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Ohkawa, Jiro
Oimomi, Munetada
Baba, Shigeaki

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FAMILIAL HYPERCHOLINESTERASEMIA

JIRO OHKAWA*, MUNETADA OIMOMI
AND SHIGEAKI BABA

*Department of Pathology
Hyogo Medical Center for Adults
Kitaouji-cho, Akashi 673, Japan

The Second Department of Internal Medicine
Kobe University School of Medicine

INDEXING WORDS

hypercholinesterasemia; serum cholinesterase; familial hypercholinesterasemia; cholinesterase isoenzyme

SYNOPSIS

A case of familial hypercholinesterasemia was presented. Cholinesterase isoenzyme study revealed the extra C_5 band nearer to the cathode than C_4 on the gradient polyacrylamide gel electrophoresis in 6 out of 8 subjects in the family. No significant difference in the effect of inhibitors and activator on serum cholinesterase activity of the family with hypercholinesterasemia was found compared to that of the normal control.

It was considered to be clinically useful for differential diagnosis of patients with elevated serum cholinesterase to find subjects with familial hypercholinesterasemia.

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INTRODUCTION

Serum cholinesterase (E.C.3.1.1.8) activity is decreased by various disorders and lowered activity of serum cholinesterase is a good indicator of depressed protein synthesis by the liver and indicates poor prognosis for the patient. High serum levels of cholinesterase, on the other hand, are seen in diabetes mellitus, fatty liver syndrome, and hyperthyroidism.

In our clinic, we have seen unexplainable elevated serum cholinesterase levels. In this report, we describe the polymorphic variants of this enzyme in his family. We used the test of polymorphism described by Harris et al.,[2] in which an additional C_5 band was seen upon enzyme electrophoresis.

MATERIALS AND METHODS

1) Assay of the activity of cholinesterase

Total serum activity of cholinesterase was determined with 5,5'-dithio-bis-(2-nitrobenzoic acid) method with substrate, acetylthiocholine[4] using a Hitachi 736/40 (Tokyo, Japan) chemistry autoanalyzer. Clinical reference value for serum cholinesterase activity was between 1844 and 4878 IU/L.

2) Inhibitors[1]

Dibucain, fluoride and sodium chloride (NaCl) as well as the activator; butanol, were purchased from the Wako Pure Chemical Co. (Osaka, Japan).

3) Isoenzyme study

Electrophoresis was performed overnight with a 4 to 15% gradient polyacrylamide gel which was home made.

After electrophoretic run the cholinesterase was stained by the cupper method using butylthiocholine as a substrate.[3] The released thiocholine was coupled with a cupper reagent forming a white precipitating line in the gel corresponding to the enzyme activity. Incubation time for the enzyme reaction was 30 minutes at room temprature.

4) Case report

The propositus, the patient is a 59-year-old man who came to the clinic asking that his liver be checked, because he had been told several years before that he had elevated levels of serum cholinesterase. He had no complaints otherwise and appeared healthy. He had a history of pleuritis when he was 14.

On physical examination the liver was palpable 1 finger width at the right midclavicular line. No other abnormality was present. His pertinent findings of blood chemistry included; aspartate aminotransferase 21 IU/L, alanine aminotransferase 21 IU/L, gamma glutamyl transferase 45 IU/L, total bilirubin 0.6 mg/dl, alkaline phosphate 90 IU/L, total cholesterol 259 mg/dl, triglyceride 200 mg/dl, total protein 6.7 g/dl, albumin 4.2 g/dl and cholinesterase was 16080 IU/L. Abdominal ultrasonic examination showed no sign of fatty liver.

RESULTS

1) Family study (Fig. 1 and Fig. 2)

Cholinesterase activity of the propositus was about 3 times the upper normal limit. Cholinesterase isoenzyme study showed an extra C_5 band cathodic to the C_4 band.

Two out of his three brothers and 2 of his sisters tested positive for the extra band and both of his sons also showed the C_5 band.

The total activity of their cholinesterase ranged from 3578 to 16082 IU/L. The members affected with an extra C_5 band did not necessarily have an elevated total activity level. The density of the C_5 band appeared to be propotional to the total acitivity.

The propositus, his brothers and sisters and his two sons were screened as negative for fatty liver by employing an ultrasonic abdominal examination.

2) Effect of inhibitors and activator (Table 1)

The effect of inhibitors was studied with dibucaine, fluride and NaCl and that of activator with butanol. No significant difference was observed when compared with the normal control.

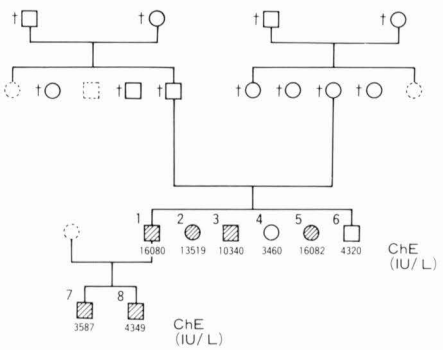

Fig. 1 The pedigree of the patient with hypercholinesterasemia.
Stripes indicate subjects with a C_5 band.
Dots represent subjects not yet examined.
Superscript numbers are that person's designation in this report, while subscript numbers are that person's total enzyme activity.
Superscript No.1 represents the propositus.

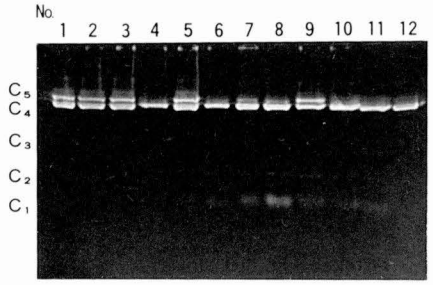

Fig. 2 Zymograms of serum cholinesterase on 4-15% gradient polyacrylamide gel electrophoresis. Substrate is butylthiocholine.
No.1 to No.8: Case No.1 to No.8 of this family are presented.
No.9: Another known case of hypercholinesterase with C_5 band.
No.10 to No.12 are normal subjects.

DISCUSSION

1) The family study of the propositus showed the extra band in 6 out of 8 subjects examined; 4 of the propositus's brothers and sisters out of 6 siblings were affected and two of his sons also tested positive for the C_5 band although their enzyme activity was

Table 1 Effect of inhibitors and activator on serum cholinesterase of the family with hypercholinesterasemia. Dibucain No., fluride No. and NaCl No. were calculated as follows;

$$\frac{\text{total activity of enzyme} - \text{enzyme activity with inhibitor}}{\text{total activity of enzyme}} \times 100$$

Butanol No. was calculated as follows;

$$\frac{\text{enzyme activity with butanol}}{\text{total activity of enzyme}} \times 100$$

Cases	Total Activity	C_5+	Dibucain No.(%)	Fluoride No.(%)	NaCl No.(%)	BuOH No.(%)
Control	1844−4878	−	55	20	4	112
1	16080	C_5+	54	22	4	112
2	13519	C_5+	56	25	4	112
3	10340	−	55	20	4	148
4	3460	C_5+	55	21	2	112
5	16082	−	60	25	4	112
6	4320	C_5+	55	22	3	111
7	3587	C_5+	56	21	4	112
8	4349	C_5+	56	22	4	111

within the normal limit, which suggested that the inheritance pattern of the C_5 band is autosomal dominant.

The enzyme activity of the subjects with the C_5 band varied widely, ranging from markedly elevated to within normal limit. The density of the extra C_5 band appeared to be in proportion to the total enzyme activity. The subjects with the less dense C_5 band as well as those with acitivity within the normal limits could be heterozygotes. Then X-linked dominant inheritance could be ruled out.

2) Effects of inhibitors and activator

No difference in the effects of the inhibitors and activator was observed between the healthy, normal control and the subjects with the extra C_5 band. It was suggested that the catalytic properties of the extra C_5 band appeared to be the same as that of

the normal control and increased activity was caused by the increased enzyme protein; the additional C_5 band.

3) Frequency of C_5+ phenotype in normal population

Frequency of C_5+ phenotype was 1.2% in our healthy normal population,[6] which is much less than that of 10% reported by Harris et al.[2] in the English population measured using the starch gel electrophoresis method. The frequency of C_5 band cholinesterase of our normal population was also less than that of Canadian Indians or Eskimos which ranged from 7 to 13%.[5,7] The great difference in incidence between our population and their populations seems to be racial because our electrophoretic separation with acrylamide gel is more sensitive than the starch gel that Harris et al.[2] used.

The clinical significance of the additional C_5 band is that they occur frequently in patients with hypercholinesterasemia of unknown origin.

In the differential diagnosis of fatty liver an elevated cholinesterase often shows abnormal chemistry. When we are able to exclude a familial innocent hypercholinesterasemia due to a C_5 band, the diagnosis of fatty liver would be more precise.

The pathological elevation of cholinesterase should be differentiated from innocent genetic variants with hypercholinesterasemia caused by an additional C_5 isoenzyme band.

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