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Osteopetrosis: review of dominant cases and frequency in a Brazilian State

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As was mentioned in the preceding paper (Ilha and Salzano, 1961) it was thought, at first, that the disease which afflicted several members of the family studied there was osteopetrosis. A review of the literature concerning this condition showed that English and French general treatises were greatly confused with regard to the inheritance of the disease. Thus Touraine (1955) fails to distinguish osteopetrosis from osteopoikilosis; McKusick (1956) states that osteopetrosis is inherited through a recessive gene, while Gates (1946) and Falls (1953), although mentioning the possibility of dominant inheritance, place much more emphasis on the cases inherited through recessive genes. Already in 1944, however, Schinz had presented a clinical-genetic classification of the disease in four types, generally accepted by the investigators of German language. These four types could be described as follows: *Type* 1: inheritance through a dominant gene, with very little intra-familial variability, mild development and good prognosis; *Type* 2: inheritance through a dominant gene with high intra-familial variability, for example, benign manifestation in one generation and severe anemia in the following; *Type* 3: inheritance through a recessive gene with a relative benign development; *Type* 4: inheritance through a sub-lethal gene with great variability and early malignant development.

Hanhart (1948) has made an excellent review of the recessive cases, but no such review is available for cases where a dominant gene appears to be present. It seemed therefore to be worthwhile to present a list of these last cases. Such a list is presented in table 1.

It is the author's opinion that at least types 1 and 2 of Schinz should be treated collectively as different expressions of the same gene. But when possible a classification of cases in types 1 or 2 was tried; several authors, such as Hanhart (1948) and Cocchi (1950) for instance, have already tried to classify these cases. Statements were generally homogeneous with the exception of Pirie's patients who were classified by Hanhart (1948) as belonging to type 1 while Cocchi (1950) classified them as being of type 2.

The eleven reports listed give a firm basis to the existence of a dominant form of osteopetrosis. There still rests a doubt if the patients of Lauterburg (1931) can be

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included in the list. Cocchi (1950) consider them as being affected by the Camurati-Engelmann disease. The work of Bonomini and Gregoris (1951) was not included because both authors state that their cases could represent a new variant of osteopetrosis.

The only reference to twin studies with regard to this anomaly seems to exist in the paper of Hesseling (1948-49) in which he reports the recessive malignant form of the disease in one of a pair of probably monozygous twins. The other member of the pair had already died, probably due to the same condition.

It is interesting to mention that the disease was also found in rabbits (Pearce and Brown, 1948; Pearce, 1948, 1950a and 1950b). In this species its inheritance is due to a recessive gene.

At the time this study was started, there existed only one report about the frequency of osteopetrosis. It was Karshner's (1926) information that he had found four cases during the two-year period from July 1, 1924 to July 1, 1926 out of 2,752 new patients under twelve years of age admitted for various causes to the Roentgen-Ray Department of the Childrens' Hospital where he was employed. This would indicate a high frequency of the disease (1 in 688), at least in a hospital population. Higher than it could be supposed by the relative scarcity of published reports. A survey was therefore made among the radiologists and orthopedists of the larger cities of the State of Rio Grande do Sul, in order to ascertain the frequency of the disease in the State. All the radiologists and orthopedists of Pôrto Alegre were interviewed personally by the author or by a field worker. With regard to the other cities a questionnaire was sent to all representatives of the State Medical Association asking: *a*) If he were a radiologist or orthopedist; *b*) If he was, the incidence of the disease in his clinic; *c*) If he was not, the name of the radiologists or orthopedists of the city. The number of answers to the questionnaire were very poor; it was therefore decided to complete them by making personal interviews with all radiologists and orthopedists of the larger cities. This was done by the author personnaly. The total result of the survey disclosed 11 cases in a total of 1,130,437 radiograms. This would imply a frequency of approximately 1 in 100,000 individuals. But there was a clear difference between the frequency obtained in Pôrto Alegre (9: 589,200 or 1: 65,467) and those from outside Pôrto Alegre (cities included: Pelotas, Rio Grande, Santa Maria, Passo Fundo, Cachoeira do Sul, Cruz Alta, Vacaria, Carazinho, Canoas, Sao Jerônimo, Caxias, Taquara, Novo Hamburgo, Roca Sales and Horizontina. Frequency 2: 541,237 or 1: 270,618). It is possible that the lower frequency observed outside Pôrto Alegre was due to the fact that some affected persons were undetected, which is not very likely, however, due to the striking characteristics of the disease. Another explanation would be that those affected with the malignant form of the disease would die before they had X-rays taken, since the percentage of persons X-rayed is much higher in Pôrto Alegre than in other localities of the State. On the other hand there exists the possibility that some of the cases reported in Pôrto Alegre were not real cases of the disease (remember that the condition described in the foregoing paper was initially diagnosed as osteopetrosis). Summing up it is pos-

Table 1. Recorded Instances of Dominant Inheritance of Osteopetrosis

Author	Propositus	Type	Members of the family studied [1]
Ghormley (1922)	Male; age 8	1	*Siblings*: only child; a previous child of the couple died at the age of 2 months. *Parents*: father affected, mother normal.
Pirie (1930)	Female; adult	1	*Siblings*: not studied. *Children*: 1 boy (5) and 2 girls (8, 11), all affected.
Zaleski (1932)	Male; age 41	1	*Siblings*: a brother has had several fractures. *Children*: the author mentions only one daughter (4), also affected.
Pagenstecher (1935)	Male; age 65	1	The author mentions only a son (25), affected.
Mc Peak (1936)	Female; age 13	1	*Siblings*: 1 sister, normal (9); 2 sisters, affected (3, 11 months); 2 brothers, affected (15, 6). *Parents*: mother (43) affected. *Other members*: a maternal aunt (41) and the maternal grandmother (70) of the propositus also presented the disease. The maternal aunt has had a son (18) and a daughter (20), both normal.
Harnapp (1937)	?	1	*1st generation*: a man (54) and his wife (60); both normal. *2nd generation*: They have had one daughter (27), normal; one son (29) also normal and another son (31), affected [3]. *3rd generation*: This affected male married a normal female (38). They have had two affected sons (8, 7), two normal daughters (6, 2) and three affected daughters (5, 4 and 11 months).
Heine (1941)	Male, adult (?) [2]	2	*Siblings*: only child; the propositus married but has had no children. *Parents*: mother (80), affected. The original description of the disease by Albers-Schönberg was based on the propositus.
Winter (1945)	Male, age 18	?	*Parents*: mother (55), affected.

[1] The number after the individual indicates his age at the time of the investigation.

[2] It is not clearly stated if the X-ray studies performed in the old lady were before or after it was realized that she was the mother of Albers-Schönberg patient.

Author	Propositus	Type	Members of the family studied
Thomson (1949)	Male, 5 months	2	*Siblings*: a brother, normal. *Parents*: father normal, mother (29) affected. *Mother's siblings*: three sisters (37, 32, 31) and two brothers (34, 22). Only the older brother was X-rayed, and shown to be normal. *Maternal grandparents*: normal [3].
Cocchi (1950)	Male, age 20	2	*Siblings*: one brother (23), affected. *Parents*: father affected. *Father's siblings*: four sisters (54, 52, 50, 48) examined, normal; one sister (died at 35) not examined, but her son (34) was normal. Two dead brothers (22, 46), one affected, the other not examined. *Paternal grandparents*: not examined. A grandfather's brother was crippled and is mentioned as probably affected.
Theilkäs (1950)	?	1	Father (51) and son (21) affected.
Klein (1952)	Male, age 64	1	*Siblings*: two brothers, affected; four sisters, normal. *2nd generation*: of the three men affected, two have had one normal daughter each; the other has had two sons and one daughter, all normal. *3rd generation*: the normal daughter has had an affected son [4]. It is not stated who of the three brothers of the 1st generation is the propositus.
Welford (1959)	Male, age 11 [5]	1(?)	*Siblings*: a brother (8), affected (o.). *Parents*: Father affected (o., f.p.). *Grandparents*: paternal grandfather affected (o., f.p.), according to hospital records. 9 other members of the family, all males, are reported to be affected. The pattern of inheritance seems most striking, affected fathers transmitting the condition to their sons only. It would be highly desirable to check the information given by the members of this family.

[3] Instance of irregular penetrance or mutation.

[4] This could be a case of irregular penetrance or, as discussed by the author, of recessive sex-linked inheritance.

[5] The propositus presented osteopetrosis (o.) and facial paralysis (f.p.).

sible that the figure arrived at for the total result (1: 100,000) is a good compromise between the two other figures, and it is the author's opinion that it indicates the approximate frequency of this condition in the State of Rio Grande do Sul.

Recently Stevenson (1959) has made an estimate of the frequency of osteopetrosis and other hereditary defects in Northern Ireland. In regard to the condition under discussion he arrived at a much lower frequency than the one obtained here: 1: 200,000 at birth and 1: 500,000 in the living population. As he does not give any details as to the way his estimate was obtained, no discussion regarding the differences between the figures arrived at by him and by the author of this report is possible at the present time.

Summary

Eleven reports of osteopetrosis due to dominant genes (table 1) establish in a firm basis the existence of such a genetic variant. By personal interview with all radiologists and orthopedists of Pôrto Alegre and larger Rio Grande do Sul cities, an estimate of 1: 100,000 was obtained for the frequency of osteopetrosis in this Brazilian State.

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RIASSUNTO

Undici reperti di osteopetrosi da geni dominanti (tav. 1) stabiliscono una base solida, in relazione alla esistenze di una tale variante genetica.

Per mezzo di una inchiesta fatta personalmente con tutti i radiologi e ortopedici di Pôrto Alegre e delle più popolose città dello stato di Rio Grande do Sul, si è ottenuta una stima di 1: 100.000 per la frequenza dell'osteopetrosi in questo stato brasiliano.

RÉSUMÉ

Onze rapports d'ostéopétrose due à des gènes dominants (table 1) fournissent une base sûre à l'égard de l'existence de cette variante génétique. Moyennant une interview personnelle avec tous les radiologues et les orthopédistes de Pôrto Alegre et des plus grandes villes du Rio Grande do Sul, on a obtenu une évaluation de 1: 100.000 pour la fréquence de l'ostéopétrose dans cette province brésilienne.

ZUSAMMENFASSUNG

Elf Berichte über Marmorknochenkrankheit durch ein dominantes Gen verursacht, sind eine feste Grundlage für das Vorhandensein dieser genetischen Variante. Durch persönlicher Zusammenkunft mit Röntgenspezialisten und Orthopäden aus Pôrto Alegre und anderen grösseren Städten von Rio Grande do Sul wurden wir gewahr dass die Häufigkeit der Marmorknochenkrankheit in Rio Grande do Sul (Brasilien) schätzungsweise 1: 100.000 ist.