Hereditary Ovalocytosis in Melanesians

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A distinctive type of hereditary ovalocytosis has been found in Papua New Guinea and a few areas of Southeast Asia. Its main features include a high incidence among tropical lowland dwellers, autosomal recessive inheritance, specific depression of a number of red cell antigens, a characteristic morphology in blood films, and an effect on the erythrocyte sedimentation rate.

Speculation has occurred as to whether the high incidence of ovalocytosis in malarious areas may be related to a selective advantage possessed by ovalocytics with regard to severe malaria. Preliminary data tend to support this hypothesis, but the evidence is not conclusive and much further work is needed.

PRELIMINARY NOTE ON NOMENCLATURE

The terms ‘ovalocytosis’ and ‘elliptocytosis’ have long been used interchangeably for the sporadic type of hereditary elliptocytosis which is inherited in an autosomal dominant manner and which has been known for over 70 years. Since the condition which is the subject of this review, although also hereditary, differs in several important ways from the sporadic type, we shall not use the terms interchangeably. Rather, ‘ovalocytosis’ will refer to the high-frequency type discussed in detail below, and ‘elliptocytosis’ will denote the sporadic type.

INTRODUCTION

A distinctive type of hereditary ovalocytosis is common among Papua New Guineans of coastal and insular origin. In this article, we review the salient features of this condition: its incidence, geographic distribution, inheritance, appearance in blood films, clinical significance, serological findings, and the question of whether the abnormality confers a selective advantage; in addition, the chief differences between this type of ovalocytosis and the sporadic type of hereditary elliptocytosis will be summarized.

INCIDENCE

The first mention of a high frequency of ovalocytosis in this part of the world was made almost 40 years ago in a Dutch language journal by Bonne and Sandground (1939); the phenomenon was mentioned incidentally in an article on echinostomiasis in Celebes. To our knowledge, the first systematic study of high-frequency ovalocytosis was reported by Lie-Injo in 1965; this article mentions a frequency of 12.3% among 440 healthy and hospitalized aboriginal Malayans.

Other studies have revealed high incidences of ovalocytosis among several populations: 6.6 to 20.9% in several groups of Malayan aborigines (Lie-Injo, Fix, Bolton and Gilman, 1972); 12.7% among the land Dayaks and 9.0% among the sea Dayaks of Sarawak (Ganesan, Lie-Injo and Ong, 1975); and 1.7% among the Batak and 7.2% among the Minangkabau in North Sumatra (Sembiring, Siregar and Kosasih, 1975).

Although the condition has been known for some years in Papua New Guinea (P.N.G.), its first mention in the literature did not occur until 1975 (Isbister, Amato and Woodfield, 1975). In that same year, a study of 1,020 blood films of in-patients and out-patients at the Port Moresby General Hospital (P.M.G.H.) found ovalocytosis in 11.2%; analysis of smaller numbers of films from Pari and Hisiu villages in the Central Province showed frequencies of 22.4% and 16.8%, respectively (Amato, 1975).

Its incidence among 334 Waskia Kar Kar Islanders (Madang Province) was 13.8% (Booth, Serjeantson, Woodfield and Amato, 1977); and that among 583 residents of Kikori, Malalaua and Kerema in the Gulf

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Province was 12.9% (Amato, 1976). It is also seen frequently at Wewak Hospital in the East Sepik Province, and at the Angau Memorial Hospital in the Morobe Province (Spark, R., and Crane, G.G., personal communications).

Thus its incidence among coastal populations in P.N.G. appears to be between 5 and 20 per cent, i.e., of a similar order to the frequencies reported from the Malaysian and Indonesian populations mentioned above. This is several hundred times more frequent than the sporadic type of elliptocytosis, the incidence of which is about 0.02 - 0.05 per cent (Cooper and Jandl, 1972).

GEOGRAPHIC DISTRIBUTION

In the P.M.G.H. study (Amato, 1975), of 97 patients with ovalocytosis whose home province was ascertained, 96 came from 10 coastal or island provinces. The one highlander was from the Tari Sub-province of the Southern Highlands Province. Serological studies (see below) provide further evidence for a coastal distribution of the trait, with the exception of parts of the Southern Highlands (Booth, 1972; Booth and Homabrook, 1972b). Moreover, there is evidence, from other genetic markers, of coastal affinities of some Southern Highlands populations, especially those from the Lake Kutubu area (Booth and Homabrook, 1972a). To date, ovalocytosis and/or antigenic depression has not been found in any person from the other highland provinces (Booth, 1972; Booth and Homabrook, 1972b; Bashir, H., personal communication; Amato, D., unpublished observations).

There is little doubt, then, that the type of ovalocytosis under discussion is found only among groups originally of coastal or island (i.e., lowland) origin.

INHERITANCE

It has long been known that the sporadic type of elliptocytosis is inherited as an autosomal dominant (Cooper and Jandl, 1972).

In contrast, data from Kar Kar Island (Booth et al., 1977) are consistent with an autosomal recessive inheritance for the high frequency type of ovalocytosis seen in P.N.G.

It has been stated (Lie-Injo, L.E., personal communication) or implied (Baer, Lie-Injo, Welch and Lewis, 1976) that the ovalocytosis found in Malaysia and Indonesia is autosomal dominant; however, the type of rigorous statistical study of families necessary to distinguish a dominant from a high-frequency recessive character has not yet been reported from those populations.

It is clear from family studies in P.N.G. (Booth et al., 1977) that individuals heterozygous for ovalocytosis usually display normal red cell morphology. There is evidence (Serjeantson, S., personal communication) that occasionally the red cells of an obligate heterozygote assume the oval shape after storage for a few days in EDTA.

MORPHOLOGY

The high-frequency type of ovalocytosis is readily recognized on a well prepared thin blood film. Under low power (100 x), examination of the thicker area of the film reveals that the red cells are ‘piled together’; i.e., they do not form rouleaux as seen in the thick areas of non-ovalocytic films.

At higher power (400 x), in the thin part of the film the great majority of cells are seen to be oval in shape, some of them only mildly so (Figure 1). A few oval macrocytes are usually present, as are a small number of elongated cells with blunt or squared-off ends (‘bacillary’ forms). Stomatocytes (red cells with a slit-shaped central pallor) and knizocytes (cells with a double pallor separated by a well haemoglobinized narrow area) are commonly seen; their numbers range from few to many.

The autosomal dominant type of elliptocytosis is occasionally seen in P.N.G. (Pryor and Pitney, 1967; Crane, G.G., personal communication; Amato, D., unpublished observations). In the families studied with this type, the morphology has been different from the high-frequency type: the red cells of the former have a greater length-to-width ratio, i.e., they are more cigar-shaped. In addition, rouleaux can be seen in the thick part of the film; and stomatocytes, knizocytes and oval macrocytes do not form part of the picture.
Occasionally, a film is seen with a smaller proportion of oval cells (i.e., < 50%), and these may show some of the characteristics of the high-frequency type mentioned above. Whilst it is possible that the gene for ovalocytosis may show variable penetrance, it is our opinion that such films should not be classified as ovalocytic, especially since there are many other conditions which can be associated with small numbers of oval or elliptical cells.

The presence of a few oval macrocytes raised the question of megaloblastosis. However, among 26 patients with ovalocytosis who underwent marrow aspiration in a 2½ year period, only 4 had definite megaloblastic changes. This proportion did not differ significantly from that seen in non-ovalocytics (chi-square = 0.07, p < 0.75) (Amato, D., unpublished observations).

The megaloblastic ovalocytics did not show greater numbers of macrocytes in the peripheral film than those ovalocytics without megaloblastosis. However, other changes were seen in the former which can be associated with megaloblastosis: hypersegmented neutrophils in all 4, Howell-Jolly bodies in 3, basophilic stippling in 1, leucopenia in 1 and thrombocytopenia in 1.

**CLINICAL SIGNIFICANCE**

It has long been known that sporadic hereditary elliptocytosis may be associated with haemolysis. While the majority of cases show no evidence of haemolysis, a minority (10-15%) have a compensated haemolytic state; i.e., there is a mild degree of haemolysis, but this does not exceed the erythropoietic capacity of the marrow and thus there is no anaemia. In an even smaller minority, there is overt haemolytic anaemia which is usually improved or corrected by splenectomy (Cooper and Jandl, 1972).

In contrast, high-frequency ovalocytosis does not appear to be associated with haemolysis. In the survey of P.M.G.H. patients (Amato, 1975), the frequency distribution of haemoglobin concentrations was essentially similar when comparing ovalocytic and non-ovalocytic patients of either sex; the modal range of haemoglobin was the same (9.1 - 11.0 g/ dl) in all four groups.

Thus, while patients with ovalocytosis may certainly be anaemic, they are anaemic for the same reasons that other Papua New Guineans may be anaemic, e.g., iron deficiency, infection, folate deficiency, malaria, beta-thalassaemia minor, tropical splenomegalic syndrome, etc. Even when there is evidence of haemolysis, causes other than ovalocytosis can be found.
We have yet to see a patient with the high-frequency type of ovalocytosis who is haemolyzing on the basis of the red cell membrane defect. A similar situation appears to obtain for the high-frequency ovalocytosis seen in Malaysia and Indonesia (Lie-Injo et al., 1972).

The main significance of this type of ovalocytosis for the clinician would appear to be its effect on the erythrocyte sedimentation rate (ESR). The ESR depends on a number of factors, one of the most important being the degree to which the red cells form rouleaux in the sedimentation tube (Dacie and Lewis, 1975). This property is in turn enhanced by several factors, such as high levels of serum globulins, especially fibrinogen (an acute phase reactant) and gamma-globulins, and an increased ratio of plasma to red cells (anaemia).

Yet patients with the high-frequency type of ovalocytosis usually do not develop an increased ESR in association with many conditions where such an increase would be expected. Thus we have seen 3 ovalocytic patients with acute rheumatic fever, 2 with multiple myeloma, and numerous others with acute infections and/or anaemia, in whom the ESR was within normal limits. This phenomenon is most likely due to the inability of these ovalocytes to form rouleaux.

Thus, if a patient has a normal ESR in a situation where one would have expected an elevated rate, the blood film should be checked. If it is typically ovalocytic, then the ESR is of no value in diagnosing or following the patient’s illness.

SEROLOGICAL CORRELATIONS

In 1966, Booth, Jenkins and Marsh reported that a cold-acting auto-antibody commonly encountered in Papua New Guinean sera, recognized a ‘new’ blood group antigen, related to Li and designated I'. It was soon apparent that selective depression of I' occurred in some 15% of coastal Melanesians (Booth, 1972), and this was shown by family studies to be inherited as an autosomal recessive characteristic (Booth and Hornabrook, 1972b).

Unfortunately, during the early work, other antibodies selected to show that the I' weakness was not artefactual (anti-H, -N, -P, and -I') were not among those directed at antigens subsequently shown to be of the depressed series, and so the more widespread nature of the antigenic depression remained unrecognized until in 1974 investigations in Christchurch, New Zealand, of warm type autoimmune haemolytic anaemia antibodies of anti-LW specificity, demonstrated that LW was depressed on I' weak cells. Further investigations have shown that the depressed series of antigens include I', I', LW, D, C, e, S, s, U, Kp, Jk, Xg, Wr, Sc, En, and D\(\text{b}\), which are simultaneously affected when present. Reactivity of H, A, B, I', I, P, M, N, Lu, k, Fy, Co, Vel, Ge and Jr appeared to be within the normal range (Booth, 1975).

It was eventually realized that the work on ovalocytosis, and that on antigenic depression, represented complementary investigations of the same hereditary condition. A series of 235 bloods previously screened for antigenic weakness was examined, blind, for ovalocytosis, and the statistical test for association of antigenic status and red cell morphology gave chi-square > 179.0, thus removing all doubt about the correlation.

The antigens of the depressed series include those against which haemolytic auto-antibodies act, which suggests that another common factor affecting these antigens may be a propensity to undergo changes resulting in the body failing to recognize them as part of itself, and treating them as foreign antigens.

The antigenic status of the Indonesian and Malaysian ovalocytic bloods is not yet known, but when ascertained should immediately either confirm or rebut the hypothesis that these arise from the same hereditary condition as exits in P.N.G.

The I' strength of cells of individuals from 6 different families with (sporadic) elliptocytosis, both haemolytic and non-haemolytic, has been found to be normal (Booth et al., 1977; Woodfield, D.G., Ama-pto, D., unpublished data), thus providing a further distinguishing feature between the two conditions.
THE MALARIAL HYPOTHESIS

Geographical location rather than ethnic or linguistic group appears to determine the occurrence of ovalocytosis/antigenic depression in P.N.G. Also, the incidence of the condition is notably constant from population to population, which is in contrast to the very variable distribution of blood group alleles in the same populations. These considerations suggested (Booth, 1975; Amato and Andrews, 1975) that some selective mechanism might apply, though as the incidence of ovalocytosis seemed not to exceed 20%, it might be that the condition conferred advantage at some period of life, and disadvantage at another, supposing that equilibrium gene frequencies for the hereditary condition have been attained in coastal regions and that ovalocytosis is not neutral in effect. If ovalocytics were advantaged during childhood and disadvantaged in utero or in adulthood, a balanced polymorphism could result.

The congruent distribution of ovalocytosis and malaria in P.N.G. has prompted some preliminary investigations, which have provided results tantalizingly suggestive, but not, in general, statistically significant of an increased resistance to malaria in ovalocytic children. The main difficulty arises from the relative paucity of ovalocytic compared to normal subjects in any random series, and, of course, this is compounded by the need to sub-divide the subjects into those with and without malarial parasites present.

The data of Serjeantson, Bryson, Amato, and Babona (1977), on children aged 2-14 years from Kar Kar Island and Gogol Valley, show that the likelihood of infection in ovalocytic children is about 75% that in normocytic children for Plasmodium falciparum, P. vivax and for all species combined. Of 397 children examined, 52 were ovalocytic, and of these only 15 had demonstrable parasites. These workers emphasize the very large sample size needed to demonstrate significant differences in parasitaemia rates between normocytic and ovalocytic.

In an attempt to overcome this problem, Babona and Amato (1976) studied 255 children aged 6 months to 5 years presenting at Madang Hospital with fever (>38°C). In this way, it was hoped to secure a greater proportion of malarious subjects. However, a possible disadvantage emerged, as only 14 ovalocytic (5.5%) were found in the series, while among 84 afebrile children (controls) the rate was 8.3%. Even so, 119 of 241 normocytic children had malarial parasitaemia, compared with 3 of the 14 ovalocytic, which is a significantly lower rate (p<0.05). When the analysis was restricted to those with falciparum malaria, there was a lower, but non-significant rate of parasitaemia among the ovalocytics.

Baer et al. (1976) have reported resistance to higher grades of malarial parasitaemia among ovalocytic Temuan people in Malaysia (two-thirds of malaria seen in the region is due to P. falciparum). They also found a higher frequency of ovalocytosis among adults than among children, which would be expected if ovalocytosis possessed a selective advantage. However, Serjeantson et al. (1977) found no significant difference in the incidence of ovalocytosis between adults and children in P.N.G.

It is noteworthy that the protection afforded by the sickle-cell trait (Hb S trait) against malaria is most obvious when the deficiency of sicklers among children dying of malaria is treated statistically (Motulsky, 1964). Whether an analogous study would prove feasible in regard to ovalocytosis and malaria in P.N.G. is doubtful.

Clearly, an apparently relatively minor change in red cell membrane composition can profoundly affect susceptibility to malaria. In the absence of the Duffy blood group antigens (Fy⁺ and Fy⁻), as occurs in 80-90% of West Africans, P. vivax cannot gain entry to the erythrocytes (Miller, Mason, Clyde, and McGinniss, 1976), presumably because in this situation the receptor normally activated by this parasite is also absent. Fy (a-b-) cells have normal morphology and survival.

If ovalocytosis confers any resistance to malaria, then the mechanism for this protection seems likely to occur after entry into the red cells by the parasites, as ovalocytic subjects can be seen with para-
parasitaemia, and more specifically, parasites can be seen in oval cells.

**COMPARISON OF ‘ELLIPTOCYTOSIS’ AND ‘OVALOCYTOSIS’**

The main features which help to differentiate these two conditions are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elliptocytosis</th>
<th>Ovalocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence on world scale</td>
<td>Worldwide</td>
<td>Apparently limited to parts of Southeast Asia and Melanesia</td>
</tr>
<tr>
<td>Geographic restriction</td>
<td>None</td>
<td>Lowland tropical areas; congruent with regions of malarial endemcity</td>
</tr>
<tr>
<td>Incidence</td>
<td>0.02 - 6.65%</td>
<td>2 - 70%</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Morphology of red cells</td>
<td>Mainly elongated oval</td>
<td>Mainly oval (often with stomatocytes, knizocytes, oval macrocytes, and ‘bacillary’ shapes); lack of rouleaux formation.</td>
</tr>
<tr>
<td>Haemolysis on basis of red cell defect</td>
<td>Occurs in minority of cases</td>
<td>Probably does not occur</td>
</tr>
<tr>
<td>Effect on ESR</td>
<td>Probably none</td>
<td>Expected rise of ESR in inflammatory and other states not seen</td>
</tr>
<tr>
<td>Selective antigenic depression</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

**NATURE OF THE MEMBRANE DEFECT**

Very little is known about the nature of the red cell membrane defect(s) in either of these two abnormalities. No consistent differences between patients with the haemolytic and non-haemolytic forms of hereditary elliptocytosis have been found.

It is probable that the defect in ovalocytosis associated with antigenic depression involves the portions of the membrane where the depressed antigens are normally expressed. One might assume either that the antigens subject to depression all depend, for their full expression, upon the same membrane component(s), or alternatively that the membrane anomaly in some way physically obscures the antigenic sites. The series of depressed determinants would thus be associated by structure and/or spatial orientation on the red cell membrane.

**ADDENDUM**

Professor Sir John Dacie has recently brought to our attention an article (Honig, G.R., Lacson, P.S., and Maurer, H.S. [1971] A new familial disorder with abnormal erythrocyte morphology and increased permeability of the erythrocytes to sodium and potassium. *Pediatric Research* 5:159), in which the authors describe ovalocytosis without anaemia or evidence of haemolysis in several members of a Filipino family. From their description and photomicrographs, it appears that the condition is identical with the one seen in P.N.G. The significance of the report with respect to this type of ovalocytosis is twofold:

1. Several in vitro abnormalities (without apparent clinical significance) are identified in this condition, including decreased osmotic fragility, increased autohaemolysis after 48 hr incubation, increased glucose consumption by red cells, and decreased intracellular potassium;

2. The disorder is documented in yet another country of the Southeast Asia-Melanesia region (though we are not aware of any reports bearing on its incidence in the Philippines).
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REFERENCES


