Microcephaly is one of the most severe congenital anomalies found in man. Its main characteristics are the strikingly small skull, "Aztec-type" physiognomy, extreme idiocy, undersized body and some neuropathic symptoms. These characteristics are common to cases found in both Caucasian and Mongolian races. In both occidental and oriental countries these idiots are spoken of in a popular way somehow in connection with its apparent similarity to apes. The etiology of microcephaly has long been subject of great interest and intense discussion among neurologists and psychiatrists. It has been established that X-ray irradiation during the early stage of pregnancy may induce microcephaly (Zappert 1926, Goldstein and Murphy 1929, Goldstein 1929, Murphy 1947). Recently, Plummer (1952) reports seven microcephalics among children in Hiroshima due to atomic bombing in their early stage of intra-uterine life. Other causes are also suspected, though none of them is convincing, except probably for maternal rubella (Murphy 1947).

On the other hand, it has been believed that many microcephalics have a genetic cause, and they have been studied from this viewpoint. Most of these studies, however, are based on a few pedigrees and cases, and there remains a great deal to be elucidated. The present authors, by their conjoined efforts, have been able to accumulate 119 cases belonging to 61 sibships from among Japanese population. This figure includes some cases examined by other Japanese investigators.

The Gene for Microcephaly

More than half (63/119) of these cases are children of first-cousin marriages. Microcephalics who are the progeny of consanguineous marriages of other degrees are also common. Besides, there are some kindreds which contain several cases in different sibships. These facts favor the view of the genetic origin of the majority of the cases of microcephaly. Since the parents of this kind of idiots are normal persons almost without exception, a recessive gene should be postulated. Apert-Bernstein's apriori method was used to test this postulate, first
on all the sibships collected by us. It has been found that the observed number is 119, while the expected number is 105.689. The difference 13.311 slightly surpasses twice the standard error 6.60, suggesting the presence of some other cause than the recessive gene. Halperin (1944) has obtained a similar result, in his examination by the same method of the pedigrees collected from literature which are mostly European.

Eight sibships in our collection contain more abnormals than could be expected on the postulate of a recessive gene with probability lower than 0.05. This suggests that some other genetic or non-genetic cause is at work in the production of microcephalics in these sibships. If calculation is made excluding these sibships, the observed number of abnormals becomes 91, while the expected number is 93.730. The difference 2.73 is much smaller than the standard error 6.32. Thus, it seems safe to conclude that the majority of the cases of microcephaly is due to a single autosomal recessive gene. There are, however, apparently some other cause, either genetic or non-genetic, which makes abnormals appear in greater proportion than could be expected on this postulate. The latter cause may be either a modifying gene, or something in the physiology of the fetus, or of the mother, or of both. At any rate, this cause seems to be at work in cooperation with the basic gene for microcephaly. This conjecture seems warranted, since four of the eight sibships are progeny of first-cousin marriages, and one forms a part of a large kindred which contains several abnormals. Moreover, in none of these cases is there a record of radiation therapy, nor of trauma or disease of mother which might have affected, the developing fetus.

The disparity between the sexes, 79 males and 40 females, among the microcephalics in our collection, seems significant. We have also tested the possible effect of birth-order or of mother's age on the production of microcephalic children. Such an effect has been confirmed or suggested in the production of other congenital anomalies apparently allied to microcephaly, namely, Mongolian idiocy, anencephaly, hydrocephaly and spina bifida (Penrose 1938, 1939, 1946, Buchi 1950). However, nothing suggesting this effect has been disclosed.

**Incidence of the Gene for Microcephaly and Its Mutation Rate**

Next, the incidence of the gene for microcephaly among Japanese population has been estimated by means of Dahlberg's formula (1948):

\[
q = \frac{c (1 - k)}{16k - 15c - ck},
\]

where \( q \) denotes the incidence, \( k \) the rate of cousin marriages among the parents of the microcephalics and \( c \) the rate of cousin marriages
in the whole population. Excluding for the reason stated above the 28 cases belonging to the 8 sibships, the remaining 91 cases belonging to 53 sibships were used for this purpose. In the present material, \(k\) is 0.54, and for \(c\) we have used the value 0.06 which has been found by the investigators in ABCC in Hiroshima and used by them for the estimation of the incidence of the genes for other rare abnormalities among Japanese population. Thus, the value 0.0036 has been obtained for \(q\). This value comes very close to the values found by these investigators for the genes for albinism (0.0029–0.0075), infantile amaurotic idiocy (0.0007–0.0034), ichthysis congenita (0.0003–0.0022), congenital color-blindness (0.0041–0.0069) and xeroderma pigmentosum (0.0057–0.0075) (Neel et al. 1949).

Based on this value of \(q\), the rate of mutation of the recessive gene for microcephaly has been estimated by the formula:

\[
m = (1 - f) [\alpha q + (1 - \alpha) q^2]\]

(Li 1948),

where \(m\) stands for this rate, \(f\) for the relative fertility of microcephalics as compared with normals, and \(\alpha\) for the coefficient of inbreeding. For microcephalic idiots \(f\) is almost zero, but a few of them have children. So we have put \(f = 0.05\). Then, from the values \(c = 0.06\), \(q = 0.036\) and \(\alpha = 0.005\), we find \(m = 3.0 \times 10^{-5}\). This value also is close to the mutation rates found by previous authors for genes of various kinds of congenital abnormalities in man, such as: Albinism, hemophilia, retinoblastoma, microphalhmia, total color-blindness, etc. (Neel and Falls 1951).

It is to be noted that here is apparently a rather strong isolate effect such as pointed out by Dahlberg (1948) and Dunn (1947), primarily for the infantile type of amaurotic idiocy among the Swedish population. There are in Japan undoubtedly districts where microcephalics are commoner than elsewhere. For instance, we have found a kindred containing eight unquestionable and one probable cases in the suburbs of Yokosuka. Komai also has located a family containing three microcephalics at a village near Atami. This family had come from a village near Yokosuka, and it is more than probable that it shares the same gene for the abnormality with the kindred mentioned above. Ozaki has found in an isolated village in Toyama-ken at least ten microcephalics. On the other hand, there are several districts where the effect of consanguineous mating has been systematically studied, and no case of microcephaly has been found. Thus, it is very likely that a rather considerable unevenness occurs in the distribution of the gene in question among the Japanese population at large.

Summary

1. 119 cases of microcephalics belonging to 61 sibships found
from among Japanese population were used as the material for the study. More than half of these cases are children of first-cousin marriages. The analysis of the pedigrees shows that the great majority of microcephalics are due to a simple recessive autosomal gene.

2. In 8 sibships the number of abnormals significantly exceeds the proportion expected on this basis, and it is likely that some additional genetic or non-genetic cause is at work for their production. It is doubtful whether any case of microcephaly entirely free of the genetic cause is included in the present material.

3. Nothing suggesting the effect of birth order or of the maternal age for the production of microcephaly has been disclosed.

4. The incidence of the gene for this abnormality among the Japanese population has been estimated approximately at 0.0036, and the rate of new mutation at $3.0 \times 10^{-5}$. These values are close to the corresponding values estimated by previous authors for various kinds of rare abnormalities occurring in man. The distribution of the gene, however, is probably rather uneven among the population at large.

References


———: Familial data on 144 cases of anencephaly, spina biphida and congenital hydrocephaly. Ann. Eug., 13, 73-78 (1946).

Plummer, G.: Anomalies occurring in children exposed in utero to the atomic bombs in Hirosima. Pediatrictics, 10, 687-693 (1952).