Influenza A virus and Reye's syndrome in adults

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SUMMARY We report fatal Reye's syndrome in two adults following proven influenza A viral infections. Reye's syndrome is, therefore, not confined to children but may also occur in adults. Many reported cases of postinfluenza A encephalopathy have clinical and pathological features of Reye's syndrome suggesting that they are not due to postinfectious perivenous demyelination.

In 1963, Reye, Morgan, and Baral described 21 children who, following a prodromal illness, developed vomiting, seizures, coma and death.¹ Noninflammatory cerebral oedema and fatty metamorphosis of the liver was found at necropsy. An increasing number of similar cases have since been reported worldwide. Reye's syndrome is generally thought to occur only in children. The aetiology is unknown, but the syndrome has been associated with epidemics of influenza B virus² and varicella zoster virus.³

We describe two adults with mild influenza virus illness followed by clinical, biochemical and pathologic features of Reye's syndrome. We suggest that this syndrome can occur in adults in association with influenza A virus infections.

Case reports

Case 1 A 57 year old, previously healthy, white male developed fever, cough and myalgia on 6 March 1978, during an epidemic of influenza A/Victoria/3/75. The patient was mildly ill and was recovering. Three days later vomiting, confusion and seizures developed. He was hospitalised with a temperature of 38.9°C, stuporous with bilateral Babinski signs. No papilloedema or focal neurological signs were present. The liver was not enlarged and no other abnormalities were present. The patient rapidly progressed into a coma with fixed, dilated pupils and absent reflexes. The next day the electroencephalogram (EEG) showed electrocerebral silence and the patient

died. No one in his family had ever had illnesses suggesting abnormalities of the urea cycle.

Laboratory tests included a normal brain computerised tomogram (CT), blood count, and serum electrolytes. A traumatic lumbar puncture done on admission had a normal opening pressure. The cerebrospinal fluid (CSF) contained 900 fresh red blood cells per mm³, 5 lymphocytes per mm³, 250 mg per dl protein, 150 mg per dl glucose, and sterile bacterial and fungal cultures. The SGOT level was 114 milli-International Units per ml (mIU/ml) (normal 9 to 41) and lactic dehydrogenase (LDH) level was 800 mIU/ml (normal 60 to 100). Total serum bilirubin was normal. Toxicology studies demonstrated moderate salicylate levels in the blood, but no toxins.

Case 2 An 18 year old waitress with no previous health problems became ill with influenza. Two days later, she developed nausea and vomiting. The next day confusion and seizures developed. Initial neurological examination was normal except for confusion. Five hours after admission, she became comatose without localising signs. Three hours later the patient had fixed dilated pupils, absent reflexes, and no spontaneous respirations. An EEG showed electrocerebral silence. She was maintained on a respirator for four days before death. She had had no previous episodes of encephalopathy or liver disease and there was no family history of individuals with abnormalities of the urea cycle.

Laboratory tests included a normal blood count, serum electrolytes, drug and toxin screen, skull x-ray and isotope brain scan. Lumbar puncture showed a normal opening pressure. The CSF contained 95 RBC per mm³, no WBCs, 23 mg per dl protein, 105 mg per dl glucose, nonreactive

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Venereal Disease Research Laboratory results, and sterile bacterial and fungal cultures. On admission the SGOT was 198 mIU per ml, LDH was 250 mIU per ml, and serum total bilirubin was normal; these tests remained abnormal thereafter.

Necropsy findings of cases 1 and 2

Brain The brains were swollen with flattened gyri, narrow sulci, and compressed ventricles. They weighed 1580 grams in case 1 and 1330 grams in case 2. Histological findings in both brains were similar. There were numerous empty pericellular, perivascular, and interfibrillary spaces in sections from all parts of the cerebrum. Within the convolutional white matter, there was astrogliosis with swollen, often lobulated nuclei and pale, eosinophilic, ill-defined cell bodies. Microgliosis was also present. Blood vessels within the brain were dilated and rare foci of recent haemorrhage could be seen. No inflammatory cells were seen in meninges, brain parenchyma, or spinal cord. There were no defects of myelin in the brain or spinal cord. Many cells in the choroid plexus contained cytoplasmic vacuoles (fig 1). These vacuoles were similar to those described in Reye's syndrome by Brown and Madge.⁴

Liver The livers of both patients were normal in size and shape. Histologically, fine vacuoles were

present in most of the hepatocytes which did not displace the nucleus (fig 2). Numerous fine lipid droplets in hepatocytes were seen on the oil red O stain (fig 2 inset). These lipid droplets were often present in higher concentrations at the periphery of the lobules and were typical of fatty metamorphosis found in Reye's syndrome.

Kidney Case 1 had normal kidneys. Case 2 had fine lipid droplets in the cells of the collecting tubules.

Lungs There were foci of bronchopneumonia and disseminated zones of atelectasis in both cases.

Virology and serological studies

Viral cultures were obtained in case 1 from cardiac blood, trachea, frontal, temporal and occipital cortex, and thoracic and lumbar spinal cord. No virus isolation studies were attempted on the other case. Influenza virus was isolated from ten-day embryonated eggs following intra-amniotic inoculation with 10% suspension of trachea and thoracic spinal cord. The other tissue samples contained no virus. Both influenza isolates were identified as influenza A/Victoria/75 at the World Health Organization Influenza Reference Laboratory at the Center for Disease Control, Atlanta, GA.

Serological studies on blood obtained at nec-

Fig 2 Fatty metamorphosis of liver; A (case 1), B (case 2), H & E. Insets show fine lipid eosin (original magnification $\times 64$).

Fig 2 Fatty metamorphosis of liver; *A* (case 1), *B* (case 2), H & E. Insets show fine lipid droplets within hepatocytes, oil red O (original magnifications $\times 130$).

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ropsy of case 2 showed a complement fixation (CF) titre of 1:1024 against influenza A virus antigen and a titre of 1:16 against influenza B viral antigen. The influenza A antibody titre was considered by the WHO Influenza Reference Laboratory to demonstrate concomitant or recent infection with influenza A virus. No CF antibodies to western equine encephalitis, Venezuelan encephalitis and Saint Louis encephalitis viruses were present.

Discussion and review of literature

In both cases, the diagnosis was not made before death. Prothrombin times, ammonia levels, and ultrastructure of the liver were, therefore, not available. In retrospect, both cases presented with typical features of Reye's syndrome. There was a mild influenza illness followed by an abrupt onset of vomiting, seizures and an encephalopathy terminating in death. Biochemical evidence of hepatocellular damage and severe fatty metamorphosis of the liver were found. Toxic causes of acute liver damage were not found. Cerebral oedema without inflammatory or demyelinating

changes were present. Thus, the clinical and pathologic criteria for the diagnosis of Reye's syndrome were met in both cases.⁵ Virological or serological evidence of an acute influenza A virus infection was present. This suggests the association of Reye's syndrome with influenza A virus in these patients.

Although Reye's syndrome has been associated with prior influenza B² and varicella virus³ infections, a virus has only rarely been recovered from the liver or brain.⁶ The isolation of influenza A virus from the spinal cord of case 1 is difficult to interpret as it was recovered in only one of seven brain and spinal cord samples and histological examination of the spinal cord did not suggest a myelitis.

Central nervous system complications of influenza A virus infection are often called influenza encephalomyelitis. This term is used to describe patients of all ages who developed stupor, coma, and seizures following influenza. The pathology is often described in textbooks as a postinfectious encephalitis, with perivenous demyelination of the white matter.^{7, 8}

To determine how often central nervous system

Table Fatal cases of proven influenza A virus infection and encephalopathy

First author	Case number	Age/sex	Vomiting preceding neurological symptoms	Seizure	Normal CSF	Duration of neurological symptoms to death (days)	Liver dysfunction and/or fatty degeneration	Brain oedema without inflammation or demyelination
Horner ¹⁶	4	14/F	+	—	+	1	—	+
Flewett ¹⁶	1A	11/M	+	—	+	1	0	+
	1B	3	0	+	0	0	0	+
	1C	4	0	+	0	0	0	+
	17	10/F	+	—	+	1	0	+
Oseasohn ¹⁷	27	9/M	—	+	0	1	0	+
Ongerboer ⁹	1	48/M	—	—	—	30	+	— ^a
Kapila ¹⁸	1	0	+	+	+	3	+	+
	3	0	+	—	+	3	+	+
	5	0	+	—	+	3	+	+
	17	0	+	+	+	6	+	+
	24	0	+	—	+	2	+	+
	28	0	+	+	+	5	+	+
Bamatter ¹⁹	1	15/F	+	+	+	1	0	+
Horvath ¹⁴	1	64/F	0	—	+	1	+	+
Bennett ²⁰	1	16/F	+	+	+	1	0	+
Beswick ²¹	3	19/F	—	—	0	5	—	0
Hall ²²	1	13/F	+	—	+	3	+	+
Joshi ²¹	1	1/12/M	—	—	0	12	+	+
Nicholls ¹⁰	2	10/M	—	+	+	60	+	— ^b
Crandall ²³	1	6/M	+	+	+	5	—	+
Kaji ²⁴	6	10/M	0	0	0	2	—	+
Finland ²⁵	A-1	18/F	+	+	0	1	0	0
Noble ^c	1	14/M	+	+	0	3	+	+
	2	5/F	+	+	0	4	+	+
Ruben ²⁶	4	8/F	+	0	0	8	+	0
	5	12/M	+	0	0	6	+	0
Murphy ²⁷	1	44/F	0	0	0	4	—	+
Present	1	57/M	+	+	+	1	+	+
	2	18/F	+	+	+	4	+	+

+ = present; — = absent; 0 = not reported; a = coexistent EB virus infection present; b = late in clinical course a brain abscess developed; c = two cases on Reye's syndrome file at Center for Disease Control, Atlanta, Georgia.

complications of influenza A infection were actually postinfectious encephalitis or were likely to have been Reye's syndrome, a review of the literature was undertaken. A summary of 30 cases dying of encephalopathy and proven influenza A viral infection is given in the table. Cases without virological or serological confirmation were excluded. In those cases where details were available, the median age of onset was 12 years with a range of one month to 64 years. Fifty-five per cent of the cases were female. The mean duration from onset of neurological symptoms to death was six days. Vomiting preceded neurological symptoms in 67%, seizures developed in 50%, and coma occurred in all. The CSF was abnormal in only 4%. Changes in the brain, other than cerebral oedema, were found in two cases, and both had evidence of coexisting infection with Epstein-Barr virus⁹ or a fungal brain abscess.¹⁰ Twenty-seven per cent of reports did not mention liver function studies or morphological findings in the liver. Nevertheless, liver dysfunction was noted in 57% and fatty degeneration was found in 40%. We conclude, therefore, that most cases of proven influenza A encephalopathy have histological evidence of brain oedema without inflammation or demyelination. Over half also have clinical evidence of liver dysfunction or fatty degeneration at necropsy. We suggest that some cases previously called "influenza encephalopathy" or "postinfectious influenza encephalopathy" were, in fact, Reye's syndrome.

Several investigators have suggested that Reye's syndrome results from sudden defects in the urea cycle enzymes.^{28, 29} Neither of our cases had a past history or family history suggesting urea cycle abnormalities. However, since we did not measure blood ammonia or liver urea cycle enzyme levels, we cannot consider this hypothesis further.

Our two cases of Reye's syndrome in adults emphasise that the disease is not confined to children. The syndrome occurs in infants,¹¹⁻¹³ as well as adults.^{9, 14, 30} The diagnosis must, therefore, be considered in patients of all ages who suddenly develop vomiting, seizures, and coma, particularly during an influenza epidemic.

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