Genetic Studies On Keloid

P. OMO-DARE, M.D., Ch.M. (BIRM.), F.R.C.S. (EDIN.), F.M.C.S. (NIG.), F.R.C.S. (ENG.),
Department of Surgery,
College of Medicine,
University of Lagos,
Lagos, Nigeria

THERE are several reports in the world literature which show that keloid has a pronounced family clustering and point to the possible existence of a hereditary factor in its genesis.[1-4]

Bloom, in a very comprehensive review of the literature in 1956, collected reports on 89 cases which occurred in 31 families and added another 14 which he discovered during a personal study of an Italian family pedigree which spanned five generations.[1] He concluded that keloid is inherited as an autosomal dominant character. He, however, did not provide an explanation in his paper on how he arrived at this conclusion. As the report is the only one in the literature which, to the best of my knowledge, had attempted an analysis of the family pattern of occurrence of this lesion—an analysis which is now contended as unsatisfactory. It is obvious that the hypothesis that there is a hereditary predisposition to keloid formation[1] remains to be satisfactorily proven and the genetic mechanism in its formation, remains to be determined.

The purpose of this paper is to report the results of a recent investigation of the family pattern of occurrence of keloid in the rural Western Nigerian town of Igbo-Ora with a population of nearly 30,000 people. It aimed at determining the role of inheritance, if any, and the mechanism of its operation in the aetiology of keloids.

MATERIALS AND METHODS

In a previous epidemiological study in this rural township, 75 of a randomly sampled sub-population of 1,317 were found to have keloids.[5]

For this study, detailed inquiry was made into the family history of each of the 75 people in so far as they relate to the formation of keloidal scars after injury. The information on a relative reported as having keloids was considered reliable only if the relative was seen and examined personally. This latter approach has resulted in limitation of the tracing of cases at the most to three generations.

In order to study the mode of inheritance, pedigree charts were constructed from the data thus obtained. Each member of the pedigree was represented on the chart as a keloid/or a non-keloid former.

RESULTS

Five people who were recorded as having keloids in the original survey[5] refused re-interview and re-examination. Two others gave information on their relatives which could not be verified personally. The pedigree of these seven individuals were excluded from the present analysis.

Parental consanguinity was denied in all of the remaining 68 patients. It was repeatedly emphasised that this type of marriage/interrelationship was taboo in the community. Multiple births were not recorded in any of the families studied.

In all, 34 family pedigree charts were constructed from the data obtained. The total number of family units (consisting of father, mother and their children) and hence the number of marriages embraced within these 34 pedigrees, totalled 77. Of these, there were:

1) Two marriages (families), in each of which, both partners were keloid-scar formers. There was a total of two children in these families (one in each). Both of them were keloid formers, an incidence of 100%.

2) Twenty marriages (families), in each of which, one of the partners (male/or fe-

male) only was a keloid-scar former. The total number of offsprings in this group was 67; of these, 14 were keloid formers and 53 non-keloid formers (an incidence of 20.9%.

3) Twenty-five marriages, in each of which, both partners were apparently non-keloid scar formers. None of the 170 offsprings was a keloid former.

4) Thirty marriages between partners, each of whom was apparently non-keloid formers, but 41 of the 158 offsprings (25.9%) were keloid formers.

The incidence of keloids found in the random sample of the population of Igbo-Ora itself was 5,94%.[5]

Table 1. EXAMINATION FOR HETEROGENEITY OF KELOID INCIDENCE IN ALL THE MOTHERS AND IN THE MALE OFFSPRINGS OF THE 14 KELOID-FORMING MOTHERS IN THE SUB-POPULATION RE-STUDIED

	Mothers	*Male Offsprings*	*Total*
Keloids	14 (*15.1)	7.7 (*5.9)	21
Non-Keloids	63 (*61.9)	23 (*24.1)	86
Total	*77*	*30*	*107*

X^2 (1) = 0.509 p > 0.30
*Expected Incidence

Fourteen mothers of the 77 families in the study had keloids. This represents an incidence of approximately 18.1% of the mothers in this sub-group of the population.

Of the 49 offsprings of these 14 mothers, 11 had keloids (seven of 30 males and four of 19 females). This gives a keloid incidence of 22.45% (23.3% for male offsprings and 21.1% for female offsprings). A comparative examination of keloid incidence in mothers and offsprings of mothers with keloids in the same generation showed no statistically significant difference between the two (p 0.5) and therefore indicate that the incidence of keloids from one generation to another, in this study, is approximately the same. This finding is consistent with what is expected if an inherited mechanism is operating in keloid genesis.

The same conclusion emerges when keloid incidence in all mothers of this sub-group of the population on the one hand, and the male/or female offsprings of keloid forming mothers—the scientifically reliable tracing tags in this study—are compared (Tables 1 and 2).

Table 2. EXAMINATION FOR HETEROGENEITY OF KELOID INCIDENCE IN ALL THE MOTHERS AND IN THE FEMALE OFFSPRINGS OF THE 14 KELOID-FORMING MOTHERS IN THE SUB-POPULATION RE-STUDIED

	Mothers	*Female Offsprings*	*Total*
Keloids	4 (*3.6)	14 (*14.4)	18
Non-Keloids	15 (*25.4)	63 (*62.6)	78
Total	*19*	*77*	*96*

Fisher Irwin Test (Since the expectancy of the smallest cell column is 4 and thus less than 5) makes p > 0.3.
*Expected Incidence

Similarly when the incidences in the sibs (i.e. brothers and sisters) were compared, no statistically significant difference was found (Table 3). If keloid formation has a genetic basis it must follow from this latter finding that the underlying gene is autosomally inherited.

DISCUSSION

The high incidence of keloids in mothers and offsprings of the sub-group in relation to the general population of Igbo-Ora[5] may be due, either to an underlying genetic predisposition to keloid formation in the sub-group or due to the same environmental mechanism influencing the family units differently from the rest of the population. It is well known that members of the same family are more likely to be exposed to the same environmental influence—food, work, ventilation pattern, etc.—and are thus more likely to suffer from the same infectious diseases, like tuberculosis, than the general population. In Igbo-Ora, however, Barber had pointed out that there are hardly any marked differences between the living standards, ways of life, or eating habits of the individuals within the community.[6] It therefore appears as if envi-

ronmental factors should be considered unlikely to be predominating, if at all. They are determinants in keloid genesis, because they do not appear to form the unifying factors that separate the families of keloid formers from the rest of the population.

Is keloid formation genetically determined? Three types of mechanisms are usually considered in a genetically determined condition: a) Dominant inheritance; b) Recessive inheritance; and c) Multifactorial or polygenic inheritance.

Table 3. EXAMINATION FOR HETEROGENEITY OF KELOID INCIDENCE IN THE SIBS (BROTHERS AND SISTERS) OF THE 14 KELOID FORMING MOTHERS IN THE SUB-GROUP RE-STUDIED

	Female Offsprings	*Male Offsprings*	*Total*
Keloid Formers	4 (*4.3)	7 (*6.7)	11
Non-Keloid Formers	15 (*24.7)	23 (*23.3)	38
Total	*19*	*30*	*49*

Again since the expectancy of the smallest cell column is 4.3 and thus less than 5, Fisher Irwin Exact Test is used and gives $p > 0.80$.
*Expected Incidence

In the case of a trait determined by two genes, one of which is dominant to the other, there will be two classes of persons: those manifesting the dominant phenotype and those manifesting the recessive phenotype. Emery[7] had shown that if a frequency distribution of a lesion, the occurrence of which is genetically determined, were plotted, the curve in such a case is discontinuous. When the heterozygotes are the same phenotypically with the dominant homozygote, the curve has two humps. If the heterozygotes however were different phenotypically from the two homozygotes, then the frequency distribution curve would have three humps. In multifactorial inheritance on the other hand, there is no dominance and the frequency distribution curve is a smooth curve which is bell-shaped—the so-called Gaussian distribution.

An examination of the graphic representation of the incidence of keloids, according to age groups in the population of Igbo-Ora found in the present study is shown[1] (Fig. 1). The prevalence distribution curve is discontinuous and has two humps suggesting thus that the keloid character is most probably determined by two genes one of which is dominant to the other.

When one is dealing with a "single gene" character, it is usually possible in a system of mating that is sharply controlled, i.e., in a "laboratory" population, to predict the mode of inheritance from the determination of the proportion of offsprings of affected parents who were similarly affected.

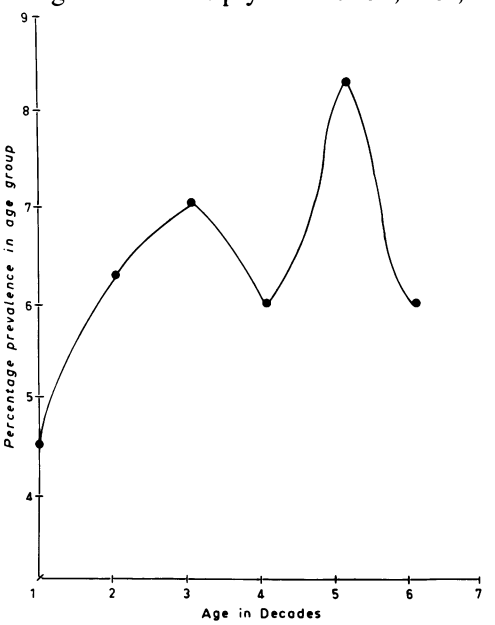

Fig. 1. Age specific prevalence/age decades "Keloids".

It will be observed that the proportion of affected offsprings of mothers who had keloids in the present study—11/49 (22.45%) does not agree with any of the expected proportions in dominant gene inheritance.

It was found at the initial epidemiological survey in Igbo-Ora, that the character keloid can not be scored until an individual has reached an age over one year and has had the requisite exposure to trauma.[5] The precise moment when this transition, from non-keloid forming to keloid forming in the individual who has the inherent predisposition, takes place is still unknown but appears from observations in that survey to be before the age of two years.

In the present study: a) Two matings of keloid by keloid formers gave rise to two

keloid forming offsprings; and b) 20 non-keloid by non-keloid matings (i.e. families) produced offsprings in whom some were keloid formers.

These are in keeping with expectation on the recessive inheritance hypothesis. Furthermore the percentage of offsprings of keloid-forming mothers with keloid, 22.45%, is not significantly different from that expected on Mendelian law when the determinant is recessive.

In natural populations, mating is generally left to chance; furthermore other factors, like birth control, may result in proportions that on first observation appear to be incongruous with Mendelian ratios.

75 people in the randomly sampled population of 1,317 in Igbo-Ora were keloid formers.[5] The corrected incidence for keloid in the sample calculated after subtracting those under the age of one year in whom the keloid character does not manifest is $75/(1,317 - 55) = 75/1,262 =$ (approximately 0.06). The frequency of keloid in the population (q^2) is therefore 6%, which is equal to the mating frequency where both partners are keloid formers.

Analysis of the pedigree charts,* had shown that out of 77 mating pairs, only in 22 are one or both members keloid formers.

Hence, the number of matings (families) in which both pairs would be expected to be keloid formers are 6% of 22 or 1.32. But the observed figure in this series is two. By the same token, the expected number of mating between keloid and non-keloid formers is (22 – 1.32) or 20.68, whereas the observed number is 20.

The difference between the expected and observed figures in each case is not statistically significant. It must be concluded therefore that mating in the population of Igbo-Ora is random and that this finding casts doubt on the declarations that there is no co-sanguinous marriages/or matings.

If we take a look at the phenotype analysis of all the offsprings from all matings between keloid and non-keloid formers, the following ratio is determined:

$$\frac{\text{Keloid Formers}}{\text{Total Offsprings}} = \frac{0.0216}{(0.0216 \quad 0.0912)} = \frac{0.0216}{0.1128}$$

(offsprings of this type of mating expected to be keloid formers).

When all matings of keloid by non-keloid formers and vice versa were abstracted from the pedigree charts and detailed, steps have been taken to avoid counting an individual more than once in computing the data. The results show that of 67 offsprings of this type of mating, there were 53 non-keloid and 14 keloid formers.

The expected numbers were 0.0216×67 keloid formers and 0.0912×67 non-keloid formers (i.e. 12.8 and 54.2, respectively). There is no statistically significant difference between observed and expected figures and thus there appears to be no cause to set aside the hypothesis that keloid is inherited as a recessive character.

Similarly if we analyse the "scorable" offsprings of matings between keloid and keloid-formers, we find that the expected number of keloid forming offsprings is 0.0036 of the total number of offsprings which is two in the study. The observed and the expected numbers of offsprings with keloids in this type of mating are in total agreement and thus again, this finding is not against accepting the hypothesis of recessive gene mechanism of inheritance for keloid.

Finally, if we analyse the "scorable" offsprings of unselected non-keloid forming by non-keloid forming matings, the expected number of keloid forming offsprings of all such matings (i.e. the four possible types of this mating on genotypic basis—KK × KK; KK × kK; kK × KK and kK × kK) should be $0.0324/0.8836 \times (158 + 170)$ approximately equal to 12. This figure is significantly different from the observed figure of 41. If however the mating between the apparent non-keloid former by non-keloid former were limitedly interpreted as involving the heterozygote genotype kK × kK, then the expected number of offsprings with keloid is $0.0324/0.1296 \times 158 = 39.5$. This is not significantly different from the

* These charts may be obtained from the author on request.

observed figure of 41 ($X^2 = 0.0549$: $p > 0.80$), and the hypothesis that there is a recessive gene mechanism is keloid formation is thus again upheld.

The findings in this study therefore have led to the conclusion that the predisposition to keloid formation is inherited as an autosomal recessive character.

SUMMARY

The pattern of occurrence of keloid in the families of 68 people, in a rural Western Nigeria town of 30,000 people, was investigated.

Fourteen of the 77 mothers (18.1%), in the families studied, were found to be keloid formers. Eleven of the 49 offsprings (22.45%) of these keloid formers were also afflicted by the lesion. It was therefore concluded that there was no statistically significant difference in keloid incidence from one generation to another in this group.

Observations had shown that environment did not appear to play an important role in the differences in keloid incidences in family pedigrees in which individuals have keloids and those in which predisposition to the lesion was not found in the rural population.

As no significant difference was found in the keloid incidence between male and female offspring, it was concluded that the predisposition to its genesis is autosomal in character.

Comparison between observed and expected incidence of the lesion in the offsprings of different mating patterns, indicate that the genetic mechanism operating in the formation of this lesion is recessive in character.

LITERATURE CITED

1. BLOOM, D. Hereditary of Keloids. New York State Med. Jour., 56: 511, 1956.
2. GEOGEROT, H. and F. LAMY, A Propos D'une Syphillise sur Cheloide. Ann. Mal. Veneriennes, 9: 363, 1908.
3. JACOBSON, F. The Treatment of Keloids at Radumhemmet 1921-1941. Acta. Radiol. (Stockh), 29: 251, 1945.
4. SCHRAMEX, M. Cited by Bloom, D. (1956): New York State Med. Jour., 56: 511, 1956.
5. OMO-DARE, P. MD Thesis, Univ. of Birmingham, Birmingham, Eng. 1972.
6. BARBER, C. R. A Sociological Report on the Ibarapa Project Ibadan. Oxford Univ. Press. 1966.
7. EMERY, A. E. H. Hereditary Disease and Man. Univ. of Calif. Press, Los Angeles, 1958. pp. 108.

(Hara & Krohn, from page 446)

and both have a history of noncompliance with prescribed medication. One patient underwent subtotal thyroidectomy and developed hypothyroidism and hypocalcemia. Duration of medical treatment ranged from 30 to 50 months and no patients had drug toxicity. The most common problem observed with medical treatment was noncompliance.

LITERATURE CITED

1. VAIDYA, V. A. and A. M. BONGIOVANNI, J. S. PARKS, A. TENORE, and R. T. KIRKLAND. Twenty-two Years Experience in the Medical Management of Juvenile Thyrotoxicosis. Pediat., 54:565-570, 1974.
2. GROSSMAN, A. and G. F. GROSSMAN. Protein Bound Iodine by Alkaline Incineration and a Method for Producing a Stable Cerate Color. J. Clin. Endocrinol., 15:534, 1955.
3. KONTAXIS, N. E. and D. E. PICKENING. A Micromethod for the Determination of Butylalcohol Extractable Hormonal Iodine in Serum. J. Clin. Endocrinol., 18:774, 1958.
4. BRAVERMAN, L. E. and A. G. VAGENALAIS, A. E. FOSTER, and S. H. INGBAR. Evaluation of a Simplified Technique for the Specific Measurement of Serum Thyroxine Concentration. J. Clin. Endocrinol., 32:497, 1971.
5. DONIACH, D. and R. V. HUDSON. Thyrotoxicosis Emerging into Hashimoto's Disease. Proc. R. Soc. Med. 52:178, 1959.
6. DONIACH, D. and R. V. HUDSON, and I. M. ROITT. Human Autoimmune Thyroiditis: Clinical Studies. Brit. Med. J., 1:365, 1960.
7. VANHAELST, L. E. and F. HAYEZ, M. BONNYUS, and P. A. BASTENIE. Thyroid Autoimmune Disease and Thyroid Function in Families of Subjects with Down's Syndrome. J. Clin. Endocrinol., 30:792, 1970.
8. ALEXANDER, W. D. and R. M. HARDEN and J. SHIMMINS. Emotion and Nonspecific Infection as Possible Etiological Factors in Graves Disease. Lancet, 11:196, 1968.
9. STARR, P. and H. L. JAFFEE, and L. OETTINGER, Jr. Later Results of ^{131}I Treatment of Hyperthyroidism in 73 Children and Adolescents. J. Nuclear. Med., 10:586-590, 1969.