Discussion

Fungal infection in neutropenic patients is common. In one postmortem study of young cancer patients, 23 out of 88 fatalities showed evidence of systemic fungal infection.¹

Our patient was at particular risk of such an infection. The risk factors included prolonged neutropenia, prolonged steroid treatment, diabetes, and an indwelling Hickman catheter.² In addition he was on prolonged broad spectrum antibiotics, the most important factor in the aetiology of serious and fatal candidiasis. The stopping of antibiotics in those who remain febrile and neutropenic, however, carries a very high risk of serious bacterial infections.³

Empirical antifungal treatment is advocated for neutropenic patients with an antibiotic resistant fever.^{1 4 5} Amphotericin is the only antifungal with proved efficacy in neutropenic patients and its use as a single agent in this situation is therefore recommended.^{4 5} Indeed in one study nearly complete elimination of fungal infections was seen if amphotericin was started in those who remained febrile and neutropenic after a week of antibiotic treatment.¹ Starting antifungals only late in antibiotic resistant neutropenic fever is known to result in an increased mortality from fungal infection, but the optimal time to start remains uncertain.^{1 5}

In our patient amphotericin was started after six days of fever resistant to antibiotics. Despite this, symptomatic presentation of mycotic cerebral abscesses occurred 12 days later and viable *Candida* was isolated from these three weeks after the start of amphotericin treatment. Doubt about the efficacy of amphotericin alone as empirical treatment has been expressed previously.⁶

The use of flucytosine combined with amphoteri-

cin has been suggested, not least because of its synergistic activity against *Candida*.⁶ This combination, however, has been considered to have a number of disadvantages—namely, the need to lower the dose of amphotericin, the problems of determining flucytosine concentrations, and myelotoxicity.⁵ While using this combination therapeutically in our patient none of these problems were seen. Amphotericin dosage was reasonable (1 mg/kg on alternate days), flucytosine concentrations were readily determined by our laboratories, and myelotoxicity was not an important problem. The addition of itraconazole seemed justified by the extremely high mortality previously documented for this condition.

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Hypothermia and sudden infant death syndrome

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SUMMARY We recently reported an association between recurrent episodes of severe apnoea requiring vigorous resuscitation for which no cause could be found and episodic hypothermia. Two similar cases are now reported that give further evidence of a link between hypothermia and acute life threatening episodes of apnoea.

Our first report concerned a baby boy who at the time of writing this paper was 4 years old.¹ He has had no further apnoeic attacks, but does have recurrent attacks of hypothermia (rectal temperature 32–35°C). The only new development is that he now has occasional episodes of sweating and hypoglycaemia that have been documented while he was under observation in hospital. He is being monitored at home with a skin temperature probe.

We now report two similar cases that give further evidence of an association between severe apnoea for which no cause could be found and hypothermia.

Case reports

CASE 1—A normal baby boy was born at term weighing 2270 g. There was no family history of sudden infant death syndrome (SIDS) or hypothermia. He was referred from another hospital at the age of 2 months having had recurrent episodes of apparent lifelessness during sleep when he became pale, grey, cold, and limp, and had required vigorous mechanical or mouth to mouth resuscitation by his mother (a trained nurse) from the age of 4 weeks. Observations showed excessive periodic breathing when compared with age matched controls, and mild regurgitation was seen on barium swallow examination. He was treated with oral theophylline 5 mg/kg/24 hours and given a home apnoea alarm (MR-10, Graseby Dynamics Ltd). Between 1 and 12 months there was a gradual improvement both in the frequency and the severity of his attacks. The apnoeic episodes stopped when he was 15 months old. From the age of 10 months he had recurrent episodes of hypothermia with a rectal temperature of less than 35°C recorded while he was under observation in hospital. These episodes were accompanied by extreme pallor and he was cold to touch (described as 'snow white' by his mother) but had no sweating. Rectal temperatures during the day were normal, and he became feverish (38°C) when he had an upper respiratory tract infection. Physical examination yielded normal results, and development at the time of writing was normal.

CASE 2—A baby girl of 38 weeks' gestation was delivered by caesarian section (because of a bicornuate uterus) weighing 2892 g. She had a brief cyanotic attack at the age of 2 days, possibly associated with secretion of mucus. She was seen when she was 6 weeks old with a three week history of multiple recurrent episodes of apnoea, limpness, and cyanosis that had required vigorous resuscitation. Observations and investigations showed excessive periodic breathing, and a bradycardia of less than 90 beats/minute was recorded on cardiorespiratory tracing. She was given a home apnoea alarm but theophylline 5 mg/kg/24 hours was stopped because it made her irritable. She had recurrent apnoeic attacks requiring vigorous resuscitation every four or five weeks until she was 12 months old, and recurrent episodes of hypothermia during which she became pale and cold with a rectal temperature of less than 35°C occurred during sleep throughout the summer while she was under observation in

hospital. These started when she was 8 months old. Physical examination yielded normal results, and development at the time of writing was normal.

All three babies had the following measurements made, all of which yielded normal results: full blood count; erythrocyte sedimentation rate (mm in the first hour); serum urea and electrolyte concentrations; and calcium, glucose, and creatine phosphokinase concentrations. Serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase activities, were normal as were screening tests for autoantibodies, serum concentrations of immunoglobulins, chest radiographs, cultures of cerebrospinal fluid, and Mantoux tests. Wasserman reactions were negative, as were serological tests for toxoplasma, rubella, cytomegalovirus, herpesvirus, mumps, Q fever, and psittacosis. The electrocardiograms and electroencephalograms were normal. Computed tomography of the brain yielded normal results in each case with normal copora callosa. The patient previously reported had also had magnetic resonance imaging of the brain, which was normal.

Estimations of the serum concentrations of thyroxine, thyroid stimulating hormone, and prolactin (samples taken at rest) were normal. Pronounced hypoglycaemia induced by insulin produced normal serum growth hormone and cortisol concentrations. There were normal responses to thyroid releasing hormone, and the gonadotrophin responses were also normal. Cortisol concentrations showed normal diurnal variations. Early morning urine specimens concentrated normally.

Discussion

All three infants had recurrent unexplained life threatening episodes of apnoea followed later by episodes of hypothermia. This association may be more important that has previously been recognised.

We have reviewed the presentation and management of 73 cases of acute life threatening episodes of apnoea diagnosed at this hospital from 1980–84.² We studied all patients with episodes of lifelessness that required vigorous mechanical or mouth to mouth resuscitation to revive the infant, and in whom investigations failed to show a cause. Twelve parents (16%) stated as a presenting complaint that the child was 'cold'. This could simply be explained by the vasoconstriction that occurs in any ill child. Six children (8%), however, had recurrent severe apnoeic attacks, and three of these later developed episodic hypothermia.

Although the pathophysiology of both apnoea and hypothermia is uncertain, the most likely link between severe apnoeic attacks and temperature

disturbances is a defect in hypothalamic function.¹ Episodic hyperthermia is rare, and usually associated with episodic hyperhidrosis, and absence of the corpus callosum.³ This link with agenesis of the corpus callosum is presumed not to be functional but developmental, perhaps occurring in the hypothalamus. One patient had gliosis and neuronal loss in the premamillary area of the hypothalamus at necropsy.³ As the hypothalamus also controls regulation of sleep, it is interesting to note the differences in sleep patterns between normal controls and infants with severe apnoeic attacks.⁴

Neurones sensitive to local temperature extend from the hypothalamus far down into the spinal cord in an interlinked system. It has been postulated that the defect causing episodic hypothermia may be below the hypothalamus. We have reported normal brain stem potentials evoked by auditory stimuli in one patient.¹ This, however, does not exclude a brain stem lesion with possible effects on respiration.

Altered autonomic function may affect both temperature and respiratory control, and play a part in the pathogenesis of SIDS. We have previously reported a child with poor short term variability of heart rate who died of SIDS. There are, however, few data on normal controls to compare with variability in heart rate among these patients, and we could not test their autonomic function fully because they were too young.

The association between severe apnoeic attacks and SIDS has not been proved, though some of these infants have died from SIDS.² Abnormally high temperature has been postulated as a cause of some deaths from SIDS, despite the fact that most of the deaths occur in winter. Stress caused by cold may be a sufficient trigger for the abnormalities in fatty acid metabolism recently implicated in the pathogenesis of SIDS. A defect in heat production that is metabolically mediated and accentuated by a cold environment may be a possible explanation for the increase in such deaths during the winter months. The metabolic state of these children is currently being investigated.

The presence of brown adipose tissue may also be

important. There is evidence that brown adipose tissue is present and functional in normal babies.⁵ Aherne and Hull, quoted by Blaza, however, found that the brown adipose tissue was depleted of fat in 42 of 394 necropsies of infants who died before the age of 4 weeks. Most of the 42 deaths were due to starvation and the brown fat was only partially depleted. In six infants with injury from cold, however, they found total depletion of brown fat. A similar depletion was found in two elderly adult patients who had died of hypothermia. There were no cases of SIDS in their series.

Contrary to earlier reports, Emery and Dinsdale found less periadrenal brown fat in babies who died of SIDS compared with controls aged less than 5 months.⁶ As the largest mass of brown adipose tissue in the abdomen envelops the kidneys we postulate that these infants may have been at greater risk of hypothermia.

Abnormal temperature regulation should be sought in infants with recurrent life threatening apnoeic attacks, and should be investigated closely in the search for the causes of SIDS.

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