Case Report

A Case of Hereditary Elliptocytosis Associated with Constitutional Indocyanine Green Excretory Defect

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A 24-year-old woman was diagnosed as having hereditary elliptocytosis and post-transfusion hepatitis. On admission, a marked delay in indocyanine green (ICG) plasma clearance was noted while bromosulphalein excretion was almost normal. Even when her levels of serum bilirubin and transaminases were decreased to the normal ranges and a liver biopsy revealed no evidence of any liver cirrhosis or active hepatitis, ICG excretion still remained abnormal. These findings were compatible to those of constitutional ICG excretory defect.

Key Words: Elliptocytosis, Constitutional indocyanine green excretory defect

Hereditary elliptocytosis is an uncommon disorder and the incidence is from 0.03% to 0.05% in white race. In Japan, the incidence is approximately 0.05% and about fifty families have been listed in Japanese literatures. This disorder is inherited as an autosomal dominant trait. Interestingly, it is known that hereditary elliptocytosis is associated with some other genetically inherited anomalies such as γ-thalassemia, hemoglobin Lepore Boston, hemoglobin C, hemoglobin E, high level of hemoglobin F, hemoglobin S, hemorrhagic teleangiectasia, divergent strabismus, bone deformities, and microspherocytosis.

Constitutional indocyanine green (ICG) excretory defect is also considered as a congenital disorder. It has been reported to occur more commonly among Japanese than among other races. The distinctive feature of this disorder is a marked delay in ICG plasma clearance, while a bromosulphalein (BSP) test is normal and the histology of the liver shows no evidence of liver disease. Several Japanese families with this disorder have been reported and the pattern of inheritance is considered to be an autosomal recessive trait.

In this paper, a case of elliptocytosis associated with constitutional ICG excretory defect is presented and her family and relative members were examined to investigate the relationship between the two disorders.

CASE

A 24-year-old house wife was admitted to the Oita Prefectural Hospital in April, 1979 because of malaise and elevation of serum transaminase levels. She was well until two months before admission, when she delivered a daughter. At that time she was found to be severely anemic and was transfused with six units of packed red
blood cells.

On admission, her bulbar conjunctivae were not icteric. There was neither struma nor lymphadenopathy. Examination of the lung and heart revealed no particular abnormalities. The abdomen was normal except that the edge of liver with smooth surface extended 1 cm below the right costal margin. There was no rash, hemangioma, or petechiae on skin. Neurological examinations showed no abnormalities.

Her blood counts were; Hb 14.1 g/dl, PCV 41.5, RBC $4.75 \times 10^{12}/l$, reticulocytes $219 \times 10^9/l$, and WBC $5.0 \times 10^9/l$ with 57% neutrophils, 49% lymphocytes, and 4% monocytes. Marked elliptocytosis was noted on the blood smear (Fig. 1). The eccentricity ratios of red blood cells were calculated by the method described in detail in Materials and Methods. The result was as follows; group I 9.0%, group II 6.8%, group III 25.8%, and group IV 58.4%. The blood type was A and CCDee. An osmotic fragility test was normal. A bone marrow aspiration revealed normal cellularity with M/E ratio of 2.3. There was no evidence of erythroid hyperplasia. The erythroblasts in the bone marrow were round and were not elliptocytic.

The prothrombin time and partial thromboplastin time were normal. The serum total bilirubin 3.3 mg/dl, conjugated bilirubin 2.2 mg/dl, serum GOT 516 U, serum GPT 420 U, LDH 669 U, alkaline-phosphatase 333 U, and γ-GTP 113 U. These values were above the normal ranges. The followings were within normal ranges; LAP 40 U, cholinesterase 0.79 ΔpH, total cholesterol 186 mg/dl, creatinine 1.0 mg/dl, glucose 98 mg/dl, total protein 7.6 g/dl (the albumin 5.0 g/dl and the globulin 2.6 g/dl), and blood urea nitrogen 10 mg/dl. The serum hepatitis B surface antigen and antibody were negative.

The retention rate of ICG 15 min after dye injection (R_{15ICG}) was 94%, while that of BSP 45 min after dye injection (R_{45BSP}) was 12%. The plasma disappearance curve of ICG showed a step formation between 15 and 25 min after the injection and was different from that of BSP (Fig. 2).

The patient was diagnosed as having post-transfusion hepatitis and she was treated by bed rest. Two months after admission, her serum bilirubin and transaminases subsided to normal levels, while elliptocytosis still remained. At that time a liver biopsy and a ICG test were performed. The liver biopsy revealed that the liver was white and its...
surface was smooth. Histological examination of the liver showed slight infiltration of inflammatory cells around the Glisson's sheaths, which was compatible to the findings of convalescent hepatitis (Fig. 3). There was no evidence of liver cirrhosis. The R_{15}ICG value was still elevated as high as that on admission.

**MATERIALS AND METHODS**

**Family study**

The pedigree is shown in Fig. 4. A consanguineous marriage was demonstrated between the patient's grandmother on mother's side and her grandfather on father's side. Thus, the patient's parents were cousin each other. Ten out of twelve living family and relative members were examined for elliptocytosis and constitutional ICG excretory defect.

**Elliptocytosis**

Wright-Giemsa stained blood smear was examined for elliptocytosis by the method of Günther. Red blood cells were classified into the four groups by their eccentricity ratios calculated by the Formula as follows:

\[ e^2 = 1 - \left( \frac{\text{short diameter}}{\text{long diameter}} \right)^2 \]

In the group I, e is from 0 to 0.47; group II, 0.47 to 0.62; group III, 0.62 to 0.74; group IV, 0.74 to 1.0. The diagnosis of elliptocytosis was made when the total percentage of groups III and IV is more than 25% based on the examination of 500 red blood cells.

**RESULTS**

The blood smears obtained from 10 family and relative members including the patient on three generations were examined. Total percentages of groups III and IV ranged from 7.4% to 89.2%. Five out of the 10 members showed elliptic deformation of more than 73% of red blood cells (Table 1). As to the relationship between elliptocytosis and Rh types, 4 of the 5 members with elliptocytosis had CC phenotype and the remaining one had Cc phenotype.

The values of R_{15}ICG of the 9 members are shown in Table 1. Six out of the 9 members showed R_{15}ICG of more than 78% and one of the remaining 3 showed a moderately elevated value of 31.5%, whereas the remaining two showed values within normal limits.

The patient's parents were also examined on BSP test. They showed normal R_{45}BSP values. Therefore, they were strongly suspected to be associated with constitutional ICG excretory defect. Other data involving liver functions are shown in Table 1 and they were found to be normal or almost normal. No relationship between the values of R_{15}ICG and the Rh types was ob-
Taketzu et al

TABLE

<table>
<thead>
<tr>
<th>Case</th>
<th>Elliptocytes</th>
<th>R15ICG</th>
<th>R45BSP</th>
<th>sGOT/sGPT</th>
<th>Total bilirubin</th>
<th>Hb</th>
<th>RBC</th>
<th>PCV</th>
<th>Reticuloocytes</th>
<th>ABO</th>
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<tr>
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<td>15.8</td>
<td>4.95</td>
<td>44.7</td>
<td>0.6</td>
<td>O</td>
<td>CcDee</td>
<td>CDe/cDe</td>
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<td>14.0</td>
<td>4.63</td>
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<td>ND</td>
<td>ND</td>
<td>CcDee</td>
<td>CDe/cDe</td>
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</tbody>
</table>

* Case numbers are compatible with those in Fig. 4. The patient reported here is represented as IV-2.
** ND, not determined.

Four of the 10 family and relative members studied had both elliptocytosis and high values of R15ICG, whereas no significant correlation between the values of R15ICG and percentages of elliptic deformation was observed.

The patterns of genetic behavior were compatible with those reported before. Namely, the elliptocytosis was inherited as an autosomal dominant trait and the constitutional ICG excretory defect as an autosomal recessive trait. No evidence of genetic linkage between the both disorders was shown.

**DISCUSSION**

Hereditary elliptocytosis has been reported in association with several other hereditary disorders, but not yet with constitutional ICG excretory defect. Several disorders such as liver cirrhosis, chronic active hepatitis and Roter syndrome are known to show a delay in ICG plasma clearance. The case reported here showed the discrepancy between plasma disappearance of ICG and BSP, while laboratory findings as well as liver biopsy study excluded the possible existence of liver diseases. Thus, the patient was diagnosed as having elliptocytosis and constitutional ICG excretory defect.

The gene for “nonhemolytic” elliptocytosis has been proven to be linked with the Rh blood type. In this study, the Rh genotype of CDe which would be derived from anyone of the patient's parental grandparents, may be linked to a elliptocytosis gene.

As to the genetic linkage between elliptocytosis and constitutional ICG excretory defect, 3 of the 10 members examined had both disorders, while no association between the two disorders was shown. The genes for hereditary elliptocytosis and for constitutional ICG excretory defect were thought to be inherited independently.

**REFERENCES**


