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Case Report

Myelitis associated with influenza A virus infection

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We report a patient presenting with myelitis after respiratory symptoms. A high level of antibodies to influenza A virus was measured in serum and cerebrospinal fluid (CSF), and the serum/CSF antibody ratio was 1.7, suggesting specific antibody production in the central nervous system. Magnetic resonance imaging of the spinal canal showed a contrast-enhanced swelling on the cervical medulla. Such a case would have warranted the use of antiviral therapy and calls to mind the neurotropic potential of influenza A viruses.

Keywords: influenza A; myelitis; paresis; MRI

Influenza A virus infection may be associated with a range of central nervous system (CNS) complications (Nicholson, 1992). Medullar involvement is rare, although several patients in southeast Wales with transverse myelopathy were described during the winter of 1969–1970 (Wells, 1971). The diagnosis was based on detection of specific antibodies in the patient's serum. The outbreak of influenza A in Finland in 1993–1994 was caused by H3N2 subtype viruses closely related antigenically to the reference strains A/Beijing/32/92 and A/Hong Kong/23/92. This epidemic sent us a patient who had ascending myelitis with radicular and medullar symptoms, culminating in quadriparesis. A high level of antibodies to influenza A virus was found in the CSF, and the serum/CSF antibody ratio was low, suggesting specific antibody production in the CNS.

Myelitis may be associated with a variety of infections: herpes simplex, Coxsackie, polio and immunodeficiency viruses, Borrelia burgdorferii and syphilis (Gero *et al.*, 1991; Omasits *et al.*, 1990; Scotti *et al.*, 1993) and with immune disorders, multiple sclerosis (MS), and malignancies (Boumpas *et al.*, 1990; Fukazawa *et al.*, 1990; Joubert *et al.*, 1995). Abnormal neuroradiological findings are rare in myelitis (Färkkilä *et al.*, manuscript in preparation). Typically, T2-weighted MR scans show an increased focal or diffuse intramedullary signal, with or without a mass effect. In our patient, MRI showed striking alterations in the cervical medulla and we present the case here.

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Case history

A 62-year-old woman, who had had brain infarcts 4 years earlier but had made a good recovery, experienced respiratory symptoms and weakness in her left leg. She was admitted to the regional hospital after a few days and found to have pneumonia with respiratory symptoms and high fever. She was treated with antibiotics. The weakness spread to her right leg. On suspicion of a lacunar stroke, the patient was transferred to the University Hospital for further examination. A computed tomography scan of the head showed old lacunar infarctions, but no recent alterations. Her muscle weakness progressed, reaching the body musculature and both arms. Deep tendon reflexes were absent, but the Babinski sign was bilateral. Within 3 weeks quadriparesis was complete, and she had apparent difficulty in swallowing and speaking. MRI of the spinal canal showed evident swelling and contrast enhancement extending from the Medulla oblongata to at least the T3 level (Figure 1). A T1-weighted scan without contrast medium showed hypointensity, and a T2-weighted scan showed hyperintensity compared with the surrounding tissue. The patient received antibiotics, antituberculotic and antiinflammatory medication, and prednisolone in decreasing doses starting with

80 mg/day, lasting for 6 weeks. She was alert throughout the illness and her mental functions were normal, though depression was apparent. At follow-up after 12 months, her condition was found to be unchanged. Namely, her respiratory function has been minimal but sufficient, her voice is hoarse, and her swallowing sluggish and she is able to move the fingers of her left hand.

Laboratory tests

The first CSF specimen, obtained 15 days after the onset of symptoms, showed WBC 17×10^6/L, RBC 945×10^6/L, a normal glucose level, an elevated protein content of 2358 mg/L (normal 150–450 mg/L), and negative bacterial staining and cultures (Table 1). Blood WBC, Hb, serum electrolytes, creatinine, and liver enzymes were normal. Antibody screening of serum with an enzyme immunoassay [EIA] to 21 microbes was unremarkable, except that the response to influenza A virus was high. The level of antibodies to influenza A virus was clearly increased in the CSF as well. No other antibodies were found in the CSF. A polymerase chain reaction assay for HSV type 1 and HSV type 2 from the CSF was negative. Urinalysis was also negative. The level of antibodies to CMV in the serum increased from 86 EIU (EIA units) to >390 EIU during prednisolone therapy; IgG avidity was high, suggesting an old infection, and only traces of antibodies to CMV were present in the CSF.

The level of antibodies to influenza A virus was high in both the serum and the CSF, the antibody ratio being 1.7 (normal >20) (Table 1). The antibody index (AI) was 9.9 (normal <1.9; AI=[Influenza A antibody level in CSF : Influenza A antibody level in serum] × [total IgG in serum: total IgG in CSF]) (Ukkonen *et al.*, 1981). In immunoblot analysis with an IgG concentration of 8.8 mg/L for CSF and 9.7 mg/L for serum against a recent reference strain, A Beijing/353/89 (H3N2), the antibodies appeared reactive (Kapaklis-Deliyannis *et al.*, 1993). In nonreducing conditions, both serum and CSF gave distinct bands to HA2 and M proteins and a weaker band to NP. All the bands were stronger for CSF than for serum. In hemagglutination inhibition (HI) tests, a titer of 1 : 20 was detected when the neuraminidase-treated CSF was studied for antibodies against a representative epidemic strain (A/Finland/280/93), which was propagated in MDCK cell cultures and known to be sensitive to HI antibodies. No antibodies were found (a titer of 1 : <5) when a recent H1N1 subtype virus (A/Finland/164/91) was used as antigen in the HI test.

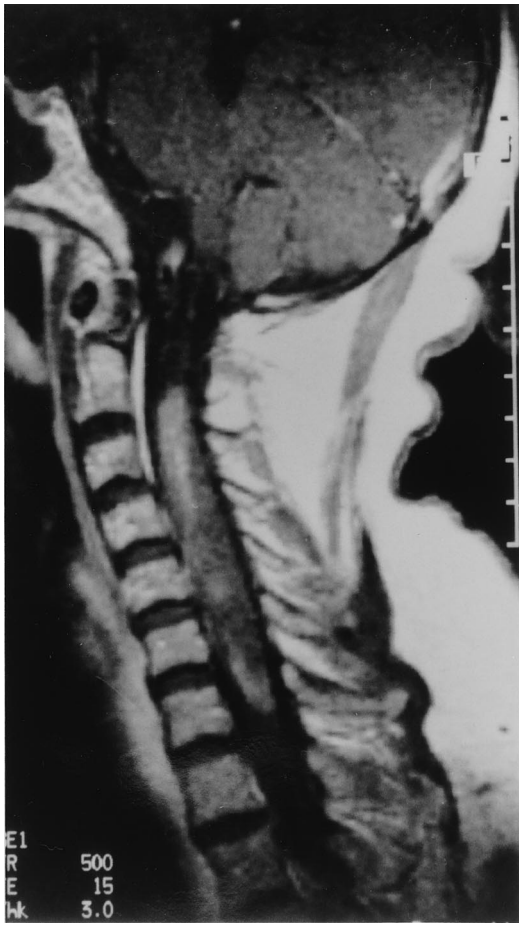

Figure 1 Magnetic resonance imaging of the spinal canal showed contrast-enhanced expansion over a large area, on this T1-weighted image from C-2 to C-7; without contrast medium the lesion appeared hypointense. In the T2-weighted scan this same lesion appeared clearly hyperintense against the gray medulla.

Table 1 Results of tests on serum and cerebrospinal fluid (CSF) during the course of the disease. The IgG content of the CSF was 440 mg/L, and the IgG index 1.23 (IgG level in CSF : IgG level in serum) × (albumin level in serum : albumin level in CSF), normal ≤0.60. Specific antibodies were determined by enzyme immunoassay (EIA) using antigen-coated microtiter plates with positive and negative controls in serial dilutions. The respective optical densities (ODs) at a dilution 1 : 200 were divided by the OD of the positive reference serum multiplied by 100. The positive control serum represents a EIA unit level of 100, the negative control <20

		Cerbrospinal fluid				
*Days**	*CRP mg/L*	*WBC 10^6/L*	*RBC 10^6/L*	*Gluc mmol/L*	*Prot. mg/L*	*S/CSF-Ab** Ratio of EIUs*
15	13	17	945	2.2	2358	ND
22	50	8	0	4.2	1749	ND/62
26	10	ND	ND	ND	ND	1.7
33	10	1	104	4.6	582	ND
48	44	5	2580	3.6	620	6.4
69	13	2	5	2.5	927	4.0

*Days from onset of symptoms
**Level of antibody to influenza A in serum and in CSF. Usually, no antibodies are present in the CSF (EIUs<5), and if present, the ratio of EIUs in serum : CSF is >20 in a normal case.
ND= not done.

Discussion

The MRI and CSF findings in our case are characteristic for severe myelitis. In addition, the patient had radicular symptoms. Cases with myeloradiculopathy were observed during an outbreak of influenza in 1969–1970 (Wells, 1971; Owen, 1971). Our case is the first with evidence of intrathecal production of virus-specific antibodies and abnormal MRI findings. An elevated level of antibodies to influenza A virus but not to other viruses was found in the CSF. The serum/CSF antibody ratio was highly abnormal, indicating production of antibody to influenza A virus within the CNS. Oligoclonal bands in sodium dodecyl sulfate gel were detected specifically with an H3N2 influenza A strain. Unfortunately, the influenza A viral RNA was not amplified because CSF specimens were no longer available for the assays.

MRI showed marked swelling and extensive contrast enhancement of the cervical medulla. The finding was nonspecific, suggesting an inflammatory process or medullar neoplasm (Gero *et al.*, 1991). Myelitis may often be difficult to distinguish from a neoplasm or demyelinating diseases on MR images. The prodromal respiratory symptoms and concomitant pneumonia were consistent with influenza A virus infection. No signs of bacterial or other infections or malignancy were found. The relentlessly progressive course, involving the entire medulla and spreading to the pontine regions with cranial nerve involvement, was life-threatening and the patient has been left with severe sequelae.

Our case was unexpected and is alarming. Specific antiviral therapy with ribavirin is available, which makes rapid diagnosis imperative (Gilbert and Knight, 1988). The case is also alarming, since it reminds us that influenza A virus has the potential for neurotropism and may cause specific antibody production in the CNS as in our case. In future cases, a reverse transcriptase polymerase chain reaction for influenza A viral RNA should be used to further document viral invasion of the CNS.

The presence of radicular symptoms in the absence of a prior neurological clinical history, or of central lesions visible on MRI or of antibodies to other viruses in the CSF make the diagnosis of MS unlikely (Sibley and Weinshenker, 1992). The present-day influenza A viruses are young human pathogens which evolve at a high rate (Webster *et al.*, 1992). Neurotropic influenza viruses have been detected but have been infrequent (Stuart-Harris and Schild, 1977). The rapid evolution and adaptation may be reflected in the clinical features. In conclusion, when features typical of myelitis are detected, by MRI, influenza A virus should be among the viral etiologies considered.

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