SUXAMETHONIUM APNOEA IN AN INFANT

EXPRESSION OF FAMILIAL PSEUDOCHOLINESTERASE DEFICIENCY IN THREE GENERATIONS

BY

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The cause of apnoea in association with anaesthesia is often beset with difficulty in interpretation, for so many variable factors may be present. The effects of pre-existing disease may well modify the response of a patient to respiratory depressant drugs, while abdominal surgery is known to cause impairment of respiratory function (Anscombe, 1957). Not infrequently, the label of "scoline apnoea" is applied to the patient who is not breathing at the end of an operation, despite a normal level of plasma pseudocholinesterase. Such an apnoea may be evoked by respiratory depressant drugs in the presence of some pre-operative disability such as emphysema or kyphoscoliosis.

Bourne, Collier, and Somers (1952) and Evans, Gray, Lehmann, and Silk (1952, 1953) drew attention to the prolonged apnoea in man after suxamethonium in the presence of a low pseudocholinesterase. Whereas it had been accepted that plasma cholinesterase could be low owing to acquired deficiency of liver function, Lehmann and Ryan (1956a) observed a familial incidence of low pseudocholinesterase level in the absence of disease. The following report of prolonged apnoea in an infant after suxamethonium shows that this can occur in early infancy, and also contributes new information on the nature of the inheritance of low pseudocholinesterase level.

Case Report

A girl aged 15 months was admitted to hospital for the excision of a small symptomless lumbar meningocele. She was otherwise in good health. Her weight was 13 kg. and haemoglobin 12.3 g./100 ml. Atropine 0.6 mg. intramuscularly was given one hour pre-operatively.

Induction was carried out with cyclopropane and oxygen until the child was asleep, when 20 mg. of suxamethonium chloride was given intravenously and the cyclopropane discontinued. After being inflated with oxygen the child was intubated with a No. 1 flexometallic tube, which was connected to a T-piece and double-ended bag (500 ml. capacity). Artificial respiration with nitrous oxide and oxygen (4 litres/2 litres) was started at the rate of 30–40 a minute. The operation was performed with the child in the prone position, and when it was completed, 45 minutes later, spontaneous respiration was still absent. Discontinuance of the nitrous oxide, movement of the endotracheal tube, painful stimuli, and a few breaths of CO_2 elicited no respiratory response. Fifteen minutes later—that is, 70 minutes after induction—shallow jerky diaphragmatic movements were seen, but respiration had to be augmented for the next two hours until spontaneous respiration was considered to be adequate. Though the child was ventilated with only oxygen from the end of the operation, she did not appear to be awake, though bronchial secretions were profuse and were frequently aspirated. Her temperature was not recorded. Extubation was performed without difficulty, and subsequent recovery was uneventful.

Blood was withdrawn during the period of apnoea for serum pseudocholinesterase estimation. The level of pseudocholinesterase was measured in the serum as described by McArdle (1940). This technique measures the CO_2 liberated from a bicarbonate buffer by the products of ester-hydrolysis. The activity of the enzyme is expressed in units, one unit being equivalent to 1 μl. of CO_2 formed per minute by 1 ml. of serum at 37° C. It was found to be 24 units, which was well below normal. As there was no explanation for the low pseudocholinesterase level, such as liver disease or anaemia, the family of the child was investigated for evidence of familial low pseudocholinesterase level. The findings are recorded in the Diagram.

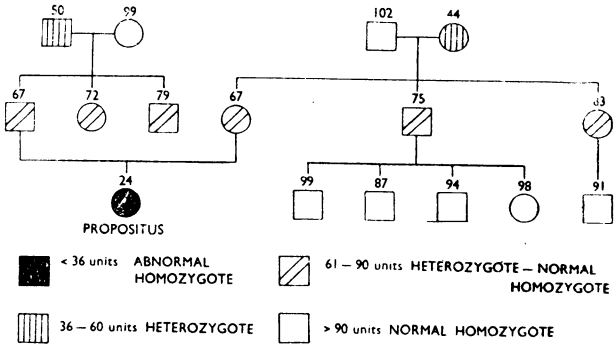

Diagram showing the family tree and the individual pseudocholinesterase levels in units. It is suggested that in the range 61–90 units heterozygotes as well as normal homozygotes can be found.

Discussion

The absence of central respiratory depressant drugs, apart from a few breaths of cyclopropane for induction, suggested the diagnosis of abnormal response to suxamethonium; the low plasma cholinesterase was subsequently confirmed in the laboratory. It is tempting to speculate on the possibility of a further action of suxamethonium besides that of depolarization at the end-plate, for from animal experiments Harmel, King, and Kao (1958) have demonstrated a central effect. Treatment of the apnoea consisted of ventilation until spontaneous respiration became adequate. Drugs were not considered for fear of clouding the diagnosis and possibly even further delaying the return of respiration.

In order for the child to be homozygous for the gene causing a low pseudocholinesterase level, both parents would have to be heterozygotes. McArdle (1940), in a series of normal individuals, found the range of pseudocholinesterase units to be from 55 to 121. From ten years' experience at St. Bartholomew's Hospital, it is considered that a value below 65 units is not truly normal; though, for the purpose of testing the liver function, a result is not reported as significantly abnormal unless it is below 55 units. The parents (67 units) would fall within the lower level of normal individuals, even by the former assessment. However, both parents themselves have one parent in whom the pseudocholinesterase level is definitely abnormally low. Following Allott and Thompson (1956) (see also Lehmann and Ryan, 1956b) Lehmann, Patston, and Ryan (1958) have suggested that there is a considerable overlap of the enzyme levels of heterozygotes and of

normal homozygotes within the range of 61–90 units. Seventeen people with a pseudo-cholinesterase level below 36 units were selected as the propositi of family studies. All of them had come to attention because of suxamethonium apnoea unassociated with a disease which might cause a low pseudo-cholinesterase level. These results can now be further extended by taking into account the present family and eight others examined since, making a total of 26 (Table I).

TABLE I.—*Relatives of Patients Presenting with Suxamethonium Apnoea Unassociated with Diseases Causing a Low Pseudocholinesterase Level*

People with Plasma Pseudocholinesterase <36 Units	Relatives		Plasma Pseudocholinesterase (Warburg Units)			
	Group	No.	<36	36–60	61–90	>90
26	Parents and children	52	3	22	27	0
17	Siblings	31	11	6	11	3
10	Spouses	10	0	0	5	5

If it is presumed that the propositi are homozygous, their first-degree relations—parents and children—should be heterozygotes. It is clear from Table I that none of 52 first-degree relatives of the 23 propositi had a pseudocholinesterase level above 90 units. Thus it can be considered fairly safe to rule out the heterozygous state for the abnormal gene when a level above 90 units is found. On the other hand, more than half of the 52 first-degree relations assumed to be heterozygotes showed a pseudocholinesterase level within the lower range of normality—from 61 to 90 units. Thus, within this range an overlap occurs between normal homozygotes and heterozygous carriers. The present family tree shows this particularly well. The enzyme levels of both parents of the propositus are found within this "normal" range—61 to 90 units. Yet each of these two, in turn, has one parent with a clearly abnormally low level of 50 and 44 units, respectively. Together they have a child with an enzyme level of 24 units.

There is, obviously, also an overlap at the lower range of the enzyme levels, and values below 36 units seem to include both abnormal homozygotes and heterozygous carriers. Three individuals in the parents-and-children group (Table I) showed values of less than 36 units (26, 28, and 35 units, respectively), and two of these were children of a propositus and a spouse with a pseudocholinesterase level above 0 units. Thus, in at least two of these it seems possible to rule out the homozygous state. Not enough data have yet been accumulated, but it may well be that the values below 36 units will have to be subdivided into those below 26 units, designating definite abnormal homozygotes, and those from 26 to 35 units, designating both abnormal homozygotes and heterozygotes. Kalow and Staron (1957) have demonstrated that an abnormal enzyme can be the cause of idiopathic familial low pseudocholinesterase level. Investigations are in progress, in collaboration with Dr. H. Harris and Dr. Mary Whittaker, London Hospital Medical College, to examine the correlation between the findings of the Canadian workers and those of this country. Possibly these studies will throw light on the subdivision of phenotypes proposed in Table II.

TABLE II.—*Abnormal Gene Causing Low Pseudocholinesterase Level*

Pseudocholinesterase	Abnormal Homozygotes	Heterozygotes	Normal Homozygotes
<26 units	+		
26–35 ,,	+	+	
36–60 ,,		+	
61–90 ,,		+	+
>90 ,,			+

Summary

Suxamethonium apnoea is described in a child aged 15 months. This is believed to be the first such recorded observation in an infant. The family has been studied in detail. There was a deficiency of pseudocholinesterase in one paternal and in one maternal grandparent, yet only low normal values for pseudocholinesterase were found in both parents. The overlap of enzyme levels found for presumed heterozygotes for the abnormal pseudocholinesterase gene and for normal individuals is discussed.

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EOSINOPHILIA IN CHILDREN WITH ASTHMA AND BRONCHIECTASIS

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It is well known that asthmatic attacks are often associated with an eosinophilia in the circulating blood and that the bronchial secretions also may contain an excess of eosinophils (Stickney and Heck, 1944; Urbach and Gottlieb, 1946). Blood eosinophilia is regarded as typical of allergic reactions in general, and can be produced experimentally by injections of protein material (Biggart, 1932) or histamine (Vaughn, 1953). It is suggested that the eosinophils are concerned in the transport of histamine which is produced in allergic reactions (Code, 1952; Vaughn, 1953).

The present paper provides evidence that eosinophilia in asthmatic children is not confined to the times of the asthmatic attacks and in general is unrelated to the degree of ventilatory impairment. In addition, eosinophil counts on a group of children with asthma and a group with bronchiectasis are compared in order to evaluate their usefulness in differentiating these conditions.

Methods

Eosinophil counts were performed on 83 children (40 with bronchiectasis and 43 with asthma). These were

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