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Case Report

Myelin insults differentials on MRI in children: In the light of an ADEM case ☆,☆☆

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an acute and rapidly progressive autoimmune demyelinating disorder in the central nervous system. It is a rare disease but is more frequently observed in the pediatric population. We report a case of a monophasic postvaccination ADEM, which presented with paraparesis associated with fever. It showed a favorable evolution under corticosteroids, without recurrence after 3 years of follow-up. The diagnosis was established due to the postvaccination context and the MRI abnormalities characteristics. This case prompted a general discussion about the etiologies of myelin insults in children, especially demyelinating disorders, by shedding the light on their MRI features.

Introduction

Acute disseminated encephalitis (ADEM) is an acute, rapidly progressive inflammatory demyelinating disorder in the central nervous system (brain and spinal cord). It is an autoimmune process secondary to a preceding infection, or less frequently, a vaccination. Nevertheless, there may be no preceding event found in about 25% of cases [1].

ADEM is a rare disease that is more common in children, younger than 10 years old in most cases [1]. Its incidence varies from 0.07 to 0.9 per 100,000 children per year [2].

Case report

A 5-year-old female child with unremarkable personal and family history, with no anomalies during pregnancy and delivery nor psychomotor development retardation, presented for a motor deficit of the lower limbs 15 days after receiving the fifth dose of the Diphtheria-Tetanus-Pertussis combined vaccine intramuscularly, and the sixth dose of Poliomyelitis vaccine orally, as part of the national immunization program in Morocco. The physical examination found lower limbs paraparesis and hyperreflexia, Babinski sign, neck stiffness, and fever (temperature at 38°C). There was no sensory abnormali-

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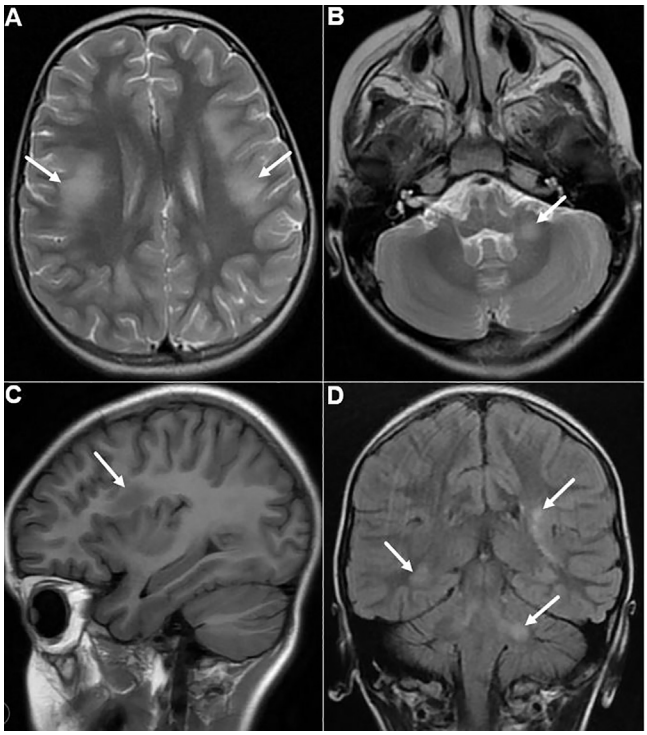

Fig. 1 – T2 axial (A and B), T1 sagittal (C), and FLAIR coronal MRI images (D) of the brain, showing multifocal bilateral and asymmetrical supra and infra-tentorial WM abnormalities, hypointense on T1 and hyperintense on T2 and T2 FLAIR abnormalities (arrows).

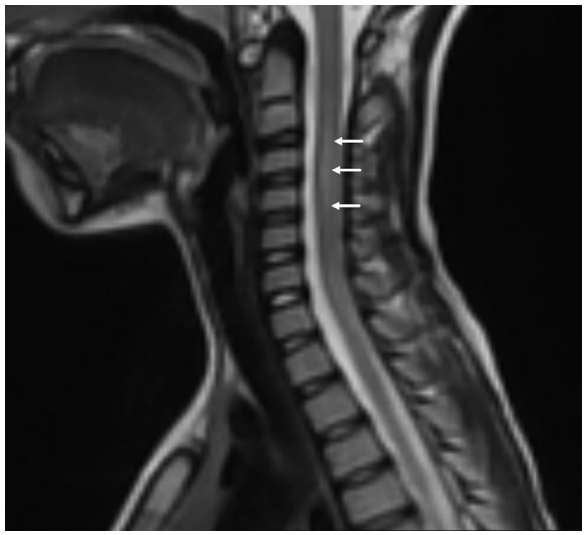

Fig. 2 – T2 sagittal image of the cervical spine, showing hyperintense signal abnormalities (arrows), longer than 3 vertebral bodies in length (longitudinally extensive transverse myelitis).

ties nor other nervous system anomalies. The rest of the physical examination was unremarkable.

Biological workup showed a neutrophilic leukocytosis and slightly elevated platelets. The cerebrospinal fluid was clear at lumbar puncture, and showed hyperproteinorachia (0.73 g/L) and a slight lymphocytic pleocytosis (53/mm^3).

A brain computed tomography (CT) was performed, which came back normal.

Next, a brain and spine magnetic resonance imaging (MRI) was performed, showing multifocal, bilateral and asymmetrical supra and infra-tentorial brain lesions, involving the subcortical and deep white matter (WM), sparing the U-fibers and somewhat sparing the periventricular WM, they were focal and confluent with somewhat ill-defined contours, measuring more than 1cm (most of them), and they were of hypointense signal on T1, hyperintense on T2 and T2 FLAIR, without diffusion restriction nor postcontrast enhancement (Fig. 1). In the spine, T2 hyperintense anomalies longer than the length of 3 vertebral bodies were found in the cervical, dorsal, and lumbar floor (Fig. 2).

WM lesions can be caused by many diseases including ADEM, infectious encephalitis, multiple sclerosis (MS), posterior reversible encephalopathy syndrome (PRES), neurometabolic and toxic causes. Nevertheless, ADEM was the most probable diagnosis based on the clinical setting (age, postvaccination context, acute setting, and clinical signs), the biological markers (low lymphocytic pleocytosis), and the MRI appearance.

The patient received boluses of corticosteroids at a dosage of 600 mg per day for 3 days, resulting in clinical improvement with recovery of the ability to walk. Afterward, the patient was discharged with a prescription for oral corticosteroids at a dosage of 20mg per day, with a gradual reduction in dosage over a total treatment period of 2 months (associated with potassium and calcium supplements in addition to a low salt diet).

The patient has remained symptom-free and has not experienced any recurrence for more than 3 years after the episode.

Two follow-up MRIs were conducted 9 months and 18 months respectively after the initial episode. Both revealed the disappearance of the WM lesions (with the persistence of a single frontal punctate lesion on T2 FLAIR, considered to be nonspecific) which established a definitive diagnosis of ADEM (Fig. 3).

Discussion

Myelin makes up most of the substance of the white matter in the central nervous system and is crucial for nerve fiber function. It originates from and is part of oligodendrocytes, which envelop and myelinate specific axon segments [3,4]. Myelination occurs with temporal diversity in topographic patterns: some areas myelinate before birth (dorsal brainstem, dorsal brainstem, and perirolandic WM), while others do so after birth during the first 2 years of life. Myelination follows a fixed pattern, roughly speaking, it progresses from caudal (spinal cord) to rostral parts (brain) and spreads from central (diencephalon, pre- and postcentral gyri) to peripheral parts of the brain [3].

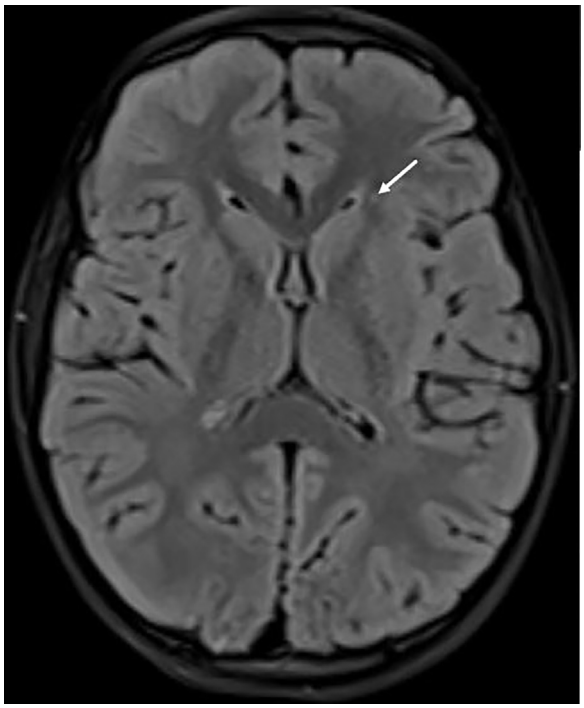

Fig. 3 – T2 FLAIR axial image of the brain, performed 18 months after the ADEM episode, showing the persistence of a single punctate WM lesion (arrow).

The term demyelination refers to myelin loss, the term hypomyelination describes insufficient myelin accumulation, and the term dysmyelination involves abnormal myelin composition, potentially leading to myelin collapse and degeneration [4].

WM myelin abnormalities in children have a large number of etiologies which can be summarized in an algorithm based on MRI (Fig. 4):

- Developmental myelin abnormalities: Most of these disorders are characterized with confluent and essentially symmetrical cerebral WM abnormalities instead of multifocal and isolated ones [5]. Two subgroups to distinguish:
  +Acquired: represented by the secondary delayed myelination which is a short and transient delay in myelination for age in infants (Less than 6 months discrepancy in comparison with normal myelination for age). The areas affected with delay in myelination appear mildly hyperintense on T2. This delay is secondary to a situation of stress (eg, prematurity, infection). A follow-up MRI should be performed more than 6 months after the initial MRI in a child older than 1 year in order to prove the transient nature of the delay in myelination [5].
  +Genetic:
  -The hypomyelinating disorders: Genetic abnormalities causing errors of metabolism, leading to a deficiency in myelin formation. They manifest since birth with psychomotor development retardation, and manifest on MRI as an unchanged pattern of deficient myelination on 2 MRIs at least 6 months apart in a child older than 1 year, or as a severely deficient myelination in a child older than 2 years [5].
  -The dysmyelinating disorders: Genetic abnormalities causing a defective enzyme that leads to dysmyelination [3]. These disorders can be subdivided based on the predominant location of the abnormalities: Frontal, parieto-occipital, periventricular, subcortical, diffuse cerebral, and posterior fossa [5].
- The demyelinating disorders: we distinguish primary and secondary ones:
  - The primary demyelinating disorders:
    - Multiple sclerosis: We call it pediatric MS when it starts before the age of 16. It is a rare entity, especially before the age of 10 [6,7]. Lesions are disseminated in time (simultaneous presence of enhanced and nonenhanced lesions, or appearance of a new lesion on follow-up), and are disseminated in space; with at least 1 lesion in at least 2 out of 4 of these regions: the juxta-cortical WM and the cortical grey matter, the periventricular WM, the posterior cerebral fossa, and the spine. Presenting a hyperintense signal on T2 and FLAIR sequences, with an oval or round-shape, and measuring ≥ 3 mm in the long axis, with an asymmetrical distribution [8]. Most lesions are in the cerebral hemispheres, perpendicular to the lateral ventricles. Involvement of the corpus callosum (CC) is very suggestive, and the periventricular location is commonly predominant initially. The presence of associated deeply hypointense lesions, which are nonenhancing after contrast (black holes) during the first demyelinating episode is highly suggestive of MS in children [9]. The spine is usually affected, often in the cervical floor, with short lesions (≤2 vertebral bodies in length) in the periphery of the spine [8,10]. Active lesions manifest a ring enhancement or especially an open ring enhancement (which helps differentiate between demyelinating diseases and neoplasms), and manifest diffusion restriction [11]. An MS lesion occurs in a perivenular pattern with a central vein. It is called the “central vein sign” when it is visible on MRI, on T2* and susceptibility-weighted-imaging (SWI) sequences [8,12].
    - Neuromyelitis optica spectrum disorder: Is an auto-immune disorder characterized by antibodies targeting the astrocyte water channel protein Aquaporin-4. Abnormalities have a typical distribution, with the following features:
      -Spine lesions presenting the following characteristics: Long (more than 3 vertebral bodies in length), central (around the central canal), post-contrast enhancement, and swelling.
      -Optic nerve lesions presenting the following characteristics: Long (more than half the length of the optic nerve), bilateral, posterior, and post-contrast enhancement.
      -Nucleus tractus solitarus lesions.

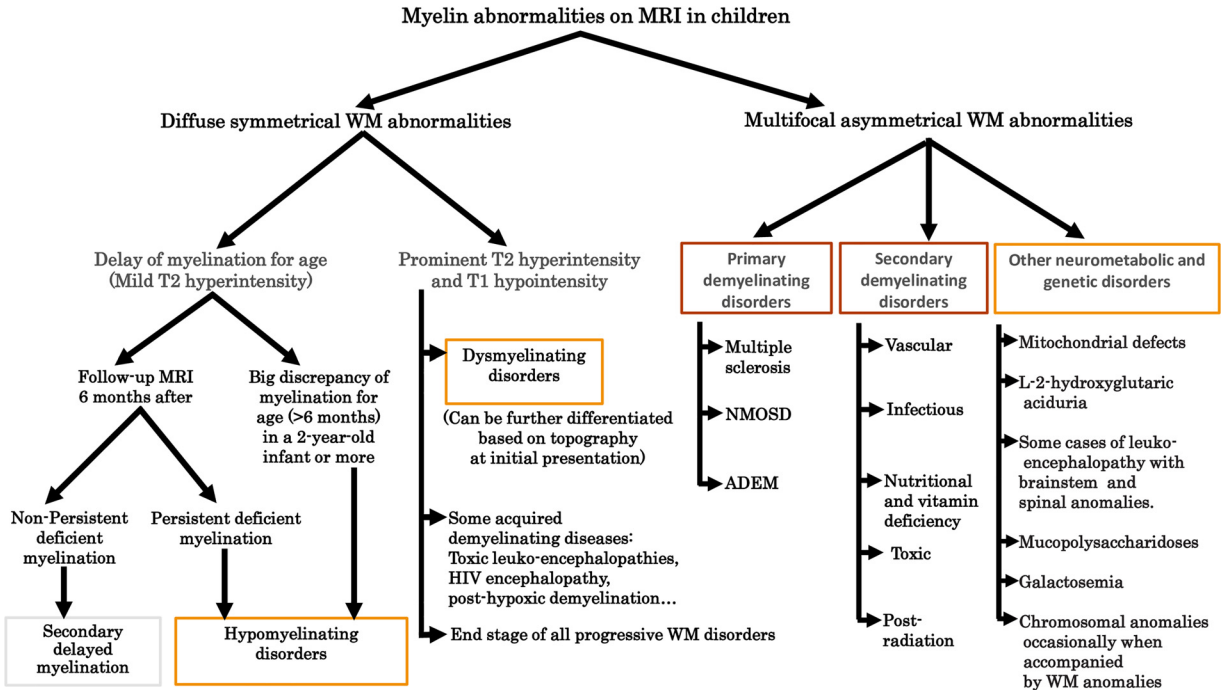

Fig. 4 – Algorithm for myelin abnormalities in children on MRI: Secondary delayed myelination, hypomyelinating, dysmyelinating, and demyelinating disorders.

-Optic chiasmal lesions.
-Periaqueductal lesions.
-Third ventricular periependymal lesions.
-Area postrema lesions.
-Hypothalamic lesions [13].

- ADEM: Is an inflammatory demyelinating disease that typically follows a monophasic course, characterized by the occurrence, worsening, recurrence, or appearance of new symptoms within a 3-month period. If a second event meeting the criteria for ADEM takes place after 3 months, it is referred to as multiphasic ADEM. While it is rare to establish a diagnosis of MS after a first event of ADEM, it is still possible if the child experiences 2 subsequent events without encephalopathy or 1 subsequent event accompanied by the emergence of new MS specific MRI lesions dispersed across time and space [2].The initial presentation of ADEM and MS can lack clear differentiation, necessitating years of follow-up to establish a definitive diagnosis [14].

  On MRI, the most frequent pattern of ADEM is a bilateral, supra and infra-tentorial subcortical WM involvement of few hazy lesions often larger than 2 cm. Spinal cord involvement is not uncommon, it usually presents with lesions traversing more than 3 vertebral bodies in length (longitudinally extensive transverse myelitis). The thalami, the basal ganglia, and the brainstem are less frequently affected, and involvement of the cortex is rare. The lesions are hyperintense on T2 and T2 FLAIR, and often without diffusion restriction [15,16]. When diffusion restriction is present, it tends to be faint, and is correlated with a poor prognosis, it indicates cytotoxic edema which is reflective of necrosis. Lesions enhance in a minority of patients (18-50%), in this case, they uniformly enhance since they have the same age, however, there is no specific pattern of enhancement in ADEM (complete or incomplete ring-like, spotty, nodular, amorphous, and gyriform are all possible patterns). Follow-up often shows complete disappearance of abnormalities, nevertheless, the persistence of some lesions has been reported in some cases (like in our patient) [6].

➢ The secondary demyelinating disorders:

- Nutritional/vitamin deficiency:

  -Central pontine: Characterized by lesions within the central pons, in a context of chronic malnutrition or alcoholism.

  -Wernicke encephalopathy: Its characteristic locations are the thalami, mammillary bodies, tectal plate and periaqueductal areas. And it occurs in a context of vitamin B1 (thiamine) deficiency [17].

- Toxic exposure: It is necessary to search for an exposure to a toxic substance. Carbon monoxide poisoning can lead to brain damage, with the most well-known being the involvement of the basal ganglia, but abnormalities in the WM are also common. Chronic exposure to heavy metals, particularly lead, can manifest as an acute

encephalopathy with abnormalities limited to the periventricular WM, but occasionally diffuse, depending on the severity of the poisoning [10].

- Postradiation injuries: Have a nonspecific appearance on MRI, and are a consequence of radiotherapy [17].
- Infectious (excluding fetal/new born infections):
  -HIV-related encephalopathy: A neurocognitive disorder usually found in the advanced stages of the disease. It manifests on T2 and FLAIR sequences with a diffuse hypersignal in the bilateral deep WM, and rarely, within the subcortical structures or the brain stem [18].
  -Progressive multifocal leukoencephalopathy: It occurs in a context of immunodeficiency and it manifests with asymmetrical and confluent WM lesions, initially located in 1 lobe and increasing in size. They present no mass effect and no enhancement (or a faint peripheral one) [10,19].
  -Subacute sclerosing panencephalitis (SSPE): A rare and progressive encephalitis caused by a persistent infection with the measles virus [20,21]. MRI can be normal, however, when it's abnormal, the findings are nonspecific, showing bilateral and asymmetrical lesions in the WM of the parietal, occipital and temporal lobes that can extend to basal ganglia and CC. Rarely, the grey matter and brain stem can be affected too. Later, encephalomalacia and atrophy take place [20,21]. The diagnosis relies on electroencephalogram, anti-measles antibodies, in addition to clinical findings [21].
- Vascular:
  -PRES: A neurotoxic syndrome characterized with vasogenic edema caused by endothelial damage and hyperperfusion secondary to hypertensive peaks. It manifests on imaging as areas of signal abnormalities (edema), that tend to be symmetrically located in the posterior lobes [17].
  -Stroke and stroke-like disorders: The absence of diffusion restriction which is characteristic of acute stroke and the absence of lacunar infarcts eliminates these diagnoses [17].
  -Primary central nervous system angiitis: Abnormalities exhibit vascular systematization with ischemic areas and infarcts in the subcortical WM and deep gray matter with evidence of vasculitis. Angiography can manifest multiple "beading" or segmental narrowing in large, intermediate, or small arteries with regions of ectasia or normal lumen in between, along with collateral blood flow [22].
  -CADASIL: An autosomal dominant microvasculopathy which is rare in children. It is characterized by recurrent infarcts of different ages (affecting WM, basal ganglia, and thalami) and vascular leukoencephalopathy, without vascular risk factors [23].
  -Susac syndrome: A microangiopathy of undetermined cause which is extremely rare in children. It manifests with lesions within the CC and periventricular WM in a clinical context of encephalopathy, hearing loss, and vision disturbances [24].

In summary ADEM has multiple differential diagnoses on MRI, however, MS remains the main one. It is very difficult to distinguish the 2 on MRI, as they are both demyelinating disorders with similar appearance on MRI. When "black holes" are present, it largely favors the diagnosis of MS. When spine involvement manifests with long lesions (>3 vertebral bodies of length), it largely disfavors the diagnosis of MS. Some clinical and biological signs strongly favor the diagnosis of ADEM: An age below 10 years old, a postinfection/postvaccination context, elevated anti-MOG antibodies, and a monophasic evolution (less than 3 months).

Conclusion

This article reports a case of ADEM, which manifested on MRI with supra-tentorial and infra-tentorial WM lesions, in addition to spine involvement. And we discussed the numerous differential diagnoses of myelin insults on MRI in children.

MRI is an important tool to help differentiate between different etiologies, however, it has limitations due to overlapping imaging appearances and atypical presentations. Hence, it is important to consider clinical signs and context, biological markers, and follow-up.

Ethical approval

No ethical approval is required for de-identified single case reports based on our institutional policies.

Patient consent

Written informed consent was obtained from a legally authorized representative.

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