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RESPIRATORY SYNCYTIAL AND OTHER VIRUSES ASSOCIATED WITH RESPIRATORY DISEASE IN INFANTS

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Summary

Diagnosis by virus isolation and serology was attempted in 377 cases of respiratory-tract infection in infants under one year of age admitted to hospital during two winters. A diagnosis of infection with respiratory syncytial (R.S.) virus was made in 40%, rhinovirus in 6·1%, adenovirus in 3·7%, parainfluenza in 2·1%, enterovirus in 1·9%, and influenza in 1·3%. R.S.-virus infections were more severe than others and occurred mostly in the first five months of life, with a peak at two months. Rhinovirus infections occurred at all ages, and often involved the lower respiratory tract. Of the 12 deaths, only 1 (due to R.S. virus) was not associated with a contributory cause. Maternal antibody to R.S. virus did not notably affect the incidence or severity of R.S.-virus infections.

Introduction

There have been few intensive studies of respiratory-virus infections of infants. To prevent these infections, it is necessary to know which viruses cause the most severe illness and whether maternal antibody plays any part in their prevention. We report here the results of a survey of respiratory-virus infections in infants under one year of age in hospital.

Patients and Methods

Patients

All infants under one year of age in Southmead Hospital and Bristol Children's Hospital who had respiratory infections during a period covering two winters (Nov. 1, 1965, to July 2, 1966, and Sept. 10, 1966, to April 30, 1967) were included. 360 had respiratory infections on admission and 17 developed respiratory infections in hospital. Soon after admission (or onset) nose and throat swabs were taken by one of us (J. W. J.) from each infant. The throat swabs were taken with a gagging technique, so that the infants coughed over the swab. At the same time blood was taken from most of the mothers. Paired serum samples were obtained from some of the infants with an interval of 4–6 weeks.

Examination of Swabs

One throat swab from each infant was inoculated into Bristol hela-cell tissue cultures at the bedside, and was examined thereafter in the University of Bristol department of bacteriology. A second throat swab and the nose swab were put together into 50% milk-saline transport medium and inoculated in the Public Health Laboratory into hela cells and primary monkey-kidney tissue culture within 90 minutes. They were also inoculated (often after storage at −40°C, and if not already yielding a virus) into human embryo kidney and WI-38 human embryo fibroblast tissue cultures and into suckling mice. The methods used have already been described.

Serology

Sera were tested by complement fixation (c.f.) against respiratory syncytial (r.s.) virus antigen but not against other viruses. The methods of preparing the antigen and conducting the test have already been described.

Severity of Illness

This was graded retrospectively according to a scheme developed during the survey. Signs in order of severity were:

(1) Upper-respiratory-tract infection.
(2) Specific treatment (excluding nasal drops but including humidified air, physiotherapy, or antibiotics) or temperature >38·8°C.
(3) Chest signs found by radiography, auscultation, or aspiration for less than three days.
(4) Chest signs for three days or more unless the patient died.
(5) Oxygen therapy for one or more days, or respiration-rate 70 or more per minute, or peripheral cyanosis.
(6) Digoxin therapy or heart-rate of 170 or more per minute.
(7) Additional treatment (cortisone, intubation, or tracheostomy).
(8) Death.

The grade was the most severe sign the patient showed, providing that all the less severe signs were also present. For example, an infant showing signs 1, 2, 3, and 6 was said to have a severity grade of 3. In practice it was rare for an infant not to show an intermediate sign.

Results

Virus Infections Diagnosed

377 illnesses were studied among three hundred and forty-seven infants. The 377 nose and throat swabs yielded 184 viruses (table I). Seven of the specimens yielded 2 viruses, so viruses were isolated from 177 (47%) of the illnesses. In addition, 100 paired sera were obtained. Of 70 illnesses from which R.S. virus was not isolated, a diagnosis of R.S. virus infection was made serologically in 24. From 1 of these, adenovirus type Z had been isolated, and from another rhinovirus H. Thus there were 9 double infections, so virus infections were recognised in 199 (52·8%) of the illnesses.
TABLE I—DIAGNOSIS OF VIRUS INFECTIONS IN INFANTS OF DIFFERENT AGES

| Age (mo.) | Total | % of total |
|----------|-------|------------|
| (<1)     |       |            |
| 1        |       |            |
| 2        |       |            |
| 3        |       |            |
| 4        |       |            |
| 5        |       |            |
| 6        |       |            |
| 7        |       |            |
| 8        |       |            |
| 9        |       |            |
| 10       |       |            |
| 11       | 377   | 52.8       |

No. specimens tested: 377, R.S. virus recognised: 199.

**Bacteriological Examination**

In 272 cases routine bacteriological examination was undertaken. *Staphylococcus aureus* was isolated from 15%, and *Streptococcus pneumoniae* from 7%. Several β-haemolytic streptococci were isolated, but none were group A. *Haemophilus influenzae* was isolated from 8% (3%), in 6 of which R.S. virus infection was also diagnosed.

**Repeated Admissions**

Twenty of the infants were admitted with respiratory infections twice, and two were admitted three times. From one infant, two different M rhinoviruses were isolated—type 1B at the age of two months and type 2 at the age of ten months. One infant, a premature baby, was admitted seven times over a period of four months (table II). 4 different viruses were isolated. There was no evidence of hypogammaglobulinaemia.

**Type of Illness**

Table I shows virus infections diagnosed in infants of different ages. Two-thirds of the specimens came from infants under six months of age. The rate of virus diagnosis was higher under six months of age, with a peak at three months. This was because most infections were caused by R.S. virus, and the peak for this virus was in the age range one to five months. Parainfluenza and influenza viruses were found only over four months of age; and rhinoviruses, enteroviruses, and adenoviruses were found at all ages. The viruses recognised in the first month of life were R.s. (5), rhinovirus M, and coxsackie B5.

**Age**

Table I shows virus infections diagnosed in infants of different ages. Two-thirds of the specimens came from infants under six months of age. The rate of virus diagnosis was higher under six months of age, with a peak at three months. This was because most infections were caused by R.S. virus, and the peak for this virus was in the age range one to five months. Parainfluenza and influenza viruses were found only over four months of age; and rhinoviruses, enteroviruses, and adenoviruses were found at all ages. The viruses recognised in the first month of life were R.S. (5), rhinovirus M, and coxsackie B5.

**Sex**

Of the fifty-four infants in whom R.S.-virus infection was diagnosed and both isolation and serology attempted, the diagnosis was made in twenty-four by serology alone (nineteen infants showed a fourfold rise and five a change from secondary to primary antibody), six by isolation alone, and in twenty-four by both methods (twenty-two showed a fourfold rise and two a change from secondary to primary antibody).

**R.S. virus was isolated more frequently from throat swabs inoculated direct into tissue culture at the costside (115/127) than from swabs put into transport medium and inoculated within ninety minutes (69/127 isolates).**

**R.S. virus was isolated more frequently from specimens taken three to six days after the onset of the illness (43% of 189 specimens) than from those taken before three days (25% of 72 specimens) or after six days (26% of 93 specimens) from onset.**

**Diagnosis of R.S.-virus infection**

A serological diagnosis was made either by a fourfold or greater rise in titre between acute and convalescent specimens, or a change from passive maternal (secondary) type of antibody to an active (primary) type of antibody in a chequerboard c.f. test with a potent antigen.
TABLE III—ASSOCIATION BETWEEN VIRUSES AND CLINICAL DIAGNOSIS

| Virus recognised | Upper-respiratory-tract infection | Laryngotracheitis | Bronchiitis | Bronchiolitis, pneumonia | Unclassified, lower-respiratory-tract infection | Total |
|------------------|----------------------------------|------------------|-------------|--------------------------|-----------------------------------------------|-------|
| R.S. virus*      | 4                                | ..               | 10          | 100*                     | 29*                                           | 151   |
| Parainfluenza    | 1                                | 3                | 2           | 1                        | 8                                            | 8     |
| Influenza        | 1                                | ..               | 2*          | 2*                       | 5                                            | 7     |
| Rhinovirus       | 6                                | 1                | 12*         | 3                        | 23                                           | 23    |
| Enterovirus      | 1                                | ..               | 1           | 2*                       | 7                                            | 7     |
| Adenovirus       | 1                                | ..               | 1           | 6*                       | 14                                           | 14    |
| Total infections diagnosed | 15 | 4 | 15 (81%) | 125 (64%) | 40 (21%) | 199 (82%) |

* By isolation and serology. The remaining viruses by isolation only.
a Refers to illnesses where more than one virus recognised.

TABLE IV—SEVERITY OF ILLNESS ACCORDING TO VIRUS INFECTION

| Virus recognised | No. of infants with severity grade: | Total | Mean grade |
|------------------|-----------------------------------|-------|------------|
| R.S. virus*      | 1 2 3 4 5 6 7                       |       |            |
| Parainfluenza    | 4 3 2 1                            |       |            |
| Influenza        | 1 2                               | 2     | 3          |
| Rhinovirus       | 1 2                               | 1     | 2          |
| Enterovirus      | 1 2                               |       |            |
| Adenovirus       | 1 2                               |       |            |
| Viruses not recognised | 14 | 21 | 18 | 30 | 18 | 15 | 8 | 5 | 129 | 3.9 |
| Total illnesses studied | 17 | 31 | 55 | 89 | 73 | 35 | 17 | 11 | 328 | 4.2 |

* By isolation and serology. The remaining viruses by isolation only.
a Refers to illnesses where more than one virus recognised.

Rhinoviruses were often associated with lower-respiratory-tract illnesses. An eight-month-old boy was admitted with a ten-day history of wheezing getting worse two days before admission. Coarse crepitations in right and left lower lobes. Intercostal recession. Pneumonia confirmed radiologically. Chest signs persisted four days. Respiration and heart rates up to 70 and 180 per minute. Temperature up to more than 40.5°C. Oxygen and cortisone given. Discharged after ten days. Nose and throat swabs taken on the second day in hospital yielded rhinovirus H. There was no evidence of R.S.-virus infection by either serology or isolation. No bacteria implicated.

Enteroviruses also were often associated with lower-respiratory-tract illness. A four-month-old girl was admitted with a three-day history of worsening coryza. Inspiratory wheeze and coarse rales. Bronchopneumonia confirmed radiologically. No fever. Respiration and heart rates up to 65 and 145 per minute, respectively. Liver enlarged. Cyanosis. Chest signs lasted two days. Discharged after nine days. Echo-22 virus isolated from swabs taken on the second day in hospital. There was no evidence of infection with R.S. virus by serology or isolation. No bacteria implicated.

Severity of the Illness

The grade of severity was calculated for all illnesses in which definite viruses were implicated and in 129 others (table iv). Infants with R.S.-virus infection were more severely ill than other infants. Illnesses due to rhinoviruses were of moderate severity. The small numbers of parainfluenza, influenza, and enterovirus infections were mild.

Table v shows the severity of illness of the infants with R.S.-virus infections divided according to age. Except possibly during the first month of life, the younger the infant, the worse the illness.

TABLE V—SEVERITY OF R.S.-VIRUS INFECTIONS AT DIFFERENT AGES

| Age (mo.) | No. of infants with severity grade: | Total | Mean grade |
|-----------|-----------------------------------|-------|------------|
| 0         | 1 2 3 4 5 6 7                       | 5     | 3.4        |
| 2         | 2 2 15 6 3                         | 28    | 5.2        |
| 3         | 4 8 5 4                            | 23    | 4.7        |
| 1         | 1 10 6 2 1                         | 22    | 4.4        |
| 5         | 10 5                               | 16    | 4.6        |
| 6-7       | 3 6 4 2                            | 15    | 4.3        |
| 8-11      | 4 9 2                              | 17    | 4.1        |
| Total     | 1 2 19 50 50 18 8 3                | 151   | 4.6        |

Deaths

Twelve infants died (table vi). R.S.-virus infection was diagnosed in three, parainfluenza type 3 in one, rhinovirus H in one, and adenovirus type 2 in one. There was a contributory cause of death in eleven; ten had congenital defects and one had gastroenteritis due to Escherichia coli O119.

The remaining infant was first admitted aged four months with severe bronchiolitis. Discharged after twenty-five days, but readmitted two days later with bronchopneumonia. Coarse rales in upper anterior chest and right axilla. Temperature slightly raised. Respiration and heart rates up to 80 and 200 per minute, respectively. No viruses or other organisms were implicated during the first admission, but the throat swab taken on the day of second admission yielded R.S. virus. No other organisms implicated. Died three days after admission. At necropsy, mucopurulent in larynx, trachea, and bronchi. Generalised congestion of lungs. Normal aeration in only a few small peripheral areas. The microscopic appearance resembled hyaline-membrane disease of newborn. No other abnormalities.
TABLE VI—DEATHS

| Age at death | Respiratory condition         | Contributory causes of death | Organisms in respiratory tract |
|--------------|------------------------------|------------------------------|-------------------------------|
| 5 mo         | Pneumonia                    | E. coli O119 gastroenteritis | R.S. virus                    |
| 4 mo         | Bronchopneumonia             | v.d., A.S.D., bilateral hydrenephrosis | Rhinovirus H                 |
| 1 mo         | Pneumonia                    | Down's syndrome, v.d., P.D.A., patent foramen ovale | R.S. virus                  |
| 1 mo         | Bronchopneumonia             | Glänzhalke ataxia, re nutritia, A.S.D., v.d., left hydrenephrosis | Parainfluenza 3             |
| 7 mo         | Bronchopneumonia             | Persistent trunca arteriosus |                  |
| 2 mo         | Bronchiolitis                | Coarctation of aorta, P.D.A., hydrenephrosis, | Adenovirus 2, Pseudomonas aeruginosa, Staph. aureus |
| 2 mo         | Bronchopneumonia             | Meckel's diverticulum         |                  |
| 1 mo         | Pneumonia                    | Aoetic stenosis, P.D.A., Meckel's diverticulum | Staph. aureus               |
| 3 mo         | Pneumonia                    | Adrenogenital syndrome       |                  |
| 4 mo         | Bronchopneumonia             | Fibrocystic disease of the pancreas | Ps. aeruginosa               |
| 5 mo         | Lower-respiratory-tract infection | Fibrocystic disease of the pancreas, probable necrosis |                  |
| 11 days      | Postnatal pneumonia          | Bilateral renal-vein thrombosis, acute tubular necrosis |                  |

V.S.D. = Ventricular septal defect.  A.S.D. = Atrial septal defect.  P.D.A. = Patent ductus arteriosus.

Passively Acquired Antibody in R.S.-virus Infections

Acute-phase sera were collected from two hundred infants. Table VII shows the numbers of infants of different ages with antibody to R.S. virus at the beginning of their illnesses. There was no indication that passive antibody potentiated infection. Table VIII shows that passive antibody also had no detectable effect on the severity of R.S.-virus illness.

R.S. virus C.F. antibody was measured in one hundred and ninety-three mothers of infants in the survey and in thirty-five mothers of infants admitted without respiratory infection. Titres of 20 or more were found in 67% of the mothers of infants shown to have R.S.-virus infections, but in only 55% of mothers of other infants with respiratory infections, and in 54% of the mothers of infants who had no respiratory infection at all.

Discussion

Diagnosis of R.S.-virus Infection

Although Holzel et al. and Berglund et al. recommended inoculation at the bedside for the isolation of R.S. virus, they did no direct comparisons. We isolated R.S. virus more frequently when the throat swabs were inoculated at the bedside than when they were inoculated up to ninety minutes later. However, these tests were done in two different laboratories with two different stocks of Bristol hela cells, so the results are not directly comparable. We isolated R.S. virus more frequently from swabs taken between three and six days after the onset of symptoms than during the first two days. Higgins et al. isolated viruses from patients with respiratory infections with equal frequency on each of the first four days of the illness.

In our hands the C.F. test was a more sensitive method than isolation for diagnosis of R.S.-virus infections in the infants where both methods were attempted. R.S.-virus infections were diagnosed by demonstrating a change from passive to active antibodies, for which it is necessary to do a cumbersome checkerboard titration, but most showed straightforward rises in titre when a large amount of antigen was used in the C.F. test. Berglund and Strählmann conclude that isolation is better than serology. Much will depend on the potency of the C.F. antigen, the number of antigen units used, and the time of taking the convalescent serum; and the sensitivity of the cell line used for isolation and the timing of inoculation are also important.

Other Respiratory Pathogens

The diagnosis-rate for all respiratory pathogens of 53% might have been higher if paired sera had been obtained from all the infants, and if serology for viruses other than R.S. virus had been performed. We did not look for Mycoplasma pneumoniae or corona-viruses or cytomegaloviruses, all of which are known to cause respiratory infections, especially cytomegalovirus in the first year of life. There is no convincing evidence that the bacteria we isolated (Staph. aureus, Str. pneumoniae, and Hemophilus influenzae) are a frequent primary cause of respiratory illness in infants. All are common in healthy infants.

Double Infections

These were found on 9 occasions. In 5 double infections an adenovirus was isolated, but here the second virus (R.S. and influenza) probably caused the illness, the adenovirus being carried in the tonsils. The findings in one patient (table II) support this.
Similar double infections have been described by Holzel et al. and Hilleman et al.

**Association of Infection with Illness**

In table I we have assumed that the virus isolated was the cause of the illness. However, in infants a quarter of rhinovirus infections, half enterovirus infections, and about half adenovirus infections are subclinical. However, when one of these viruses is isolated from a child with a respiratory infection, it is probable that it is the cause of the illness. It is even more probable that illnesses associated with R.S. and parainfluenza viruses are due to these viruses.

**Type of Illness**

We found that rhinoviruses often produced a severe lower-respiratory-tract illness, as did Hamparian et al. The finding of lower-respiratory-tract illness in association with echo 22 virus is interesting in view of similar associations described by Berkovich and Smithwick.

**Deaths**

Of the twelve infants who died with respiratory infections, eleven had a contributory cause of death. It seems, therefore, that respiratory viruses are not frequent killers of otherwise healthy infants in Bristol. In Newcastle only a quarter of infants who died with respiratory infections had congenital defects. It seems that viruses, especially R.S. virus, are more important as a cause of severe illness and death among infants in Newcastle than among infants in Bristol. There may be socioeconomic reasons for this.

**Importance of Different Viruses**

In this survey, as in others, R.S. virus was the commonest cause of respiratory illness requiring admission at this age (40%), and the illnesses were more severe than those associated with other viruses (table I). Rhinoviruses were the next most important (6%) and often caused severe illnesses. In this age-group, adenoviruses, influenza, and parainfluenza viruses were relatively unimportant. This is supported by work with respiratory viruses in the Bristol Public Health Laboratory over the past nine years (unpublished).

**Sex**

We found a heightened susceptibility of males to respiratory infections, previously noted by Moss et al.

**Effect of Maternal Antibody**

The few parainfluenza virus infections observed in this survey occurred only in infants more than four months of age. Over the past nine years in the Bristol Public Health Laboratory, among large numbers of parainfluenza viruses isolated, parainfluenza types 2, 3, and 4 have only occasionally been isolated from infants under four months of age, and type 1 never. This is not a new observation, and there is evidence that maternal antibody protects against these viruses. Our experience with influenza virus is similar, and in this survey there were no influenza virus infections below the age of four months. Maternal antibodies probably played a role here also. On the other hand, rhinovirus infections were detected from a very early age, and this is to be expected because mothers would not have antibodies against all rhinovirus types at the time of delivery. Indeed maternal antibody may protect against infections with this group of viruses.

The position with regard to R.S.-virus infections is less clear-cut. For instance it is widely accepted that the majority of severe infections occur in the first three months of life. In our series the peak of incidence was at two months, and infections have been recorded as early as ten days after birth. There is no multiplicity of antigenic types to account for this early incidence as there is for rhinoviruses. On the other hand, the incidence of antibodies to R.S. virus in the adult population—and by implication exposure to R.S. virus—is very high. One would expect, therefore, the epidemiological features of this infection in infants to resemble influenza more closely than the common cold.

The series we investigated may have been a selected group, in that for some reason we saw principally infants of mothers who lacked antibodies to R.S. virus. Unfortunately a retrospective survey such as this cannot distinguish between maternal-antibody levels present before birth and those acquired at the time of, or just before, the infant's illness; and it is far more likely that the mother of an infected baby has just had an antigenic stimulus from the same virus. The high levels of antibody we observed in mothers of infected infants are thus meaningless in terms of protection afforded to the population studied.

The vaccination studies carried out by some American workers, using killed virus vaccines, have often been quoted in support of the idea that antibody to R.S. virus actually increases the severity of a subsequent infection. However, other types of R.S.-virus vaccines prepared differently may not have the same effect.

Neither is there any concrete evidence in table VII to support the hypothesis of antibody potentiation, for although at two months of age the geometric mean titre of antibody is higher in the group with R.S.-virus infections, as is the percentage of acute sera with antibody present, this trend is reversed at one month of age. Similarly there is no correlation between high antibody titre and mean severity grade. Although the numbers are extremely small, there was evidence in table V that in the first month of life infants had less severe R.S. infections than older infants. This could be taken as evidence that maternal antibody may actually have a protective effect.

Chanock et al. found that the titre of R.S.-neutralising antibody was two times lower in the acute sera of infants with R.S. infections than in those without, and suggests that antibody-antigen complexes in the lung may lead to depletion of antibody in the serum.

Gardner et al. present persuasive evidence in support of the postulate that the development of immediate hypersensitivity plays a dominant role in the pathogenesis of acute bronchiolitis in R.S. infections. However, they favour the idea of a Gell and Coombs hypersensitivity response, and to sustain this argument they postulate a previous exposure to R.S.-virus antigen. Again we find no evidence to support this hypothesis, since, where antibody was detected in the acute-phase sera, it behaved like adult antibody in the C.F. test and was thus, presumably, maternal in origin.

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REVERSAL OF ACUTE CLINICAL AND EXPERIMENTAL ORGAN REJECTION USING LARGE DOSES OF INTRAVENOUS PREDNISOLONE

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Summary

The ability of single large (1 g.) doses of intravenous prednisolone to reverse rejection episodes has been investigated clinically and experimentally. Sixteen renal-transplant recipients have been treated in this way. The oral dose of prednisone was not increased during these episodes and no additional treatment was given. This therapy reversed 86% of rejection crises without any toxic effects. One patient has died from infection, 1 month after transplantation. Using the heterotopic rat-heart-transplant model the ability of intravenous prednisolone, antilymphocyte serum (A.L.S.), intraperitoneal prednisolone, and azathioprine to reverse rejection in recipients immunosuppressed with a single dose of A.L.S. at the time of transplantation were compared. Intravenous prednisolone was the only successful agent and prolonged survival by 9±3 days.

Introduction

One of the major problems in clinical organ transplantation is the detection and reversal of rejection episodes. Centres differ in their methods of overcoming such episodes, but most administer an increased dose of oral steroids. Actinomycin C, 1-3, and antilymphocyte globulin, 1,2,7 and local graft irradiation 1,2,7 have been used to the same end.

At the start of our clinical renal-transplant programme we decided to use prednisolone given as a single 1 g. intravenous dose over a period of 2 hours for the treatment of acute rejection crises. This decision was made for several reasons. Firstly, prednisolone at this dose level is lytolyticic and has a short half-life of 60-90 minutes, giving maximum lymphocyte damage with relatively little in the way of chronic side-effects. Secondly, we were impressed by the results published by Kountz and Cohn, who used large doses of intra-arterial steroids, but we felt that this method was potentially dangerous and, perhaps, unnecessary. Thirdly, we hoped to avoid the high oral doses of steroids normally used to control rejection and thereby avoid serious complications in the first few months after transplantation.

The ability of a high dose of intravenous prednisolone to reverse acute rejection episodes was also investigated using the heterotopic rat-heart-transplant model. We present here the clinical and experimental results of this type of antirejection treatment.

Patients, Materials, and Methods

CLINICAL

Patients

Sixteen patients were transplanted over a 24-month period. Three patients received kidneys from sibling