More or less living according to your blood type

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Over a period of almost a century, many have attempted to find a relationship between ABO blood group and predisposition to certain diseases (e.g., pernicious anaemia, gastric cancer, pancreatic cancer, venous thrombosis, coronary heart disease, duodenal ulcer)[1,2]. The ABO blood group system is the most important blood type system in human blood transfusion. The antigens of the ABO system (A, B, and H determinants, respectively) consist of complex carbohydrate molecules. The A and B alleles encode slightly different glycosyltransferases that add N-acetylgalactosamine and D-galactose, respectively, to a common precursor side chain, the H determinant, and convert it into A or B antigens. The O alleles do not encode a functional enzyme and consequently OO carriers, who lack the transferase enzymes, continue to express the basic, unmodified, H structure, which has a solitary terminal fucose moiety attached[3].

The ABO blood group certainly has a profound influence on haemostasis. The most well-known is the major quantitative effects that the ABO blood group exerts on plasma levels of von Willebrand Factor (vWF) and consequently of factor VIII (FVIII), since vWF acts as a specific carrier of FVIII and protects it from proteolytic degradation[2]. The ABO blood group locus on chromosome 9q34 is the most important genetic determinant of plasma levels of the vWF-FVIII complex after the *vWF* (12p12) and *F8* (Xq28) genes. Indeed, plasma vWF levels are 25-35% lower in subjects with O blood group than in individuals with non-O blood group. Several investigators have studied the clinical implications of this biological interaction, including the influence of the ABO blood group on the risk of developing bleeding or thrombotic events[2,4,5]. In brief, as compared with O group, non-O blood group is associated with a higher probability of developing venous thrombosis. Similarly, as compared with O group, non-O blood group is associated with higher incidence rates of myocardial infarction, angina pectoris and other ischaemic events.

The above-noted research has logically extended to studies on the potential association of the ABO blood group with *longevity*, in an attempt to explain differences in life span among individuals with different blood groups. Prior to the report by Mengoli and Colleagues in the past issue of Blood Transfusion[6], there have only been a few reports in English on a potential association between certain ABO phenotypes and longevity. Murray was the first to publish his findings in 1961 of increased prevalence of group A in 125 healthy elderly males (65-89 years)[7]. Eight years later, a study carried out on 50 inhabitants of eastern Turkey allegedly aged >90 years (interestingly, one individual claimed to be 155 years old) found no correlation between the ABO system and longevity; instead the authors reported a significant difference in the prevalence of P and Lewis types in the senescent group compared to 110 controls[8]. In a survey of German doctors aged >75 years, group O appeared to be associated with longer life expectancy[9]. Findings of two studies performed on centenarians were contradictory. Blood type B was observed more frequently in 269 Japanese centenarians (29.4%) than in controls (21.9%)[10]. By contrast, in the only study using molecular ABO typing, Vasto and Colleagues failed to demonstrate significant differences in the distribution of ABO groups between a group of 38 centenarians and healthy controls (age range, 45-65 years) from western Sicily[11]. Finally, following a review of 772 deaths in their hospital in the United States, Brecher and Hay concluded that B type, rather than being associated with longevity, was a marker of early death[12].

In view of the conflicting reports, Mengoli and Colleagues examined the association between ABO blood group and longevity at their hospital by conducting a retrospective review of electronic records of outpatients and blood donors[6]. They stratified the blood group of 28,129 subjects according to age and gender and found that group A was statistically more represented in the male population (43.40% *vs* 40.50%), whilst the opposite was true for group B (10.70% *vs* 13.48%). The Authors observed that the proportion of individuals with group B declined significantly with age regardless of gender. For example, 17.62% of the individuals aged between 20 and 29 years were type B compared to only 9.05% of those aged 80-89 years. Some other associations were confined only to females: the prevalence of group AB declined with age, while the prevalence of group A tended to increase

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with age. Of note, although not statistically significant, 70% of subjects aged over 99 years had type O blood.

Unfortunately, as with the studies investigating the association between the ABO system and certain diseases, the reports of an association between blood group distribution and life expectancy are inconsistent. While Shimizu and Colleagues[10] found that blood type B was associated with longevity, Mengoli and Colleagues[6] and Brecher and Hay[12] concluded that group B was inversely correlated with age. In addition, there are isolated reports of group A[7] and group O[9] being associated with longevity. Finally, neither Vasto and Colleagues[11] nor Sturgen and Colleagues[8] found any correlation between life expectancy and ABO system. There may be several explanations for these discrepancies. For example, any identified associations might be population- or location-specific. Alternatively, different conclusions might be unpredictably affected by methodological differences including potential pitfalls common to studies in this field, as outlined in detail by Manuila[1] as early as 1958. Sampling error and racial or ethnic stratification might also be responsible for divergent conclusions by different research groups. Importantly, ethnic and racial factors also account for differences in the distribution of ABO genes of up to 5-20% within a given population of the same country or even the same city. Similarly, sampling errors may account for differences of up to 4% between samples from 1,000 individuals.

Mengoli and Colleagues[6] have acknowledged the possibility of multiple confounders in their observational study. Although their sample of more than 28,000 individuals is considerable, it was comprised of two essentially disparate groups of subjects: the younger group included healthy blood donors and pregnant women while the older age group cohorts were presumably over-represented by non-pregnant and potentially "less healthy" outpatients. Thus, out of the entire study population, 74.3% were female, with an excess of individuals in the reproductive age, so that 89.65% of the subjects aged <40 years were female. In addition, males were significantly older than females (57.2 *vs* 40.8 years).

In conclusion, the investigation by Mengoli and Colleagues[6] should motivate inception of large well-designed studies with particular effort to address and minimise potential confounder effects that, in addition to small sample sizes and modest statistical significance, have hindered progress in this field of medical research. If the association between a blood group and life expectancy were to be unequivocally confirmed, it would be important to elucidate the mechanisms accounting for this interaction, in part to then potentially assess for any feasible modifications to negative impacts on longevity. However, as ABO group is currently a non-modifiable human characteristic, investigation of any association between ABO blood group and life expectancy might simply be relegated to that of a "quite interesting" rather than a "clinically practical" fact. Finally, such relationships are simply part of the rich tapestry of physiological and pathophysiological interactions, and other chapters of the story yet to unfold may concern the relationship between aging and other components such as haemostasis,[13] as well as ethnicity, thrombosis risk and longevity[14]. In short, it may take some time to unravel these mysteries.

Finally, we should highlight that Blood Transfusion has recently published several other papers that may contribute to the unfolding story[15-19]. To add further complexity to the saga, the main moderator of vWF function *in vivo* is a protease called ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin-1-like domains, member 13). Levels of plasma vWF are known to increase with age[13]. Given the association of elevated vWF levels with risk of thombosis, this may contribute to the perceived increased thrombotic risk observed with aging[13,14]. This may or may not be compounded by plasma levels of ADAMTS-13, which have not been observed to increase in parrallel with vWF[19,20], although strangely, in contrast to antigen levels, measured ADAMTS-13 activity did appear to fall in one of these studies[19]. May we have the longevity to resolve all these issues during our lifetime.

The Authors declare no conflict of interest.

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