Sudden Infant Death Syndrome, as First Expression of a Metabolic Disorder


Pediatrics Clinic, Children's University Hospital Reine Fabiola, Free University of Brussels, Avenue J J Crocq 15, 1020 Brussels; and *the V.U.B., Brussels, Belgium

INTRODUCTION AND DEFINITIONS

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is the sudden death of a young child which is unexpected, given the child’s history, and for which no explanation can be found despite postmortem examination (1). The need for a complete postmortem investigation is shown by the fact that in up to 15% of the autopsies, an explanation for the death can be found (1). In 5% of the cases, a “fatty liver” is found, revealing a possible prior metabolic disorder (2). The prevalence of SIDS is between one and three deaths per 1,000 live births. In Belgium, the SIDS rate is 1.72 per 1,000, and represents one third of all deaths occurring between the age of 1 month and 1 year, by far the most frequent cause of death in the postnatal period.

Apparent Life-Threatening Event

Pediatricians have been asked by anxious parents to care for an infant who has survived an apparent life-threatening event (ALTE). The child was found unresponsive, pale or cyanotic, and apparently not breathing. The accident occurred unexpectedly, and only prompt intervention by one of the parents revived the child. The initial episodes appear to occur during periods of sleep, waking, or feeding, and are most commonly described as some combination of apnea, color change (usually cyanosis or pallor, occasionally erythema), marked change in muscle tone (usually limpness, but in rare cases rigidity), and choking or gagging. In most cases observers reported the episode as being potentially life threatening, and in some cases they stated that the child had actually died (1,2). There is epidemiological evidence that some of the infants studied after an ALTE might have survived a potential SIDS episode (3,4).
Metabolic Abnormalities, Sudden Infant Death Syndrome, and Apparent Life-Threatening Events

The possible role played in SIDS by inherited metabolic diseases could be illustrated by some epidemiological characteristics of these deaths, such as the tripled death rate in families with a SIDS case, or the frequent observation of gastrointestinal infections or fasting in the days preceding a SIDS event (1,4,5). Fasting could have enhanced the occurrence of metabolic crises related to acylcoenzyme A dehydrogenase deficiency. The inherited metabolic disorder is associated with life-threatening episodes of hypoketotic hypoglycemia, accompanied by dicarboxylic aciduria, and steatosis in various tissues. The clinical findings are similar to those of Reye’s syndrome with fulminant hepatic encephalopathy following a minor illness with diarrhea and/or vomiting (8). Subtle clinical symptoms, as seen in some future SIDS or ALTE victims, are also compatible with an underlying metabolic problem, such as the observation of recurrent episodes of “fatigue” during feeds, muscular hypertonia, or excessive sweating during sleep (1,5).

As early as 1976, an unrecognized but specific disease was suspected in a small number of the SIDS cases in which a diffuse fatty change was found in the liver (2). Since 1984, several cases of “sudden Reye-like deaths” and SIDS have been attributed to defects of free fatty acid metabolism or to a systemic carnitine deficiency (7–12). Deaths have also been related to nesidioblastosis-induced hypoglycemia, or to a deficiency of pyruvate dehydrogenase (13), thiamine (14), or bioinidase (15). It was estimated that up to 1 of 10 SIDS cases could be attributed to inherent errors of metabolism, and that at least 31 metabolic defects could be potential candidates for SIDS (16).

RETROSPECTIVE ANALYSIS OF APPARENT LIFE-THREATENING EVENTS RELATED TO METABOLIC ABNORMALITIES

Retrospective Analysis of Data

We have reviewed the available data on the 844 infants admitted between 1977 and 1984 after having survived an apparent life-threatening event (ALTE). The mean age was 9 weeks (range 1 to 52 weeks). After a systematic clinical investigation was conducted to rule out possible causes for the event, a medical or surgical cause was found in 563 infants (67%). In decreasing order of frequency, the main abnormalities were digestive (47%), neurological (30%), and respiratory problems (10%). Impaired breathing regulation during sleep was found in about a third of the infants (3,6). In five infants a metabolic cause was found (0.6% of all ALTE cases, or 0.9% of the “explained” ALTE cases) (3).

Results

The results are shown in Table 1.

Infant 1. The child with Leigh’s syndrome was a 9-week old girl admitted 5 days
TABLE 1. ALTE infants with metabolic abnormalities: retrospective study (1977–1984)

<table>
<thead>
<tr>
<th>Number of infants studied</th>
<th>844</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with a metabolic disorder</td>
<td>5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2/3</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.8 ± 1.0</td>
</tr>
<tr>
<td>Legal age (weeks)</td>
<td>8.8 ± 1.7</td>
</tr>
</tbody>
</table>

**Diagnosis:**
1. Subacute necrotic encephalopathy (Leigh) | 1 |
2. Menkes’ syndrome | 1 |
3. “Reye’s syndrome” | 1 |
4. NEFA oxidation deficiency (?) | 1 |
5. Fructosemia | 1 |

after an upper airway infection. She was found limp, pale, and with irregular shallow breathing. On admission she was in a coma and hypothermic. She had severe metabolic acidosis, with normal aciduria. She died 15 days later, and the diagnosis was confirmed by the postmortem.

**Infant 2.** A 3-month-old boy was found in a state of respiratory arrest and metabolic acidemia. His rectal temperature was 39°C, his hair was sparse, and he had palmar hyperkeratosis. The diagnosis of Menkes’ syndrome was supported by the finding of pili torti, an abnormal carotidography, and low plasma copper (<2 μg/dl) and ceruloplasmin levels (<2 mg/dl). After frequent seizures, he died 5 months later. The autopsy confirmed the diagnosis of Menkes’ syndrome.

**Infant 3.** A 4.5-month-old boy was found in a coma, after having vomited the day before. Hepatomegaly and hypoglycemia (40 mg %) were noted, together with increased levels of plasma ammonium (367 mg %), BUN (40 mg %), and transaminases (GO 162 IU, GP 157 IU). There was an increased excretion of adipic acid without cetonuria. A liver biopsy revealed the presence of perilobular steatosis, and a diagnosis of “Reye’s syndrome” was made. At 9 months of age the child was readmitted because of anorexia, fever, diarrhea, and muscle weakness. He had been fasting for 6 hours. He was found to be hypoglycemic (10 mg %), and died suddenly despite treatment. At the postmortem, both myocardium and liver were yellow and enlarged, with large vacuoles of perilobular steatosis. The final diagnosis was carnitine deficiency, although the carnitine blood level was not measured.

**Infant 4.** A 7-month-old girl was found unconscious in her crib after 5 days of fever, anorexia, and vomiting. No hepatomegaly was noted. Blood glucose was 21 mg %, and the plasma pH was 7.49. There was an increase in the levels of ammonium (746 mg %), BUN (68 mg %), and transaminases (GO 612 IU, GP 1100 IU). The Quick test was 55% of normal. Generalized amino aciduria was noted. A liver biopsy revealed microvesicular steatosis. The child survived but developed West’s syndrome.

**Infant 5.** A 6-week-old girl developed a state of pallor and hypotonia following her first ingestion of fruit. A slight hepatomegaly was found. Blood glucose was 50 mg %. A liver biopsy showed no fructose-1-phosphate-aldolase activity. Given a
sucrose- and fructose-free diet, the child developed normally and is now 10 years old.

Comments

The retrospective nature of the analysis precludes any detailed confirmation of the suspected abnormalities. Based on the available evidence, the first two infants (children 1 and 2) could be diagnosed as having suffered from a defect of the mitochondrial respiratory chain, probably affecting cytochrome c oxidase. The ensuing mitochondrial myopathy would account for the observed hypotonia, lactic acidemia, and the poor outcome.

Patients 3 and 4 could be classified as showing an impairment of fatty acid oxidation, although a primary carnitine deficiency was ruled out. The last infant showed a standard abnormality of carbohydrate metabolism that was treated with an appropriate diet.

PROSPECTIVE DETECTION OF METABOLIC ABNORMALITIES IN INFANTS WITH A HIGHER RISK OF SIDS

We have prospectively evaluated 86 infants classified as having a higher risk of SIDS. To scan for possible metabolic disorders the infants were carefully selected and subjected to a systematic series of tests, including a 15-h fasting period.

Infants Studied

Forty girls and 46 boys were admitted to the hospital to evaluate their SIDS risk factors. There were 56 siblings of sudden infant death victims (siblings), and 30 infants who had survived an apparent life-threatening event (ALTE), and for which no cause was found. The median age of the infants was 28 weeks (range 42 to 118 weeks). The criteria used for the selection of the infants included several characteristics potentially associated with metabolic abnormalities, such as the occurrence of an ALTE after an infection or a period of fasting, or when the SIDS had occurred at an unusual age—before the fourth week or after the first 12 months of life (9). Asymptomatic infants were included if they were born to families in which at least two siblings had died of SIDS or in which a sibling suffered from a metabolic abnormality. All but one of the infants were considered healthy. No medication was being given at the time of the evaluation.

Clinical Evaluation of the Infants

A detailed family and personal history was obtained for each infant, and a standard physical and neurological evaluation was made. Before initiating the fasting period,
blood samples were taken to measure the levels of 3-hydroxybutyrate, transaminases, free and total carnitine, amino acids, and nonesterified fatty acids (NEFA). Urine samples were collected to determine the level of free and total carnitine, amino acids, and organic acids. The 15-h fasting test was then conducted under close medical supervision. Glycemia was monitored by hourly Dextrostix checks, and blood was taken after 9 and 11 h of fasting. Oral glucose was administered in cases of hypoglycemia. After the fifteenth hour of fasting a determination was made of 3-hydroxybutyrate, free and total carnitine, amino acids, blood glucose, lactic acid, pyruvic acid, NH₃, NEFA, and plasma pH. The presence of ketoacids, carnitine and organic acids was evaluated in the urine. Cultures of fibroblasts were performed when acyl-CoA dehydrogenasis deficiency was suspected. The findings related to enzyme activity were not yet available when this report was written.

Results

In 80 of the infants no fasting-induced hypoglycemia or abnormal metabolites were found. In the remaining six infants (one ALTE infant and five SIDS siblings) the following results emerged.

Infant 1. A 13-week-old girl was a SIDS sibling. Her brother and a cousin both died of SIDS at the age of 2.5 and 20 months, respectively. Failure to thrive, anorexia, and muscular hypotonia had been noted since the age of 9 weeks. On admission she showed global muscular hypotonia; the liver edge was felt 1 cm under the costal margin. Blood lactic acid was 29 mg/dl (normal 9–16 mg/dl), and pyruvic acid 1 mg/dl (normal 0.2–1 mg/dl). Increased levels were noted of SGOT (103 U/liter), CPK (489 IU/liter; N: 6–147 IU/liter, and LDH (1724 IU/liter; N: 162–340 IU/liter). Serum NH₃, amino acids, and free, esterified, and total carnitine levels were normal. During the fasting test blood glucose remained normal, but there was an increase in lactates (29 mg/dl) and acetone in the plasma, and two unidentified peaks of organic acids were noted in the urine. A muscle biopsy revealed such nonspecific abnormalities as fatty microvacuolar infiltrations and mitochondrial swelling. An enzymatic defect in the mitochondrial respiratory chain was suspected. Carnitine supplements were nevertheless given orally (100 mg/kg-day), accompanied by a fat-free diet. A delay in gross neuromuscular development was noted at the age of 1 year, with a persistent elevation of the level of muscular enzymes. The activity of the mitochondrial respiratory enzymes is being evaluated.

Infant 2. An 86-week-old boy, a SIDS sibling, had a sister and brother who died of SIDS at 2 and 2.5 months, respectively. A physical examination was normal. After 15 h of fasting, his blood glucose fell to 40 mg/dl, and rose slowly only after glucagon and glucose injections. There were no other abnormal findings. The fasting test had been performed less than 1 week after a viral infection. It was repeated 4 months later, at which time no abnormality was found. Two years later, the child appears to be normal.

Infant 3. A 16-week-old boy had lost two cousins to SIDS at the ages of 2.5 and
16 months. One cousin is suspected of suffering from lactic acidosis (infant 1). His physical examination was normal. The fasting test induced mild plasma lactic acidosis (27 mg/dl; normal 9–16 mg/dl), but no other abnormality was found. A muscle biopsy revealed microvascular steatosis and swollen mitochondria. Despite the lack of a precise diagnosis, oral carnitine was given for 9 months (100 mg/kg-day). At 1 year of age the child’s development is normal.

**Infants 4, 5, and 6.** Mild dicarboxylic aciduria (adipic and 3-OH butyrate) was found in three infants: two SIDS siblings aged 9 and 23 weeks and one 33-week-old ALTE infant. The fasting test was repeated in all three infants within one month of the initial study and was found to be normal. All infants survived the first 2 years of life uneventfully, without treatment.

**Comments**

Infant 1 was a “floppy baby,” who combined both clinically evident hypotonia and lactic acidemia. The most probable diagnosis was that of mitochondria myopathy related to the existence of a respiratory chain enzyme defect (type I or IV). As an enzymatic deficiency has not been identified, we can exclude a deficiency of MCAD or pyruvate metabolism. A defect of the fatty acid oxidation mechanisms was suspected in infant 2, because of the induced hypoglycemia. The diagnosis could not be proven, as a control fasting challenge failed to disclose any abnormality. We do not know whether the viral infection that preceded the fasting challenge contributed to the disruption of the glucose homeostasis. Deficient enzymatic activity in the mitochondrial respiratory chain was suspected in infant 3 because of a mild increase in blood lactate during fasting, abnormal findings in the muscle biopsy, and his familial relationship with infant 1, who suffered from mitochondrial myopathy. The child’s clinical development could indicate that the enzymatic deficiency may be a mild one. In the last three infants (4, 5, and 6), fasting induced mild dicarboxylic aciduria but no hypoglycemia. The aciduria was not found a few weeks later during a repeat of the fasting challenges. No clinical symptom was seen, and the children’s development was normal. A mild, transitory FFA oxidative defect was postulated, but we were unable to identify any metabolic abnormality in these infants.

**DISCUSSION**

Our retrospective study revealed that five out of 844 infants (0.6%) studied after an apparent life-threatening event suffered from a metabolic disease. Three of the children died, and one suffered from severe neurologic sequelae. Infants thought to be at higher risk of SIDS were studied prospectively to screen for unidentified metabolic abnormalities. Specific loading challenges have been advocated for the screening of acyl-CoA deficiencies, such as the administration of L-carnitine, or phenylpropionate (10). To extend the range of metabolic defects screened, we performed a fasting challenge. In infants, starvation tests lasting 15 h have been reported to
require close monitoring, and to contribute efficiently to the identification of various enzymatic deficiencies (9,17,18). The finding of abnormal results in six out of 86 infants (7%) is close to the incidence of metabolic abnormalities reported in SIDS (8,16). But when the tests were controlled, no abnormality could be confirmed. Only one infant (infant 1) had a clearly abnormal response during the fasting challenge. That child was clinically abnormal, with gross delay in growth and psychomotor development, metabolic acidosis, and elevated levels of liver enzymes.

While the preliminary character of this study precludes any definite conclusions, the lack of correlation between the results of the challenge and the clinical diagnosis, together with the discrepancy between the results of the initial and control studies, raise questions as to both the nature of the abnormalities and the sensitivity of the test procedures. Within the limits of our investigation protocol, the number of SIDS or ALTE infants who suffer from a metabolic dysfunction appears to be limited.

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REFERENCES

DISCUSSION

Dr. Saudabay: I would like to make some comments about the difficulty in finding the right protocol for the investigation of SIDS. Of the list of the investigations you presented, I have done many over the last two years which I have found to be very questionable. For example, when you choose a 15-h fast for investigation, this is either very dangerous or absolutely useless, because if you want to investigate fatty acid oxidation during a fast, the investigation must take place at a time when fatty acid oxidation is stimulated; if the patient is still using liver glycogen stores you are not studying fatty acid oxidation. So it is a false security, because even if all measured variables are completely normal, you cannot rule out the possibility of a fatty acid oxidation defect. The same holds true for everything else. For example, amino acids in plasma are not really informative; if they are normal, what does it mean? As for carnitine, it has known incredible success; but when I reviewed my own experience after 3 or 4 years of carnitine measurement, not only for sudden infant death but for every patient with suspicion of inborn errors, I stopped measuring carnitine as a screening system; if it is low, you don’t know what this means, and if it is normal, you cannot rule out the possibility of an inborn error.

Dr. Kahn: There is sufficient evidence in favor of a 15-h fast if you want to stress a child less than 1 year of age. As reported in the literature and in our own experience, a 15-h fast is not dangerous as long as you monitor the child very closely.

Dr. Holton: Can I comment on this question of the incidence of metabolic disease in SIDS patients? To answer this question we do need some systematic studies of unselected sudden infant death victims. Fortunately, three studies have been proceeding. One was reported at the Münch meeting recently, from Lyon. They had studied 109 cases of sudden infant death and had looked at available body fluids using GCMS. They also examined skin fibroblasts in these cases, using the CO₂ release assay for MCAD. In Bristol we have examined 100 cases, using almost identical methods. In Edinburgh they have looked at 200 sequential cases of sudden infant death, using the CO₂ release assay. In all these cases, over 400 now, not one metabolic disorder was detected.

Dr. Bartlett: I would like to present a dissenting view. We have done a rather limited study, looking at postmortem plasma octanoate concentrations. We studied 40 cases of sudden infant death. We found five who had raised octanoate concentrations, but of that five only one also had octanoate-carnitine present. However, we had no tissue available to confirm the diagnosis by direct enzyme assay.

Dr. Holton: I don’t think it is a dissenting point of view. Metabolic disease, particularly MCAD, does cause sudden infant death, but I think only in a very small percentage.
Dr. Kahn: I agree completely with that comment. Again, let me stress that the problem of the definition of the prevalence of metabolic abnormalities in sudden infant death syndrome is a methodologically difficult one to solve. But from the clinical point of view we should not forget that, as clinicians, we also have access to information on the child’s condition and on the family history that may contain a lot of information. For instance, I mentioned excessive sweating during sleep; in normal infants this is rarely seen in such studies, but in studies on 150 SIDS victims, sweating was excessive in 25%, while only 3 to 5% of the control population were reported to be sweating. The same applies to difficulty in feeding these infants. Such information could contribute to the identification of infants in whom metabolic investigations should be performed.

Dr. Roe: Part of the problem is not knowing the actual frequency of some of these disorders in the general population. It is not at all clear what the frequency of MCAD is. To make matters worse, we are further confounded by variation in the definition of sudden unexplained death in children: up to 12 months of age in my country, for example, whereas the British consider SIDS up to 24 months of age. There are a lot of variations. From the slide I showed on the situation with MCAD, one would expect to find more deaths in the second year of life than in the first. One of the things that I have found interesting while working closely with the examining medical officers is that pathologists know what SIDS is, and they will tell you precisely what the findings are or are not. When they have a sudden death and observe significant hepatic steatosis or some degree of cerebral edema at autopsy, that death is not usually considered to be SIDS. However, cases with those findings often prove to be a metabolic disorder.

Dr. Duran: I may perhaps add a comment on the age of death in children dying unexpectedly with inherited disorders of fatty acid metabolism. We know four families in which children with the medium chain acyl-CoA dehydrogenase deficiency or hydroxyacyl-CoA dehydrogenase deficiency have died. Three families had children dying in the second year of life. One family had a child who died in the first week of life. So all these children died outside the generally accepted period of sudden infant death.

Dr. Kahn: That is a comment I would like to emphasize. This is why we are also focusing mostly on those infants where a previous child died at an unusual age. We know that 85% of the infants will die of sudden infant death syndrome between 2 and 6 months of age. We also know that less than 10% occur in the first 4 weeks of life, and less than 1% of all the SIDS cases occur after 1 year of age. So whenever a child is reported to have died after the first year of age, the risk of there being a metabolic abnormality could increase, and we are therefore much more concerned with those deaths. Likewise, the prevalence of sudden death in the same families for no apparent reason is fairly small, since 97% of all siblings are normal. Whenever more than two children have died in one family with the same unexplained death we should wonder whether we are not dealing with a metabolic abnormality.

Dr. Saudubray: What is the possible influence of dietary medium chain triglyceride supplementation on the postmortem levels of decanoic, decenoic, and marginally medium chain fatty acids in plasma? Do you have any experience in this field?

Dr. Bartlett: Of the five patients in our study who had elevated octanoate concentrations, one had been on a formula containing medium chain triglycerides, but this was not the case in whom there was also octanoylcarnitine.

Dr. Duran: We don’t have much experience with MCT diet in postmortem material. What we do know is that in postmortem diagnosis of MCAD deficiency, we find the unsaturated C10 fatty acid, the cis-4-decenoic acid, which we consider quite characteristic of this disorder.

Dr. Endres: We recently had a discussion with Dr. Ann Burchell, who published in the Lancet many cases of glucose-6-phosphatase deficiency in patients who had died suddenly (1). There
was no agreement on the reliability of this work and I would like to ask you what you think about this publication.

*Dr. Van Hoof*: We have been involved in the diagnosis of more than 100 patients with type I glycogenosis. None of them developed sudden infant death syndrome.

*Dr. Van den Berghe*: The paper by Burchell et al. (1) claimed that glycogen storage disease type I was present in 10 of 38 cases of SIDS. Together with Dr. Van Hoof, we scrutinized this study in detail and found the following shortcomings: (1) although all children were necropsied, no information is given with respect to liver size in a disorder in which hepatomegaly is a major sign; (2) apparently neither optical nor electron microscopic examination of the liver was performed, which could have demonstrated glycogen accumulation; and (3) glucose-6-phosphatase is known to be very unstable, rendering its assay in autopsy liver highly problematic.

*Dr. Hobbs*: In the 1960s, Professor J. L. Emery brought me samples from 68 cot-death children which were analyzed for immunoglobulin deficiency. I regret this is one paper we did not publish, but for the record, we did not find a single abnormality.

*Dr. Saudubray*: Beside the true sudden infant death syndrome, we have observed sudden death several times in patients affected with respiratory chain disorders presenting with cardiomyopathy. Five patients who on admission did not appear severely ill died 5 or 6 h after admission. Of course, these were not sudden infant death syndrome cases, but when you make a diagnosis of respiratory chain disorders you must tell the parents the child is in constant danger of dying unexpectedly.

**REFERENCE**