BLOOD GROUPS AND DISEASES

SYNOPSIS

The literature on the association of blood groups, abnormal haemoglobins, serum proteins and red cell enzymes in some common diseases is critically reviewed. The scope of the article has been limited only to the studies of diseases in which the author has been actively involved. An attempt is made to examine the significance of some of the associations observed as for example i) Pulmonary tuberculosis and ABO-Lewis a blood groups; ii) Diabetes mellitus and red cell G6PD deficiency; iii) Lack of association of blood groups with coronary heart disease and risk factors; iv) Malaria and haemoglobin E; v) Interrelationship of haemoglobin, haptoglobin, transferrin, red cell G6PD and acid phosphatase phenotypes.

N Saha

Department of Physiology
National University of Singapore
Kent Ridge
Singapore 0511

N Saha, BSc, MBBS, MD, PhD (Med)
Association Professor

This is a review of the work carried out by the author and his colleagues.
It is now generally believed that susceptibility of most of the diseases in man is influenced by genetic characteristics of man. The evolutionary significance of diseases in man has been suggested by Haldane (1, 2). Even prior to that, immediately after the discovery of ABO blood groups by Landsteiner, the geneticists were looking for the significance of the occurrence of different blood groups by studying the association of certain blood groups in diseases.

The present paper focuses on studies on the association of blood groups with some of the common diseases in man. The progress in the area had been phenomenal, but in most of the studies only the ABO blood groups were used as a marker. There has been very limited work done on the association of other blood groups such as Rhesus (D), MN and HLA types. The literature available on the subject had been reviewed in a book form by Mourant and colleagues (3). It is beyond the scope of the present paper to deal with the hundreds of papers published on the topic. I would therefore like to restrict the discussion pertaining to our own studies, and bringing in others work occasionally, only in the studies of diseases, in which we had been actively involved.

1. Pulmonary Tuberculosis

The results of twin studies in pulmonary tuberculosis are suggestive of a strong genetic factor involved in the aetiology of the disease (4). Studies on the association of blood groups in pulmonary tuberculosis date back to 1926 when Hilber and Hirzfeld (5) first reported their negative finding on the association of ABO blood groups in the disease. Since then conflicting reports have appeared in the literature published on work in different population groups. We have observed a significant association of the B-antigen in pulmonary tuberculosis with a higher incidence of B and AB-antigen persons (P<0.005) in the Chinese in Singapore (6, 7). Since then the same association has been reported in diverse groups of populations: Indians (8); Japanese (9); Eskimos (10). In spite of the other conflicting reports published, there seems to be a presence of a true association of ABO blood groups in pulmonary tuberculosis. The study of genetic association is complicated by the selection of a proper healthy control. Singapore had the unique advantage of being served by only one Blood Bank for the whole country at the time of investigation. The Japanese study was based on a sample of 21,365 patients in the whole nation whose blood groups were known. This association fits well with the antigenicity of tubercle bacillus having B-like antigen (11). The observed excess of B blood group people in the pulmonary tuberculosis series may be attributed to the lack of protection in persons of groups B and AB who lack anti-B to neutralise the tubercle bacilli by reacting with antigen on the bacilli when a person is infected with the tubercle bacilli. This is similar to the hypothesis put forward by Vogel (12, 13) for small-pox and blood group A (A-like antigens of vaccinia virus). In order to further the possible mechanism of action a study on the serological status of 354 Chinese patients suffering from the disease showed a trend indicating involvement of secretor locus in the association of B-antigen in pulmonary tuberculosis. No significant association of red cell G6PD deficiency was observed in pulmonary tuberculosis (14). However an excess of abnormal haemoglobin was observed in Chinese patients, as compared to the normal control (15). The significant association of ABO blood groups in pulmonary tuberculosis should be explored further. Pulmonary tuberculosis is one of the oldest diseases of mankind, documented by the presence of bone tuberculosis in Egyptian mummies. It may have a great evolutionary significance in man.

2. Leprosy

The extensive literature on the association of ABO blood groups in leprosy has been reviewed by Vogel (13) and on the basis of 33 published papers an association of O:A has been suggested (P<0.0027). However there is wide degree of variation of the association in these series even in the same population group (Japanese). We failed to observe any deviation of the distribution ABO, Rhesus (D), abnormal haemoglobins and G6PD deficiency in lepers and the healthy control series (16). In a study in Thailand Vogel et al (17) reported the relative incidence of 0.8551 for A/O and 1.1345 for B/O in 335 leprosy patients. The similar relative risk was observed in our series of Chinese patients (16). There was also no significant different in the frequency distribution of ABO blood groups between lepromatous and non-lepromatous patients. The reported positive association of red cell G6PD deficiency in leprosy (18) may be a chance finding unless it is observed in some other populations.

3. Syphilis

No association of ABO, Rh (D) blood groups, red cell G6PD deficiency and abnormal haemoglobins was noted in 1041 patients suffering from syphilis (19). Schofield (20) also failed to detect any association of ABO and Rh (D) blood groups with syphilis. There is very limited data on the distribution of genetic markers in this common condition. More work needs to be carried out in future to look into the genetic susceptibility in the development and prognosis of venereal diseases in man.

4. Malaria

It has been postulated that the heterozygous form of haemoglobin S, and probably also haemoglobin E and G6PD deficiency offer protection against Plasmodium falciparum infection. Allison (21) demonstrated that 13 out of 15 subjects with the sickle-cell trait were resistant to the induced Plasmodium falciparum infection whereas 14 out of 15 control subjects showed no such resistance. Subsequent studies confirmed that the presence of sickle-cell trait offers protection against P. falciparum but not P. malariae. Ray, et al (22) observed that E-thalassaemia also offers protection against P. vivax infection. In general, the geographical distribution of the sickle cell gene and the red cell G6PD deficiency gene run parallel with the past incidence of malaria. However wide variations of abnormal haemoglobins and G6PD deficiency in different populations in same geographical areas cannot be adequately explained and is contrary to the hypothesis. Only when more data will be available on the population genetics of these gene markers, will it be possible to examine the mortality hypothesis adequately. The incidence of the E haemoglobin and red cell G6PD deficiency in East and South-East Asia in relation to past malarial endemcity is more conflicting. In a study of the incidence of red cell G6PD deficiency and abnormal haemoglobins among the ethnic groups of Singapore we could not evidence support the malarial hypothesis in conferring resistance in the presence of E haemoglobin or G6PD deficiency (23). Similar lack of association of these genes with malaria was observed.
5. Coronary Heart Disease

From the study of the concordance in twins it is evident that there is a strong genetic component in the development of coronary heart disease (29). The genetic component has been worked out by a computer model on the basis of the distribution of the most important risk factor (serum total cholesterol) in families by several authors. In recent years an association with ABO blood groups with higher incidence of Coronary Heart Disease, has been observed among A group persons in most of the populations studied and the literature has been reviewed by Mourant et al (3). The incidence and mortality from coronary heart disease in the Chinese of Singapore has been reported to be very low compared with that in the Indians of Singapore (1:4) and Caucasians in the west (26, 27). The multiracial population of Singapore with differential mortality of coronary heart disease provided a unique opportunity to study the genetic association in myocardial infarction. Several series of studies have been published on the association of ABO blood groups in myocardial infarction (27, 28). The average relative risk has been estimated as 1.29 for A/O and 1.19 for B/O in the ranges from .78 to 3.0 and .77 to 2.37 respectively. In a study of the incidence of ABO, Rh, Le*, Xg* blood groups, G6PD deficiency and haemoglobin types in myocardial infarction patients of Chinese, Indian and Malay origin we failed to establish genetic association with any of these markers for myocardial infarction (Saha et al., 1973; Sahai, 1974). However a marginal association of ABO blood group was observed only in Indian patients (P < 0.05). It seems that the question of association in a disease may be influenced by the ethnic composition — probably it is different in Mongoloid and Caucasoid subjects. This is also true of the association of O blood group in duodenal ulcer with lack of association in Negro patients. Serum cholesterol and triglycerides are known to be important risk factors for myocardial infarction (29, 30). In another study, a higher level of serum cholesterol ester was observed in A group persons in Indian subject (P = 0.02) which fits well with the higher incidence of myocardial infarction in A groups Indians (31, 32). The influence of blood groups in the control of serum cholesterol level is probably expressed in the post-natal period resulting from the interactions of genes and environment (33). In an extensive study to examine the genetic markers association in the regulation of serum cholesterol, we have investigated more than 5000 subjects of Caucasian, Mongoloid and African origins. The results are being processed. X-linked genes (Xg* blood group and G6PD) did not have any influence on serum cholesterol levels (34, 35). The higher incidence of myocardial infarction in Indians compared to the other reports from Singapore and India (26, 36), however it failed to elucidate further as to the reasons for these striking ethnic differences in the incidence and mortality of coronary heart disease. Though some epistatic genetic factors may be involved — it seems, environmental factors may be playing a more important role in the expression of the genetic predisposition in the causation of coronary heart disease. There was highly significant positive correlation of both serum total and esterified cholesterol levels with body weight (r = 0.78 and 0.84) and calculated body-fat content (r = 0.73 and 0.84) (31). The socio-economic status of Indians and Chinese in Singapore is very comparable excepting the differences in their traditional dietary habits. In a nutritional survey we have recorded an intake of about 30% of calories from fat in Chinese (37-40). In an earlier study in Indian medical students, similar intake of fat was recorded (41). However the sources of dietary fat in Chinese and Indians in Singapore are different — coconut oil is the main cooking medium in the former while lard in case of Chinese food. In another study of dietary intakes in Singapore populations we observed no difference of the intakes of energy, fat (saturated and unsaturated), protein and cholesterol though Chinese took significantly higher amount of nicotinic acid and thiamine (39). Customary higher intake of these two vitamins by Chinese may have some protective effect against the higher even though coronary heart disease in a population. The hypercholesterolemic effect of therapeutic doses of nicotinic acid is well-established. It appears that the appropriate environmental factors are required for the expression of genetic predisposition resulting in disease.

6. Diabetes Mellitus

The genetic association of diabetes mellitus has been studied in the past mainly by studying the rate of concordance in twins, family materials and calculating the relative incidence of blood groups and serum proteins (3). The results are rather conflicting, In a series of six hundred male Chinese patients suffering from maturity-onset diabetes mellitus we could not establish the reported association of ABO blood groups. However, a significant positive association of red cell G6PD deficiency was observed with higher relative risk of diabetes in G6PD deficient subjects. (Relative risk 2.2 in Chinese and 3.39 in Indians (P < 0.002 and 0.03 respectively). The relative risk of G6PD deficient subjects was higher even for diabetics (42, 43). The observed association of G6PD deficiency in diabetes mellitus supports the hypothesis put forward by Kessler (44) — suggesting a negative association of G6PD deficiency in cancer and a positive relationship in diabetes mellitus. Naik and Anderson (45) observed a negative association of G6PD deficiency in cancer in American Negro patients, but only in females. In our series we observed a positive correlation of G6PD deficiency in diabetes mellitus in two ethnic groups of Singapore. It will be interesting to look into the phenotypic expression of red cells G6PD in diabetes mellitus in different populations of the world as there are many populations with a high incidence of diabetes, but with a low or no red cell G6PD deficiency. The underlying significance of the association of G6PD deficiency in diabetes mellitus is not clear at the moment.

7. Vitiligo

The etiology of vitiligo is not known, however the genetic factors are probably involved. There have been many studies in the past to examine the association of ABO blood groups and the secretary status in vitiligo patients (46-51). The results are far from being definitive. We investigated the distribution of A,A,BO, MNs, Rhesus (C, D, E, c, e), Kell and Duffy blood groups; haptoglobins and transferrins; and red cell enzymes (acid phosphatase, 6-phosphogluconate dehydrogenase, phosphoglucomutase and glucose-6-phosphate dehydrogenase); and haemoglobins in a series of 170 Sudanese patients suffering from vitiligo, and compared them with those in a control series of
random subjects (52, 53) and another series of blood donors. No significant association was observed with ABO, Ss, Rhesus, Kell and Duffy blood groups in vitiligio. However, a significant association was observed for the MN system with an excess of homozygotes and of the M gene in vitiligio for homozygote excess and 6.6 for M gene excess (ξ² = 29.87, 21.91; P<0.001; 54). There was no association with the serum protein markers or red cell enzyme markers excepting glucose-6-phosphate dehydrogenase deficiency. An excess of G6PD deficiency was present in this patient group (P<0.05). However there was no association with any specific phenotype (GdA or GdB) of the enzyme (53).

8. Infertility

Differential fertility and mortality are two of the important selective factors in the maintenance of the genetic characteristics of a population. Infertility is at the lowest end of the scale of the former and is expected to exert a selective influence on a population. There have been many studies on differential fertility in relation to ABO blood groups in different population groups. The most commonly cited series with positive associations are those of Waterhouse and Hoggan (55); Allan (56); Kirk et al (57, 58); Matsunaga and Itô (59). At the same time many authors have failed to confirm this association of fertility with ABO blood groups (60-62). There have been relatively limited studies on the association of ABO blood groups in infertility (63-65) with conflicting observations. Morgan et al (66) had suggested the involvement of the secretor locus in infertility on the basis of sperm-antibody and antigenicity of uterine secretion. Cohen (67) had suggested an interaction of ABO and Rhesus genes in infertility. With the above in view we studied the distribution of ABO, LeA, Rhesus (C, C, E, c, e) blood groups, red cell G6PD deficiency and abnormal haemoglobins in a group of 308 Chinese and 70 Indian infertile women in Singapore and compared them with those in controls. There was a relative excess of blood groups A among the Chinese infertile women, which probably worked through the secretor locus (relative excess of LeA negative, ξ² = 5.12). R, R, R, gene complex of the Rhesus system was deficient in infertile groups (ξ² = 9.55). There was no significant difference in the distribution of red cell G6PD deficiency and haemoglobin types infertility (58).

9. Schizophrenia

It is one of the commonest mental illnesses which may disturb the balance in a population due to lower fertility among schizophrenics. The family studies had conclusively established the importance of genetic involvement in the disease though the extent of heritability had not yet been ascertained. The concordance rate in twins was inconclusive due to the small size of the sample (25). There has been a very limited amount of work done on the genetic association in this common disease and the scanty studies have been limited to only ABO blood groups and some serum proteins (3). We have studied the distribution of ABO (AA, A, B); Rhesus (C, C, E, c, e); LeA; MN blood groups; some serum protein (Gc, Hp, T1) and red cell enzyme markers in a group of Chinese Schizophrenics. An interesting new association with an excess of LeA+ had been observed in Schizophrenics (69). Other blood groups did not reveal any association. The results of other markers are being processed.

10. Goitre

It is generally believed that goitre is prevalent in areas of iodine deficiency. However, not everyone living in the area develops goitre. It seems that some genetic factors may be involved in the genetic predisposition for the development of goitre. There have been many studies carried out on the distribution of ABO blood groups among various population groups of the world (3) with inconclusive diverse results. However another aspect of the studies on the genetic association in goitre had been more promising — that is its association with PTC (Phenyl thiocarbamid) tasting system with lower incidence of goiter among the goitrous patients particularly in female patients (3). In a study of genetic association in endemic goitre in goitrous areas of Jabal Merah in the Sudan a similar association of PTC sensitivity has been observed while no other association was identified with the other blood genetic markers studied (Hb, Hp, G6PD, GPGD, PGM, AP, T1, etc). Further in the same study a strong genetic component in the etiology of the disease was observed by studying the relative incidence of the disease (age and sex-matched) among the offsprings of the consanguineous (sharing more similar genes) than those of non-consanguineous matings (70).

11. Interrelationships of haemoglobin, serum haptoglobin, transferrin; red cell G6PD and acid phosphatase phenotypes

These polymorphisms have been suggested to have some selective importance in having common interacting ecological backgrounds (e.g. malaria, temperature, humidity etc (71-75). The phenotypic expression of red cell acid phosphatase was examined in relation to various haemoglobin, haptoglobin and G6PD phenotypes in three populations of the Sudan and Nilgiris, India. No consistent association of red cell acid phosphatase types was observed in different haemoglobin, haptoglobin and G6PD phenotypes excepting a lack of AB phenotype of acid phosphatase in G6PD deficient subjects of Nilgiris. However the G6PD deficient subjects had a lower level of red cell acid phosphatase activity compared with those with normal G6PD activity and normal thalassaemia carriers in Sudanese patients (76).

12. G6PD Deficiency

Distribution of ABO and LeA blood groups in G6PD-deficient persons was similar to that in non-deficient subjects. There was a significant lack of the R, gene in G6PD-deficient subjects (77-79; 23).

13. Serum Uric Acid

Gout and hyperuricemia is generally a familial disorder, so one would expect some genetic control of this parameter. There have been several studies in the past to examine the influence of blood groups on serum uric levels with inconsistent results (80-81). In another study we examined the genetic association of serum uric acid using several genetic markers (ABO, Rhesus, LeA blood groups; haptoglobin, transferrin, C3 and transferrin subtypes; red cell acid phosphatase, phosphoglucomutase (PGM), esterase D, G6PD phenotypes and PGM subtypes). No association of serum uric acid was observed with any genetic marker. However a marginal association was revealed with PGM subtypes — PGM1+ phenotype tends to be associated with higher serum uric acid than the other
phenotypes (82). However a stronger influence of environmental components on serum uric acid was observed in most of our studies (83).

14. Miscellaneous
Several interrelated findings were observed in the course of the genetic association studies. Sickle cell trait was associated with hepatic dysfunction (84) and at the same time had some selective advantage in stimulation of haemoglobin (85). β-thalassaemia trait also had similar selective advantage. Red cell G6PD deficiency was associated with lowered red cell acid phosphatase (76), increased haemoglobin (85), isocemic variations (86). Total iron-binding capacity of serum is influenced by TI subtypes, haemoglobin types and G6PD deficiency (87, 88).

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