Respiratory viruses and cot death

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Summary and conclusions

Respiratory viruses and histological appearances of the lung were studied prospectively in an unselected series of 104 children who died between 1 week and 2 years of age. Thirty-one of the cases were cot deaths. Seven of these showed evidence of active virus infection in the lower respiratory tract. Similar evidence was found in two children who died from known causes and did not have a severe respiratory illness terminally.

Although in some cases of cot death respiratory viruses may be responsible for a severe and rapidly overwhelming illness, the present results are compatible with an alternative hypothesis—namely, that minor respiratory illness may trigger sudden apnoea.

Introduction

Whether respiratory viruses play a part in cot deaths remains uncertain despite much circumstantial and some direct evidence. Cot deaths occur more often in winter and in large families, and it has been reported that in the days before death the incidence of respiratory symptoms is higher than that among control babies.¹ These observations, together with the close similarity in age distribution between children in cases of cot death and those admitted to hospital with respiratory syncytial (RS) virus bronchiolitis,² have led to the hypothesis that the mechanism in some cot deaths may be a rapidly developing bronchiolitis that leads to death before symptoms of severe illness have been observed or fully appreciated.

After some cot deaths viruses have been identified in the respiratory tract at necropsy, particularly since the introduction of the sensitive fluorescent antibody technique.³ The correlation between histological changes in the respiratory tract and the identification of viruses strongly suggests that there is active virus infection in these cases.²⁻⁴ The problem is to know if such infection plays a part in death, since these studies have not attempted to control virus and lung histology findings by including babies dying at a similar age from known causes. The studies are also open to the criticism of possible selection, since the reported series were not consecutive.

On 1 January 1974 we therefore began a prospective study of all children dying in Newcastle between the ages of 1 week and 5 years for whom permission to carry out necropsy was obtained. We report the virus and lung histology findings in 104 such children who died up to 31 March 1976.

Methods

The study included 52 children whose home addresses were within the Newcastle city boundaries and who were therefore part of the

continuing Newcastle survey of deaths in early childhood. The investigative methods in this survey have been reported.⁵ In addition, 52 children from neighbouring districts were investigated by the same standardised necropsy. The methods for identifying viruses in necropsy material have been described.⁴

Histological changes in lung tissue were categorised by a single pathologist as follows. Type 1, varying degrees of congestion, oedema, increased cellularity of alveolar walls, and intra-alveolar haemorrhage; no histological evidence of respiratory tract infection. Type 2, varying degrees of peribronchiolar lymphocytic infiltration, and abnormalities of bronchiolar epithelium; bronchioles often plugged with mucus, cell debris, and inflammatory cells. Type 3, polymorphonuclear inflammatory exudate filling bronchioles and adjacent alveolar sacs; inflammation mainly lobular. Type 4, easily identifiable lymphocytic infiltration of alveolar walls and interstitial lung tissue, sometimes associated with minor peribronchiolar lymphocytic infiltration.

Viruses were identified and lung histology assessed independently without previous exchange of information.

Results and comment

Table I shows the viruses identified and the categories of lung histology in the 104 cases. As in previous series²⁻⁴ there was a close correlation between the viruses known to be associated with lower respiratory tract illness—in this series RS virus, parainfluenza virus type 3, rhinovirus, and adenovirus—and type 2 histology. Of the 14 cases in which these viruses were identified, 10 had type 2 lung histology; two of the remaining four had adenoviruses, which are less clearly associated with acute illness because of long periods of excretion; one had a rhinovirus, which is more often associated with upper than lower respiratory tract illness; and one was a child with cystic fibrosis who showed type 3 changes as well as the presence of RS virus. Only two children had type 4 histological changes; both had lymphoblastic leukaemia complicated by *Pneumocystis carinii* pneumonia.

The correlation between the identification of respiratory virus and type 2 lung histology suggests that the eight virus-negative cases with type 2 histology probably had virus infections that were not identified, either because of technical failure or because the infecting agent was not demonstrable by the methods used—for example, no attempt was made to identify coronaviruses.

Table II divides the cases into three categories: cot deaths (sudden unexplained deaths at home); respiratory deaths (those in which a terminal lower respiratory illness was identified clinically); and others (comprising 15 children with major congenital abnormalities, seven with acute non-respiratory infections, six who died after accidents, five with malignant disease, and seven with miscellaneous conditions). The second and third categories were further subdivided into children aged under and over 1 year, so that a more reasonable comparison could be made with the cot deaths, all of which occurred during the first year of life. Table II shows the numbers of children within each

TABLE I—Classification of lung histology and viruses found at necropsy in 104 children

Virus	Lung histology categories				Total
	1	2	3	4	
RS virus	..	5	1		6
Adenoviruses	2	2			4
Parainfluenza viruses	..	2			2
Rhinoviruses	1	1			2
Coxsackie virus B ₄	1				1
Echovirus 22	1				1
Herpesvirus hominis	2				2
Cytomegalovirus	..			1	1
Total virus-positive	7	10	1	1	19
Total virus-negative	55	8	21	1	85
Grand total	62	18	22	2	104

RS = Respiratory syncytial.

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category in whom evidence of virus infection in the lower respiratory tract was found—that is, those who had type 2 lung histology with or without an identified virus. The proportion of cot deaths with evidence of virus infection in the lower respiratory tract (seven out of 31; 23%) was greater than that of “other deaths” under 1 year (one out of 23; 4%), but the difference was not significant.

RS virus was identified in two children from each of the three categories. The case histories of the two cot deaths and two “other deaths” were as follows.

Case 1—Cot death at age 2 months. The baby developed a minor cough and runny nose. After two days he was seen by the general practitioner, who prescribed an antibiotic. He remained generally well but two mornings later was found dead.

Case 2—Cot death at age 4 months. On the day before death the baby was seen for a routine check by her general practitioner, who found her well. Next day she appeared well to her parents, although possibly she took her 8 am feed less hungrily than usual. At 11.30 am she was found dead.

Case 3—Death from medulloblastoma at age 5 months. Hydrocephalus was diagnosed in this girl at the age of 9 weeks and relieved by a shunt operation. At 3 months she was readmitted with signs of increasing intracranial pressure, and air studies suggested a tumour. At the age of 5 months, while still in hospital, she became ill suddenly one evening, with irregular respiration but no signs or symptoms of respiratory infection; she died three hours later. Postmortem examination showed a medulloblastoma and coning, as well as RS virus in the lungs and type 2 lung histology.

Case 4—Death from road-traffic accident at age 3 years. Three days before death the child had developed a slight cold but was not considered to be ill. His brothers and sisters had similar colds. He was run over in the street by a reversing van and died immediately. At necropsy there was extensive brain damage, but also RS virus in the lungs and type 2 lung histology.

Discussion

These results confirm the findings of smaller studies^{2,4} and show that evidence of respiratory virus infection may be found at necropsy in about a quarter of cot deaths. Such evidence seems to be more common in case of cot death than in children dying from known non-respiratory causes; but as children in this second group are few it is difficult to draw firm conclusions at a single centre. Pooling results from several centres raises major problems in standardising techniques for identifying viruses, which have yet to be solved.

Nevertheless, virus and lung histology findings similar to

TABLE II—Numbers of children, grouped according to category of death, with postmortem evidence of virus infection in lower respiratory tract

	Virus infection in lower respiratory tract*		Total
	Present	Absent	
Cot deaths	7	24	31
Respiratory deaths			
Under 1 year	6	12	18
Over 1 year	3	12	15
Other deaths			
Under 1 year	1	22	23
Over 1 year	1	16	17

*Regarded as present if lung histology categorised as type 2, even if no virus identified.

those in some cot deaths seem to occur in at least a few children dying from known non-respiratory causes. Although a rapidly overwhelming or inadequately appreciated severe respiratory infection remains a possible mechanism in some cases of cot death, our results are compatible with the hypothesis that sudden fatal apnoea may be triggered by a minor illness. Considerable non-virological evidence in support of this hypothesis is accumulating.^{6,7}

References

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SHORT REPORTS

Orbital cellulitis related to an influenza A virus epidemic

Orbital cellulitis is rare, being a complication of ethmoid sinusitis, and may result in blindness, cavernous sinus thrombosis, meningitis, and death.¹ Three patients are described, all being admitted in the same week during an epidemic of influenza.²

Case reports

Case 1—A 19-year-old woman presented with a three-day history of upper respiratory tract infection, swelling of the left eyelids, and axial proptosis. A conjunctival swab was sterile, but the nasal swab grew *Staphylococcus aureus*. The organism was sensitive to ampicillin and the condition responded to treatment with antibiotics and local decongestants. X-ray films showed a pansinusitis. At no time was her vision affected.

Case 2—A 6-year-old boy presented with a six-day history of upper respiratory tract infection and swollen left eyelids. The globe was proptosed forwards, laterally, and downwards and the eye movements were restricted. Nasal swabs grew *Staphylococcus aureus*, but a conjunctival swab was sterile. X-ray films showed an ethmoid sinusitis but the antra were radiologically clear. He had already been taking penicillin V syrup, 250 mg four times daily, for six days without improvement, and was therefore submitted to surgery. The ethmoid was explored through the nose, and a subperiosteal abscess was found on the medial orbital wall. Postoperatively, the proptosis

resolved slowly leaving no muscle imbalance. His visual acuity was not affected.

Case 3—An 11-year-old boy presented with a ten-day history of upper respiratory tract infection and swelling of the left eyelid for three days. The left eye was proptosed forward and laterally and he complained of pain. On the morning of admission he developed chemosis and limitation of movement. Thirty-six hours later he had a total ophthalmoplegia and no perception of light. He was treated with ampicillin intramuscularly. Eye swabs were sterile initially but later grew *Staphylococcus aureus*, as did nasal swabs. An x-ray film showed pansinusitis. There was no response to medical measures. At operation a subperiosteal abscess communicating with the ethmoid labyrinth was found. The lamina papyracea was missing but a sequestrum was present within the abscess. This abscess was in continuity with an orbital abscess and both were drained through the same incision. This procedure proved to be inadequate and four days later a loculus was drained through the orbital septum at the level of the inferior orbital margin. He made a full recovery but at the height of his disease the left eye showed a congested optic disc, retinal haemorrhages, and retinal folds, and visual acuity was down to no perception of light. The intraocular pressure at time of operation was 33 mm Hg. (Mean normal 16 mm Hg applanation.) His visual acuity was 6/6 on discharge.

Discussion

In 1937 Ehlers³ classified orbital cellulitis into three types. Firstly, collateral oedema occurring as a reaction to an infected focus near the orbit; case 1 with ethmoiditis fits into this group. Secondly, subperiosteal and preseptal abscess formation; case 2 with a subperiosteal