; polysymptomatic presentation; or large lesions which are poorly limited to the white matter. MS in children probably has a slightly better outcome than MS in adults. Initial treatment mainly relies on methylprednisolone, while the treatment with beta interferon in children with MS has a little information about its results (6).

MS plaques of uncharacteristic location or that appears as tumefactive like lesion may be diagnostically confused with demyelination process secondary to acute disseminated encephalomyelitis (ADEM), vasculitis, ischemic areas, neurosarcoidosis and neoplasams (7).

PATIENTS AND METHODS

-The study was carried in the time frame between February 2014 and January 2016, as 8 patients with isolated brain stem lesion were retrospectively selected among 65 patients with acute neurological disease as proved both clinically and radiologically, their age ranged between 6months-16 years. The cases were referred for imaging work-up in Diagnostic Radiology Department from Pediatrics and Neurosurgical Departments, Zagazig University Hospitals. The study was approved by the local ethical committee.

Laboratory investigations were performed to narrow the differential diagnosis and to rule out infection and autoimmune disorders in children.

-MR imaging was performed during the acute phase of the disease using 1.5 T clinical imager (Philips Medical System-Achiva-class II, USA) equipped with a standard head coil. The following protocol was used:

a-Non contrast axial, coronal and sagittal T1WIs (TR 400–550 m/s, TE 15 m/s, FOV 250, matrix 256 x 256, section thickness 6 mm, interslice gap 1 mm).

b-Axial and coronal T2WI (TR 3500–4800 m/s, TE 110 m/s, FOV 250, matrix 256 x 256, slice thickness 6 mm, interslice gap 1 mm).

c-Axial and coronal FLAIR (TR 70008000 m/s, TE 140m/s, FOV 250, matrix 256x256, 6mm slice thickness, 1mm interslice gap).

d- Post contrast axial, coronal and sagittal T1WI after administration of gadolinium 0.2 ml/kg body weight.

e- Prior to contrast agent administration, breath hold DWI was done with a single shot spin-echo echo-planner sequence (TR/TE: 2000/33–55, matrix size128 · 128, section thickness 6 mm, interslice gap1 mm, FOV 38 cm, b values 0 and 1000 s/mm2).

f-ADC maps were calculated automatically and ADC values were measured by using circumferential ROI(8–50 mm2) in the central of the lesion.

-The signal intensity changes on different cMR sequences and pattern of contrast enhancement were interpreted. DWI and ADC map were evaluated to differentiate between vasogenic and cytotoxic edema. Lesions with iso- to hyperintense signal on DWI and hyperintense on ADC were considered as vasogenic edema while those with high signal intensity on DWI and hypointensity on ADC map were considered cytotocic edema.

g- Single Voxel Spectroscopy (SVS)

The voxel was placed in the indeterminate area identified on the axial post contrast T1WIs and in a comparable contralateral region. Voxel size was chosen to provide adequate signal and to be small enough to prevent partial volume averaging of adjacent structures. Voxel sizes varied between 1.5 and 2ccm.

Point resolved spectroscopy (PRESS) pulse sequence was used for volume localization, because of its improved S/N ratio, less sensitivity to motion and to multiple quantum effects.

-Cases with brain stem glioma (6cases) were not included in this case series as brainstem glioma is the commonest of all brainstem lesions and has characteristic clinical and imaging findings.

RESULTS

-Case (1):

We report a case of 12-year-old girl, presented to pediatric Department by left sided diplopia for 1day followed by disturbed conscious level (DCL) as her GCS was 9/15and intermittent generalized convulsion for which she received anticonvulsant in the form of phenytoin, the family gave history of upper respiratory tract infection 2weeks before admission with high fever for 4 days and for which she received antibiotics in the form of amoxicillin-clavulanic acid and antipyretics and she was fever free 12 days before presentation, with no family or medical history of systemic disease, no fever and all laboratory investigations were unremarkable apart from elevated platelet count and slight elevated WBCs in CSF.

The case was diagnosed as ADEM lesions after exclusion of possible diagnoses of brain stem lesions as the initial MR imaging revealed solitary brain stem lesion in the pons that displayed hypointense signal on T1WI, hyperintense signal on T2WI and FLAIR, no significant enhancement on post Gd DTPA images with no diffusion restriction on DWI and ADC map as the lesion showed imaging findings consistent with vasogenic edema, hypointense signal on DWI, hyperintense signal on ADC map and had high ADC value (1.5 x10-3mm2/sec).

This child was treated with high dose methylprednisolone (20 mg/ kd /day) for 3 days followed by oral steroid thereafter with gradual withdrawal in the next 4weeks. The clinical improvement was observed on the third day with better conscious level and control of convulsions; the patients discharged home on 7th day of starting treatment and the parents were asked to be on regular follow up for the next 3 months.

No clinical or radiological evidence of relapse in the follow-up MRI which was performed 3 months later and revealed complete resolution and clinical recovery.

Our diagnosis of ADEM was supported as there is no diffusion restriction with elevated ADC value of the lesion, so it is not neoplastic or ischemic process, no abnormal laboratory findings, no history of medical disease with the aid of MRS that revealed mild decrease in NAA peak, elevated Cho and MI peaks. Follow-up MRI revealed complete recovery after medical treatment (fig 1).

Case (2):

A 14-year-old female, presented to Neurology Department 3 days after the onset of headache, diplopia, ataxia and sleep rhythm abnormality with longer time of night sleep and multiple daytime napes, her past history together with family history were irrelevant; her routine laboratory and serology for immunological disorders were normal e.g (normal C3, ANA, AntiDNA); The case was diagnosed clinically as MS in correlation with laboratory findings of CSF electrophoresis that reveal oligocolonal bands and increased IgG index.

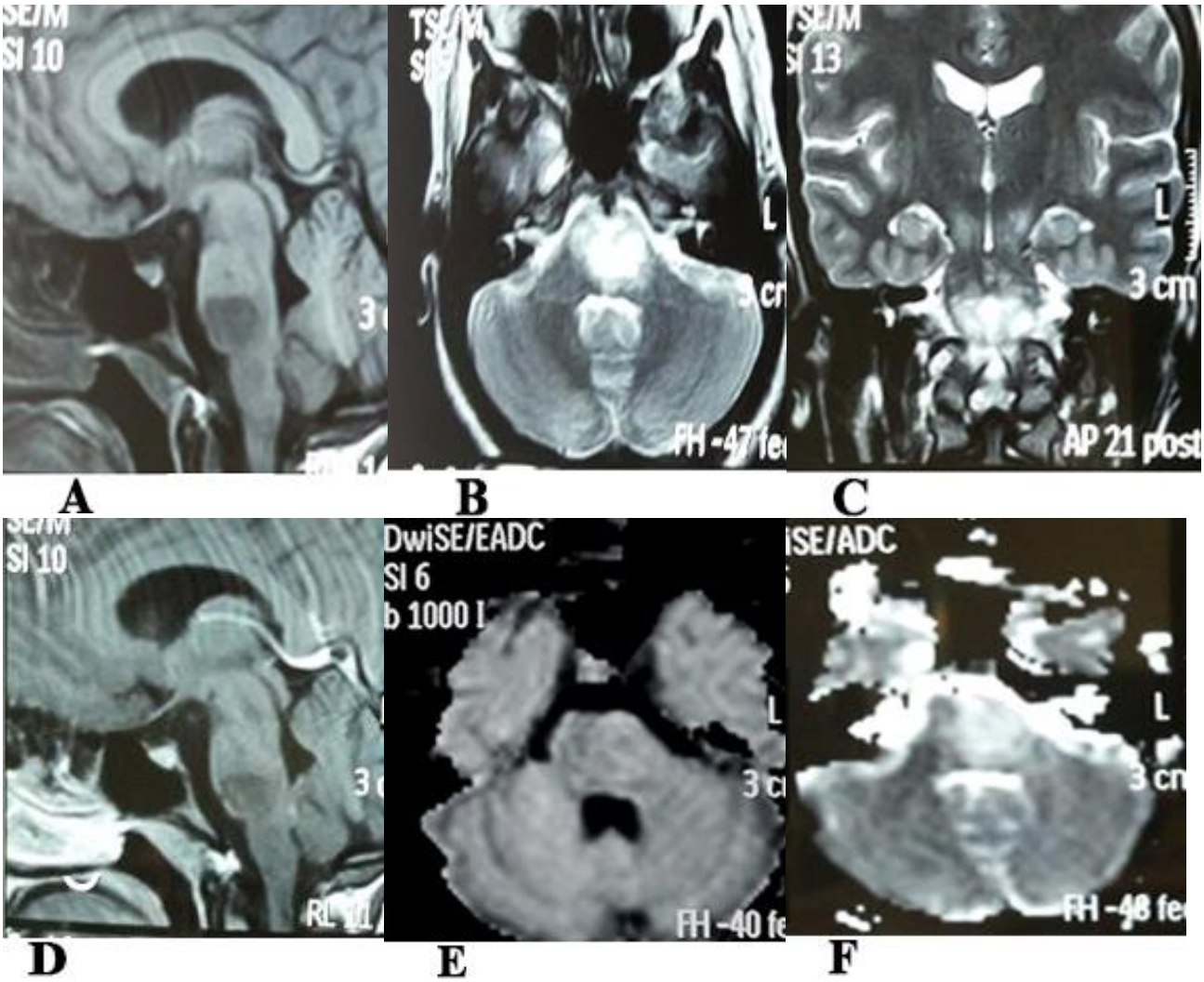
MRI revealed abnormal signal intensity lesion at the lateral aspect of pons and the related middle cerebellar peduncle, displays high signal intensity on T2WI and FLAIR. Initial diffusion MRI reveals no restricted diffusion with elevated ADC value (1.4x 10^{-3}mm²/sec) while MRS reveal mild elevated peak of choline, elevated MI and reduction of NAA on the MR spectrum (fig 2).

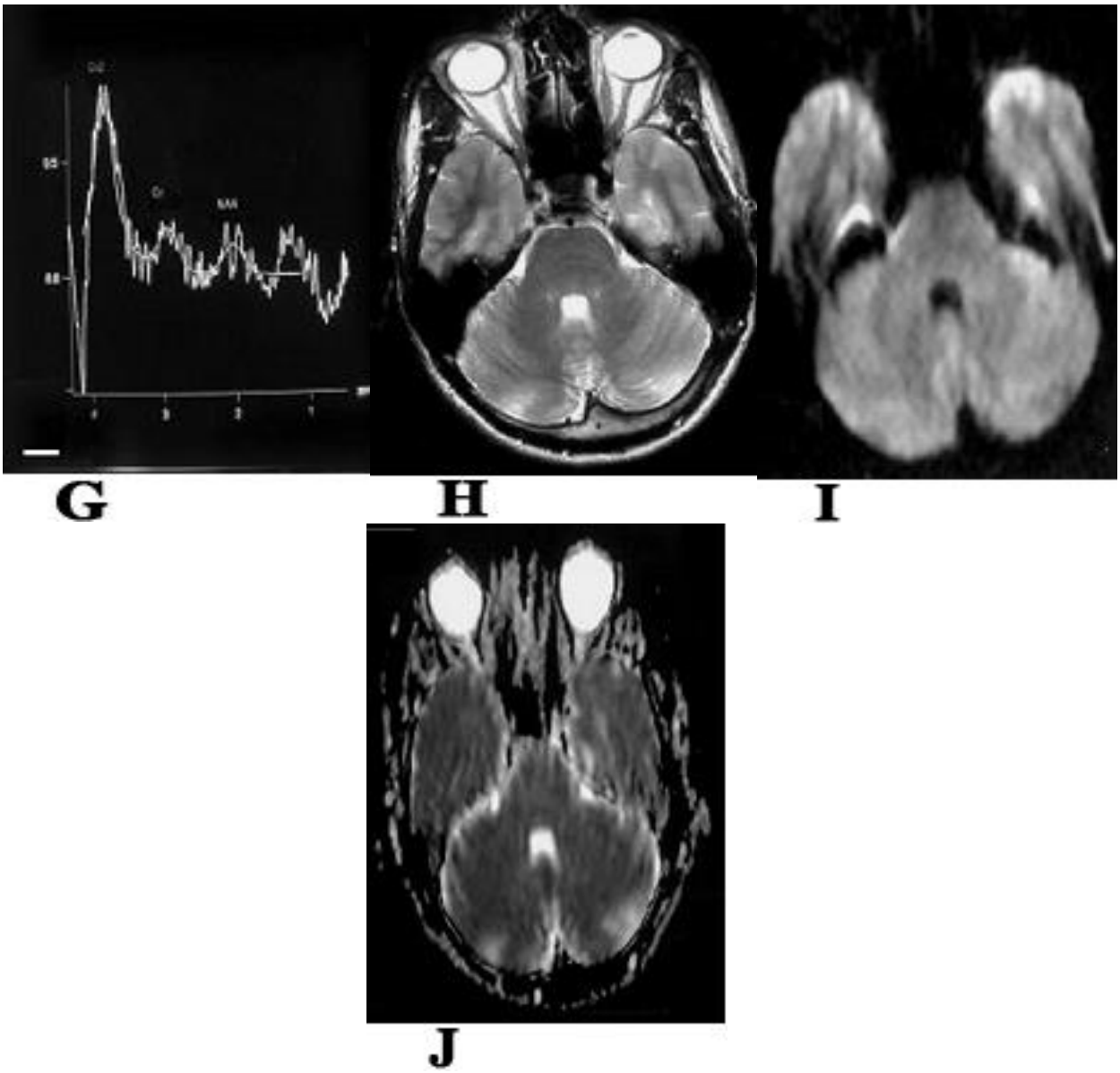
The patient started treatment with methylprednisolone 1gm (the maximum dose in children) for 5 days followed by gradual oral withdrawal, diplopia and ataxia improved on the 5th day and regained normal sleep pattern.

Three months later, Follow-up MRI revealed newly detected lesions in the supra-tentorial peri-ventricular white matter and in the cervical cord, denoting dissemination in space and time.

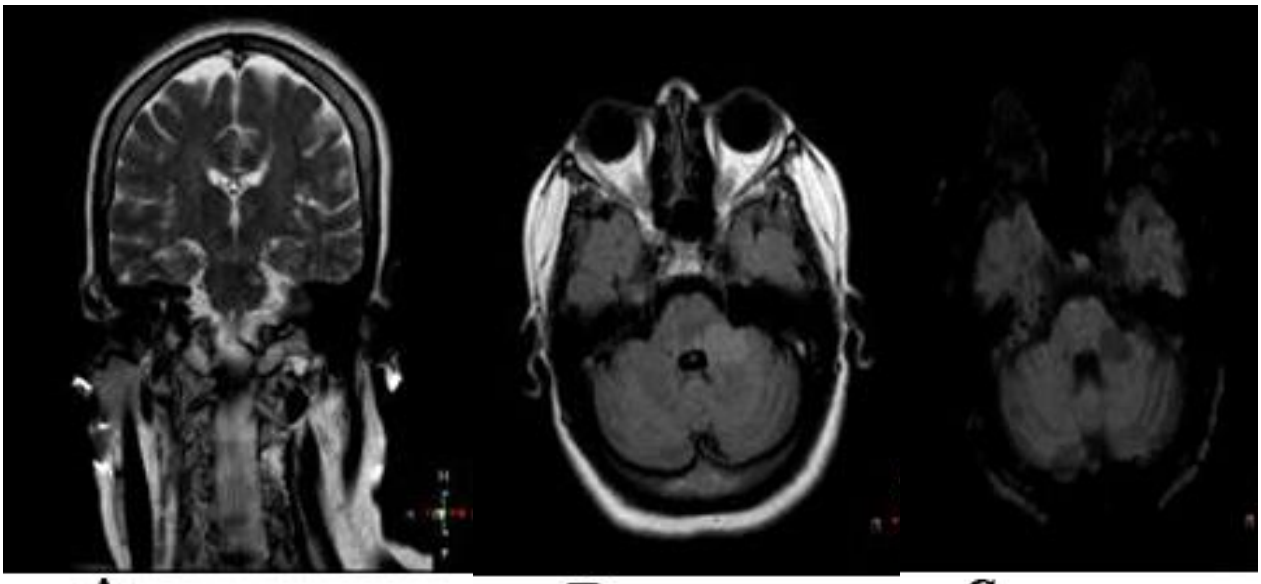
(Case 1) :12-years-old female patient presented by diplopia.

(A) MID-Sagittal T1WI: reveal hypointense lesion in the pons with no pontine enlargement. B&C): axial and coronal T2WI : show hyperintensity of the lesion sparing the antero-lateral aspect of pons and the cortico-spinal tracts. D) Post Gd DTPA mid-sagittal T1WI reveal no enhancement. E & F) Axial DWI (b1000) & ADC map: the lesion is relatively hyperintense on DWI and hyperintense on ADC map and had ADC value 1.5 x $10^{-3}mm^2/sec$ denoting free diffusion. G): SVS (TE: 135 ms): there is reduction in NAA and Cr peaks associated with elevation of the cho and MI peaks. H, I, J): Follow-up T2WI, DWI and ADC map reveal complete resolution of the lesion.





Case (2): 14-years-old female patient presented by headache, diplopia and ataxia. A & B): coronal T2WI and and Axial FLAIR reveal hyperintense lesion in the left aspect of pons and the related cerebellar peduncle. C&D) Axial DWI (b1000) & ADC map: the lesion is relatively hyperintense on DWI and more hyperintense on ADC map and had ADC value 1.4 x 10^{-3}mm²/sec denoting free diffusion. E): SVS MRS (TE: 135 ms): there is reduction in NAA and Cr peaks associated with mild elevation of the cho and MI peaks. F&G): Follow up brain Axial FLAIR and cervical Sagittal T2WI reveals newly developed plaques in the supra-tentorial periventricular white matter and in the cervical cord.



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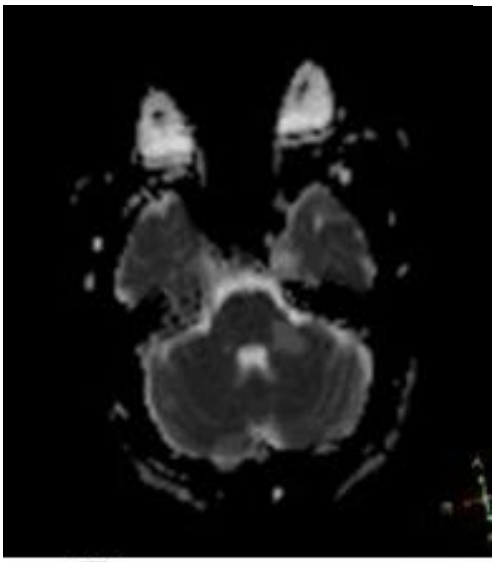

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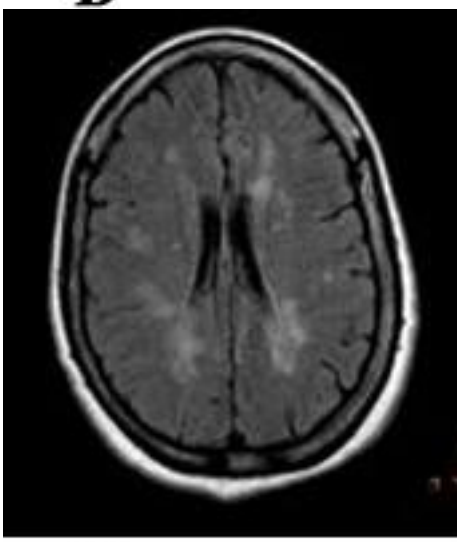

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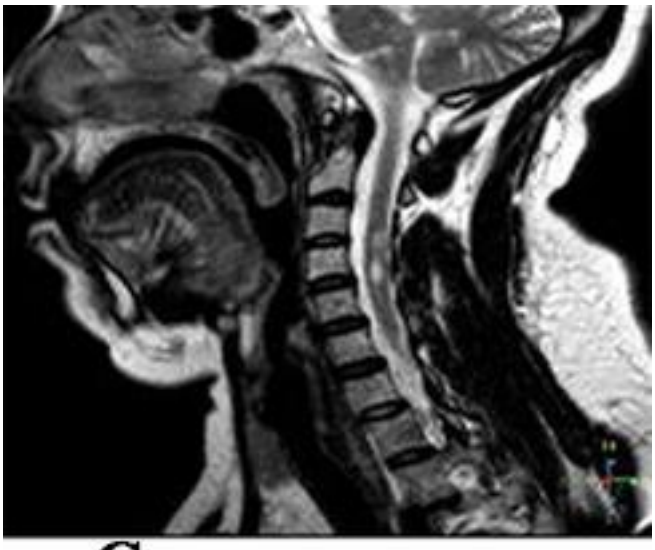

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DISCUSSION

ADEM is atypical diagnosis for isolated brainstem lesion which usually presents with asymmetrically located multifocal lesions and is associated with multifocal neurologic deficits (8).

Multiple edematous white matter T2 and FLAIR hyperintense lesions occurring at the same time are classic for ADEM. Asymmetrically distributed lesions affect the central white matter and cortical graymatter junction of both cerebral hemispheres and infratentorial (8).

Neuroimaging plays a key role in establishing the diagnosis of ADEM because there is no biomarker available. Modern MR imaging tools such as DWI are currently used in the characterization of acute demyelinating lesions (10,11).

Diffusion characteristics were analysed in children with ADEM diagnosis by IPMSSG criteria, and the study demonstrated that ADC is increased in ADEM lesions whereas isotropic diffusion maps appear to have normal findings, consistent with vasogenic edema in most patients (12). Enhancement of ADEM lesions is variable, usually absent or moderate (13).

We report a case of ADEM in which the diagnosis is made up by clinical and radiological correlation after exclusion of a number of possible diagnoses. Advanced neuroimaging by diffusion MRI and MRS play a complementary role to cMRI in diagnosis of ADEM and excluding neoplastic or ischemic insults. The case had a solitary lesion in the brainstem with high signal intensity on T2WI and FLAIR, no post Gd DTPA enhancement and no diffusion restriction. Its ADC value was high ($1.5x\ 10^{-3}mm^2/sec$) relative to the normal appearing white matter. MRS supports demyelinating insult by detected mildly elevated cho and MI peaks.

Follow-up MRI after 3 months of the diagnosis and medical treatment helps in confirming our diagnosis of ADEM as there is no newly developed lesions in consistent with Alper et al.,(1),. who stated that ADEM is a treatable disease, but a delay in treatment may results in complications as axonal loss and further progression of disease, which can be catastrophic, particularly if lesions involve crucial locations such as the brainstem. Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible and to speed up clinical recovery.

The initial diagnosis of MS is more difficult in children than adults as the classic MS diagnostic criteria used for adult patients are not easily applicable to children, and there are no criteria specifically designed for children who are under the age of 10 years. A first demyelinating event in children may be an episode of monophasic acute disseminated encephalomyelitis or a first episode of a macrophage activation syndrome, angiitis affecting the CNS or MS (6).

The most frequent initial symptoms of MS in pediatric age group seem to be sensory system disturbances, cerebellar and brain stem abnormalities, long tract dysfunction and optic-neuritis. The diagnosis can only be confirmed by a relapsing clinical course. The percentage of MS patients with childhood onset is between 2.7% and 4.4% of all MS patients, and between 0.2% and 1.6% have onset before age 10 (6).

Conventional MRI offers the most sensitive way to detect MS lesions and their changes and plays a dominant role in ruling in or out a diagnosis of MS. Although MS plaques can be found throughout the brain, they have a predilection for the periventricular white matter and tend to have an ovoid configuration with the major axes perpendicular to the ventricular surface (14).

The typical diffusion imaging feature for tumefactive demyelintaing lesions is variable ADC. Most lesions have an elevated ADC values, although occasionally, acute demyelinating lesions may have areas of reduced ADC values (15).

Early investigators used diffusion weighted MR imaging in the evaluation of MS. These studies showed increases in ADC values in MS lesions and perhaps also in the ADC values of normal- appearing white matter (NAWM) of MS patients. Although the reason for the increase in ADC is not known, it is believed to be related to the disruption of myelin, leading to an increased extracellular space (16).

We report a case of tumefactive MS in the lateral aspect of pons and its related cerebellar peduncle of a child female presented by diplopia and ataxia;T2WI and FLAIR hyperintensity with no diffusion restriction on DWI and ADC map as well as elevated ADC value, that was correlated by MRS findings where ischemia was ruled out by abscent lactate doublets on MRS and the presence of mild peaks of Cho and MI in consistent with Bernarding, Braun &Koennecke, 2002 (15), parallel to clinical and laboratory analysis. Follow-up MR studies 3 months later confirmed the diagnosis by dissemination as newly developed plaques are evolved in the supra-tentorial white matter and in the cervical cord in consistent with Horowitz etal., 1989 (14).

Follow up MRI in our cases helped in establishing the diagnosis as dissemination in time and space was characteristic for MS in consistent with Poser et al., 1983 (17) and McDonald et al., 2001 (18) who stated that the distinction between early signs of MS and ADEM is difficult, but of major importance for informing families and making therapeutic decisions. In the absence of specific biological characterization, the occurrence of relapses is the only absolute criteria for distinguishing between these two closely related diseases. The chance of observing relapses depends on the duration of the follow-up period.

It is important to assess the definition of these two conditions. Childhood MS is defined, in most published cohorts, according to the Poser criteria that require a classical dissemination in space and time (17). The McDonald criteria, which include MRI aspects, are also used (18).

Conclusion:

ADEM and Tumefactive MS are rarely involving the brain stem as isolated lesions; however, they should be included in the differential diagnosis of isolated brainstem lesions in children. DWI with elevated ADC value supports the diagnosis of vasogenic edema in both conditions. Follow-up MRI revealed full clinical and imaging recovery in ADEM while dissemination was seen in MS to support the diagnosis in both conditions.

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