GENETICS

Abnormal Distribution of Haemoglobin Genotypes in Negro Children with Severe Bacterial Infections

SEVERE pneumococcal infections (meningitis and/or septicaemia) in children in this department have been unexpectedly frequent in cases of sickle cell anaemia (SCA). We have investigated this situation by examining the distribution of haemoglobin genotypes in a group of children with acute, generalized bacterial infections.

All records of patients hospitalized in our department from 1959 until December 31, 1966, with bacteriologically proved acute meningitis and/or septicaemia were reviewed. Salmonella infections were excluded because of their particular tendency to cause chronic osteitis in patients with sickle cell anaemia.

Altogether 265 cases were examined, of which sixty-nine had to be rejected because the haemoglobin genotype had not been determined. Haemoglobin electrophoresis was not carried out either because the young age of the patient made paper electrophoresis unreliable, or because the patient died quickly after admission, before an appropriate blood specimen had been taken. In the remaining 196 cases the haemoglobin genotype was known and the diagnosis of septicaemia and/or meningitis was substantiated by a positive bacteriological culture from the blood, from the cerebrospinal fluid or from both.

Haemoglobin genotype was determined routinely by paper electrophoresis with a *tris*-barbiturate buffer. After November 1964 agar gel electrophoresis with citrate–citric acid buffer was used in the case of children less than 6 months old. The last method gives clear-cut results, even in the newborn. Bacteriological diagnosis was made according to standard cultural and immunological techniques. The distribution of haemoglobin genotypes in the patients was compared with the expected distribution by standard statistical methods.

The distribution of haemoglobin genotypes was similar in patients with septicaemia and in patients with meningitis, so the two types of infections were connected. The causative organisms fell into five groups: pneumococci (forty-five cases), coliforms (fifty-seven cases), staphylococci (thirty-three cases), *Haemophilus influenzae* (twenty-five cases) and a miscellaneous group (thirty-six cases) including *Neisseria meningitis*, streptococci, proteus group, pseudomonas group, clostridia, and *Flavobacterium meningosepticum*. The distribution of the haemoglobin genotypes for the five bacterial groups is shown in Table 1.

Table 1. DISTRIBUTION OF HAEMOGLOBIN GENOTYPES

Bacterial groups	*AA*	*AS*	*SS*	Total
Pneumococci	18 (40·0%)	4 (8·9%)	23 (51·1%)	45 (100%)
Coliforms	40 (70·2%)	8 (14·0%)	9 (15·8%)	57 (100%)
Staphylococci	20 (60·6%)	7 (21·2%)	6 (18·2%)	33 (100%)
H. influenzae	19 (76·0%)	3 (12·0%)	3 (12·0%)	25 (100%)
Miscellaneous	28 (77·8%)	4 (11·1%)	4 (11·1%)	36 (100%)
Total	125 (63·7%)	26 (13·3%)	45 (23·0%)	196 (100%)

Haemoglobin S is the only abnormal haemoglobin known to be present in a significant frequency in the Bantu population of Kinshasa (formerly Leopoldville). The incidence of the sickle cell trait (SCT) in 488 adult women living in Kinshasa has been found to be 26·6 per cent (unpublished work of Vandepitte, Van Baelen, Cornu and Eeckels); the local incidence of sickle cell anaemia in a group of 1,000 newborn babies was 20 per thousand. The figures agree well with each other: assuming an equal frequency of sickle cell trait of 26·6 per cent in adult males and females, it can easily be calculated that the frequency of the genotypes *AA*, *AS* and *SS* in a newborn population has to be 75·1 per cent, 23·2 per cent and 1·7 per cent, respectively. This distribution can be considered to modify itself during childhood to reach in adults the figures 73·4 per cent, 26·6 per cent and 0 per cent.

The average age of our 196 cases of severe bacterial infection was 26 months. At that age the exact distribution of the three haemoglobin genotypes is unknown. For the purpose of this communication, it will be assumed that it is still the same as at birth, namely, 75·1 per cent *AA*, 23·2 per cent *AS* and 1·7 per cent *SS*. Compared with this expectation, the observed distribution is markedly abnormal for each bacterial group taken separately as well as for the whole 196 cases. The observed frequencies for the genotype *SS* are constantly greater than expected, whereas the observed frequencies for *AS* are constantly lower, except in the case of the staphylococci group. This abnormal distribution is most pronounced in the pneumococci group.

Using the Kolmogorov-Smirnov test[1], the distribution observed in the pneumococci group can be shown to differ significantly from the expected distribution ($P < 0{\cdot}01$). The same is true for the total of all groups ($P < 0{\cdot}01$). There is, however, some doubt as to the homogeneity of this total group; the distribution observed in the case of pneumococci differs significantly from the distribution observed in the total of other bacterial groups ($P < 0{\cdot}01$). After eliminating the pneumococci group from the total, the distribution of haemoglobin genotype in the 151 remaining cases can be shown to differ from the expected distribution in a way which is probably significant ($0{\cdot}01 < P < 0{\cdot}05$). Finally, it must be noted that when only the *AA* and *AS* cases are considered, the differences between the observed and expected frequencies of both genotypes are not statistically significant, neither in the pneumococci group nor in the total of the remaining cases.

In forty-five cases of pneumococcal septicaemia and meningitis, the proportion of patients with sickle cell anaemia was found to be significantly greater than expected. The only explanation which presents itself is an abnormally high sensitivity of children with sickle cell anaemia to pneumococcal infections. A markedly increased incidence of meningitis, mostly caused by pneumococci, has been described[2] in patients with sickle cell anaemia. In 151 other cases of acute bacterial meningitis or septicaemia caused by various germs (excluding pneumococci), the proportion of cases of sickle cell anaemia is also greater than expected; the difference is probably significant. Although apparently to a lesser degree, as with pneumococci, cases of sickle cell anaemia might also present an increased sensitivity to other bacteria.

In all bacterial groups observed, except staphylococci, the proportion of sickle cell trait is unexpectedly small. Although the difference between observed and expected frequencies is not statistically significant, the possibility that sickle cell trait is linked with a lowered sensitivity to bacterial infections must be considered.

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