PAPERS AND SHORT REPORTS

Defects of metabolism of fatty acids in the sudden infant death syndrome

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Abstract

Two hundred consecutive cases of the sudden infant death syndrome were reviewed for the presence of fat in the liver; 14 showed diffuse panlobular microvesicular fatty change indistinguishable from that found in Reye's syndrome. Samples of frozen liver were available in five of the 14 cases; histochemical analysis showed well preserved cytochrome oxidase and succinate dehydrogenase activity in all five, uncharacteristic of Reye's syndrome. Fatty acyl-coenzyme A dehydrogenase activity in the liver was assayed biochemically in two of the same five cases with severe hepatic fatty infiltration; both showed a defect in medium chain acyl-coenzyme A dehydrogenase activity using the substrate octanoyl-coenzyme A. Both cases also showed cerebral oedema in association with fatty infiltration of renal tubules, myocardium, and skeletal muscle, characteristic of Reye's syndrome.

It is concluded that diffuse panlobular microvesicular fatty change of the liver in victims of the sudden infant death syndrome, although essentially non-specific, indicates that the state of mitochondrial enzymes should be investigated.

Introduction

A subgroup among cases of the sudden infant death syndrome showed severe fatty infiltration of the liver.[1] This pathological indicator is also characteristic of both Reye's syndrome[2 3] and some inborn errors of metabolism of fatty acids.[4 5]

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In Reye's syndrome, an acute childhood illness with vomiting and coma that typically occurs a few days after an apparently mild infection, diffuse fatty infiltration of viscera is accompanied by cerebral oedema.[2] The pathogenesis is usually attributed to generalised mitochondrial dysfunction caused by a viral or toxic agent in a genetically suceptible host.[6 7] The pathological diagnosis rests on evidence of decreased activity of mitochondrial enzymes, most notably succinate dehydrogenase.[8 9] Diagnosis, however, is made often on clinical grounds alone, possibly aided by a liver biopsy showing the typical pattern of fatty change.[10 11]

On the other hand, inborn errors of fatty acid metabolism can also present as an illness similar to Reye's syndrome and manifest pathological changes identical with those seen in Reye's syndrome.[4 5] Infants with such conditions may die suddenly and unexpectedly[5] and may be classified on clinical grounds as victims of the sudden infant death syndrome. Some have diffuse fatty infiltration of the viscera and cerebral oedema.[12] The differential diagnosis of defects of fatty acid β-oxidation therefore rests on the finding of a single enzyme deficiency rather than a generalised decrease in all mitochondrial enzymes as seen in Reye's syndrome.[12]

This study was conceived to document the proportion of cases of the sudden infant death syndrome with diffuse fatty change of the liver and to determine whether any of these deaths could have been caused by defects of fatty acid β-oxidation.

Patients and methods

Two hundred consecutive infants and children aged 1 month to 2 years who had been classified as having died from the sudden infant death syndrome were selected from the files of this hospital. Cryostat sections stained for fat with oil red O were reviewed together with slides stained with haematoxylin and eosin. Those showing diffuse panlobular microvesicular fatty change were further investigated histochemically for cytochrome oxidase and succinate dehydrogenase activity with standard techniques when frozen liver tissue was available[13]; cryostat sections of kidney, myocardium, and skeletal muscle stained with oil red O were also reviewed in these cases. Assays of fatty acyl-coenzyme A dehydrogenase activity were performed on frozen liver using techniques previously reported.[14] A control group of 10 cases of the sudden infant death syndrome

without serious liver fat were also examined. Liver samples had been stored at −80°C for up to a year.

Results

Fourteen cases showed diffuse panlobular fatty change in the liver (fig 1), which generally corresponded with small and large cytoplasmic vacuoles on conventional staining. Frozen liver was available

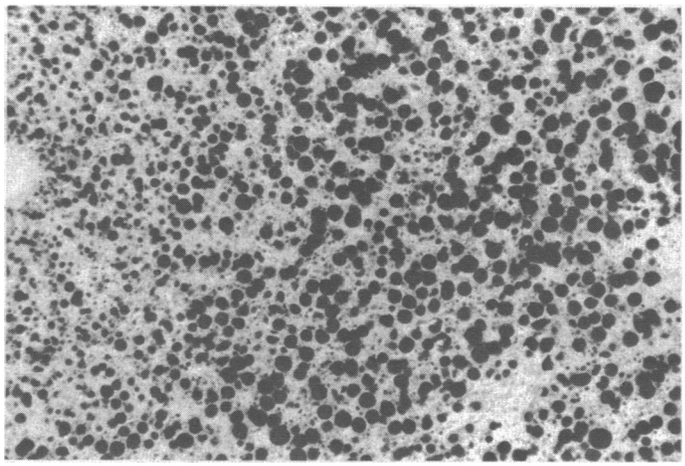

FIG 1—Diffuse panlobular fatty change in liver. Oil red O ×360 (original magnification).

in five cases for enzyme histochemistry. All five showed preservation of cytochrome oxidase and succinate dehydrogenase activity. Table I shows details of two cases with a defect in medium chain acyl-coenzyme A dehydrogenase activity using octanoyl-coenzyme A as substrate, with low to normal activity of glutamate dehydrogenase and short and long chain acyl-coenzyme A dehydrogenase. These two cases also showed considerable fatty infiltration of renal tubules, myocardium, and skeletal muscle; these features were also present in the remaining three cases. The control group showed well preserved enzyme activities. Included in table I is the interval between death and necropsy, with postmortem vitreous humour glucose concentrations. Both cases of deficiency of medium chain acyl-coenzyme A dehydrogenase showed severe hypoglycaemia. There was no mention of salicylates in the histories of the five cases analysed enzymatically.

Discussion

An earlier study reported that severe fatty change of the liver occurs in 5% of cases of sudden infant death[1]; it was suggested that these children had been in some state of "poisoning" or had suffered from an acute metabolic abnormality, such as is seen in Reye's syndrome. Our finding of severe diffuse panlobular fatty change of the liver in 7% of otherwise unexplained infant deaths agrees with that study.

Included in the mitochondrial damage of Reye's syndrome are enzymes that are thought to act in β-oxidation of fatty acids; their dysfunction is known to lead to accumulation of intracellular triglyceride.[5] Exhaustion of glycogen stores due to lack of acetyl-coenzyme A for gluconeogenesis leads to hypoglycaemia. Similar effects and pathological findings are seen in disorders of isolated enzymes that act in fatty acid mitochondrial β-oxidation.[15,16] The difference between inborn errors of metabolism and true Reye's syndrome is that the errors are familial whereas Reye's syndrome is, by definition, sporadic.

Those cases of sudden infant death with panlobular fatty change of the liver probably represent a special group in which inherited defects of fatty acid metabolism should be investigated. The incidence of cases of sudden infant death increases from 1:500 live births in the general population to 1:50 in siblings,[17] which raises the possibility that inborn errors of metabolism may have a role in some such deaths.[12]

The five cases of panlobular fatty change in the liver showed histochemical preservation of cytochrome oxidase and succinate dehydrogenase activity, which argued against a diagnosis of Reye's syndrome.[7] Two of these cases also showed considerable fatty change of other viscera similar to that described in Reye's syndrome.[2] Both showed deficiency of medium chain acyl-coenzyme A dehydrogenase, an enzyme with a role in the β-oxidation of fatty acids in mitochondria to produce acetyl-coenzyme A (fig 2). The prevalence of such inborn errors of fatty acid metabolism among sudden infant deaths is still unknown.

Besides Reye's syndrome and deficiency of medium chain acyl-coenzyme A dehydrogenase there are other recognised causes of microvesicular fatty infiltration of the liver,[18] and hypoglycin and valproate have been shown to inhibit β-oxidation of fatty acids in animals.[19] Systemic carnitine deficiency prevents fatty acids from entering the mitochondria for β-oxidation,

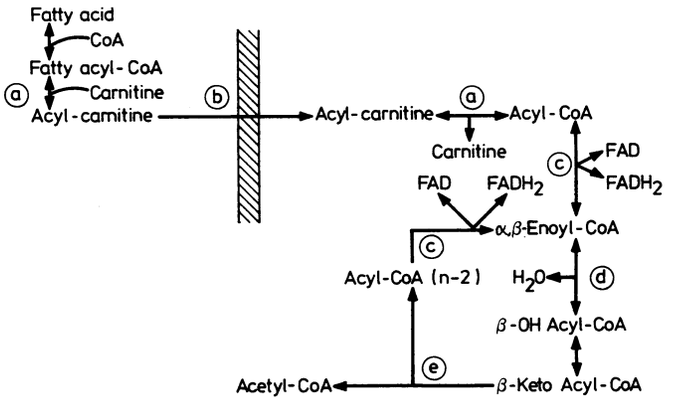

FIG 2—Diagram of mitochondrial β-oxidation of fatty acids to produce acetyl-coenzyme A. Long chain fatty acids are brought into mitochondria via acyl-carnitine transport mechanism (hatched line represents inner mitochondrial membrane). Enzymes are: (*a*) acyl-coenzyme A carnitine transferase; (*b*) acyl-carnitine translocase; (*c*) acyl-coenzyme A dehydrogenase; (*d*) enoyl-coenzyme A hydratase; and (*e*) β-ketothiolase.

TABLE I—*Details of two cases of medium chain acyl-coenzyme A dehydrogenase deficiency compared with 10 cases showing well preserved enzyme activities*

	Acyl-coenzyme A dehydrogenase specific activity (μmol dichlorophenolindophenol reduced/min)						Glutamate dehydrogenase activity (μmol NA dehydrogenase formed/min) (×10⁻²)	Interval from death to necropsy (hours)	Vitreous glucose (mmol/l)
	Butyryl-coenzyme A (short chain)		Octanoyl-coenzyme A (medium chain)		Palmitoyl-coenzyme A (long chain)				
	/mg protein (×10⁻³)	/unit glutamate dehydrogenase (×10⁻¹)	/mg protein (×10⁻⁴)	/unit glutamate dehydrogenase (×10⁻²)	/mg protein (×10⁻⁴)	/unit glutamate dehydrogenase (×10⁻³)			
Cases									
Case 1	0·98	0·62			0·19	1·2	1·59	25	0·2
Case 2	4·02	1·5			0·1	0·4	2·68	19	<0·5
Comparative group (n = 10)									
Mean	5·53	1·78	5·7	1·7	1·24	4·06	2·98	25	0·9
Range	1·34-16·6	0·89-2·85	0·96-18·7	1·03-2·5	0·16-4·7	1-10	0·7-8·4	4-77	<0·5-3

which results in accumulation of intracellular fat. The liver fat in Reye's syndrome is presumably caused by a temporary dysfunction in mitochondrial β-oxidation. It seems reasonable to assume that cases of sudden infant death with such fatty changes also have abnormalities of fatty acid β-oxidation, whether congenital or acquired.

Implicit in the currently accepted definition of the sudden infant death syndrome is that necropsy must be thorough to exclude adequate causes of death.[20] Our findings indicate that all such investigations must include histological examination of the liver, and those livers showing diffuse panlobular fatty change should be further subjected to thorough histochemical and biochemical analysis of the state of mitochondrial enzymes. Conversely, the diagnosis of Reye's syndrome cannot be confirmed by the characteristic liver fatty infiltration without tests for mitochondrial enzyme activity (table II).

TABLE II—*Histochemical and biochemical activity of mitochondrial enzymes in Reye's syndrome, medium chain acyl-coenzyme A dehydrogenase deficiency, and sudden infant death syndrome, showing diffuse fatty change of liver*

Enzyme activities	Reye's syndrome	Medium change acyl-coenzyme A dehydrogenase deficiency	Fatty change in sudden infant death syndrome*
Cytochrome oxidase	↓	Normal	Normal
Succinate dehydrogenase	↓↓	Normal	Normal
Glutamate dehydrogenase	↓↓	Normal	?
Short chain acyl-coenzyme A dehydrogenase	presumed ↓↓	↓ or normal	?
Medium chain acyl-coenzyme A dehydrogenase	presumed ↓↓	↓↓	?
Long chain acyl-coenzyme A dehydrogenase	presumed ↓↓	↓ or normal	?

*Excluding two cases of medium chain acyl-coenzyme A dehydrogenase deficiency.

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Changes in incidence and prognosis of ischaemic heart disease in Finland: a record linkage study of data on death certificates and hospital records for 1972 and 1981

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Abstract

The components of the decline in mortality from ischaemic heart disease in Finland were studied by analysing the changes in incidence and prognosis between 1972 and 1981. Using personal identification numbers, hospital discharge records and death certificates were linked for all men and women aged 40-64. During this period mortality decreased 15·9% in men and 23·5% in women, incidence 14·2% in men and 19·3% in women, being greatest among 40-49 year olds living in urban areas, and case fatality 7·3% in men and 10·3% in women, owing primarily to a decrease in patients dying of ischaemic heart disease without being admitted to hospital; survival was also better among patients admitted to hospital.

Factors explaining these changes remain unknown because data on risk factors and factors influencing prognosis are limited and largely ecological.

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Introduction

The epidemic of ischaemic heart disease in industrialised countries has been waning in some countries while waxing in others over the past 10-15 years.[1-7] Ischaemic heart disease mortality has been declining in Finland since 1969-70 by a yearly 2%.[8 9] This decline may be due either to factors improving the prognosis of incident cases or to a decline in incidence of the disease. Because data on changes in incidence of ischaemic heart disease world wide are few we examined data on admission to hospital for and mortality from ischaemic heart disease in Finland for 1972 and 1981 to assess relative changes in mortality, survival, and incidence.