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Relation between Incidence of Small-pox and the *OAB* System of Blood Groups

BY M. R. CHAKRAVARTTI
Indian Statistical Institute, Calcutta
AND
F. VOGEL
Institute for Anthropology and Human Genetics, Heidelberg University, Heidelberg

Introduction

Though means for the prevention of small-pox have been known since the end of the eighteenth century, the disease is still endemic in most countries in Asia and Africa. Europe, North America and Oceania are free from indigenous infections but are becoming increasingly liable to the importation of infection from persons incubating the disease or suffering from mild attacks, as has been shown by recent experience in England, Western Germany, Poland, and Sweden (WHO, 1964). In the past twelve years the reported number of cases in the world has fallen from about half a million to less than 1,00,000. These cases, however, represent only a fraction of those that occur. About 88,000 attacks and 25,000 deaths were recorded throughout the world in the first 11 months of 1963. Most of these, about 73,000 attacks and 24,000 deaths, occured in Asia, where India, as in previous years, reported the largest numbers—59,000 attacks and 18,000 deaths. In second place was Pakistan, which notified over 7,000 attacks and 5,000 deaths. The case fatality appears much higher in India than in any other place in the world. Even when allowance is made for unreliable reporting and the inclusion in some countries of cases of chicken-pox, this difference, explained by the WHO expert committee on small-pox as the difference in the variola strains, seems to be important. A series of investigation was carried out in Madras infectious diseases hospital to shed new light on a number of problems still unsolved in the epidemiology, immunology and specially of prevention and treatment of small-pox. The case mortality in Variola major after vaccination is approximately 20%, although in unvaccinated patients it may be 40-50%. By contrast, in Variola minor it is 1% after vaccination (WHO, 1964).

The Problem

The particular problem with which this paper is concerned is whether individuals belonging to different *OAB* system of blood groups do or do not differ in their susceptibility to small-pox disease. The purpose of the present survey, therefore, is to discover possible relationship between *OAB* blood groups and the incidence and intensity of small-pox. This topic is not only important for understanding the *ABO* gene frequencies in the world population but can also have practical consequences for the understanding of the epidemiology of small-pox and is thought of being an important study from the point of view of public health policy. The present study is also aimed at verifying the earlier conclusions, among others, of Vogel *et al* (1960) and to probe deeper into other aspects of the incidence and virulence of small-pox.

Earlier Works

It has been discovered by Vogal *et al* (1960) that the small-pox virus contains *A*-like antigen, so that antibodies useful against the disease may also attack the red cells of persons of group *A* and *AB*. A positive correlation exists between group *A* and small-pox which may cause some selective pressure against I^a. This was further elaborated by Vogel (1961) by proposing that small-pox selects against blood groups *A* and *AB*. As evidence they cite the predominance of group *B* over *A* in Central Asia than in the rest of the world, the alleged greater antiquity of small-pox in Asia. Pettenkoffer *et al* (1962) suggest that the cow-pox strain contained attenuated small-pox virus and refer to preliminary, unpublished observations of a significant association with groups *A* and *AB* of severe small-pox scars in India and of post-vaccination reactions in West Germany. They defend the thesis that *A*-like antigen in their experiments was viral rather than avial, but Harris *et al* (1963) have found that egg materials possess *A*-like substance while the lister strain of cow-pox does not.

Thus the unpublished epidemiological studies are the principal evidence in favour of a simple relation between *A* gene and susceptibility to small-pox.

Azevedo *et al* (1964) surveyed 6,414 persons submitted to a medical examination in which the adults were asked if they had ever had small-pox or had ever been vaccinated against small-pox. Persons responding affirmatively were asked if they retained the scars and, if so, to demonstrate them while persons answering negatively were questioned about the cause of suggestive scars were concordant. As a result, they found 1.4% cases were affected with small-pox and 22% were vaccinated. Out of 683 medically examined *O* and *B* mothers, only 15 had small-pox scars. The incidence of small-pox scars with *A* group was stated to be 1.45% while with *O* and *B* gene 1.91%. This difference is non-significant and is opposite in direction to the results obtained by Vogel (1961) and the present study.

Present Small-pox Project

At the first International Congress of Human Genetics at Copenhagen in 1956, a project was designed by the expert on the respective fields to study the association between *OAB* system of blood groups and various diseases. Since 1954, a great deal of literature has accumulated on the study of peptic ulcer, cancer, etc., but unfortunately no study was undertaken to see the relationship between variola and blood groups in India prior to this survey. A project designed to investigate the association of small-pox to *OAB* system of blood groups was undertaken in March, 1965. By courtesy of the Deputy Director General of Health Services (Public Health), West Bengal, a complete thana-wise statistics with regard to small-pox cases of Burdwan District in 1964 could be secured. In 1964, there were 749 attacks and 347 deaths in the two sub-divisions of Burdwan District, West Bengal. A pilot survey was, therefore, launched in the two sub-divisions of the district. The survey was in the form of a complete enumeration of 29 villages of Katwa and Kalna sub-divisions of Burdwan District, which experienced an epidemic of small-pox during summer of 1965. A total of 602 cases of incidence was covered by the survey. Of these 402 are those who survived a previous attack in the summer of 1964, when the epidemic was less virulent than in 1965, while the 200 were still in the incubation period at the time of survey when the current epidemic was still present. All these are non-inoculated cases.

A parallel sample of 250 inoculated persons (have had no attacks of small-pox) was also taken for purposes of comparison. These controls were selected from the very families of those who had an attack or survived an attack, and preferably of the same sex, i.e., if a brother was found to be attacked or survived, his inoculated brother who had no attack of small-pox was subjected to blood examination. A follow up study was also made of the 200 fresh attack cases and those who survived were recorded.

The incubation period has been calculated since the date of the onset of fever and not that of the onset of rash. The incubation period of Variola major has been found to be reasonably constant at 13-14 days. Occasionally, it may be as short as 9 days or as long as 21 days. In Variola minor the incubation period appears to be the same. A shorter incubation period occasionally occurs in severe cases where any other possible source of infection can be ruled out.

It is a really good public health policy to regard the incubation period to the onset of fever as 12 days, and a quarantine period of 16-18 days is a reasonable safe-guard against the spread of infection.

The 200 cases of fresh attacks had also been classified according to a 4 degree scale with regard to the virulence of attack, as suggested by Helmbold (1965). The field work was undertaken in two instalments, during the months of June-August, 1965. The design of the survey was prepared by Prof Dr B. P. Adhikari while the first author along with the assistance of Sri V. K. Verma was responsible for the field work. Sri Hanurao did the satistical analysis of the data.

The test sera as well as all the blood grouping appliances were supplied by Prof. Vogel. The schedule prepared in connection with the survey contained a number of items which were necessary from anthropological background.

Method

The method and technique employed in the field for ascertaining the *OAB* system of blood grouping was followed after Helmbold (1965). The results of the laboratory analysis, regarding the *OAB* system have been subjected to tests of consistency of laboratory technique. One technician analysed the blood samples for *OAB* classification at the rate of availability of small-pox cases. Out of these two were selected at random and given to him after coding them so that he may not know which of the samples were given in duplicate. The agreement between the duplicates afforded a check on the consistency of the technique adopted by him. Two more samples were duplicated and given to another technician so that neither of the technicians know which samples were selected for this purpose. The agreement between the two technicians regarding the grouping afforded a check on any personal biases operating. In all the cases tested, there was a full agreement so that there was no reason to suspect any misclassification save an account of impurities, if any, present in the test sera employed.

Analysis of Data

Owing to the small size of the sample for the extensive subdivisions than the standard statistical procedure required, the suggestion of Roberts (1957) has been followed using the technique that allows pooling of data. In this way combined weighted estimate of the strength of the association has been obtained. Of the two techniques suggested, we have followed that of Woolf (1955) as this can be used for combining and comparing populations with widely different blood group frequencies ; furthermore, as Roberts state, this has the advantage that the results, expressed as a relative incidence, come out in the form with a simple and direct physical meaning, it being natural to think of disease in terms of incidence.

Table 1

Showing Differential Incidence Rates

Blood Groups	Frequency Attacked	Control	Total
O	37	84	121
A	106	38	144
B	48	66	114
AB	9	12	21
Total	200	200	400

$\chi^2_3 = 44.5$ *Highly Significant*

As will be evident from Table 1, there is a differential incidence rate. The rate is highest among *A* group people.

Table 2 shows that there is differential vulnerability rate. The rate is highest among *A* group. But the differences in these rates are not as high as those for incidence rates.

Table 2

Showing Differential Vulnerability Rates Among 22 cases

Blood Groups	Frequency Survival	Death	Total	
O	22	15	37	
A	43	63	106	
B	30	18	48	} Amal-
AB	2	7	9	gamated
Total	97	103	200	

$\chi^2_2 = 6.1$ *Significant*

Table 3

Showing Differential Virulence Rates

Blood Groups	T-1 Mild	T-2 Severe	T-3 Very severe	T-4 Haemarr	Total
O	23	14	0	0	37
A	40	58	8	0	106
B	30	17	1	0	48
AB	2	5	2	0	9
Total	95	94	11	0	200

CONDENSED TABLE

Blood Groups	Virulence T-1 Mild	T-2+3 Severe	Total
O	23	14	37
A	40	66	106
B+AB	32	25	57
Total	95	105	200

$\chi^2_2 = 12.3$ *Highly Significant*

Table 3 shows that the virulence of attack is different for the different groups. *A* group people are more susceptible to more virulent attacks.

Table 4 shows that the attack rates are same for primary and secondary cases. The difference between attack rate from a member of the same household and that from a member of a different household is negligible for a closely knit clustered population as is found in the villages.

Table 4

Comparing the primary and secondary attacks

Blood Groups	Type: Primary	Type: Secondary	Total
O	35	2	37
A	95	11	106
B	42	6	48
AB	8	1	9
Total	180	20	200

CONDENSED TABLE

Blood Groups	Type: Primary	Type: Secondary	Total
A	85	9	94
Not-*A*	95	11	106
Total	180	20	200

$\chi^2_1 = 0.03$ *Not significant*

The relative incidence (R1), based upon blood group frequencies of patients and controls, has also been calculated after using Woolf's method and has been recorded as 3.09.

Discussion

For many years since the discovery of the blood groups it was generally believed that the blood group substances were of no particular significance in physiological and pathological processes. Among persons of different blood groups there must be, to a greater extent or lesser extent, differences in resistance or susceptibility to diseases or in viability. In order to understand the dynamical aspect of the selection in *ABO* polymorphism in all its complexity, further studies may be carried out on a much wider scale. The research will no doubt be of great significance to both human biology and medical science. Considering a population as a whole, the *ABO* polymorphism is undoubtedly due not only to random genetic drift but also to natural selection.

Substances serologically related to human *OAB* blood groups are found in a variety of organisms, including bacteria. This has led Mourant (1954) and Livingstone (1960), among others, to speculate that the antigens of infecting organisms are the primary factors responsible for the *ABO* polymorphism in man. Mourant's question whether the antigens of infecting organisms are the primary factors responsible for the polymorphism of *OAB* blood groups has stimulated some recent reports on the subjects.

In these reports it is claimed that the present blood group distribution in large areas of the world is most probably due to *H*(*O*) activity of the causative agent in plague and a postulated blood group *A* activity of Variola (small-pox) virus grown in chicken eggs. It has been asserted that individuals of blood group *O*(*H*) or *A* would be unable to form sufficient antibodies against the respective micro-organisms, and therefore would be more susceptible to fatal infection.

It has been rightly claimed by Pettenkoffer *et al* (1962) that people with the blood group *O* or *B* in case of small-pox infection have an immunological advantage compared to people with blood group *A*. It is found in the present survey that *A* group people are not only more susceptible to attack of smallpox, but more vulnerable to die of an attack and are more prone to have virulent attacks.

The serum of persons with the blood group *O* or *B* always contains anti-*A*. In the case of small-pox infection, the virus has to react with the antibody anti-*A* during the stage of viraemia and thus will be inhibited. It is well known that many people have the blood group substance *H* independently of their blood groups *ABO*. However, a certain percentage of persons of group *A* and *AB* do not possess the substance *H*. It is this group that is involved in the selection mechanism.

Summary

It is found that *A*-group people are not only more susceptible to attack of small-pox, but are more vulnerable to die of an attack and are more prone to have virulent attacks. There is no indication of differences between the two sexes. The highly significant values as also the differences between the various incidence rates and mortality rates, the differences among the corresponding rates for the milder and more virulent epidemics suggest that there is a positive correlation between group *A* and small-pox. A probe into possible specific allelic action is worth investigating.

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Authors' addresses : Dr M. R. Chakravartti,
Research and Training School,
Indian Statistical Institute,
203 B. T. Road, Calcutta 35, India.
Prof Dr F. Vogel,
Institute for Anthropology and Human Genetics,
University of Heidelberg, 15A Monchhofstrasse,
69 Heidelberg, Germany.