Case Report

Familiar Hypercholinesterasemia. A Case Report

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A 58-year-old female who had a serum cholinesterase activity four times higher than normal is described. Investigation of her family revealed that five out of seven tested had high level of serum cholinesterase activity. The family distribution of the increased cholinesterase suggests that the inheritance is transmitted in a autosomal dominant manner. Analysis of the isoenzyme of serum cholinesterase of five cases including the patient showed that none of them had extracomponent (C5) of the cholinesterase. Examination of anti-cholinesterase antibodies in her serum was negative. Molecular weight of her serum cholinesterase by HPLC analysis was not different from that of a healthy subject. It was speculated that the overproduction of usual components (C1, C2, C3, C4), decreased clearance of cholinesterase by a certain mechanism(s), and/or the presence of cholinesterase which has more active catalysis could be responsible for her and her family's hypercholinesterasemia.

Key Words: Hypercholinesterasemia, Family studies, Isoenzyme, HPLC, Immune precipitation

Increased serum cholinesterase activity without any detectable disorders such as fatty liver, hyperthyroidism, and diabetes mellitus is very rare¹⁾. Karlow and his colleagues²⁾ noted one individual with the enzymic activity 2.5 times higher than the average in a study of 1556 healthy subjects. The subject, like our case, had no evidence of any diseases and had a normal dibucaine number. Their study, however, has not mentioned of family studies. Harris et al³⁾, on their extensive studies of distinct phenotypes of cholinesterase in Tristan da Cunha islanders, have shown several cases with familial hypercholinesterasemia. Neitlich⁴⁾ has found in his study of 1029 military personnel between the age of 17 and 35, only a case (26-year-old male) who had cholinesterase activity 2.5 times higher than normal. As far as Karlow's and Neitlich's reports are concerned, the prevalence of elevated cholinesterase activity 2.5 times more than the mean in normal individuals is approximately 2 per 2600. In this communication

a case of hypercholinesterasemia found incidentally by laboratory tests is described. Examination of her family disclosed that the disorder is a familial which transmitted in a autosomal dominant manner. The inheritance, characteristics and significance of hypercholinesterasemia on this patient and her family are reported.

CASE REPORT

A 58-year-old Japanese house wife visited the Department of Neurosurgery of Takayama Red Cross Hospital for the treatment of left hemi-facial spasm which she had been suffering from for two years. She had no remarkable past history and never received blood transfusion and continuous drug ingestion. She had never been pointed out to have liver disease, diabetes mellitus and hyperthyroidism. Family history was not contributory except for her mother died of apoplexy at age 49 had hypertension. She was admitted to the Department of Neurosurgery of our hospital

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and was pointed out to have extremely high level of serum cholinesterase incidentally and was referred to our department for the evaluation of hypercholinesterasemia.

On physical examination, she appeared healthy except for left hemi-facial spasm. Her height was 152 cm and weighted 52 kg. Her temperature was 36°C and pulse rate was 72 per min. and was regular. Her blood pressure was 144/90 mmHg. Palpebral conjunctiva was slightly anemic. Although she did not have any signs of hypothyroidism or hyperthyroidism, she had a small struma. Chest X-p as well as auscultation of the lung did not show remarkable findings. Her heart sound was normal. Achilles and knee reflexes were both normal.

Laboratory data on admission were as follows: Urinalysis was normal. On hematological examination, she had slightly decreased levels of RBC ($363 \times 10^4/\text{mm}^3$), WBC count ($3900/\text{mm}^3$) and hemoglobin concentration (11.9 g/dl). On blood chemistries, electrolytes, total protein, albumin and lipids were all in normal range. Liver function tests (total protein, alubumin, GOT, GPT, LDH, ALP-ase) were normal except for thymol turbidity test (TTT) (TTT; 11.3U, normal range 0–5U) and zinc turbidity test (ZTT) (ZTT; 16.4U, normal range 4–10U) being slightly higher than normal range. Indocianine green test (ICG) showed normal blood retention ratio (R_{15}) of the dye. HBs-antigen was negative but anti-HBs antibodies were positive. Erythrocyte sedimentation rate was 61 mm per hour. On immunological data, rheumatoid factor measured by hemagglutination technique was positive. LE test was negative. Serum immunoglobulin levels were almost normal. Titers of anti-microsomal (Microsome test, Fuji

Zoki, Tokyo) and anti-thyroglobulin (Thyroid test, Fuji Zoki, Tokyo) antibodies were 1: 160² and 1:20², respectively. On endocrinological data, thyroid function tests (T3, T4, TSH) were normal. An oral 75 g glucose tolerance test (75 g-O-GTT) revealed that she has normal glucose tolerance with normal secretion of immunoreactive insulin (IRI, Insulin-RIA kit, Dainabott, Tokyo). Serum cholinesterase measured by using butyrylthiocholine as a substrate and Weber Ellman's method using acetylthiocholine as a substrate were 4.85 ΔpH (normal range; 0.60–1.20 ΔpH) and 21640 IU/1 (normal range; 4240–6560 IU/1), respectively. In contrast to the extremely high level of serum cholinesterase, the activity of red blood cell cholinesterase (Cholinesterase color test, Boehringer Japan, Tokyo) was 1381 IU/1, which was lower than normal range (4242–6560 IU/1). Both dibucain number and fluoride number were 85% and 70%, respectively, and were almost in normal levels.

Fig. 1 and Table 1 show a family tree and liver function tests of the patient and her relatives, respectively. Examination of serum cholinesterase in her family disclosed that five out of seven showed high levels of serum cholinesterase ac-

Fig. 1. Family tree of the patient.

Table 1. Serum cholinesterase levels and liver functions among relatives of the patient (2, 3, 4, 5, 6) who showed hypercholinesterasemia. Number of cases are the same to those in Fig. 1.

Name	Sex	Age	Ch-E (ΔpH)	GOT (U)	GPT (U)	ALP (K.A.U.)	$\gamma\text{-GTP}$ (mU/ml)
1.	F	58	4.85	15	8	6.9	4
2.	F	46	3.95	21	10	7.3	6
3.	F	35	3.09	12	12	4.4	6
4.	M	33	1.65	39	76	5.4	20
5.	M	28	3.81	14	8	5.7	4
6.	M	24	3.27	18	12	9.4	7

tivity. Concerning liver function tests among relatives who showed hypercholinesterasemia, all of them including the patient had normal levels of GOT, GPT, ALP and γ -GTP except for a case (Case T.M.) who had high level of GPT. Analysis of the isoenzyme of serum cholinesterase of five cases who had high cholinesterase level was performed by electrophoresis of polyacrylamide gel gradient (2–10%) according to the method described by Margolis and Kenrick⁶. Each 200 μ l of serum was applied to the gel followed by electrophoresis for 90 min. Staining of the gel was done according to the method described

Fig. 2. Electrophoretic pattern of serum cholinesterase isoenzyme of the patient, her relatives and a healthy control. $\square$; Male, $\circ$; Female, Numbers of cases are the same to those in Fig. 1.

Fig. 3. HPLC (TSK 3000sw column) analysis of the cholinesterase in the patient (upper panel) and a healthy subject (lower panel). IgM; immunoglobulin M; IgG; immunoglobulin G, HSA; human serum albumin, Mb; Myoglobin, T₄; thyroxine.

by Koelle and Friedenwald⁷). Briefly, butyrylthiocholine as a substrate was hydrolyzed to thiocholine by serum cholinesterase which interacted with copper ion in the reaction mixture to form copper thiocholine, and the copper thiocholine was stained with dithiooxamide. Fig. 2 shows the results of electrophoresis. None of the patient and her four relatives with hypercholinesterasemia examined had extracomponent of cholinesterase (C5).

In order to examine the presence of cholinesterase linked immunoglobulins, each of 25 μ l of patient's serum was incubated with either 200 or 100 μ l of chain specific rabbit anti-human antisera (anti-human IgG, IgM, IgA, IgD, IgE) and of rabbit preimmune serum, followed by centrifugation at 3000 rpm for 30 min, and cholinesterase activity of the supernatant was determined. None of the chain specific antisera absorbed her serum cholinesterase. Thus the possibility of the presence of anti-cholinesterase antibodies in her serum was neglected.

High performance liquid chromatography (HPLC) of her serum was performed so that to examine the possibility that serum cholinesterase in her serum might be an abnormal cholinesterase in respect to its molecular weight. As shown in Fig. 3, elution profile of TSK 3000 sw column disclosed that the molecular weight of patient's cholinesterase which was eluted between IgM (M.W.; 900,000) and IgG (M.W.; 150,000), was not different from that of a healthy subject.

DISCUSSION

The presence of hypercholinesterasemia in five out of seven members of our propositus's family supports the concept that this elevation of cholinesterase activity is familial and not acquired. The family distribution of the increased cholinesterase suggests that the inheritance is autosomal dominant manner.

Unlike the case of macroamylasemia due to immune complex of amylase with anti-amylase antibodies⁵) in which activity of serum amylase is high due to decreased clearance of amylase, result of immune precipitation using chain-specific rabbit antihuman antisera in our case was negative for the presence of anticholinesterase antibodies.

Although we have not determined the exact M.W. of cholinesterase of the patient, elution profile of cholinesterase by HPLC is comparable to the reported value of M.W. of cholinesterase being 348,000⁸⁾. In addition, unlike the cases reported by Harris et al³⁾ and Neitlich⁴⁾, whose hypercholinesterase were attributed to the presence of extracomponent (C5) of cholinesterase, we were unable to find not only C5 component but also any abnormal isozyme in our case and her relatives. These results indicate that hypercholinesterasemia in her and her family could be attributed to the over-production of usual components (C1, C2, C3, C4) which is controlled by genes at the E2 locus⁹⁾ or N locus⁸⁾, decreased clearance of cholinesterase by a certain unknown mechanism(s), and/or the presence of cholinesterase which has more active catalysis. Since the propositus and her relatives so far examined did not have extra components slower than C4 (C5–C10) components, it is unlikely that activation of N^R gene (epigenetic factor)⁸⁾ is responsible for their hypercholinesterasemia.

In summary, a family of hypercholinesterasemia which transmitted in a autosomal dominant manner is described. Examination of the propositus's serum was negative for the presence of antibodies against cholinesterase and the molecular weight of cholinesterase was not different from

that of a healthy subject. In addition we were unable to find extracomponent of cholinesterase in her and her family's sera.

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