An association between sub-arachnoid haemorrhage and influenza A infection

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Summary
The sera of 25 patients with confirmed sub-arachnoid haemorrhage were assayed by complement fixation for 14 viruses. Twenty (80%) showed elevated titres to influenza A virus compared with 3 out of 25 (12%) of control subjects matched for age, sex and district and 3 out of 17 (17%) of a group of patients with other neurological disorders.

A seasonal variation in the notification of sub-arachnoid haemorrhage appeared to be related to changes in the incidence of influenza A infection.

Introduction
The present investigation was precipitated by an observation that there was seasonal variation in the number of referrals for treatment of sub-arachnoid haemorrhage (SAH) to the Department of Neurosurgery. This is contrary to the findings of Talbot (1973) but confirmed those of Takahashi et al. (1957), Whylie (1962) and the Registrar General Hospital in-patient enquiry (1964).

Eight out of the 25 patients (32%) gave a history of a recent influenza-like illness and led to a virological study.

Patients and methods
Between March and July, 1978, the sera of all patients suffering from sub-arachnoid haemorrhage (SAH) who were referred to the Cardiff Neurosurgical Department were assayed by complement fixation for the following 14 viruses:

- influenza A, B and C; parainfluenza IV; psittacosis/lymphogranuloma venereum; Rickettsia burnetii; adenovirus; respiratory syncytial virus (RVS); Mycoplasma pneumoniae; mumps antigens V and S; herpes simplex; Epstein-Barr; cytomegalovirus; rubella.

The diagnosis of sub-arachnoid haemorrhage was confirmed by lumbar puncture but all cases of traumatic origin were excluded.

The patients with sub-arachnoid haemorrhage had a male:female ratio of 11:14, with a peak incidence in the 40-60 age group. Aneurysms were demonstrated in 16 out of 25 patients (64%) by computerized tomographic scan and carotid and vertebral angiography. Blood samples were taken between 3 and 7 days after the episode of bleeding and again 14 days later, but because patients were routinely given dexamethasone the validity of the second titres is in doubt. The first control group was a series of 17 patients in the care of the Department of Neurology who underwent screening for various suspected CNS viral disorders.

The second control group was made up of 25 patients matched for age and sex, and living in the same area, who were referred, during the same period, by general practitioners for viral screening to the Cardiff Public Health Laboratories but had no clinical involvement of the nervous system. Viral complement fixation titres were determined in batches to reduce laboratory variation.

Results
The sera of the SAH group were initially assayed against all 14 viruses and titres > 1/16 were considered positive. Only influenza A, RSV and adenovirus showed raised titres in more than one patient.

The sera of the control groups were then assayed for these 3 viruses.

For influenza A, the differences between the SAH group and the other 2 groups were statistically highly significant (P=0.001).

Table 1. Number of patients with viral complement fixation titres > 1/16

<table>
<thead>
<tr>
<th></th>
<th>Influenza A</th>
<th>RSV</th>
<th>Adenovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH group</td>
<td>20/25</td>
<td>17/25</td>
<td>2/25</td>
</tr>
<tr>
<td></td>
<td>(80%)</td>
<td>(68%)</td>
<td>(8%)</td>
</tr>
<tr>
<td>Neurology control group</td>
<td>3/17</td>
<td>2/17</td>
<td>1/17</td>
</tr>
<tr>
<td></td>
<td>(17%)</td>
<td>(11%)</td>
<td>(6%)</td>
</tr>
<tr>
<td></td>
<td>(12%)</td>
<td>(40%)</td>
<td>(12%)</td>
</tr>
</tbody>
</table>
For the RSV the P value for the difference between SAH and the matched control group was 0.025; for the difference between the neurology control and the matched group it was 0.05.

Adenovirus titres showed no difference between the groups.

Nine out of 25 of the SAH patients had changing titres to influenza A of above 1/32 initially. Eleven showed titres of 1/16 which remained static while the remaining 5 were negative.

The number of notifications of SAH per month from the University Hospital of Wales, Cardiff, was obtained from the hospital in-patient analysis records from January 1977 to August 1978. Figure 1 shows the total incidence and those with and without hypertension.

In February 1978 a peak of SAH notification occurred at the University Hospital of Wales which had not occurred in 1977 (Hospital In-Patient Analysis, 1978). Data from the Department of Virology indicated that an epidemic of Influenza A occurred between February and May 1978 but that there had been no major outbreak in 1977. The rise was most noticeable for SAH occurring in conjunction with hypertension. The work of Fabrictant et al. (1978) and Benditt and Benditt (1973), discusses the possible interrelationship between viral infections and vascular disorders. Virus-induced atherosclerosis or virus-induced transformation of smooth muscle cells may be the primary event in the formation of intracranial aneurysms (Editorial, 1978). However, the mode of infection of influenza A is different from that of the viruses used in the work of Fabrictant et al. and Benditt and Benditt and involves mucosal binding. Viraemia in influenza A infection is unusual (Stuart-Harris, 1965). In those cases in which severe systemic infection does occur, haemorrhagic leucoencephalitis is a (rarely) reported feature at post-mortem (Hould and Flewitt, 1960). The serotyping results appear to exclude involvement of recent influenza strains but the complement fixing assays are considered to be indicators of recent infection and do not remain elevated more than 3 months after contact with the virus. The explanation for this contradiction is unknown.

It is postulated that influenza A infection is related to smoking (Bell and Syman, 1979) and hypertension in its influence on the formation of intracranial aneurysms and their subsequent rupture.

Acknowledgments

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