CASE REPORTS

Possible Atypical Silent Heterozygotes with Extremely Low Esterase Activity

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The presence of atypical plasma cholinesterase has long been recognized as a cause of prolonged apnea after succinylcholine administration. Following the original description of atypical or dibucaine resistant cholinesterase by Kalow and Genest,[1] a fluoride resistant type was reported by Harris and Whittaker [2] (1961) and a silent type by Liddell *et al.*[3] The genes for these abnormal cholinesterases are suggested to be allelic, autosomal, nondominant and nonrecessive, although their modes of transmission are still under investigation. In addition, C_5 variant type was identified by Harris *et al.* in 1963. This report concerns a case of prolonged apnea following succinylcholine in which the propositus exhibited unusually low atypical plasma cholinesterase activity which may have contributed to the severity of the apnea.

In the following presentation, E_1^u will designate the gene for the usual type of plasma chlorinesterase, E_1^a, the gene for the atypical plasma cholinesterase, and E_1^s, the "silent" gene.

CASE REPORT

An 81 year old well-developed, well-nourished and moderately obese white woman underwent skin graft for ulcers due to peripheral vascular disease on both legs. This was her first hospital admission. She had not been seriously ill until the present illness, except for osteoarthritis. She was given premedication of 50 mg. of meperidine and 0.4 mg. of atropine. Induction was accomplished with 80 mg. of 0.4 per cent thiopental by drip, followed by 40 mg. of succinylcholine and the trachea was intubated. Anesthesia was maintained with 50 per cent nitrous oxide–oxygen, with one dose of 20 mg. of meperidine intravenously. One half hour after the induction, it was realized that the patient had not resumed respiration. Operation was started one hour after induction without evoking any respiratory response. Attempts were made to induce respiration by stimulating the trachea and by allowing carbon dioxide to accumulate, but without success. These procedures were repeated several times during the operation. Manual control of ventilation was easily maintained. Preoperative blood pressure, 120/70, and pulse rate, 76, were relatively unchanged throughout the operation. Two hours after induction, 250 mg. of nikethamide was given, which briefly increased her pulse rate to 110 without respiratory effect. Ten minutes later 10 mg. of edrophonium was administered without effect. Nitrous oxide was then discontinued. The operation was completed three hours after induction at which time the patient was totally flaccid. The pupils were mid-dilated equally, fixed centrally and the light and corneal reflexes were absent. One hour later, the pupils reacted to light for the first time transiently and sluggishly; the corneal reflex remained absent. The patient was transferred to the recovery room and placed on a respirator. Her condition remained unchanged except for sporadic fasciculations and barely visible twitchings in both arms. Vital signs were stable throughout this period. Ninety and one half hours after induction the patient appeared to respond slightly to pain stimuli. Ninety minutes later the patient was able to move a hand slightly and very slowly on repeated commands. After a further ninety minutes she attempted to move her hand voluntarily to her mouth in an unsuccessful attempt to remove the endotracheal tube.

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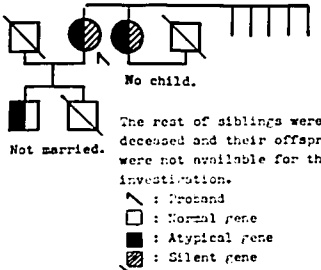

FIGURE 1

After another hour, the patient attempted to remove the tube more intently this time. This was thirteen and one half hours after induction. The following morning, eighteen and one half hours after induction, the patient was conscious and triggering the respirator. After thirty minutes of observation without respirator, the trachea was extubated. The patient stated that she did not remember anything following induction except that she could recall trying to remove the "thing" in her mouth and that she could not move her hand well because she felt "very weak." On the second postoperative day a blood specimen was drawn for the investigation of plasma cholinesterase. The method of collection and preparation of the specimen are described elsewhere.[4]

RESULTS OF CHOLINESTERASE DETERMINATIONS

On the first test the proband's esterase activity was reported as nil and it was assumed that she was a silent homozygote. However, since her son's cholinesterase was consistent with that of atypical normal heterozygote, the proband was reinvestigated ten days later. At the same time liver function tests were done and reported within normal limits. The proband's only surviving sister, quite healthy at the time, was also investigated. The results are shown in table 1 and the genealogy of the family is shown in figure 1.

COMMENT

Since the number of siblings and their offspring available for the investigation was limited, the genotype of the sisters could not be definitely established. However, from the data shown above, it was assumed we were dealing with a case of atypical silent heterozygote, although another possibility exists in that this could be an atypical homozygote. A peculiar feature of the patient and her sister is that their esterase activities were extremely low compared with previously published and genetically determined atypical silent heterozygotes. Since the patient was quite healthy until the time of admission, well-nourished at the time of operation, with normal liver function, and since the patient's sister had never been hospitalized or seriously ill and was in good health at the time of investigation, it may well be assumed that these low values were inherent to the sisters.

It is difficult to explain these findings on the current theory of the allelic autosomal genes. The existence of a gene which produces plasma cholinesterase with a dibucaine number characteristic of the atypical gene but with extremely low esterase activity may be postulated. But this is unlikely, because if it were so, the dibucaine number of the proband's son would be expected to be higher. Simpson and Kalow[5] have discussed the nonallelic theory of inheritance of the "silent" gene. Assumption was made that s(suppressor) gene and S(nonsuppressor) gene exist on some other locus and that one s gene is not sufficient to suppress two genes. They concluded that suppression is selective because otherwise, a double heterozygote ($E_1^aE_1^aSs$) would be expected to have a dibucaine number of the atypical normal heterozygote with low esterase activity. These authors also feel that suppression of the allele E_1^a is unlikely as this ex-

TABLE 1

	Hydrolysis Rate* of		D.N.†	Genotype
	Acetylcholine	Benzoylcholine		
Proband	0(1.2)	2.0	24	$E_1^aE_1^a$ or $E_1^aE_1^a$
Proband's sister	3.2	13.8	23	$E_1^aE_1^a$ or $E_1^aE_1^a$
Proband's son	55	34.9	47	$E_1^aE_1^a$
Normal male	270	80	70+	$E_1^aE_1^a$
Normal female	250	75	70+	$E_1^aE_1^a$

* μmols of substrate hydrolysed per ml. plasma/hour.
† Dibucaine number.

planation predicts too high a frequency of individuals with no esterase activity. The suppression of the allele E_1^a is again not likely, since no segregation of E_1^a has been observed from seven offspring of one critical mating ($E_1^uE_1^aSs \times E_1^uE_1^uSS$).[6] However, they suggested further study of the offspring of matings ($E_1^uE_1^aSs \times E_1^uE_1^uSS$) as a critical test of the last hypothesis. A quarter of the offspring would be $E_1^uE_1^aSS$ ($E_1^uE_1^a$ by allelic theory). Although it is not possible to draw any definitive conclusion from the data obtained, we believed that the case in question might be explained on the basis of the last hypothesis: the existence of s(suppressor) gene which is abnormally active. It is also possible that this may be due to environmental factors as could be inferred from Simpson and Kalow's study on the esterase activities in the families and twins they studied.[7]

The use of edrophonium in this case was inappropriate. Respiration and post-tetanic facilitation should have been demonstrated before the administration of any anticholinesterase. However, Vickers [8] has reported a case in which neuromuscular block worsened following neostigmine administration in spite of the demonstration of post-tetanic facilitation. Caution should be exercised in the use of anticholinesterase.

Summary

A case of prolonged apnea following 40 mg. of succinylcholine was reported. The duration of apnea was nine and one half hours. Investigation of the family showed the patient to be a possible atypical silent heterozygote with extremely low esterase activity, for which an explanation was postulated.

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