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Type A Influenza: Postmortem Virus Isolations From Different Organs in Human Lethal Cases

Brief Report

By

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With 2 Figures

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Summary

Trachea, lung, liver, spleen, pancreas and brain of 77 human patients who had died in the course of clinically diagnosed influenza were subjected to virological and histopathological examination. Type A influenza viruses closely related to the virus variants contemporarily in circulation were isolated from 12 of the lethal cases. In 10 of them, virus was demonstrated in organs other than respiratory, most often the brain. Influenza antigen was also demonstrated in brain tissue by immunofluorescence.

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Clinical experience and numerous publications supply evidence of serious disorders in the function of various organs in addition to respiratory symptoms in human influenza (2, 8, 15). In animals, influenza is known as a disease complex and virus can be recovered from different internal organs. In birds e.g., virus isolations from the brain, ovaries and cloacal specimens are sometimes more effective than from tracheal swabs (1, 14). In experimentally infected mice, influenza virus has been recovered from, and the presence of virus antigen in parenchymal cells has been demonstrated in, kidney (5), salivary gland, pancreas, spleen, liver and heart (3). There is much less information about human cases but there are a few reports that, in some circumstances, viraemia is present in human influenza (7, 11) and the virus may reach different target organs (10, 13).

In this brief communication virological and histopathological data based on virological examination of materials from patients who died in the course of influenza are presented. These cases were studied during the period from December 1971 to January 1975.

Sterile samples of trachea, lung, liver, spleen, pancreas and brain were collected during autopsy from clinically diagnosed cases of influenza. The interval between death and autopsy varied from 15 to 69 hours.

Influenza virus was isolated from 12 fatal cases by means of amniotic inoculation of chicken embryos and/or in monkey-kidney tissue cultures. In 10 of these cases the virus was found in organs other than the respiratory tract (Table 1). All positive materials came from persons debilitated by a serious underlying chronic disease or pregnancy. The only exception was a 16-year-old boy who had suffered from a febrile illness lasting 48 hours, terminally with heavy abdominal symptoms. The autopsy finding was haemorrhagic tracheitis and a strikingly hyperaemic pancreas. From this organ influenza virus was repeatedly isolated.

The most frequent isolations were from the brain. Although immunofluorescence in cryostat sections from the liver and spleen as well as from the pancreas did not

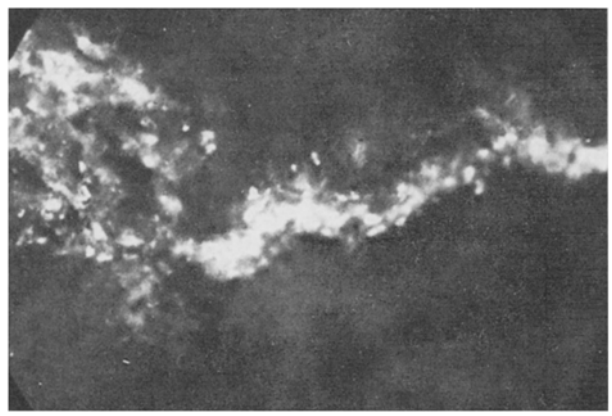

Fig. 1. Specific immunofluorescence of ependymal cells. Microscope ML 2, magnif. × 79.3

Fig. 2. Specific immunofluorescence of ependymal cells. Microscope ML 2, magnif. × 158.6
Cryostat sections were fixed with acetone and stained by means of the direct immunofluorescence technique. The globulin fraction of hyperimmune rabbit serum A/PR 8 (H_0N_1) conjugated with fluorescein-isothiocyanate (BBL, U.S.A.) was used for the staining

bring convincing evidence of intracellular presence of virus antigen, in brain tissue sections intensive specific immunofluorescence was seen predominantly in the periventricular area in the ependyma (Figs. 1 and 2). In addition to this finding, specific immunofluorescence of ovoid structures closely resembling inclusions scattered in small or greater foci was observed in the neuropil in four cases with positive virus isolations from the brain.

Both macroscopic and histological changes were, in most cases, limited to hyperaemia and oedema, without inflammatory infiltration. In one instance the walls of the lateral ventricles were rigid macroscopically. Microscopically, non-purulent encephalitis with a periventricular maximum, desquamation and alterative lesions in the ependyma were found. The character of the infiltration was pleomorphic, with lymphoid cells at different stages of development.

Without any exception, the isolates of influenza virus from dead patients' tissues were obtained during periods of maximum mortality due to influenza. During a high incidence of influenza B infection toward the end of 1973 and in the beginning of 1974, no positive result was obtained. All the strains isolated were closely related to the variants of influenza A virus prevalent in the particular area and period (18).

The positive isolations of influenza A virus from different organs were obtained in deceased persons who presumably had had depressed immune reactions (three of the 10 had been suffering from plasmocytoma and one from myeloma) (Table 1).

Table 1. *Survey of lethal cases with positive influenza A virus findings in organs other than respiratory*

Case number	Age	Duration of infl. (days)	Underlying disease	Virus isolation
1	71	2	Plasmocytom	Lung, trachea, brain
2	75	5	Heart dis.	Brain, trachea
3	71	2	Plasmocytom	Lung, liver, brain
4	4 m.	4	Mukoviscidosis	Brain, lung
5	39	1 (18 h)	(Puerperium)	Trachea, lung, brain, spleen
6	68	5	Plasmocytom	Brain
7	42	2	Kidney makrocystosis	Brain
8	81	2	Myelosis	Trachea, brain
9	16	2	—	Pankreas
10	75	1	Marasmus, bronchopneumonia	Brain

The isolations of virus from the liver, spleen and pancreas may merely illustrate the presence of viraemia in human influenza.

The relatively frequent isolations of influenza virus from the brain at postmortem were accompanied by convincing immunofluorescence in the ependyma. This is in accordance with the results obtained in animals experimentally infected with NWS influenza virus (9, 12). The influenza virus probably enters the lumen of the cerebral ventricles by penetrating the choroid plexus, and replicates in ependymal cells.

At an early stage this replication of virus is not inevitably connected with infiltrative changes, and perhaps it is only exceptionally that encephalitis develops. From this point of view, the possible connection with this finding of the long-

term persistence of influenza antigen in ganglion cells in postencephalitic parkinsonism, as described by GAMBOA *et al.* (4), is of interest. At any rate, it may be concluded that the penetration of influenza virus into the central nervous system may not be so rare as has been supposed.

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