Virus Infections in Children in a Respiratory Intensive Care Unit during an Influenza Epidemic

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SUMMARY

The incidence and severity of virus infections in a children's respiratory intensive care unit during an influenza A epidemic were studied. Infections caused by the Port Chalmers strain of influenza A or by an adenovirus were associated with severe, often fatal, pneumonia, whereas infections caused by respiratory syncytial virus or cytomegalovirus carried a good prognosis.

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A short circumscribed outbreak of influenza A caused by the Port Chalmers strain (the so-called Kiwi 'flu) occurred in the general population of Cape Town during the mid-winter months of 1974. During this period, there was a striking increase in the number of children admitted to the respiratory intensive care unit (R-ICU) with severe bronchopulmonary disease. This was unexpected, since others[1,2] have found that influenza epidemics do not generally increase the rates of serious respiratory illness in children.

This study was undertaken to analyse the events in the R-ICU which caused a marked increase in admission during the epidemic period lasting from the last week of June to the end of July 1974.

PATIENTS AND METHODS

The investigations were done on children admitted to a 6-bedded R-ICU for non-White patients in the Red Cross War Memorial Children's Hospital. Because of the limited accommodation, only those patients in severe respiratory failure, based on the following blood gas criteria, were admitted: p_aCO_2 above 60 mmHg, or p_aO_2 below 150 mmHg in F_IO_2 1,0. The diagnosis in each case was established on the usual clinical and radiographic criteria. Pneumonia and bronchiolitis were the predominant expressions of pulmonary infection. The 4 Black and 19 Coloured children were from the lower socio-economic strata of the community, evidenced by their generally low body weight for age.

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Laboratory Investigations

Nasopharyngeal secretions were collected within 24 hours of admission and sent with a minimum of delay to the laboratory for microbiological study. Tracheal aspirates were obtained from those patients with endotracheal tubes needing assisted ventilation. As a rule, only one specimen was obtained from each patient for virological investigation. Paired sera were not routinely collected.

Virus isolations were achieved by standard methods, using human fibroblasts for cytomegalovirus, HeLa cells for adenovirus and respiratory syncytial virus, and primary vervet monkey cells for herpesvirus, para-influenza virus, and influenza virus in which viral presence was recognised by cytopathic effect or by haemadsorption. The influenza virus strains were also isolated in embryonated eggs. Viruses were identified by the appropriate neutralisation, haemadsorption inhibition or haemagglutination inhibition tests. This series of investigations did not include culture for *Mycoplasma pneumoniae*.

The Influenza Epidemic

The first isolations of A/Port Chalmers influenza virus were made from two specimens received in the laboratory on 26 June, one from an adult and one from a patient in the R-ICU. Isolations of this virus continued throughout the next 5 weeks, up to the end of July. There were no further isolations of influenza A virus from patients in the R-ICU and the epidemic in the general public gradually subsided.

RESULTS

Admissions

Coinciding almost exactly with an outbreak of influenza A virus in the general community, there was a dramatic increase in the number of non-White patients requiring admission to hospital for severe respiratory disease, but there was no similar increase among the White patients (Table I).

TABLE I. TOTAL HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASE

Patients	May	June	July	Aug.	Sept.
White	**14**	**13**	**10**	**6**	**15**
Non-White	**209**	**219**	**263**	**139**	**157**

During the month of July 1974, the number of non-White patients with acute respiratory failure admitted to the R-ICU was almost double the average monthly intake (Fig. 1). Admission returned to normal levels in August and September.

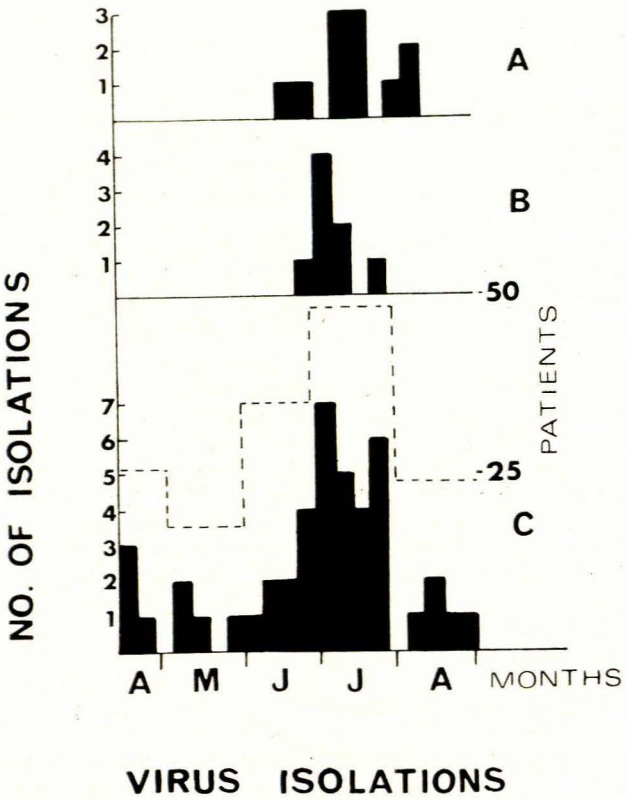

Fig. 1. Weekly virus isolations between April and August 1974 from children in the respiratory intensive care unit. A = isolations of respiratory syncytial virus; B = isolations of A/Port Chalmers influenza virus; C = total isolations. Each bar represents one week. Broken line = total monthly R-ICU admissions.

Bacteriological Culture

Surprisingly few significant bacterial pathogens were isolated from the respiratory specimens, possibly owing to the use of antibiotic therapy before admission to the ward. Only 5 species were isolated from 5 patients: *Pneumococcus, Haemophilus influenzae, Pseudomonas, Salmonella* and *Mycobacterium tuberculosis.*

Virus Isolations

From the 44 nasopharyngeal or tracheal aspirates submitted for examination, 26 virus strains were grown from 23 patients. Three children had simultaneous infections with two viruses.

Influenza A/Port Chalmers virus was isolated from 8 patients and respiratory syncytial virus from 8 others. Herpes simplex virus was cultured from 4 patients, adenovirus from 2, cytomegalovirus from 4 and para-influenza virus (type 3) was isolated only once.

Two viruses were isolated from the aspirates of 3 children: an adenovirus with an influenza virus in one, a herpes simplex virus with an adenovirus in another, and a respiratory syncytial virus with a cytomegalovirus in the third.

The virus isolations during each week of the epidemic period are shown in Fig. 1 and are contrasted with the figures for routine virus isolations from this unit in previous and subsequent months. Viruses were isolated from 59% of the nasopharyngeal and tracheal aspirates examined and just over one half of them were influenza or respiratory syncytial virus.

Specific Viral Illnesses

Influenza virus was isolated from 8 patients, of whom 4 were under 1 year of age. One of these was 3 weeks old and the other 3 months. Six of the 8 patients presented with pneumonia, one had laryngotracheobronchitis requiring an artificial airway, and in one, influenza complicated severe bilateral bronchiectasis. Three patients died. Two were severely malnourished with weights less than 70% of that expected for age, and the third had a dual infection with an adenovirus. Postmortem examination was possible on only one patient and the histological features were highly suggestive of an adenovirus bronchiolitis in addition to an influenzal pneumonia, but an adenovirus was not cultured during life or at autopsy.

The 8 patients, from whom **respiratory syncytial** virus was cultured, varied in age from 10 days to 16 weeks and stayed in hospital for periods of 5 - 10 days. All were normally developed for age. In 6 of these patients, the clinical diagnosis was bronchiolitis and in 2, viral pneumonia. A 4-week old male with pneumonia died, and at autopsy the lymphoid tissues were found to be almost totally depleted of T-cells.

Herpes simplex virus was grown from 4 children. Two presented with laryngotracheobronchitis and recovered. The other 2 died. One with kwashiorkor had miliary tuberculosis and a viral type pneumonia confirmed histologically. The other had clinical features compatible with a disseminated herpesvirus infection and had a concurrent adenovirus infection.

Cytomegalovirus was isolated from 3 aspirates from patients aged between 23 days and 9 weeks. Two presented with bronchiolitis and the third with pneumonia. All recovered and were discharged from hospital after 7 - 28 days.

Both patients from whom an **adenovirus** was cultured died. In each instance the virus was present in the nasopharyngeal secretions with another virus; in one patient with an influenza virus and in the other with a herpes simplex virus. In addition, one other patient had evidence of a combined influenzal and adenovirus infection at autopsy (*vide supra*).

Para-influenza virus was grown from a year-old female child with a relentlessly progressive pneumonia, who died after 18 days.

Ten of the 23 patients from whom viruses were isolated died.

DISCUSSION

Our attempts to explain the sudden increase in the admissions to the non-White R-ICU were largely successful. During the 5-week period under study, there were in fact two epidemics, one caused by the A/Port Chalmers strain of influenza virus and the other by respiratory syncytial virus. While the influenza outbreak in July was later than usual (March in 1973 and April - May in 1970), the epidemic of respiratory syncytial virus infections occurred as expected in July, as it had done with peak incidences in July 1972 and July 1973. Such a fortuitous coincidence of epidemics of these two viruses has been recorded by others,[3,4] who also showed that cross-infections by influenza and respiratory syncytial viruses were common in children's wards. The fact that the viruses were isolated from specimens taken within 24 hours of admission suggests that the virus infections in our patients were acquired outside the hospital.

It was interesting that a para-influenza virus was isolated only once during this period, despite the fact that it was isolated several times in May from children in this ward. This may be due to some form of interference,[5] possibly related to interferon. Viruses vary in their capacity to induce interferon production and in their sensitivity to its inhibitory action. All the dual infections were caused by viruses (cytomegalovirus, herpesvirus, adenovirus) which have been considered to be relatively resistant to the antiviral effect of interferon,[6] whereas the para-influenza viruses are relatively sensitive. This may in part explain the persistence of cytomegalovirus, herpesvirus and adenoviruses, and the exclusion of para-influenza viruses during this epidemic. The isolation on 3 occasions of cytomegalovirus from these aspirates has raised the question of their participation in the pathogenesis of lower respiratory tract disease. This virus may be present in the saliva of 9% of infants and children under the age of 4 years in the UK and it may affect the lung.[7] It is known to cause pulmonary lesions in immunologically compromised adults and children, and may well do so in malnourished children since these often have depressed cellular immune mechanisms.[8]

Adenoviruses are commonly present in the upper respiratory tract of healthy children but may cause severe lung damage in susceptible children, such as those under study in this investigation. Both of the patients from whom an adenovirus was isolated died and it may have been a contributory cause of death in a third patient with influenza.

The ages of the children with respiratory syncytial virus infection are similar to those described by others, but 4 of the 8 patients with influenza were under 1 year of age and 2 died. This is contrary to the commonly expressed view that influenzal lower respiratory tract disease rarely occurs below 1 year of age.

Serious pulmonary disease of viral origin seldom occurs in the absence of some additional factor which impairs the patients' responses. The outstanding contributory factors among our patients seem to be their low socio-economic and poor nutritional status. The importance of these factors was brought into focus by the complete absence of a similar increase in respiratory illnesses among the White children (Table I) during the epidemic. The mortality of these pulmonary viral infections was high in the underprivileged children in this study, with 10 of the 23 with proved viral infections dying. The long-term consequences for the survivors of these serious bronchopulmonary illnesses are not yet known, but it is likely that they lead to an appreciable incidence of respiratory disability in childhood and adult life.[9]

There are as yet no prophylactic vaccines against most of these viral respiratory tract infections and early influenza immunisation is not widely practised. The discrepancy between the incidences of serious pulmonary disease between the low and higher socio-economic groups (Table I) implies that this group of diseases could be greatly reduced by raising the living standards of the non-White patients. Health authorities should pursue this goal with vigour.

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