A Newly Recognized Genetic Syndrome of Tetramelic Deficiencies, Ectodermal Dysplasia, Deformed Ears, and Other Abnormalities

N. FREIRE-MAIA[1]

Congenital limb deficiencies represent a highly heterogeneous group of disorders, both etiologically and clinically (Freire-Maia 1969). Phenotypically they range from minor structural deviations to the most severe defects including acheiropodia, tetraphocomelia, and total amelia. A few of these conditions are due to autosomal dominant or recessive mutations; a small group is unequivocally caused by a predominantly exogenous mechanism (thalidomide, maternal diabetes, etc.); and a small fraction may be caused by "complex" genetic mechanisms. However, the etiology of the large majority of limb deficiencies in man is unknown. Chromosomal aberrations seem to be of little importance in this class of malformations.

This paper reports an apparently undescribed complex malformation syndrome which includes severe deficiencies of all limbs. The disorder was mentioned briefly in two preliminary notes (Freire-Maia et al. 1969, 1970).

CLINICAL DATA

Four affected individuals occurred in one sibship (see fig. 1 for pedigree).

Individual 1 (II-1): this male infant died of tetanus three days after birth. According to his parents, he had anomalies similar to those of the propositus. However, he lacked a cleft lip.

Individual 2 (propositus, II-2): this fourteen-year-old male and his affected sister (II-4) were ascertained together, as beggars; the propositus beat a timbrel and his sister played a mouth organ. The patient is mentally retarded (Pierre Weil's nonverbal test). At the age of ten months, he had a febrile convulsion.

Examination (fig. 2): body length (to knees) 88 cm; sitting height, 69 cm; head circumference, 50 cm. Compared with his sister, his growth is clearly retarded. His unusual appearance is due to a combination of ethnic traits (mulatto mother, Caucasian father) and developmental defects. The latter include an incomplete right cleft lip and abnormally differentiated auricles which were larger than normal and anteverted and showed incomplete folding of the helix so that the upper crus of the

Received October 28, 1969; revised January 6, 1970.

Our research projects are sponsored by the Rockefeller Foundation, the National Research Council of Brazil, the Calouste Gulbenkian Foundation (Portugal), the World Health Organization, and the Research Council of the Federal University of Paraná.

[1] Laboratory of Human Genetics, Federal University of Paraná, P.O. Box 756, Curitiba, Paraná, Brazil.

antihelix and the rim of the helix formed a broad plane lacking the normal scaphal depression. The lobules were quite hypoplastic. He showed moderately severe hypotrichosis of scalp and of body pelage; he had somewhat sparse eyebrows and eyelashes but lacked axillary and pubic hair. His skin (particularly of the face) appeared dry and thin and it formed an unusual number of thin wrinkles when the patient smiled or grimaced (fig. 2). He did not have a cleft of the palate. His eyes were normal.

His teeth were widely spaced, and mostly small and conical; he showed persistence of some deciduous teeth and absence of some of the permanent teeth. The thyroid gland was minimally but diffusely enlarged, and there was very slight gynecomastia. The nipples were small and were surrounded by hypoplastic and eccentric areolae. The external genitalia were normally differentiated but underdeveloped for age.

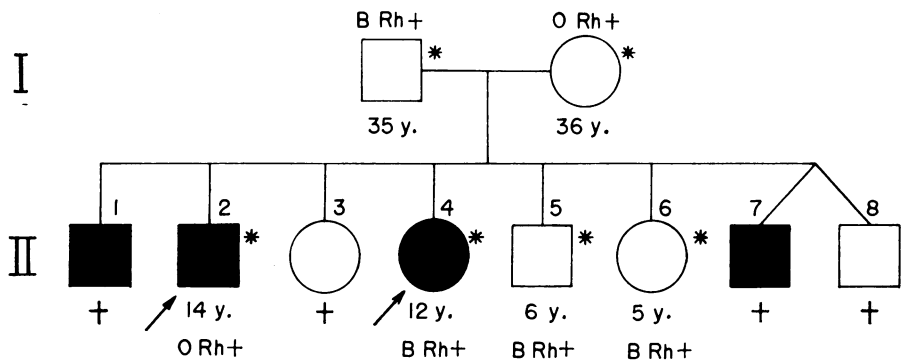

FIG. 1.—Abridged pedigree of the family showing only the sibship in which the affected individuals were born and their parents. * = examined; + = dead in infancy. The arrows indicate the propositi. The age of each individual (in 1969) is given below the corresponding symbol. The ABO and Rh blood group determinations are indicated for six of the individuals.

Limbs were seriously malformed. Upper right: very slender humerus; presence of only one abnormal forearm bone with two small bones at its distal end. Upper left: humerus slender but slightly broader than on the right; aplasia of radius; ulna short, thick, and curved; presence of only five carpal and two metacarpal bones and of two fingers with two phalanges and hypoplastic nails. Lower limbs: congenital absence of all the bones below knees; bilateral coxa vara with modification of the femoral heads and dislocation of left hip; hypoplastic patellae. Movements of some of the joints were considerably abnormal.

Heart examination and ECG were normal; blood pressure was normal. The EEG showed a diffuse abnormality most prominently in both frontal areas. Preliminary results of biochemical investigations indicated an excess of tyrosine and/or tryptophane in the urine (Freire-Maia et al. 1970).

Individual 3 (proposita, II-4, fig. 3): this 12-year-old-girl corresponded closely in most clinical details to her brother (II-2). Measurements: height (to knees), 101 cm; sitting height, 71 cm; head circumference, 50 cm. She differed from her brother in showing less growth retardation, more striking hypotrichosis of the scalp, slightly

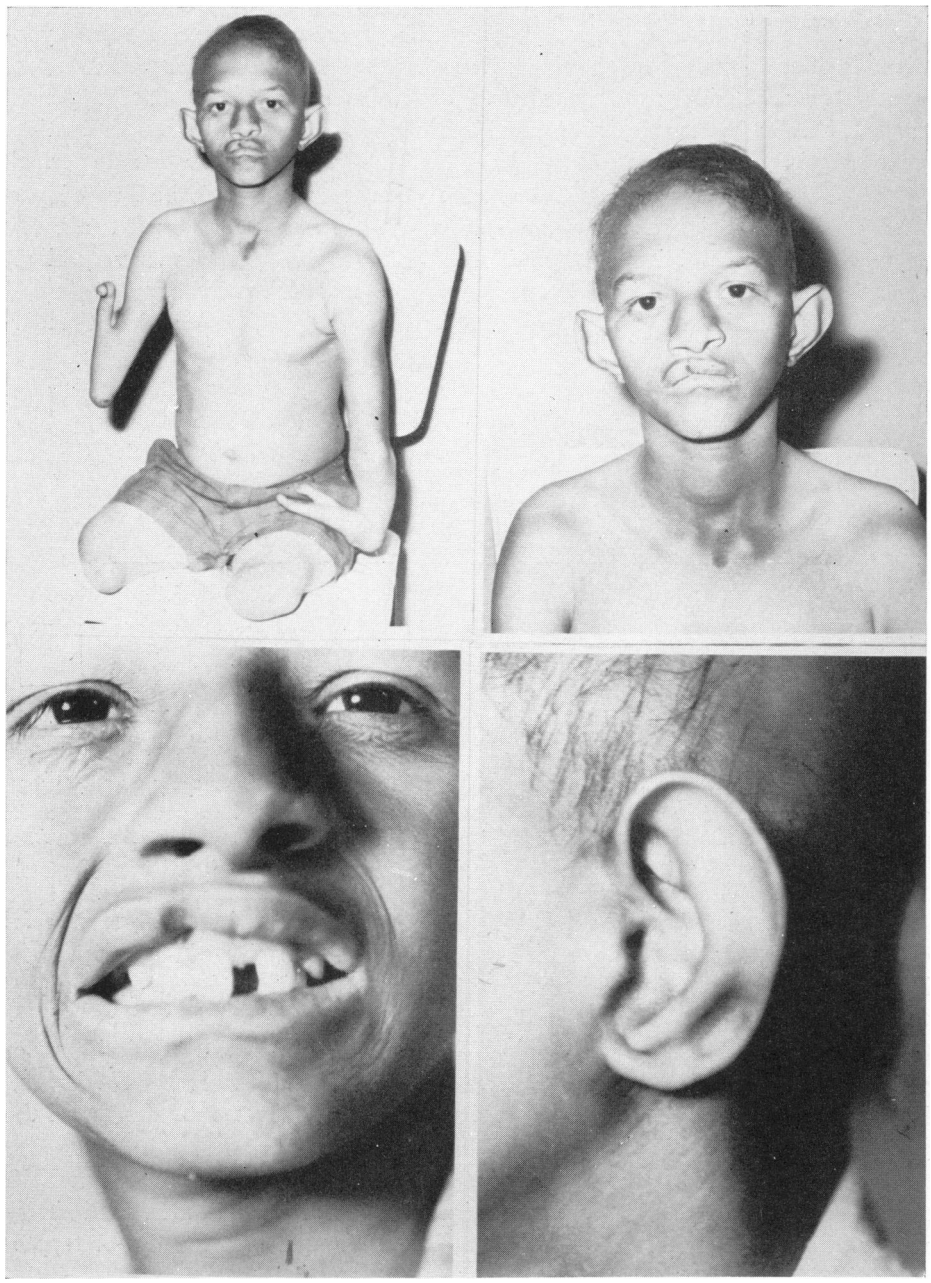

FIG. 2.—Individual 2

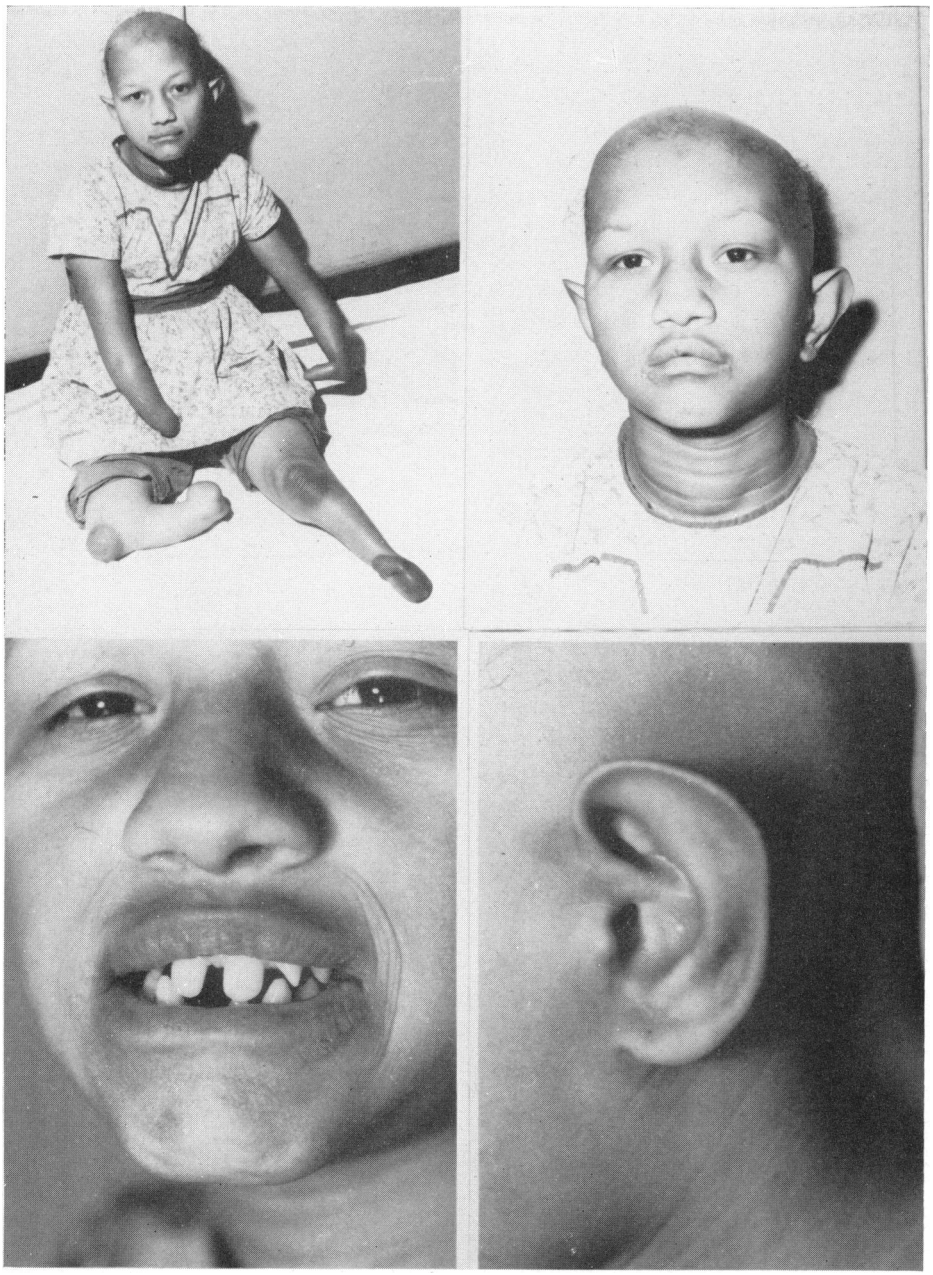

FIG. 3.—Individual 3

greater enlargement of the thyroid, normal lips (without cleft), and absent areolae. A diffuse abnormality of myocardial repolarization was observed on the ECG. Her blood pressure and clinical cardiac findings were normal. Teeth and ears were similarly affected, and eyes were normal.

Upper right limb: humerus normal, radius aplasia, ulna short and thick; two carpal bones present; total absence of metacarpals and fingers. Upper left limb: essentially identical to the right except for bowing of the ulna and the presence of one metacarpal bone. Lower limbs: femora normal except for slight slenderness and bowing of the right one. Right leg: absence of patella, severe flexion contracture of knee, absence of tibia, normal fibula, absence of all foot bones except for a deformed calcaneus. Left leg: normal patella, absence of fibula; proximal tibial epiphysis unusually flat, distal tibial epiphysis abnormally rounded; presence of only four abnormal bones in the tarsometatarsal region.

Hemogram and EEG were normal. Pierre Weil's test indicated mental retardation. This girl manifested the same metabolic defect as her brother (Freire-Maia et al. 1970).

Individual 4 (II-7): this male cotwin had anomalies like the propositus but without a cleft of the lip. He and his unaffected cotwin died at the ages of two and five days, respectively, of tetanus.

GENETIC STUDIES

It was not possible to demonstrate close consanguinity between the parents of this sibship; however, they were both born on the same farm in the state of Minas Gerais, Brazil. The mother's family had worked for her husband's parents who owned the farm on which the first four children of this sibship were born.

In 1969 the father was 35 years old and healthy; he had a slight anemia and leukopenia, and he was also found to be mentally retarded on the basis of the same test. He was the eighth in a sibship of thirteen; he also has four half sibs from a second marriage of his father and a large number (>30) of nieces and nephews.

The mother was 36 years old and healthy, but also mentally retarded. She was the fifth of a sibship of 12; she also has more than 30 nieces and nephews. Her pregnancies, labors, and deliveries were normal; she did not use drugs during gestation.

With the exception of the four affected individuals, the whole family is described as normal with respect to this syndrome. Cytogenetic studies of both parents and the proposita showed apparently normal chromosomes; chromosomal studies of the affected son were not successful (Freire-Maia et al. 1970).

Dermatoglyphic patterns of the remaining parts of the upper limbs of both patients were abnormal in many respects; their parents, however, have normal dermatoglyphics (Chautard and Freire-Maia 1970).

The mother had a total of seven pregnancies (see fig. 1) at ages 21, 22, 23, 24, 30, 31, and 34 years, respectively. The third pregnancy resulted in an otherwise normal premature female who died at 17 days of unknown cause. The fifth and sixth children were examined and found to be a normal male and female, 6 and 5 years old, respectively. The seventh pregnancy resulted in male twins whose zygosity was not

established; however, since they were discordant with respect to the syndrome, it is presumed that they were dizygous. Results of ABO and Rh determinations are indicated in figure 1.

DISCUSSION

A brother and a sister were found to share at least eight developmental defects: (1) extensive deficiencies of the four limbs with associated dermatoglyphic abnormalities; (2) hypotrichosis; (3) abnormal dentition with widely spaced teeth which are mostly small and conical, persistence of some deciduous teeth and absence of some permanent teeth; (4) hypoplastic areolae and nipples; (5) large, thin, protruding, and deformed auricles; (6) diffuse thyroid enlargement; (7) abnormalities of tyrosine and/or tryptophane metabolism; and (8) mental retardation. In addition, the propositus showed (9) hypogonadism with slight gynecomastia, (10) hypoplastic nails, (11) growth retardation, (12) incomplete, unilateral cleft of the lip, and (13) electroencephalographic abnormalities. The only additional finding in the sister was (14) an electrocardiographic abnormality without other evidence of cardiac disease or malformation.

Observations on many other similarly affected patients are required before it will become clear whether all 14 defects are common components of the syndrome or whether some of them are coincidental findings in these two siblings. The hypotrichosis, dental defects, and hypoplastic areolae and nipples seem to represent a type of ectodermal dysplasia; however, the patients did not manifest any abnormalities of sweating. It is difficult to decide whether the nail defects are the result of this dysplasia or of the process which led to the limb malformations. The dermatoglyphic abnormalities are probably an effect of this process. It is similarly unclear whether the paucity of axillary or pubic hair represents primarily a manifestation of the ectodermal dysplasia or of the apparent hypogonadism. The boy's gynecomastia is probably a eunuchoidal manifestation. Absence of pubertal signs (at the age of 12 years) in the proposita probably indicates that she also has hypogonadism. In the absence of thyroid function tests, it is not possible to define the cause of the thyroid enlargement in these two patients. Clinically they were not obviously hypo- or hyperthyroid; due to the severe limb defects it was not possible to determine their bone age. Goiter is highly prevalent in the state of Minas Gerais and its presence in the propositi may possibly be coincidental. The reason for the relative growth retardation in the propositus could not be determined. Nevertheless, the presence of thyroid, growth, and gonadal defects in one or both of the patients suggests that this syndrome may have a complex endocrine component. Clefts of lip and/or palate have not been seen in this family before; the isolated occurrence of an incomplete cleft of the lip in the propositus may therefore still represent a manifestation of the syndrome. As yet, no explanation can be offered for the ECG and EEG changes reported and for the relationship between the metabolic defect and the other abnormalities of these patients. The biochemical aberration may represent a secondary effect of the syndrome.

On the basis of a nonverbal test, the propositi were both found to be mentally retarded. However, the fact that both parents are mentally retarded, that both patients are handicapped by a mutilating syndrome, that neither patient has at-

tended school, and that the family derives from the lowest socioeconomic level of rural Brazil suggests that a major part of the mental retardation may be due to cultural factors. For a full analysis of this problem, see Mehl and Mehl (1970). The relationship between the convulsive episode, EEG changes, and the mental retardation in the propositus remains conjectural.

The occurrence of four similarly affected individuals in one sibship clearly suggests a genetic etiology of this malformation syndrome. Both sexes are affected and, with the exception of mental retardation, both parents are normal with respect to the syndrome. Parental consanguinity was denied; however, the distinct possibility exists that the parents are, in fact, consanguineous since they derive from the same farm in one of the most inbred areas of Brazil (Freire-Maia 1957). Indeed, in a low socioeconomic population sample from a large region encompassing this part of Minas Gerais, only 47%–70% of the average inbreeding coefficient was detected through pedigree analysis based on genealogical information provided by the spouses (Yasuda 1966; Azevêdo et al. 1969). It therefore seems plausible that the syndrome described in this paper is due to the homozygous state of an autosomal recessive mutation.

SUMMARY

This paper reports an apparently undescribed malformation syndrome in two personally examined siblings and two of their brothers who died in infancy. The condition consists of severe tetramelic deficiencies, hypotrichosis, deformed auricles, abnormal dentition and hypoplastic nipples and areolae; it may also include hypoplastic nails, hypogonadism, thyroid enlargement, and relative growth failure as well as incompletely cleft lip, mental retardation, and ECG and EEG abnormalities. The EEG abnormalities are possibly related to the seizure episode which occurred in the propositus. An abnormality of tyrosine and/or tryptophane metabolism has been identified in both propositi. It is postulated that this syndrome is due to the homozygous state of a rare autosomal recessive mutation.

ACKNOWLEDGMENTS

I gratefully acknowledge the help of a medical student, Mr. A. A. der Bedrossian, at the beginning of this investigation as well as the valuable contribution of Dr. Maria Carmen Schetino in a subsequent stage. I am also very grateful to Drs. Carlos Alexandre Ferreira, Claudio Sandri, Basilio Bacarin, Eleidi Alice Chautard, Alber Brito, Isac Brilman, Roaldo A. Koehler, Robinson Menon, Nicolau Eros Petrelli, Sebastião L. Carvalho, Paulo Barbosa da Costa, Herley Mehl, Nelly M. Mehl, J. C. B. Braga, Eduardo Sponholz, Jr., Carlos Américo da Silva, Nelson Maimone, Mario Peixoto, Jurema Jorge Georgi, Francisco Paolis, Joel Vieira, Oswaldo Aguiar, Oswaldo Truit, Isis S. Monte Serrat, Luiz de Carvalho, Adriano Valente, and Leonardo Grabois as well as Brother Vidal Klun for valuable help at different stages of this investigation. I am also indebted to Drs. I. Cat, John M. Opitz, R. J. Gorlin, Victor A. McKusick, and J. V. Neel for helpful discussion and reviews of the manuscript.

REFERENCES

AZEVÊDO, E.; MORTON, N. E.; MIKI, C.; and YEE, S. 1969. Distance and kinship in northeastern Brazil. *Amer. J. Hum. Genet.* **21**:1–22.

CHAUTARD, E. A., and FREIRE-MAIA, N. 1970. Dermatoglyphic analysis in a highly mutilating syndrome. *Acta Genet. Med.* (in press).

FREIRE-MAIA, N. 1957. Inbreeding in Brazil. *Amer. J. Hum Genet.* **9**:284–298.

FREIRE-MAIA, N. 1969. Congenital skeletal limb deficiencies—a general view. Pp. 7–13, pt. 3, in Daniel Bergsma (ed.), *The 1st conf. on the clin. delineation of birth defects*. National Foundation March of Dimes, New York.

FREIRE-MAIA, N.; CAT, I.; LOPES, V. L. V.; CHAUTARD, E. A.; MARÇALLO, F. A.; CAVALLI, I. J.; PILOTTO, R. F.; SCHETINO, M. C.; and DER BODROSSIAN, A. A. 1970. A new malformation syndrome? *Lancet* (in press).

FREIRE-MAIA, N.; SCHETINO, M. C.; and DER BEDROSSIAN, A. A. 1969. Dados clínicos e radiológicos sôbre um síndrome aparentemente nôvo. *Ciência e Cultura* **21**:280.

MEHL, N. M., and MEHL, H. 1970. Estudos psicológicos de dois pacientes com uma síndrome malformativa. *Rev. Brasil. Pesquisas Méd. e Biol.* (in press).

YASUDA, N. 1966. The genetical structure of northeastern Brazil. Ph.D. thesis, University of Hawaii, Honolulu.