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HPV vaccine: a cornerstone of female health – a possible cause of ADEM?

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Sirs: Referring to a recent publication on the efficacy and safety of a vaccine against infection with human papilloma virus (HPV) type 16 and 18 [3], we report on a patient who developed acute disseminated encephalomyelitis (ADEM) following this vaccination. 23 days after receiving the second part of the HPV vaccination, a 15-year-old previously healthy girl presented to our hospital with new-onset headache, nausea, fever, vertigo and diplopia. She had no history of other recent vaccination or infection. At admission the patient was somnolent and had pathological gaze-evoked nystagmus, mild tetraparesis, and bilateral pyramidal signs.

Magnetic resonance imaging (MRI) with T2-fluid attenuated inversion recovery (FLAIR) sequences revealed disseminated lesions in the right frontal subcortical area and brainstem (Fig. 1a) and the cervical spinal cord (Fig. 2a–b). Peripheral leukocyte count was increased (14.6×10^9/L), while all other routine laboratory parameters including C-reactive protein were normal. Cerebrospinal fluid examination showed 10 cells/µl, mostly lymphocytes, normal protein and glucose content, and negative oligoclonal bands. All blood cultures and extensive serologic testing on bacterial and neurotropic viral agents were negative. In view of the clinical and MRI findings the diagnosis of ADEM was made. Treatment with high-dose corticosteroids was followed by rapid neurological improvement. After three weeks neurological recovery was complete, corresponding with resolution of the MRI abnormalities (Fig. 1b, 2c).

ADEM is classically described as a monophasic demyelinating disease of the central nervous system that typically follows a febrile infection or vaccination. The characteristics include a prodromal phase with unspecific symptoms, rapid onset encephalopathy and multifocal neurologic deficits. It is now recognized that up to one-third of patients will have relapses in the future [7], and definitions for the variants "recurrent ADEM" and "multiphasic ADEM" have been suggested [6]. ADEM often poses a diagnostic and prognostic dilemma. Important differential diagnoses are clinical isolated syndrome (CIS) and multiple sclerosis (MS). Past descriptions of "ADEM confined to the brainstem" may also have been classified as CIS with brainstem involvement [6]. Some patients are diagnosed with MS in the long run. Thus repeat MRI follow-ups have been recommended to detect new lesions according to "dissemination in time" [2, 4].

The clinical presentation of ADEM is heterogeneous [2]. Furthermore, there are no uniformly accepted diagnostic MRI criteria for ADEM. Lesions on T2-weighted and FLAIR sequences are typically hyperintense, large, asymmetric, and poorly marginated. In our patient, relatively small demyelinating lesions were found in the brainstem, right frontal subcortical area and cervical spinal cord. MRI did not depict any evidence of older lesions (in particular "T1 black holes"). ADEM with small lesions has been proposed as one of four cerebral MRI patterns [5, 6], and spinal cord involvement has been described in up to 28 % of cases of ADEM [6].

The clinical picture, temporal relation to the antecedent vaccination, MRI findings, and rapid clinical response and resolution of MRI lesions after treatment with IV corticosteroids are compatible with the diagnosis of ADEM in our patient.

Several vaccines have been reported as potential triggers of ADEM, including the Semple form of the rabies vaccine, hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio [6]. For most vaccines incidence rates are as low as 0.1–0.2 per 100000 vaccinated individuals [1]. The HPV-16/18 L1 virus-like particle AS04 vaccine has recently been described as highly immunogenic, efficient and safe in the prevention of cervical cancer [3]. To our knowledge, this case is the first observation of HPV vaccine as a potential trigger of ADEM. However, a single patient case report should not lead to unjustified misperceptions about the safety of the vaccine.

Disclosure The authors report no conflicts of interest.

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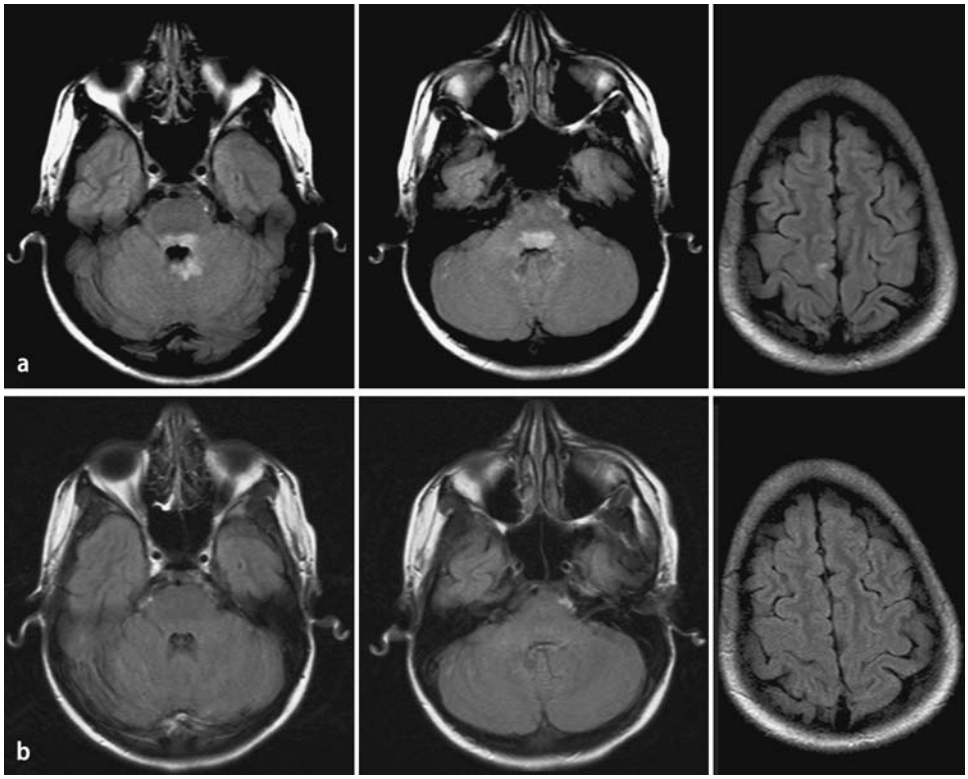

Fig. 1 Initial axial FLAIR images (**a**) showed disseminated lesions in the brainstem around the fourth ventricle and in the right frontal subcortical area. Three weeks after therapy, follow-up MRI (**b**) showed resolution of the initial abnormalities

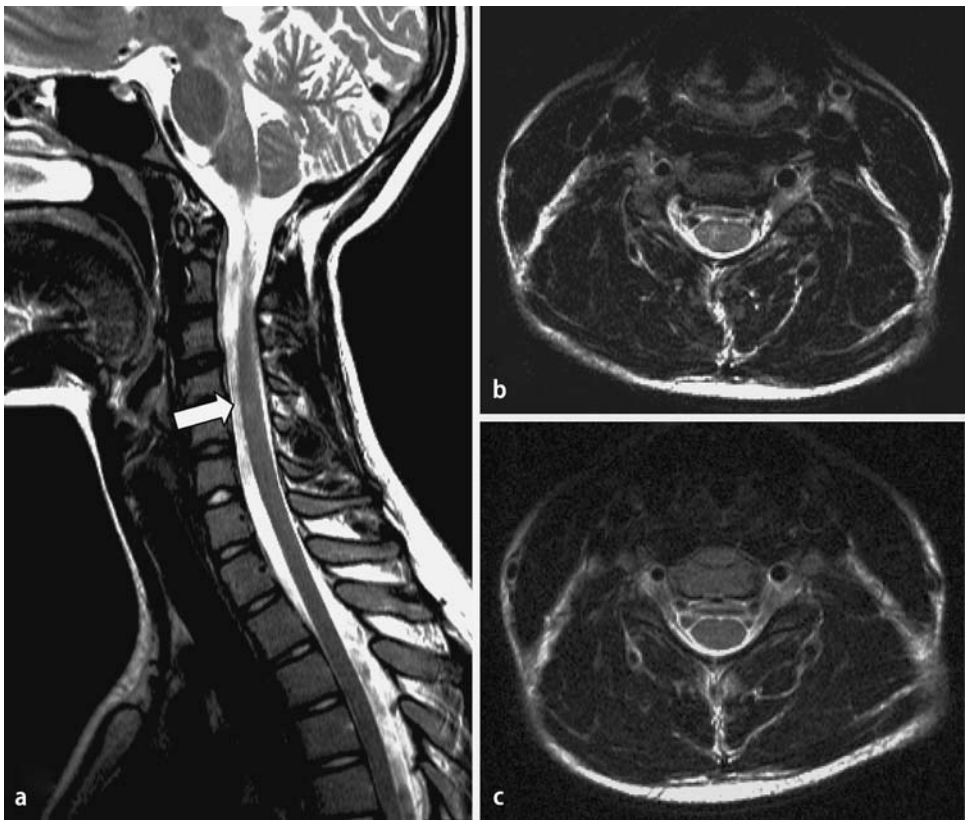

Fig. 2 Baseline MRI demonstrated high signal intensity alterations in the cervical spinal cord (**a, b**). These abnormalities had already resolved at the time of follow-up after 3 weeks (**c**)

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