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Acute Disseminated Encephalomyelitis after Rabies Vaccine: About Two Cases

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Abstract **Case Report**

The current study outlines two cases of Acute Disseminated Encephalomyelitis (ADEM) occurring in two children who received a rabies vaccine. The patients, aged 10 and 8 respectively, developed anarchic neurological symptoms after vaccination, confirming the diagnosis of ADEM through brain MRI. In the first case, bilateral abnormalities were observed in several regions, while in the second case, bilateral abnormalities of the occipital and parietal subcortical white matter were detected. Treatment included intravenous corticosteroid therapy and plasma exchange. Although slight clinical improvement was observed, neurological symptoms persisted.

Keywords: Encephalomyelitis, ADEM, child, rabies vaccine, MRI, corticosteroid.

INTRODUCTION

ADEM combines disseminated multifocal inflammation and unequal demyelination of the central nervous system. Caused by a dysregulation of the immune system and triggered by an infectious or another environmental agent in a genetically susceptible host, usually following viral infection (in 75% of cases), only 5% of cases are preceded by vaccination, usually one month before the onset of symptoms [1].

First-generation rabies vaccines, known as neuronal vaccines, have been associated with a high prevalence of neurological complications, the most common being ADEM. However, the emergence of the 3rd generation vaccines had significantly reduced this prevalence [2].

We report two cases of ADEM occurring in two children who received rabies vaccine after parental consent.

OBSERVATIONAL REPORT

Case n°1:

A 10 years old boy was bitten by a straying dog and received 4 doses of 3rd generation rabies vaccine with 2 doses at d0, one dose at d7 and one dose at d21.

Six days after the last dose of vaccine, the patient presented a paraplegia, sphincteral disorders and sensorial disorders in both lower extremities.

During the course of the disease, the patient developed intracranial hypertension, deglutition disorders, clonic seizures, altered consciousness and respiratory difficulties requiring an intubation. On clinical examination, the child was unconscious with a Glasgow score of 07/15, a fever of 38.8°C and hypertension of 139/102mmHg.

The child was admitted to the pediatric intensive care unit, under invasive ventilation for 2 days, and Ceftriaxone 100mg/kg/d. The hemogram showed a high white blood cell count of 14700, the C-reactive protein was negative, The lumbar puncture brought back a clear fluid, 70 elements pleocytosis with a lymphocytic predominance of 70%. The protein count was elevated to 1.27g/l, and the blood glucose/glucorrhagia ratio was 0.6. The culture was sterile and the PCR was negative.

Magnetic resonance imaging showed bilateral signal abnormalities of the internal capsule, lenticular nucleus and the Pulvinar, globally symmetrical (Figure 1).

The diagnosis of acute disseminated encephalomyelitis was retained on the basis of anamnestic, clinical and radiological arguments.

The patient received three boluses of methylprednisolone, one day apart at a dose of 1 gram per 1.73 m² of body surface with a relay by oral prednisone at a dose of 1mg/kg/d. The patient's clinical condition was stationary, so he received 4 sessions of plasma exchange.

The evolution, one month and a half after the beginning of the symptoms, was marked by a discrete clinical improvement, in particular: a mobilization of the two upper extremities, an improvement of the state of consciousness, the Glasgow score went to 11/15, an improvement of deglutition (he manages to deglutise a small quantity of yoghurt) and a disappearance of the seizures.

Currently, after three months from the onset of symptoms, the patient is undergoing motor physiotherapy and continuous enteral feeding.

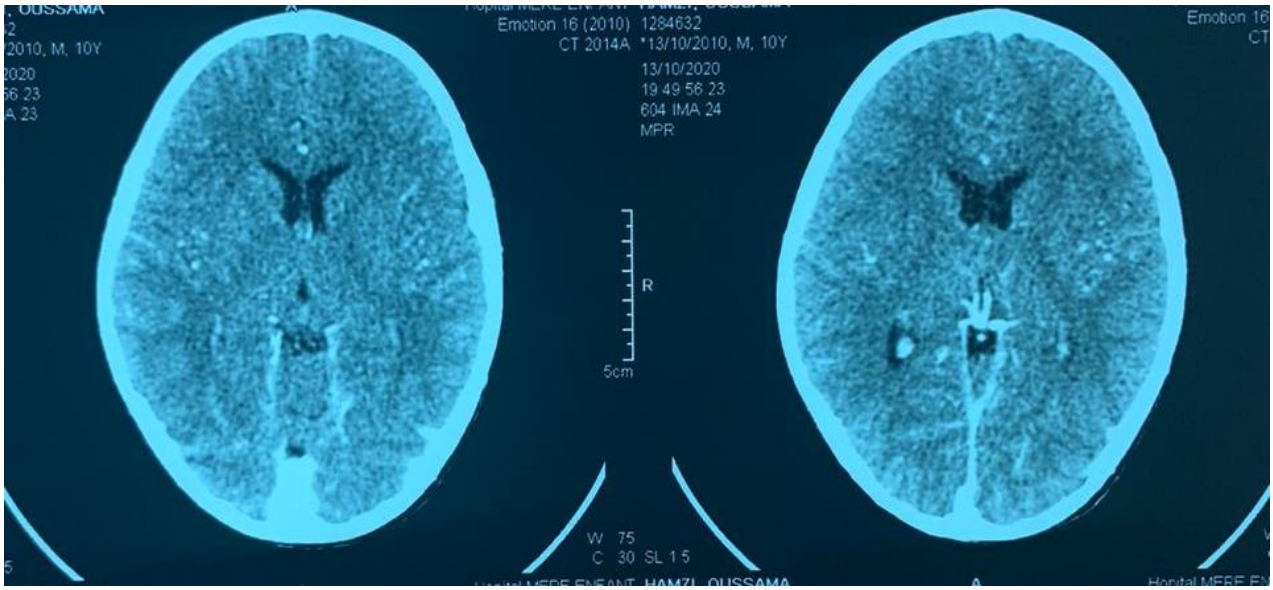

Figure 1: Frontal MRI slice of the brain showing bilateral signal abnormalities of the internal capsule, lenticular nucleus and the Pulvinar

Case n°2:

We report the case of an 8-years-old boy with a previous rabid dog bite two weeks before the onset of symptoms. The patient had received 3 doses of rabies vaccine (2 doses on day 0 and one dose on day 7).

He was admitted with a febrile meningeal syndrome one week after the last dose. On clinical examination, the child was conscious and stable on the hemodynamic and respiratory level, he was febrile at 38.5°C, he had neck stiffness, Brudzinski and Kernig's signs were positives. The patient was hospitalized and received probabilistic antibiotic therapy with Ceftriaxone 100 mg/kg/d.

The biological findings showed a 17,860-element/mm3 leukocyte count with a predominance of neutrophil cells. The C-reactive protein (CRP) was negative. The lumbar puncture brought back a clear fluid with a pleocytosis of 130 elements/mm3 with lymphocyte predominance, a protein count of 0.52 g/L and a glucose count of 0.74 g/L. The patient developed episodes of confusion and hallucinations with a persistent fever. The cerebral tomography was normal. This deterioration of the neurological condition led to the admission of the child to a pediatric intensive care unit.

At admission, the child had stable hemodynamics and respiratory status, with a Glasgow score of 13/15. Magnetic resonance imaging (MRI) was performed and revealed bilateral abnormalities of the subcortical occipital and parietal white matter with U-fibers hyper-intensity in T2 and Flair, a discrete hyper-intensity in diffusion and hypo-intensity in T1, heterogeneously enhanced by gadolinium, associated with hypoxic and anoxic lesions

Intravenous corticosteroid therapy was initiated: 3 boluses of methylprednisolone at a dose of 1g/1.73m² one day apart, followed by oral prednisone 1 mg/kg/d.

The patient's progress was marked by a recovery of consciousness and a decrease of fever. However, he still had generalized hypotonia, significant amyotrophy and quadriplegia. An enteral nutrition was introduced and physiotherapy sessions for motor and respiratory muscles allowed a modest improvement of the respiratory state and of the muscle tone.

DISCUSSION

The cases previously presented concern two ADEM cases diagnosed after the administration of rabies vaccine. The first patient received four doses of vaccine and the second three doses.

Pasteur's rabies vaccine was prepared from the spinal cord of dead rabbits infected with rabies virus and was introduced in 1885 in France [3, 4]. Neuroparalytic events have occurred in patients receiving Pasteur's rabies vaccine, with an estimated rate was 1 in 300 to 1 in 7000 [5]. With the use of purified duck embryo vaccine or human diploid cell culture vaccine, the incidence of post-rabies vaccine complications is rare or negligible.

The vaccine used in our patients was a purified inactivated vaccine belonging to the 3rd generation vaccines, prepared from human cell cultures. The symptoms appeared 1 month after the first dose of vaccine in the first case and 15 days in the second.

The most common complication is encephalomyelitis with a fatality rate of 17%. ADEM has a more aggressive and severe phenotype than acute events or relapses of multiple sclerosis, it is however less severe than hemorrhagic leukoencephalomyelitis [2].

Neurological damage occurs within 8 to 21 days after the first injection of the vaccine and is mainly represented by: encephalitis, meningitis, transverse myelitis and peripheral neuritis [5].

Clinically, regardless of its origin, ADEM is characterized by an anarchic presentation of multifocal neurological symptoms, depending on the level of demyelination (fever, headache, meningeal syndrome, coma, cerebellar syndrome, a multifocal neurological deficit, bilateral optic neuritis) [2]. The clinical presentation was different in the two patients, characterized by anarchical manifestations compatible with the ADEM definition.

CSF examination can exclude infectious meningoencephalitis that requires specific treatment and it usually reveals lymphocytic pleocytosis and high protein levels [6], as was the case in our patients. CSF may be normal in about 33% of patients [1].

The confirmation of the diagnosis is based on magnetic resonance imaging, showing lesions in the central nervous system white matter, with the absence of any previous lesion in the 3 months preceding the current episode [7].

Multifocal hypo intense white matter lesions are often found. An annular, punctiform or nodular enhancement may be seen [8]. The lesions are classified in four groups: group 1) lesions measuring less than 5 mm; group 2) lesions measuring more than 5 mm, which may be confluent and involves the white matter only; group 3) lesions affecting the white matter, regardless of their size, associated with symmetrical thalamic damage; group 4) hemorrhagic lesions. This classification has no prognostic value but can be used to differentiate ADEM from MS [9]. Therefore, MRI may be normal initially, abnormalities may appear later (between 5 and 14 days after the onset of symptoms) [10]. In our patients MRI showed exclusive subcortical occipital and parietal white matter damage in one patient and symmetrical white matter and basal ganglia damage (bilateral capsular lenticular and Pulvinar damage) in the other patient.

There is no standard treatment for ADEM. No formal clinical trial of a therapeutic agent has been published. The current treatments are based on the use of immune suppression and immune modulation [2].

The first-line treatment of ADEM, consists of high-dose boluses of intravenous corticosteroids [11]. In the last decade, there has been an improvement in survival in ADEM, associated with an increased use of intravenous corticosteroids. This use is justified by their ability to decrease inflammation and thus decrease the influx of immune cells and humoral factors contributing to demyelination [2]. A large pediatric serie of 84 patients from Argentina reported good recovery and resolution of MRI lesions with the use of high-dose corticosteroids in 80 of 84 children [12].

In our patients we used boluses of methylprednisolone at a dose of 1g/1.73m², 3 boluses administered one day apart with oral relay with prednisone 1m/kg/d without significant improvement.

Plasmapheresis should be considered as a treatment option for patients with ADEM, especially when the course is severe or if the disease has not responded to corticosteroids. It is unclear whether the use of plasmapheresis early in the disease course would alter the prognosis [13].

The overall prognosis of patients with ADEM is often favorable, with full recovery reported in 23% to 100% of patients in pediatric cohorts [11].

CONCLUSION

ADEM is a rare disease whose diagnosis is based on the anarchy of symptoms and MRI. Its management is based on high-dose intravenous corticosteroid therapy, which leads to a full recovery in most cases.

The use of 3rd generation vaccines is associated with a clear decrease in cases of ADEM after rabies vaccination.

Conflict of Interest: There are no conflicts of interest.

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