MALIGNANT HYPERPYREXIA AND SUDDEN INFANT DEATH SYNDROME

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In 1982 Denborough, Galloway and Hopkinson [1] stated that three of nine Australian families susceptible to malignant hyperpyrexia (MH) had also suffered the loss of a child through sudden infant death syndrome (SIDS). Until this time there had been no clinical suspicion of an association between these two conditions. This suggested association was avidly promoted by the media and in this country caused concern amongst both the MH and the SIDS families.

A further study [2] described “positive medical family histories” in relation to anaesthesia among SIDS families. We felt it was important to validate this association, studying both the incidence of SIDS in the MH families and the incidence of MH in the SIDS families. A further study was designed in which SIDS parents were asked to submit to a muscle biopsy similar to those performed as part of the routine screening procedure for members of MH families [3].

SUBJECTS, MATERIALS AND METHODS

First study

A simple questionnaire was sent to 195 patients previously biopsied in this department who had been shown to be susceptible to MH (MHS) who were in or above child-bearing age.

The questions included:
- How many pregnancies have you had?
- What was the outcome of these pregnancies?
- How many miscarriages?
- How many stillbirths?
- How many children died in the first year of life? (Please give dates of birth, death, cause of death as written on the death certificate.)

Second study

Another more elaborate questionnaire was sent to 106 consecutive SIDS parents, through the Foundation for the Study of Infant Deaths. This questionnaire asked for details of the death of the child, including ambient temperatures and clothing, etc., and the anaesthetic histories of both parents and their respective families. SIDS parents were also asked to provide details of any neuromuscular abnormalities including strabismus, ptosis, joint dislocations, hernia, kyphoscoliosis, muscle pains and cramps and the effects of strenuous exercise they experienced.

Third study

Following the publicity in the media, 14 SIDS parents volunteered to undergo a biopsy of the left vastus medialis muscle. These studies were accepted by the Research Ethical Committees of both Leeds East and Leeds West Health Authorities. Halothane and caffeine contracture tests were
performed *in vitro* using the European MH Group procedure [4, 5] and muscle histology was undertaken. The clinical management of these subjects was identical to that given to patients referred to this Unit for screening for MH susceptibility [3].

**RESULTS**

*First study*

One hundred and fifty-one (76%) of the questionnaires were returned, recording 511 pregnancies with 456 live births. The outcome of these live births is summarized in table I.

There were 16 deaths in children younger than 1 year of age, of which three were described as “cot deaths” occurring in apparently healthy infants. The cause of the infant deaths is summarized in table II and details of the SIDS are in table III.

Using the binomial theorem the incidence of SIDS amongst the MH live births does not differ significantly from the incidence of SIDS in the general population \((P < 0.05)\), which is taken to be 1.96 per 1000 live births [6] (but see discussion later).

*Second study*

A total of 278 anaesthetics had been recalled amongst the 106 pairs of SIDS parents who replied to the questionnaire. There were no deaths attributed to anaesthesia and five families recorded a problem which was not suspected to be MH at the time by their medical attendants. Scanty details of these complications were as follows:

Subject 1. A father had experienced an increase in postoperative temperature on several occasions.

Subject 2. A mother was pyrexial for 7 days following Caesarean section on two occasions.

Subject 3. A mother reported a postoperative respiratory depression and slow recovery.

Subject 4. A mother described postoperative stiffness for 24 h following the removal of a benign papilloma from the soft palate.

Subject 5. A maternal uncle was “packed in ice” following an acute appendicectomy.

The only case which could have been MH was Subject 5, although it should be noted he was undergoing surgery for an infected lesion, the mobilization of which can cause acute pyrexia. In our experience of over 500 proband investigations for MH screening, postoperative pyrexia has not been found to be a presenting sign of MH. Also, we have never encountered a case of MH presenting as a 7-day postoperative pyrexia. Subject 4 resembles a post suxamethonium myositis. There were no consistent reports of neuro-musculoskeletal problems.

*Third study*

The laboratory tests conducted on live muscle tissue taken from the normal SIDS parents were all within normal limits (MHN) as defined by the European protocol.

In order to compare our studies with those of Denborough, Galloway and Hopkinson [1], muscle specimens were also exposed to 3% halothane, a test not recognized in the European MH Group procedure. One of the 14 parents produced an insignificant increase in the baseline muscle tension of 0.1 g on exposure to 3% halothane.

No patient displayed any abnormal histology, and preoperative resting serum creatinekinase (CK) activity was consistently within normal limits for our laboratory.

**DISCUSSION**

It was not until 1971 that cot death or sudden death became accepted as a registrable cause of
death in England and Wales. The term sudden infant death syndrome (SIDS) came into use in 1979. The incidence of SIDS in the general population is difficult to ascertain precisely and is variously quoted as 0.62 per 1000 live births in 1971 to 2.13 in 1982 and currently is 1.96 (vide supra). Before 1971, unexpected deaths were reported as “sudden respiratory deaths” and as acute tracheobronchitis, bronchiolitis or bronchopneumonia, despite lack of conclusive pathological evidence. However, virological evidence has been found by Downham and colleagues [7] in some sudden respiratory deaths and some “cot deaths”. Since 1971 the number of sudden deaths attributed to “respiratory causes” has declined from 1.63 in 1971 to 0.46 in 1981 whereas the combined rate of SIDS and respiratory problems has stayed at a steady 2.4 per 1000 live births over the period 1971–81 [8].

The problem is compounded further because of controversy over the exact definition of SIDS, some applying the term regardless of postmortem findings [9], thus making epidemiological studies difficult. Becroft, Beckwith and Ray in 1970 [10] suggested the definition to be: “the sudden death of an infant or young child, which is unexplained by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death”.

Because of these difficulties, cases described as “cot deaths” occurring in MH families before 1971, were included. This gives an overall incidence in the MH families of three cot deaths per 456 live births as compared with 2.4 per 1000 live births for the combined SIDS and respiratory deaths in the general population. If these two cases are excluded because they could not have been registered as a SIDS or cot death on the death certificate, the incidence becomes 1 SIDS per 456 live births compared with 1.96 per 1000 live births in the general population; the latter incidence excludes the “respiratory causes” group.

The number of cases of SIDS reported in this study is too small for there to be a significant and specific link between MH and SIDS.

The incidence of anaesthetic mortality in the SIDS group was zero and the morbidity of 5 in 278 anaesthetics is gratifyingly low. With the possible but unlikely exception of Subject 5, none could be considered to be MH reactions.

From a recent study in this laboratory, MH is inherited as a Mendelian dominant characteristic [3], although differing patterns of inheritance have been described previously [11]. Should SIDS correlate with MH, the muscle abnormality should also be dominantly inherited and each SIDS parent should have a 0.5 probability for the muscle abnormality. Using sequential analysis it can be inferred that, with the 14 negative findings, the probability of a muscle defect occurring similar to that found in MHS patients is less than 0.05. We considered that further biopsy studies, with their attendant risks, would be unethical.

The apparent discrepancy between our laboratory results and those of Denborough and colleagues [1] can be explained by the method of case selection used by the latter group. In particular they encouraged SIDS families with a family history of an anaesthetic mishap to be investigated preferentially (Denborough, 1987 personal communication), thus biasing their findings in favour of an association between SIDS and MH, which we have been unable to substantiate.

REFERENCES