None of the patients studied received treatment with anticoagulants, although a few received dipyridamole. Of the 42 patients still alive at the end of the follow up period, nine had returned to work, 16 required help, and 17 were totally disabled.

Discussion

Several studies have reported the typical clinical and angiographic features of middle cerebral artery occlusion—namely, that occlusion of this artery usually develops in young patients, commonly presents as a stroke, and is associated with lesions that are often not atherosclerotic.[4-6] Knowledge of the natural long term prognosis associated with occlusion of the middle cerebral artery is, however, still largely incomplete.

Lascelles and Burrows reported that, of 59 patients with occlusion of the middle cerebral artery, 12 died from the first stroke; of the 47 survivors, three died of miscellaneous causes and one of fatal stroke.[7] Kaste and Waltimo found that of 74 survivors of a first stroke due to occlusion of the middle cerebral artery, four had a second stroke, the locations of which were not given.[8] Hinton *et al* reported on 16 patients with stenosis of the middle cerebral artery[9]: during a follow up that lasted from one month to six years two patients developed an early stroke and one had repeated transient ischaemic attacks.

In our study only four patients had a new stroke on the occluded side during follow up, representing less than 2% a year for the first five years after angiography. The risk of subsequent strokes after occlusion of the middle cerebral artery is therefore quite small. Occlusion of the internal carotid artery has been reported by Furlan *et al* (2% a year)[10] and by Norrving and Nilsson (1% a year)[11] to have a similarly good prognosis. Two recent studies, however, reported that intracranial stenosis of the internal carotid artery is associated with a high risk of subsequent strokes.[12 13]

In our study we found a high incidence of late epileptic seizures. This was probably because occlusion of the middle cerebral artery is often due to embolism and infarcts are cortical.

We thank Dr M Marinelli for statistical help.

References

1 Barnett HJM, Peerless SJ, McCormick CW. In answer to the question: "As compared to what?" A progress report on the EC/IC bypass study. *Stroke* 1980;**11**:137-40.
2 Elveback L. Estimation of survivorship in chronic disease: the "actuarial" method. *Journal of the American Statistical Association* 1958;**53**:420-40.
3 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457-81.
4 Silverstein A, Hollin S. Internal carotid vs middle cerebral artery occlusions. *Arch Neurol* 1965;**12**:468-71.
5 Sindermann F, Bechinger D, Dichgans J. Occlusions of the internal carotid artery compared with those of the middle cerebral artery. *Brain* 1970;**93**:199-210.
6 Lhermitte F, Gautier JC, Derouesné C. Nature of occlusions of the middle cerebral artery. *Neurology* 1970;**20**:82-8.
7 Lascelles RG, Burrows EH. Occlusion of the middle cerebral artery. *Brain* 1965;**88**:85-96.
8 Kaste M, Waltimo O. Prognosis of patients with middle cerebral artery occlusion. *Stroke* 1976;**7**:482-5.
9 Hinton RC, Mhr JP, Ackerman RH, Adair LB, Fisher CM. Symptomatic middle cerebral artery stenosis. *Ann Neurol* 1979;**5**:152-7.
10 Furlan AJ, Whisnant JP, Baker HL Jr. Long-term prognosis after carotid artery occlusion. *Neurology* 1980;**30**:986-8.
11 Norrving B, Nilsson B. Carotid artery occlusion: acute symptoms and long term prognosis. *Neurol Res* 1981;**3**:125-8.
12 Marzewski DJ, Furlan AJ, Louis P St, Little JR, Modic MT, Williams G. Intracranial internal carotid artery stenosis: longterm prognosis. *Stroke* 1982;**13**:821-4.
13 Craig DR, Meguro K, Watridge C, Robertson JT, Barnett HJM, Fox AJ. Intracranial internal carotid artery stenosis. *Stroke* 1982;**13**:825-8.

(*Accepted 16 February 1984*)

Respiratory viruses and sudden infant death

ALAN L WILLIAMS, ERIC C UREN, LESLEY BRETHERTON

Abstract

Viruses were shown to be present in the respiratory tract in 200 of 763 cases of the sudden infant death syndrome studied in the nine years 1974-82. Epidemiological and pathological evidence suggested that the distribution of viruses in the sudden infant death syndrome differs between infants aged 3 months or less and those aged over 3 months: the incidence of detection of virus was 14% in the younger group compared with 39% in the older group. The distribution of the viruses in these two groups was compared with that in 1341 live infants with respiratory virus infections. Adenovirus, influenza virus, parainfluenza virus, and rhinovirus had similar distribution among the victims of the sudden infant death syndrome and live controls. The incidence of detection of respiratory syncytial virus was increased in the older infants dying of the sudden infant death syndrome (90% of the cases detected) compared with the older group of live infants (53%).

Antibody studies, detection of virus, and epidemiological data suggest that respiratory syncytial virus may be a precipitating factor of sudden death in older infants.

Royal Children's Hospital, Melbourne, Australia

ALAN L WILLIAMS, MD, FRCPA, director, department of pathology, and paediatric pathologist for coroner, city of Melbourne
ERIC C UREN, BSC, virologist
LESLEY BRETHERTON, BSC, technical assistant

Correspondence and requests for reprints to: Dr Alan L Williams.

Introduction

During the past 20 years many workers have reported the isolation of viruses from infants who have died suddenly and unexpectedly and for whose death no adequate explanation can be given.[1-5] Such viruses have been isolated most commonly from faeces or secretions of the respiratory tract. We report the detection of virus by isolation or immunofluorescence, or both, in secretions of the respiratory tract from a series of 763 infants dying suddenly and unexpectedly and from controls.

Patients and methods

The 763 infants studied fulfilled the criteria for the sudden infant death syndrome proposed by Beckwith.[6] A group of 56 infants of comparable age who had died suddenly, generally after accidents, served as controls. The same protocol for necropsy was used in all cases, and about 90% of the necropsies were performed by one of us (ALW). The techniques used to demonstrate viruses in these cases have been described previously.[5] The 488 infants reported on then were included in this larger group. Throughout the entire series the time delay between death and necropsy probably militated against optimal recovery of viruses.

To determine whether infants dying of the sudden infant death syndrome had more respiratory infections before death than infants who did not die we undertook a second series of investigations to detect virus specific IgG and IgM antibodies by enzyme immunoassay.[7] In this instance infants admitted to this hospital with acute, non-respiratory illness served as controls: we excluded long term patients, who might have biased the results due to nosocomial infections, and infants with respiratory illness, so that the control group was fairly representative of the general infant population. Serum from 98 such control infants, who were matched as closely as possible for age and date to 178 infants dying of the sudden infant death syndrome during 1977-9, was used in this study.

The virus antigens used were respiratory syncytial virus prepared according to the method of Wunner and Pringle,[8] hexon antigen specific to the adenovirus group purified by the method of Spence *et al*,[9] and influenza A and B complement fixing antigens obtained from the Commonwealth Serum Laboratories (Melbourne). Rhinovirus antigen was not included, despite its frequent isolation from cases of the sudden infant death syndrome, because of the technical difficulty of preparing an antigen representative of such a large group. Parainfluenza virus types 1, 2, and 3 were also omitted owing to difficulty in obtaining suitable antigens. Antihuman IgG and IgM peroxidase conjugates were obtained from Dakopatts Laboratories (Denmark). Antigen and conjugate concentrations were optimised using block titrations against known standards. Patients' serum was used at dilutions of 1/25 and 1/100 and was considered to be positive if the optical density reading was 2·1 times the average value in 10 negative control samples.

A third series of investigations was undertaken to determine whether the pattern of incidence of respiratory virus infection with age in victims of the sudden infant death syndrome reflected that seen in live infants or whether there was a significant difference between the two. Data on all of the 1341 live infants aged 9 months or younger who were referred to this hospital with a respiratory illness during 1980-2 and from whom respiratory viruses were detected were retrieved from the virology department's data base. This age range of 9 months or less is that in which 95% of cases of the sudden infant death syndrome occur. The distributions of respiratory viruses in infants aged over 3 months and in infants aged 3 months or younger were compared between these 1341 controls and the victims of the sudden infant death syndrome.

Results

Respiratory viruses were detected in 200 of the 763 cases of the sudden infant death syndrome either by immunofluorescence or by isolation (table I). Thus the incidence of detection was 26% overall (39% in the 378 babies aged over 3 months and 14% in the 385 babies aged 3 months or younger). The incidence of detection in the control group of 56 infants whose deaths were due mainly to accident was 18%. The incidence of detection in babies aged over 3 months was significantly lower in the controls than in the babies dying of the sudden infant death syndrome ($\chi^2=4{\cdot}84$, $p=0{\cdot}028$). There was an insufficient number of controls in the younger age group for a meaningful comparison to be made with the infants dying of the sudden infant death syndrome.

Details of the pathological findings in those infants from whose respiratory tracts viruses were recovered will be presented elsewhere. Briefly, in those infants in whom changes were present they were non-suppurative inflammatory changes limited to the nasopharynx, the trachea, and occasionally the large bronchi.[10] The only infant in the series in whom bronchiolitis could be diagnosed was a control infant from whom respiratory syncytial virus was isolated. This infant's death was due to accidental drowning.

Table II shows the results of antibody studies of serum samples from infants dying of the sudden infant death syndrome and 98 control (live) infants. There was little difference in IgM or IgG positivity between the two groups, suggesting that past exposure to the viruses was no greater in the infants who died of the sudden infant death syndrome than in the controls. This was so for both infants aged 3 months and under and those aged over 3 months.

TABLE I—*Detection of respiratory viruses by isolation or immunofluorescence in 763 cases of the sudden infant death syndrome and 56 infants after accidental death (controls). (Infants were grouped into those aged 3 months or less and those aged over 3 months)*

	Sudden infant death syndrome		Controls	
	⩽3 Months (n = 385)	>3 Months (n = 378)	⩽3 Months (n = 12)	>3 Months (n = 44)
Respiratory syncytial virus	3	25		1
Parainfluenza	7	24		2
Influenza	3	20		
Adenovirus	8	28		4
Rhinovirus	33	49	1	2
Total	54 (14%)	146* (39%)	1	9*

*$\chi^2=4{\cdot}84$, $p=0{\cdot}028$.

TABLE II—*Number (%) of infants who died of the sudden infant death syndrome and control infants showing virus specific IgM and IgG antibodies to four respiratory virus antigens. (Infants were grouped into those aged 3 months or less and those aged over 3 months)*

	Sudden infant death syndrome		Controls	
	⩽3 Months (n = 89)	>3 Months (n = 89)	⩽3 Months (n = 45)	>3 Months (n = 53)
	IgM antibodies			
Respiratory syncytial virus	9 (10)	32 (36)	7 (16)	27 (50)
Influenza A	10 (11)	24 (27)	7 (16)	13 (24)
Influenza B	9 (10)	23 (26)	3 (7)	15 (29)
Adenovirus	17 (19)	41 (46)	6 (14)	19 (35)
	IgG antibodies			
Respiratory syncytial virus	86 (95)	84 (94)	41 (90)	50 (95)
Influenza A	42 (47)	48 (54)	19 (43)	16 (31)
Influenza B	23 (25)	20 (22)	13 (29)	12 (22)
Adenovirus	61 (68)	74 (83)	32 (70)	46 (87)

Table III shows the distribution of respiratory viruses between the two age groups among the 1341 cases of respiratory viral infection cases and 200 victims of the sudden infant death syndrome. Parainfluenza virus, influenza virus, adenovirus, and rhinovirus had similar age distributions in the victims of the sudden infant death syndrome and in the controls. The exception was respiratory syncytial virus:

TABLE III—*Proportions of children aged over 3 months among 1341 infants still living and 200 victims of the sudden infant death syndrome in whom respiratory viruses were detected (figures in parentheses are percentages)*

	Live infants (n = 1341)	Sudden infant death syndrome (n = 200)
Respiratory syncytial virus	295/556 (53)*	25/28 (90)*
Parainfluenza	187/246 (76)	24/31 (77)
Influenza	59/72 (82)	20/23 (87)
Adenovirus	78/94 (83)	28/36 (78)
Rhinovirus	228/373 (61)	49/82 (60)

$\chi^2=12{\cdot}7$, $p=0{\cdot}0004$.

90% of the infants dying of the sudden infant death syndrome in whom respiratory syncytial virus was detected were aged over 3 months, compared with 53% of the controls ($\chi^2=12{\cdot}7$, $p=0{\cdot}0004$).

Discussion

The 763 infants dying of the sudden infant death syndrome and the 56 control infants died within the area served by the coroner of the city of Melbourne. This is roughly the same as the Melbourne statistical area and contains about 2·5 million people.

In this area during the period under study (September 1974 to December 1982 inclusive) the number of live births ranged from 45 000 to 40 000 a year and the number of cases of the sudden infant death syndrome from 1·7 to 2·1/1000 live births. The Royal Children's Hospital is situated within this area, and its inpatient beds and outpatient areas receive most of the ill children in this community. All sudden unexpected deaths are reported to the coroner, and necropsy is performed in every case.

The question arises whether the viruses detected from these infants were in some manner associated with their sudden death or were merely incidental findings. We believe that there is circumstantial evidence to support the concept that at least some of these viruses—namely, those that cause epidemic disease—had a direct role. This evidence does not extend to those viruses that are endemic throughout the year in this area—that is, rhinoviruses and adenoviruses.

Respiratory syncytial virus and influenza and parainfluenza viruses cause epidemics of respiratory illness. In this community a significant correlation has been shown between the peak seasonal incidence of the sudden infant death syndrome and infection with respiratory syncytial virus in infants.[5] Smaller seasonal increases in the sudden infant death syndrome correlate well with epidemics of infection caused by influenza and parainfluenza viruses.[5] In a statistical study comparing the incidences of the sudden infant death syndrome in Brisbane and Melbourne it was noted that both the peak incidence of the sudden infant death syndrome and the peak isolation of respiratory syncytial virus occurred roughly six weeks earlier in Brisbane.[11] The same study found that the incidence of the sudden infant death syndrome was higher in Melbourne than in Brisbane (2·13 *v* 1·58 cases/1000 live births).[11] The increased incidence was due to an increased number of deaths of infants above the age of 3 months. Deaths of infants aged over 3 months are responsible for the increased number of deaths in winter[10 12 13]; in Brisbane at least, deaths of infants younger than this occur on a statistically random basis throughout the year.[11]

It might be argued that the deaths of some of the older infants in this series should not have been diagnosed as due to the sudden infant death syndrome—for example, the deaths of infants in whom influenza virus or respiratory syncytial virus was detected who had histological evidence of tracheobronchitis. They were all examples of "clinical cot deaths"[14] in that their deaths were completely unexpected by the parents and by the family doctor. At necropsy they were all examples of "overt cot deaths,"[14] and this diagnosis would have remained unchallenged if routine virological examination had not been undertaken. Even though it was known that the virus had been isolated and tracheobronchitis found in many infants, at the completion of the necropsy "no adequate explanation" of the mode of death was possible, and the sudden infant death syndrome was finally diagnosed.

The differing distribution of respiratory syncytial virus with age between the infants dying of the sudden infant death syndrome and the infants with respiratory viral infection seen in the hospital appears to be important. Antibody studies, particularly of virus specific IgM, suggested that there was little difference in exposure to respiratory syncytial virus between infants dying of the sudden infant death syndrome and these controls. This being so, the distribution of respiratory syncytial virus between the older and the younger age groups of infants dying of the sudden infant death syndrome should have been similar to the distribution between the same age groups of the infants with respiratory viral infections. That it was not, and that the incidence of detection of respiratory syncytial virus was significantly higher in the infants dying of the sudden infant death syndrome beyond the age of 3 months, suggests that at least for some infants aged over 3 months infection with respiratory syncytial virus may precipitate sudden death.

This concept that infants dying suddenly and unexpectedly consist of more than one group and that in those aged over 3 months certain respiratory viruses have an important role does not explain the infants' mode of death. The clinical histories indicated that death may occur before clinical symptoms have developed, or after an illness of several days. Thus anaphylaxis is unlikely to be the common mode of death, although in some infants it cannot be excluded.

One well recognised feature of the clinical illness caused by respiratory syncytial virus is the occasional occurrence of apnoeic attacks.[15 16] These may occasionally be fatal, and death may be explained by the presence of bronchiolitis or pneumonia; very occasionally, however, neither is present and at necropsy no adequate explanation of death can be given based on the limited lung disease. Apnoea may be the presenting feature of an infection with respiratory syncytial virus—that is, the infant presents as a "near miss" case of sudden infant death syndrome.[15-17] In some of the recorded cases clinical signs of infection of the respiratory tract were not present at initial presentation. Apnoea may occur in infants with respiratory infection due to influenza virus and also to parainfluenza virus.[15]

We are aware that apnoea due to respiratory syncytial virus is stated to occur more commonly in infants below 3 months of age and in infants with clinical evidence of infections of the lower respiratory tract.[18] It seems possible, however, that a fatal attack of apnoea precipitated by one of the above respiratory viruses may be one cause of infants dying suddenly, unexpectedly, and without adequate pathological change being found to explain the death.

We thank Ian Jack and his staff of the virus laboratories, Royal Children's Hospital, for advice and help and Miss V Williams for help with the manuscript.

References

1 Downham MAPS, Gardner PS, McQuillin J, Ferris JAJ. Role of respiratory viruses in childhood and mortality. *Br Med J* 1975;i:235-9.
2 Ray CG, Beckwith JB, Hebestreit NM, Bergman AB. Studies of the sudden infant death syndrome in King County, Washington. *JAMA* 1970;**211**:619-23.
3 Nelson KE, Greenberg MA, Mufson MA, Moses VK. The sudden infant death syndrome and epidemic viral disease. *Am J Epidemiol* 1975;**101**:423-30.
4 Urquhart GED. Sudden infant death syndrome studies in virology and immunology. In: Robinson RR, ed. *Proceedings of the Francis E Camps international symposium on sudden infant death syndrome in infancy*. Toronto: Canadian Foundation for the Study of Infant Death, 1974:107-36.
5 Uren EC, Williams AL, Jack I, Rees JW. Association of respiratory virus infections with sudden infant death syndrome. *Med J Aust* 1980;i:417-9.
6 Beckwith JB. Definition of sudden infant death syndrome. In: Bergman AB, Beckwith JB, Ray CG, eds. *Sudden infant death syndrome*. Seattle: University of Washington, 1970:17.
7 Engvall E, Perlmann P. Enzyme-linked immunosorbent assay, ELISA. *J Immunol* 1972;**109**:129-35.
8 Wunner WH, Pringle CR. Respiratory syncytial virus proteins. *Virology* 1976;**73**:228-43.
9 Spence D, Kenny G, McLure AR, MacFarlane DE, Sommerville RG. The preparation of an antiserum to adenovirus group (hexon) antigen. *Archiv fur die gesamte Virusforschung* 1971;**34**:340-5.
10 Williams AL. Tracheobronchitis and sudden infant death syndrome. *Pathology* 1980;**12**:73-8.
11 Deacon EL, O'Reilly MJJ, Williams AL. Some statistical and climatological aspects of the incidence of the sudden infant death syndrome. *Aust Paediatr J* 1979;**15**:248-54.
12 Fedrick J. Sudden unexpected death in infants in the Oxford record linkage area. *British Journal of Preventive and Social Medicine* 1973;**27**:217.
13 Beal SM. Seasonal variation in sudden-infant-death-syndrome. *Lancet* 1978;i:1257.
14 Emery JL. The necropsy and cot death. *Br Med J* 1983;**287**:77-8.
15 Bruhn FW, Mokrohisky ST, McIntosh K. Apnea associated with respiratory syncytial virus infection in young infants. *J Pediatr* 1977;**90**:382-6.
16 Colditz PB, Henry RL, DeSilva LK. Apnoea and bronchiolitis due to respiratory syncytial virus. *Aust Paediatr J* 1982;**18**:53-4.
17 Silva FAA, McFadyen UM, Simpson H. Clinical characteristics of 29 infants presenting as near-miss for SIDS. In: Tildon JT, Roeden LM, Steinschneider A, eds. *Sudden infant death syndrome*. London: Academic Press, 1983:653.
18 Mitchell I, Barclay RPC, Railton R, Fisher J, Conely J. Frequency and severity of apnoea in lower respiratory tract infection in infancy. *Arch Dis Child* 1983;**58**:497-9.

(*Accepted 1 March 1984*)