Severe hypoxaemia in pertussis

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SUMMARY Overnight tape recordings of breathing movements, airflow, and arterial oxygen saturation from six infants aged 3 weeks to 7 months, who had cyanotic episodes associated with pertussis, were compared with recordings from 12 age matched healthy controls. In all patients clinically apparent apnoeic episodes were associated with the rapid onset and progression of central cyanosis. When overnight recordings were compared, patients with pertussis had a greater frequency of apnoeic pauses (particularly those ≥ 12.0 seconds duration) and a greater frequency of episodes of hypoxaemia (oxygen saturation $\leq 80\%$ for ≥ 0.5 seconds) associated with apnoeic pauses. In addition to episodes of hypoxaemia associated with a prolonged absence of breathing movements, patients with pertussis had frequent dips in oxygen saturation in association with continued breathing movements with and without continued inspiratory airflow. These episodes of hypoxaemia during continued breathing movements were more common in patients with pertussis.

These findings suggest that episodes of abnormal apnoea accompanied by evidence of a mismatch between ventilation and perfusion of the lungs may produce the rapid onset of severe hypoxaemia in infants with pertussis.

Apnoeic and cyanotic episodes often occur during pertussis particularly when it occurs in early infancy.^{1 2} The underlying mechanisms responsible for this dangerous complication are, however, unknown. In this paper we describe the results of an investigation by non-invasive techniques of infants with pertussis experiencing frequent and severe cyanotic episodes and compare these results with those from 12 healthy, age matched infants.

Patients and methods

Details of the six patients are given in the table. Pertussis was diagnosed by the presence of charac-

teristic paroxysms of repetitive coughing that persisted for longer than one week and were associated with retching, vomiting, cyanosis, or convulsions in an infant who otherwise appeared to be in good health.³ Three patients had a history of recent exposure to pertussis. Nasopharyngeal swabs ('Transwab', Medical Wire and Equipment Co) from all six patients were cultured on cephalixin supplemented charcoal agar and *Bordetella pertussis* was isolated from two patients. None of the patients had suffered episodes of cyanosis before the onset of the present illness.

All patients had a paroxysmal cough and a history of apnoea associated with the rapid onset of

Table Clinical details of patients with pertussis

Patient No	Sex	Gestation (weeks)	Birth weight (g)	Age at onset of illness	Known exposure to pertussis	Results of culture for <i>Bordetella pertussis</i>	Presence of symptoms			Duration of illness at investigation (weeks)
							Whoop	Vomiting	Convulsions	
1	F	40	3210	1 week	-	-	+	+	+	3
2	F	25	680	6 months	-	-	-	+	-	4
3	F	40	3030	3 months	-	+	-	-	-	2
4	M	40	3660	7 weeks	+	-	+	-	+	3
5	M	40	3780	3 weeks	+	+	-	+	+	1
6	F	37	2000	4 months	+	-	+	+	+	2

profound cyanosis. These apnoeic cyanotic episodes began at least one week after the onset of cough in all patients except patient 1 who suffered apnoeic episodes from the outset of the illness. In all patients the cyanotic episodes had a sudden unpredictable onset. They occurred when awake and when asleep and were often not immediately preceded by cough. In many cases coughing followed the onset of the cyanosis (see below). Patients 1, 4, 5, and 6 had a history of convulsions with loss of consciousness during their cyanotic episodes. Patients 1 and 6 were cyanosed and convulsing at the time of admission to hospital. (The twin sister of patient 6, with an identical history of pertussis, died during a cyanotic convulsion while the infants were being brought to hospital.) Apart from patient 2 who had a birth-weight of 680 g at 25 weeks' gestation all the patients were delivered at term with birth weights of at least 2000 g.

All patients were nursed under close continuous supervision and were treated by positioning, oropharyngeal suctioning, and administration of oxygen via a face mask at the onset of any clinically apparent episodes of severe apnoea or cyanosis. Patients 1, 3, 5, 6 were treated with erythromycin, patients 1 and 3 were treated with phenobarbitone and salbutamol, and patients 4 and 5 were treated with aminophylline before and during investigation. Chest radiography showed normal results in all patients at the time of investigation. The recordings described in this paper were measured by non-invasive sensors, did not influence the clinical care of the patients, and were approved by the St George's Hospital ethical committee.

The case history of patient 1 shows the clinical features seen in these six infants. This 3 week old girl was brought to hospital with a two week history of paroxysmal cough and repeated episodes of apnoea with cyanosis, loss of consciousness, and generalised convulsions. Cyanosis typically occurred within 10 seconds of the onset of apnoea and loss of consciousness and convulsions followed within a further 20 seconds. On the day of admission she had twice lost consciousness. On admission she was apnoeic, cyanotic, and convulsing but quickly recovered spontaneously. After admission she had further repeated episodes of apnoea, cyanosis, and convulsions requiring resuscitation by nursing and medical staff.

Healthy term infants being studied as part of a large survey of normal breathing patterns were used as control subjects. Two age matched controls were randomly selected for comparison with each patient with pertussis.

Investigations centered around overnight tape recordings (Racal Store 4 FM with a 1 channel

multiplexer) of beat to beat arterial oxygen saturation (from a probe placed on the big toe and a modified Nellcor pulse oximeter Respro 2),⁴ airflow measured at the external nares by a thermistor (time constant 0.3 seconds, Yellow Springs Instrument Co) or by expired carbon dioxide and a scavenger tube (sampling at 100 ml/minute, with an electronic response time of 100 milliseconds, Engstrom Eliza), and breathing movements from inductance plethysmography (Studley Data Systems) or a pressure capsule (Graseby Dynamics). In order to verify the accuracy of the oxygen saturation measurements the oximeter was used in a beat to beat mode and every plethysmographic waveform representing the arteriolar pulsation used to derive oxygen saturation was recorded onto the tape recordings along with the oxygen saturation signal. Only oxygen saturation measurements accompanied by pulse waveforms of adequate quality were regarded as accurate.⁴ In three infants (patients 1, 3, 5) oesophageal pressure was monitored by either a balloon catheter (PK Morgan with Furness controls pressure transducer) or a continuously infused (3 ml/hour) naso-oesophageal tube and pressure transducer (Gaeltec). In patient 1 an electroencephalogram was recorded from a centrotemporal configuration during cyanotic episodes. Tape recordings were printed onto an ink jet chart recorder (Siemens 34T) or an electrostatic chart recorder (Gould ES 1000).

Parents of patients and controls gave informed consent for the investigations.

Recordings were analysed by a technician who was unaware of the clinical details of each subject. Periods during which signals were uninterpretable owing to movement artefact were documented and excluded from analysis. Breathing patterns were classified as regular or non-regular breathing according to previously published criteria.⁵ Regular breathing was defined as episodes of ≥ 1 minute where the breathing pattern was relatively regular in amplitude and rate, interrupted by sighs but without movement artefact. Non-regular breathing was all the remainder of the recording, and included intermittent brief periods of movement artefact. All apnoeic pauses (absent inspiratory efforts for ≥ 4.0 seconds) were counted and their durations measured and the frequency of these pauses was determined by dividing the total number of pauses by the total duration of interpretable recording. All episodes of hypoxaemia, defined for this study as a situation where oxygen saturation fell to $\leq 80\%$ for ≥ 0.5 seconds were identified. This measurement was chosen after our experience of analysing similar recordings from large numbers of healthy infants wherein a cut off of 80% was helpful in defining normality. The duration of this hypoxaemia was

measured for each episode and the breathing pattern during the preceding 12 seconds and during the period of hypoxaemia recorded. Breathing movements or airflow, or both, were regarded as absent if there was complete cessation for a period of ≥ 4.0 seconds. The frequency of episodes of hypoxaemia was determined by dividing the total number of episodes of hypoxaemia by the total duration of interpretable recording. The duration of hypoxaemia was determined by totalling the lengths of each episode and dividing this by the total duration of interpretable recording.

The frequency of apnoeic pauses of different durations, and the frequency of episodes of hypoxaemia associated with apnoeic pauses of different durations, in patients with pertussis and control subjects were compared by the Mann-Whitney U test.

Results

Clinical observations showed that although most of the overt cyanotic episodes began in association with coughing or crying, about one third, especially those occurring during sleep, began with an absence of inspiratory efforts (apnoeic pause). In all the

observed cyanotic episodes the onset of cyanosis was rapid, usually occurring between four and eight seconds after the onset of the cough, crying, or apnoeic pause. Recovery from a cyanotic episode was frequently associated with a large inspiratory effort (a gasp).

All subjects had at least 4.9 hours of interpretable recordings (patients with pertussis 5.7–9.8 hours, normal subjects 4.9–12.5 hours.) Regular breathing and non-regular breathing alternated at intervals of about 20–100 minutes throughout the recordings. Both in the pertussis patients and in the normal subjects apnoeic pauses and episodes of hypoxaemia occurred almost exclusively during the periods of non-regular breathing.

Patients with pertussis had a greater mean frequency of apnoeic pauses than control subjects (fig 1). This difference was greatest for apnoeic pauses with a duration of ≥ 12.0 seconds ($p < 0.005$). The longest apnoeic pauses for patients 1–6 were 15.0, 28.5, 11.5, 15.0, 53.8, and 17.0 seconds, respectively. The longest apnoeic pause in a control subject was 14.1 seconds. Thus five of the six patients had abnormally prolonged apnoeic pauses.

Fig 1 Frequency of apnoeic pauses (duration 4.0–7.9, 8.0–11.9, ≥ 12.0 seconds) for patients with pertussis (solid circles), and control subjects (open circles). Note logarithmic scale on the vertical axis.

Fig 2 Frequency of episodes of hypoxaemia associated with either continued breathing movements, or apnoeic pauses with durations of 4.0–7.9, 8.0–11.9, and ≥ 12.0 seconds, for patients with pertussis (solid circles), and control subjects (open circles). Note logarithmic scale on the vertical axis.

The frequency of episodes of hypoxaemia related to the duration of associated apnoeic pauses for patients with pertussis and control subjects is shown in fig 2. Patients with pertussis had a greater frequency of episodes of hypoxaemia associated with apnoeic pauses with a duration of 4.0–7.9 seconds ($p<0.005$), 8.0–11.9 ($p<0.05$), and ≥ 12.0 seconds ($p<0.05$). The greatest difference between patients with pertussis and control subjects, however, was in the frequency of episodes of hypoxaemia during continued breathing movements ($p<0.001$).

An example of a hypoxaemic episode associated with a prolonged absence of breathing movements and airflow is shown in fig 3. These episodes usually began at end expiration and were associated with a raised oesophageal pressure. Prolonged apnoeic pauses often included a period of breathing movements without airflow before normal breathing was

resumed ('mixed' apnoea) (fig 4). Some hypoxaemic episodes terminated with a period of sharply positive oesophageal pressure excursions suggesting coughing (fig 4). Patients with pertussis also had episodes of hypoxaemia associated with absent airflow despite continued breathing movements (fig 5). Patient 2 had prolonged periods of hypoxaemia despite continued breathing movements and continued airflow (fig 6) and patients 3–5 had similar but briefer episodes. Electroencephalographic recordings during prolonged pauses in inspiratory efforts with hypoxaemia in patient 1 did not show a seizure preceding the apnoeic pauses.

Discussion

All six patients in this study presented under 6 months of age and had cyanotic episodes characterised by the extremely rapid onset and progression

Fig 3 Recording of an episode of severe hypoxaemia (saturated oxygen $<50\%$) associated with a prolonged absence of airflow (A–B) and breathing movements (C–D) in patient 2. I: Arterial saturated oxygen from a pulse oximeter; scale is to the left of the signal (%). Total response time is about six seconds. IIa: Abdominal breathing movements from a pressure capsule transducer; expansion is an upward deflection. III: Arterial pulse waveform; adequate quality signals are present for most of the time during the fall in saturated oxygen. A bradycardia is shown by increased intervals between the pulses. IVa: Airflow at the nose represented by expired carbon dioxide signals; scale is to the left of the signal (vol %). Total response time is about two seconds.

Fig 4 Recording of an episode of hypoxaemia associated with 'mixed' apnoea in patient 5. A prolonged period of absent airflow (A-B) is initially associated with absent inspiratory efforts but a raised oesophageal pressure (C). Ineffective breathing efforts then occur (D). Towards the end of the episode there are sharply positive excursions in oesophageal pressure (E), suggestive of coughing. I: Arterial saturated oxygen. IIb: Oesophageal pressure from a balloon catheter: scale is to the left of the signal. Positive pressure changes are represented by upward deflections. III: Arterial pulse waveform. IVb: Airflow at the nose from a thermistor: inspiratory flows are represented by upward deflections.

Fig 5 Recording of an episode of hypoxaemia associated with continued breathing movements but absent airflow (A-B) in patient 4. I: Arterial saturated oxygen. IIa: Abdominal breathing movements from a pressure capsule transducer: expansion is an upward deflection. III: Arterial pulse waveform. IVb: Airflow at the nose from a thermistor: inspiratory flows are represented by upward deflections.

Fig 6 Recording of two episodes of hypoxaemia (A-B) and (C-D) associated with continued breathing movements and continued airflow in patient 2. I: Arterial saturated oxygen. IIa: Abdominal breathing movements from a pressure capsule: expansion is an upward deflection. III: Arterial pulse waveform. IVa: Airflows at the nose represented by expired carbon dioxide signals.

of severe hypoxaemia similar to that occurring during a condition previously termed prolonged expiratory apnoea⁶⁻⁹ and suggesting the acute onset of a mismatch between ventilation and perfusion of the lungs. Between clinically overt cyanotic events infants with pertussis showed repeated abnormal dips in arterial oxygen saturation in association with four breathing patterns: prolonged (≥ 15 seconds) pauses in inspiratory efforts (fig 3), an initial absence of effort and airflow followed by continued efforts but absent airflow (fig 4), continued breathing efforts but absent inspiratory airflow (fig 5), and continued inspiratory efforts and continued airflow (fig 6). Hypoxaemia was not seen in association with these patterns of breathing in control subjects. As with the rapidity of onset and severity of the clinically apparent cyanotic episodes, the occurrence of hypoxaemia during continued breathing movements is also characteristic of prolonged expiratory apnoea,^{6,7} and suggests that both mismatch between ventilation and perfusion of the lungs, and apnoea (absent ventilation of the lungs)

contribute to the pathogenesis of hypoxaemia in infants with pertussis.

We have previously suggested that alveolar atelectasis may be responsible for these disturbances in ventilatory perfusion relations and that the accompanying prolonged pauses in breathing movements may result from the effects of atelectasis on lung reflexes.^{7,8} This hypothesis is supported by the recordings shown in fig 6, which shows that hypoxaemia may develop despite continued airflow into the lungs. If alveolar atelectasis is the cause of the hypoxaemic episodes, a defect in lung surfactant may represent the primary pathology.⁷⁻⁹ In infants with pertussis this may be due to a direct effect of *B pertussis* toxins on surfactant synthesis, secretion or function.

Although a proportion of the cyanotic events began during coughing, some followed crying, and others, especially during sleep, followed a pause in inspiratory efforts. In this last case the infant would characteristically stop breathing, become cyanosed, arouse, and then begin coughing.

Cyanotic convulsions have been reported to precede death in pertussis,¹⁰ and changes suggesting anoxia are a consistent finding in the histology of the brains of children dying of pertussis complicated by convulsions.¹¹ Our recordings suggest that the convulsions are secondary to severe cerebral hypoxaemia.

The patterns of breathing and hypoxaemia identified above have been described in apnoea of prematurity suggesting that the pathogenesis of these two conditions might be similar.¹² Moreover, similar cyanotic episodes, sometimes with evidence of prolonged pauses in inspiratory efforts, have been reported in other respiratory tract infections during infancy. In two retrospective studies respiratory syncytial virus infection was associated with prolonged apnoea or cyanotic episodes in 10% and 20% of cases respectively.^{13 14} In the prospective study of infection by respiratory syncytial virus reported by Anas *et al*, 25% of infants showed prolonged apnoeic episodes.¹⁵ These often began early in the disease before other symptoms of infection had developed and were more frequent in infants less than 3 months of age and in previously preterm infants especially those who had suffered from apnoea of prematurity. Yolken and Murphy described cyanotic episodes in five infants with rotavirus infection, three of whom were temporarily resuscitated but subsequently died.¹⁶

Despite a distinctive clinical picture, doctors are often slow to diagnose pertussis,¹⁷ and notifications greatly underestimate the true incidence of the disease.¹⁸ Even when pertussis is diagnosed, however, clinical observation alone is likely to greatly underestimate the frequency and severity of hypoxaemia as shown by our overnight recordings.

Nicoll and Gardner¹⁹ and Cherry²⁰ have suggested, on the basis of epidemiologic studies, that pertussis may be responsible for some cases of sudden infant death. Williams and Jones have produced evidence that the convulsions and apnoea complicating pertussis may be accompanied by subsequent intellectual impairment.²¹ These data and our findings suggest that infants with a history of cough with apnoea or cyanosis, even if apparently well at initial examination, should be admitted to hospital for a period of meticulous observation. Our results also underline the need to prevent this serious and as yet untreatable infectious disease and clearly this can be best achieved by a more complete programme of immunisation.

In conclusion episodes of abnormal apnoea accompanied by evidence of a mismatch between ventilation and perfusion of the lungs may cause severe arterial hypoxaemia in infants with pertussis. This hypoxaemia may be life threatening, may result

in seizures, and may be one cause of the brain damage reported in some infants with pertussis.

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