

*Short report*

## Post-influenzal encephalitis during the influenza A outbreak in 1979/1980

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**SUMMARY** In four men a severe encephalitis developed one week after the respiratory symptoms during the influenza A outbreak in 1980. Virological studies showed that the patients had had a recent influenza A (H3N2) infection. All patients made a complete recovery.

True encephalitis complicating influenza A infections with lymphocytic pleocytosis in cerebrospinal fluid (CSF) is comparatively rare.<sup>1</sup> Benign confusional states and minor neurological signs, for example ocular muscle palsies are observed more often.<sup>2-4</sup> Reports of post-influenzal encephalitis have been sparse after the pandemic of 1957.<sup>5</sup> However, in eastern Europe and the USSR there have been numerous reports of neurological complications of influenza in the last few years.<sup>6-9</sup>

In this communication, four cases of influenza A virus associated with encephalitis are reported. According to the Central Public Health Laboratory (Helsinki), the influenza outbreak caused by H3N2 subtype viruses commenced in Finland during the last weeks of December 1979 and terminated towards the end of March 1980. Preliminary results of epidemiological surveys suggest that the outbreak covered the whole of the country and adult patients were more numerous than in any year since the epidemic 1971–1972. The strains isolated in Finland were antigenically close to A/Texas/1/77 or, in certain cases, to A/Bangkok/1/79; both variants circulated during the 1979–1980 season in many parts of the world.<sup>10</sup>

### Material and methods

The serum specimens, taken from the patients on admission and about two weeks later (exact dates in

table), were studied for haemagglutination inhibiting (HI) antibodies against the following influenza A viruses: (i) A/Finland/34/80 (an A/Texas/1/77 (H3N2)-like strain), (2) A/Finland/31/80 (an A/Bangkok/1/80(H3N2)-like strain), (3) A/Finland/23/75 (an A/Victoria/3/75(H3N2)-like strain), and (4) A/Finland/30/77 (an A/USSR/90/77(H1N1)-like strain). The principles presented by Robinson and Dowdle<sup>11</sup> were followed in the HI tests. The sera were pretreated with cholera filtrate (Philips-Duphar, BV, Holland) to remove non-specific inhibitors. Infected allantoic fluids from embryonated eggs, diluted to contain 4 HA units of virus, were used as antigens.

### CASE REPORTS

Antibody titres in HI tests can be seen in the table. A four-fold or greater rise, and in one case high titres, of antibodies against the H3N2 viruses indicates recent infection. Measurable levels of antibodies against the epidemic strains in the first specimens suggest that the patients had contracted influenza before admittance to hospital. As presented in detail below, all the patients had had an influenza-like disease a short period previously.

*Case 1* A 50 year old man became febrile in a few hours, and drowsy and disorientated seven days after influenza-like respiratory symptoms, which had subsided. On admission he was stuporous, yet conscious, and aphasic. Neurological examination was otherwise normal. CSF on the day of admission contained  $22 \times 10^6/l$  lymphocytes and the protein content was 701 mg/l. An EEG was abnormal with generalised slow activity in the theta range. Computed tomography (CT) scan was normal. Because of the suspicion of herpes simplex encephalitis a brain biopsy from the left temporal lobe was taken. No herpes simplex antigen was detected in the biopsy by an indirect

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Table *H1 antibodies in the paired sera of the cases reported*

Case no	Admission to hospital	Serum specimens and their collection dates	Titres of antibodies against:			
			A/Fin/31/80 (H3N2)	A/Fin/34/80 (H3N2)	A/Fin/23/75 (H3N2)	A/Fin/30/77 (H1N1)
1	12 2 80	I 14 2 80	24	12	< 12	< 12
		II 27 2 80	96	96	< 12	< 12
2	18 2 80	I 20 2 80	384	192	192	24
		II 20 3 80	384	192	192	24
3	18 2 80	I 19 2 80	48	48	12	192
		II 29 2 80	≥ 768	≥ 768	192	192
4	5 2 80	I 7 2 80	24	24	24	12
		II 20 2 80	192	192	24	12

immunofluorescent technique and there were no infectious infiltrates or signs of necrotising encephalitis. Adenine arabinoside for five days and dexamethasone four times daily intramuscularly were started. Next morning the patient was afebrile, orientated, but tired and spoke rationally. Recovery thereafter was uneventful. Neuropsychological examination two weeks after admission showed moderately impaired memory and sluggishness, both of which were much better three weeks later. The patient returned to his work 2½ months after admission. The EEG six weeks after admission was normal apart from some theta activity in the area of the brain biopsy.

**Case 2** A 55 year old man became febrile in a few hours, drowsy and disorientated. He had just recovered from influenza-like symptoms, which had begun a week earlier. Neurological examination on admission was normal except for drowsiness and disorientation. The CSF was clear with  $18 \times 10^6/l$  lymphocytes and a protein of 866 mg/l. An EEG showed generalised slow activity in the theta-delta range. CT scan was normal. After three days of confusion the patient returned to his normal state of mind, complaining only of tiredness. Two months later he was normal and his EEG also was normal.

**Case 3** A 43 year old man became febrile in a few hours, drowsy and finally unconscious. Seven days previously he had had an influenza-like illness, from which he had recovered. On admission the patient was unconscious, but reacted to painful stimuli. No other neurological signs were noticed. The patient was treated in the intensive care unit for 13 days, two days with controlled respiration. He received neither antibiotics nor dexamethasone. The CSF was clear with  $14 \times 10^6/l$  lymphocytes. An EEG and CT scan were not available in the hospital. The patient recovered consciousness on the fourth day of hospitalisation, but was disorientated and confused for three more weeks. Thereafter he has been normal.

**Case 4** A 36 year old man rapidly developed fever, symmetrical convulsions and unconsciousness. One week before admission he had had influenza-like symptoms, from which he had recovered in two days. On admission the patient was unconscious and reacted only to painful stimuli. There were extensor plantar response<sup>n</sup> and disconjugate gaze. The patient was

treated for eight days in the intensive care unit and on controlled respiration for four days. Cefuroxime 1.5 g thrice daily and dexamethasone 5 mg four times a day intravenously were started. The CSF was clear with  $19 \times 10^6/l$  lymphocytes and a protein of 710 mg/l. An EEG showed generalised slow activity in the theta-delta range, and a CT scan was normal. On the third day of hospitalisation the patient recovered consciousness but thereafter was intermittently unconscious and confused for two weeks. After that recovery was uneventful and the patient returned to work 2½ months after admission.

## Discussion

In these four cases of post-influenzal encephalitis the clinical picture was very uniform and resembled that of group 2 in Flewett's and Hout's study.<sup>12</sup> A week after influenza-like symptoms the patients had a rapid rise of temperature with decreased level of consciousness to the point of stupor and confusion in two cases, and unconsciousness in the other two cases who were treated in the intensive care unit. The cerebrospinal fluid showed a mild lymphocytic pleocytosis and in the EEG there was diffuse slow activity compatible with encephalitis. All four patients recovered from their dramatic symptoms of encephalitis in two to 25 days, and returned to their previous work after a few months. Virological studies showed that encephalitis in these cases was probably induced by influenza A virus (H3N2) but the exact mechanism remains undetermined.

The clinical picture of influenza A encephalitis differs from that of early herpes simplex encephalitis in that there are no localising brain symptoms, nor focal CT scan or EEG findings.<sup>13</sup> During the influenza A epidemics both possibilities should be borne in mind because of their different treatment and prognosis. An intensive general treatment should be given to the patients with influenza A encephalitis, because they are likely to recover completely. Adenine arabinoside

is the drug of choice for patients with herpes simplex encephalitis.<sup>14</sup>

The occurrence of these four cases with encephalitis during the influenza epidemic in 1979–1980 does not necessarily mean that A/Texas/1/77 variant would be more likely to cause encephalitis than other influenza A strains. Probably the number of encephalitis cases depends on the number of people infected with influenza A virus.

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#### References

- 1 Schorre W. *Die Infektionskrankheiten des Nervensystems*. München: Urban and Schwarzenberg, 1979.
- 2 Bental E. Acute psychoses due to encephalitis following Asian influenza. *Lancet* 1958; **2**:18–20.
- 3 Friedman JH, Cancellieri R. Central nervous system complications of Asian influenza. *NY State J Med* 1958; **58**:859–62.
- 4 Gerstenbrand F, Hoff H, Weingarten K. Klinischer Bericht über Enzephalitis nach Grippe. *Wien Med Wochensh* 1958; **108**:1–4.
- 5 Delorme L, Middleton P. Influenza-A virus associated with acute encephalopathy. *Am J Dis Child* 1979; **133**:822–4.
- 6 Szalka A, Mándoky F, Simon L, Endres M. Severe sequelae of influenza virus induced encephalitis during an influenza epidemic in Hungary (Hungarian). *Orvosi Hetilap* 1978; **119**:3065–7.
- 7 Vashchenko MA, Muravskaya LV, Karasovskaya LF, Maximets VG, Moyseyenko LE, Rudenko AA. Clinico-electroencephalographic correlations in lesions of the nervous system in patients with influenza (Russian). *Vrach Delo* 1978; **6**:132–6.
- 8 Gavura VV, Lymar SK. Clinical and treatment characteristics of severe forms of influenzal meningoencephalitis (Russian). *Vrach Delo* 1978; **9**:123–7.
- 9 Vashchenko MA, Trinus EK, Yatel TP, Rudenko AA, Radkevich TA, Moyseyenko PE. Encephalitis and meningoencephalitis in patients with influenza (Russian). *Vrach Delo* 1974; **1**:132–6.
- 10 WHO. Weekly epidemiological record 1980; **55**:73–80.
- 11 Robinson RQ, Dowdle WR. Influenza viruses. In: Lennette EH, Schmidt HJ eds. *Diagnostic Procedures for Viral and Rickettsial Infections*. New York: American Public Health Association, 1969; 426–7.
- 12 Flewett TH, Houlst JG. Influenzal encephalopathy and postinfluenzal encephalitis. *Lancet* 1958; **2**:11–15.
- 13 Davis JM, Davis KR, Kleinman GM, Kirchner HS, Taveras JM. Computed tomography of herpes simplex encephalitis with clinicopathological correlation. *Neuroradiology* 1978; **129**:409–17.
- 14 Whitley RJ, Soong S-J, Dolin R *et al*. Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. *N Eng J Med* 1977; **297**:289–94.