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CORRESPONDENCE

Miller–Fisher syndrome following vaccination against influenza virus A/H1N1 in an AIDS patient

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Vaccination against the novel epidemic influenza virus A/H1N1 that appeared in 2009 is associated with a number of neurological complications, including transverse myelitis [1]. The guidelines of the Italian Ministry of Health (23 July 2009) suggest that patients with immunodeficiency syndromes, including human immunodeficiency virus (HIV)-positive individuals, also be vaccinated against this virus. Here we report a case of Miller–Fisher syndrome (MFS) in a patient with acquired immune deficiency syndrome (AIDS) following vaccination against seasonal and pandemic influenza.

A 58-year-old man with diabetes, chronic renal insufficiency, and AIDS being treated with lamivudine and fosamprenavir was admitted to the Infectious Disease Unit of the Siena Hospital due to a 1-week history of painful paresthesias in the lower extremities progressing to the arms, tactile hypoesthesia, difficulty in standing, and diplopia. HIV seropositivity was detected, and the diagnosis of AIDS was established in June 2007 after admission to the Infectious Disease Unit because of weight loss, fever, and Candida esophagitis. Highly active anti-retroviral therapy (HAART) with lamivudine, tenofovir, and ritonavir was initiated in July 2007, but in November 2007, because of persistent diarrhea, ritonavir was replaced with fosamprenavir. In March 2009, tenofovir was discontinued because of progressive impairment of renal functionality and the occurrence of acute myocardial ischemia; based on low viremia (HIV-RNA <40 copies/ml), ART with two drugs (lamivudine and fosamprenavir) was continued. The nadir $CD4^+$ T cell count was 150/μl in July 2007. Prior to vaccination, in September 2009, the $CD4^+$ T cell count was 310/μl and plasma HIV load <40 copies/ml. Forty and 34 days prior to the onset of neurological symptoms, in October and November 2009, respectively, he was vaccinated against seasonal influenza viruses (Fluad, Novartis) and A/H1N1 virus (Focetria, Novartis). On admission, neurological examination showed ataxic gait, pupillary anisocoria with mydriasis in the right eye, horizontal diplopia on looking to the right, hyporeflexia in the upper limbs, and areflexia in the lower limbs. An electrophysiology study showed decreased motor and sensory nerve conduction velocities at the four limbs and reduced amplitude of compound muscle action potentials. Cerebrospinal fluid (CSF) analysis detected a slight increase in protein levels (59 mg/dl, normal range value 10–50 mg/dl), normal cell count (3 cells/μl), and a high CSF/serum albumin ratio (0.0117, normal range value <0.0063), all indicating impaired blood–brain barrier status, and the presence of several oligoclonal immunoglobulin G (IgG) both in the serum and CSF. PCR analysis for a number of neurotropic viruses, including cytomegalovirus, human papovaviruses BK and JC, herpes simplex virus type-1 and type 2, Epstein–Barr virus, and enterovirus was negative. Serum anti-ganglioside GM1 (1:640) and GQ1b (1:1,280)

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IgG antibodies were found. Following vaccination, the plasma HIV load was 296 copies/ml in December 2009 (at the onset of neurological features), decreasing to 125 copies/ml in January 2010 and <40 copies/ml in April 2010. $CD4^+$ T cell count was 349/μl in December 2009, 290/μl in January 2010, and 183/μl in April 2010. Brain magnetic resonance imaging (MRI), performed without gadolinium because of renal insufficiency, revealed a proton density-weighted image hyperintense signal in the middle anterior pons (Fig. 1). Based on the clinical and electrophysiological features as well as the presence of serum anti-GQ1b IgG, the diagnosis of MFS was made and the patient treated with intravenous immunoglobulin (0.4 g/kg/day) for 5 days; gait improvement occurred after 2 weeks and complete resolution of neurological features occurred after 2 months, except for the presence of reduced reflexes in the four limbs. An electrophysiology study performed after 6 months revealed the persistence of reduced motor and sensory conduction velocities in the lower limbs. After 5 months, serum anti-GM1 IgG antibody had decreased but anti-GQ1b IgG was still positive (Table 1). This is the first report of a case of MFS occurring after two consecutive vaccinations against seasonal influenza viruses and a vaccination against influenza virus A/H1N1 in a subject with AIDS.

A/H1N1 influenza virus has been associated with a number of neurological complications, including encephalitis [2] and acute motor axonal neuropathy [3]. In addition, a transverse myelitis has been reported in a subject after a vaccination with a nasal vaccine against A/H1N1 virus [1], and a recent preliminary report of the Center for Disease Control and Prevention showed a similar incidence of Guillain–Barré syndrome (GBS) cases among both subjects vaccinated against A/H1N1 virus and those vaccinated against seasonal influenza viruses, suggesting a similar safety profile [4]. Except for a case of MFS in an immunocompetent subject after a vaccination against seasonal influenza viruses [5], there have been no earlier reports of MFS after vaccination against influenza virus A/H1N1.

MFS is thought to be an extension of the clinical spectrum of GBS and has been associated with higher frequency of serum anti-GQ1b IgG and brain MRI lesions involving the midbrain, pons, brainstem, and middle cerebellar peduncle [6]. However, MFS has a unique immunological phenotype distinct from that of GBS as in the former anti-GQ1b IgG is closely associated with ophthalmoplegia and ataxia, both of which are absent in the classical demyelinating GBS [7]. MFS seldom occurs in AIDS subjects with severe [8] or no immunosuppression [9]. In our patient, the decreased serum $CD4^+$ T cells (<400 cells/μl) at the time of onset of neurological features as well as the subsequent $CD4^+$ T cell kinetics after vaccination (with persistent decreased count values) do not support the possibility that the neurological picture could be regarded as phenotype of an immune reconstitution syndrome, which is thought to frequently trigger autoimmune disorders in HIV-positive subjects [10]. However, the temporal relationship of the clinical features with both vaccinations (40 and 34 days prior to presentation) raises the possibility of a causal role of the influenza A/H1N1 vaccine, although a synergism of both vaccines cannot be ruled out. In our patient, the time interval between vaccination and onset of neurological features lies in the maximum temporal limit of 42 days detected in the GBS cases reported in the USA during the vaccination program against swine-origin influenza A/H1N1 subtype A/NJ76 virus in 1976 [11].

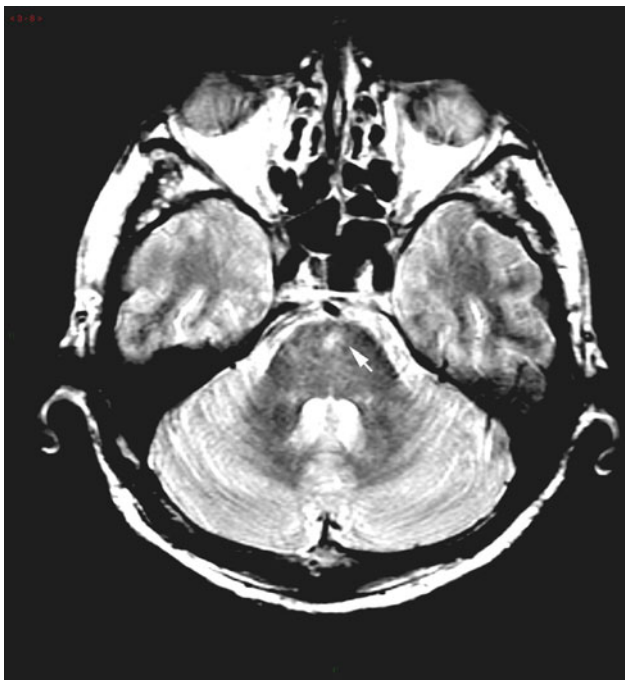

Fig. 1 Axial proton density-weighted image. Note the hyperintense lesion in middle anterior pons (*white arrow*)

Table 1 Longitudinal assessment of serum anti-ganglioside antibodies

Serum anti-ganglioside antibodies	December 2009	May 2010
Anti-GM1 IgG	1:640	1:320
Anti-GM1 IgM	1:320	1:320
Anti-GQ1b IgG	1:1,280	1:1,280

Ig Immunoglobulin

The results are expressed as titers. An enzyme-linked immunosorbent assay (ELISA) was performed to determine the titer, and the serum titer was given as the highest dilution showing an absorbance >0.050 after subtraction of the binding to bovine serum albumin

The pathogenesis of MFS after immunization is unclear, although experimental data suggest an immune-mediated mechanism. Anti-GM1 antibodies were induced in mice after the inoculation of vaccine against A/H1N1/1976 virus, suggesting that anti-GM1 IgG, but not anti-GQ1b IgG, may have been induced by the vaccine [12]. It is therefore likely that in post-immunization MFS, anti-GM1 antibody synthesis could be linked to the vaccine, whereas anti-GQ1b IgG could be linked to the underlying demyelinating process. In our patient, the different temporal pattern of the anti-ganglioside antibodies with respect to the clinical outcome, showing an early decline of anti-GM1 IgG levels and persistence of anti-GQ1b IgG after clinical improvement, supports this possibility. The clinical outcome of MFS in our patient was favorable, as previously reported [13]. Despite the undoubted efficacy of the vaccines against the influenza virus A/H1N1 in preventing death in patients affected by cardio-respiratory disorders, surveillance remains important to monitor possible neurological complications, especially in non-immunocompetent subjects.

Conflict of interest None.

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