X-linked anhidrotic ectodermal dysplasia with some unusual features*

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Summary. A total of 85 members of a family in which several individuals presented with hypodontia, hypotrichosis, and hypohidrosis were examined. Of these, 77 were evaluated clinically and the results compared with those obtained in an equal number of carefully chosen controls. The main symptoms among the affected males and females involved changes in the quantity and texture of head hair and in the distribution of body hair. More than half of the males also showed precocious baldness, and 6 of them had dyskeratosis. The average of missing teeth was 12 among men with the syndrome, but only 2 among the obligate female carriers. The sweat pore counts were lower in the two sexes (42% and 60% of the normal values, respectively), and a much higher degree of asymmetry was observed especially among the affected women. Inheritance of the syndrome seems to be the result of a dominant sex-linked gene with 78% to 87.5% penetrance in the females. Genetic data concerning anhidrotic ectodermal dysplasia are still unsatisfactory; new, more detailed studies are needed, in which special attention is given to the female carriers.

Anhidrotic (or hypohidrotic) ectodermal dysplasia is a name that designates a heterogeneous group of conditions, characterized by a triad of hypodontia, hypotrichosis, and hypohidrosis. In many cases other structures are affected as well. Inheritance of the syndrome is generally asserted to be X-linked recessive, but there are reports suggesting other types of genetic determination. A review of the published reports indicates that the amount of genetic data available is surprisingly small, if we consider the number of cases reported. In this communication we give clinical and genealogical information concerning a large family with several members affected by a relatively mild form of this condition. The benign nature of the syn-

drome is unexpected, since the X-linked forms are generally severe. The fact that almost all obligate female carriers also show the condition (though not with the same intensity as in males) should also be considered as unusual, if the above-mentioned genetic hypothesis is regarded as correct. These facts and the intrinsic interest of investigating gene action in heterozygotes for X chromosome gene mutations led to a detailed study of this kindred.

Subjects and methods

The *propositus* was ascertained in 1969 by J. A. Kulczynsky. The patient had congenital absence of 10 teeth, some of the others also having morphological abnormalities; precocious baldness and absence of hairs on the hands were also noted. Because of these features and the information that several of his relatives were similarly affected the patient was referred to our department for study. He was living at the time in Porto Alegre but his family was scattered over several other towns in Rio Grande do Sul: Camaquã, Ijuí, São Luiz Gonzaga and Carazinho. All the available members in

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these places have been approached and were studied at their homes.

The clinical data were obtained by filling a standardized form with 25 items. Special emphasis was placed on symptoms in organs and tissues of ectodermal origin, as well as on allergic manifestations. Affected and apparently healthy members of the family were studied with the same thoroughness. In addition, control unrelated individuals strictly matched for race, sex, and age were similarly investigated. Unfortunately, no x-ray studies could be performed; therefore, the information relating to missing teeth was based on visual inspection and anamnesis only, no data being available on impacted teeth. Hair samples of 13 individuals of this family were sent to Dr Paul S. Porter, of the University of Pittsburgh, for special studies.

The sweat pore counts were made using plastic imprints with a technique similar to those employed by Thomson and Sutarman (1953), Verbov (1970), and Crump and Danks (1971). Two solutions were used: A: polyvinyl glue, 70 ml; distilled water, 30 ml; crystal violet, 0.15 g. B: Polyvinyl glue, 60 ml; distilled water, 30 ml. They were applied successively to digits 2, 3, and 4 of each hand, care being taken that the first layer was dried before the second one was applied. The film was stripped off with cellulose adhesive tape and mounted on a microscope slide. The sweat pores were counted in an area of 1 cm² at $\times 45$ magnification, with a stereoscopic microscope. Because of the difficulty of obtaining good plastic impressions of a sufficient size in children less than 10 years of age, the counts in

these cases were made in three areas of 0.25 cm², which were afterwards averaged. Asymmetry in the counts of the right and left hands was measured with the indices proposed by Singh (1968).

The accuracy of this method was verified as follows: counts were made in 10 individuals (5 of each sex) and 15 days afterwards new collections and counts were performed. The average difference between the values arrived at in the two counts (9.3 pores per individual) was considered low and the method sufficiently accurate for our purposes. We also compared the impressions obtained by this procedure with those obtained using Crump and Danks (1971) technique. Six subjects were studied. In our hands, the method we describe here always gave better plastic imprints.

Results

A total of 85 members of the family was examined. Of these, 77 were evaluated clinically and the results obtained in them and in an equal number of matched controls are presented in Table I. In the anamnestic data, the frequency of non-specific skin lesions and eczema among the affected males was found to be significantly higher than those of the controls. At physical examination, significant differences between both male and female carriers of the gene and their controls were found in relation to the quantity and texture of head hair and in the distribution of body hair. More than half of the

TABLE I
CLINICAL DATA FROM AFFECTED AND APPARENTLY HEALTHY MEMBERS OF FAMILY STUDIED
AS WELL AS FROM CONTROLS

Clinical Characteristics	Males				Females			
	A (17)	C ₁ (17)	NF (17)	C ₂ (17)	A+OC (28)	C ₁ (28)	NF (15)	C ₂ (15)
<i>Anamnesis</i>								
Skin lesions	12**	2	4	2	5	3	3	1
Asthma or bronchitis in childhood	7	2	4	2	1	1	4	0
Unexplained fever	2	0	0	0	1	0	0	0
Allergic reactions	9	3	7	3	8	6	6	4
Convulsions	1	2	2	2	1	2	0	2
Puberty problems	0	0	0	0	2	0	0	0
Asthma	6	1	2	1	3	1	0	0
Eczema	5*	0	2	0	1	2	2	1
Rhinitis	4	1	5	1	3	4	2	1
<i>Physical examination</i>								
Abnormal facies	3	0	0	0	0	0	0	0
Head hair abnormalities								
Quantity	12*	5	1	5	7*	0	0	0
Texture	11***	0	0	0	7*	0	0	0
Colour	0	0	0	0	0	0	0	0
Precocious baldness	11**	1	0	1	0	0	0	0
Abnormal distribution, body hair	13***	0	0	0	10**	0	0	0
Accessory nipples	2	0	1	0	0	0	0	0
Abnormal nails	0	0	0	0	0	0	0	0
Eczema	2	0	2	0	0	0	1	0
Dyskeratosis	6*	0	2	0	3	0	1	0
Abnormalities of respiratory tract	2	0	0	0	2	0	0	0
Abnormal vision	3	0	3	2	5	4	0	1
Abnormal hearing	0	0	1	0	1	0	0	0

A: Affected; A+OC: Affected + obligate carriers; C₁ and C₂: Controls; NF: Apparently healthy relatives of affected persons. The total numbers of individuals studied are indicated in parentheses. All differences between members of the family and their controls were tested by chi-square analysis. * Significant at the 5% level; ** Significant at the 1% level; *** Significant at the 0.1% level.

TABLE II
DENTITION OF AFFECTED PERSONS OR OF OBLIGATORY CARRIERS WHO WERE OVER 10 YEARS OF AGE

Sex	No. Studied	No Missing Teeth	No. of Teeth Missing								Average $\pm$ SD	
			9	10	11	12	13	14	15	16		Unknown
Male	13	0	1	2	1	1	3	0	1	1	2	12.2 $\pm$ 2.2
Sex	No. Studied	No Missing Teeth	No. of Teeth Missing								Average $\pm$ SD	
			1	2	3	4	5	6	7	8		Unknown
Female	20	5	2	8	1	1	1	1	0	1	0	2.2 $\pm$ 2.2

Difference between the averages of males and females: $t=11.9$; $P<0.001$. SD, standard deviation.

affected males also showed precocious baldness, and 6 of them had dyskeratosis.

Table II presents the data on the dentition of persons with the syndrome or obligate carriers whose age was higher than 10 years, since the problems of this family appear mainly in the permanent teeth. The males had an average of 12 missing teeth (range: 9 to 16); females were much less affected (average: 2—generally the upper second incisors; range 1 to 8; 5 subjects showed no missing elements).

The number of sweat pores in the fingers of affected and apparently healthy adult members of the family studied as well as of their controls is shown in Tables III and IV. Male and female carriers of the gene consistently presented a lower

average of sweat pores (42% and 60% of the normal values, respectively) and a much higher degree of asymmetry, particularly evident in the Z_2 index (0.044 to 0.054, compared with 0.002 in the controls). The healthy members of this family show about the same number of sweat pores as their controls, presenting, however, an unexplained higher degree of asymmetry. Imprints were also obtained from 11 affected or obligate carriers and 5 healthy relatives of the latter, all under the age of 10 years; they were also compared with matched controls and the results obtained were similar to those of Tables III and IV. Since the numbers were small, however, no significance tests were applied. These data are available on request.

For the establishment of the pattern of inheritance

TABLE III
NUMBER OF SWEAT PORES IN FINGERS OF AFFECTED AND APPARENTLY HEALTHY MEMBERS OF FAMILY STUDIED AS WELL AS OF CONTROLS (MALES)

Hand and Finger	A (12)		C ₁ (12)		NF (12)		C ₂ (12)	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Right hand								
Finger 2	186	95	485	56	444	75	485	38
3	242	84	527	72	482	52	493	44
4	248	104	536	68	498	58	511	57
Total	225	88	517	62	475	59	489	43
Left hand								
Finger 2	178	102	478	75	437	74	473	54
3	222	108	525	82	493	79	503	53
4	231	117	549	73	523	72	528	53
Total	210	105	515	72	486	74	501	51
General total	218	91	517	67	481	64	495	46
Asymmetry								
Right + left	436	183	1032	128	961	128	991	93
Right - left	40	51	28	33	28	22	15	13
A ₂	5618	11507	2159	3156	2210	1731	996	914
Z ₁	0.057	0.048	0.013	0.009	0.015	0.006	0.009	0.006
Z ₂	0.044	0.064	0.002	0.004	0.002	0.002	0.001	0.001

A: Affected; C₁ and C₂: Controls; NF: Apparently healthy relatives of affected persons. The numbers of individuals studied are indicated in parentheses. $\bar{X}$: Average; SD: Standard Deviation. Right - Left is the mean of the sweat pore count of the right hand minus that of the left for each individual. A₂ is the mean of the square of the difference in sweat pore count between homologous fingers; Z₁ is the square root of A₂ divided by the total sweat pore count; Z₂ is obtained by dividing A₂ by the average of the sum of the squares of sweat pore counts on homologous fingers. All these calculations are done by individual. Only persons over 10 years of age were considered. The t-test showed that all the averages and asymmetry indices of the affected persons were significantly different from those of their controls.

TABLE IV
NUMBER OF SWEAT PORES IN FINGERS OF AFFECTED AND APPARENTLY
HEALTHY MEMBERS OF THE FAMILY STUDIED AS WELL AS OF
CONTROLS (FEMALES)

Hand and Finger	A + OC (20)		C ₁ (20)		NF (8)		C ₂ (8)	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Right hand								
Finger 2	267	158	474	63	476	106	535	48
3	312	185	508	51	513	107	557	54
4	332	197	514	43	512	88	569	45
Total	303	174	498	48	500	86	554	46
Left hand								
Finger 2	267	163	502	66	477	126	559	63
3	302	188	523	55	528	142	567	68
4	336	213	530	58	561	132	585	55
Total	302	187	518	57	521	131	570	58
General total	303	171	507	50	511	110	562	51
Asymmetry								
Right + Left	605	340	1016	99	1021	220	1124	102
Right - Left	74	89	29	30	42	89	18	16
A ₂	15607	37781	1958	2555	4061	3309	962	1077
Z ₁	0.059	0.055	0.012	0.007	0.018	0.012	0.008	0.005
Z ₂	0.054	0.095	0.002	0.002	0.004	0.005	0.001	0.001

A + OC, Affected + obligate carriers. C₁ and C₂, controls; NF, apparently healthy relatives of affected persons. The numbers of individuals studied are indicated in parentheses. $\bar{X}$, average; SD, standard deviation. Right - left is the mean of the sweat pore count of the right hand minus that of the left for each individual. A₂ is the mean of the square of the difference in sweat pore count between homologous fingers; Z₁ is the square root of A₂ divided by the total sweat pore count; Z₂ is obtained by dividing A₂ by the average of the sum of the squares of sweat pore counts on homologous fingers. All these calculations are done by individual. Only persons above 10 years of age were considered. The t-test showed that with one exception (A₂—with a very large standard deviation) all the averages and asymmetry indices of the affected persons were significantly different from those of their controls.

of the syndrome only those who had been subjected to the general clinical and odontological examinations, and from whom sweat pore counts had been made were considered. The data are shown in Table V. The hypothesis established was that the syndrome was conditioned by a dominant, sex-linked gene. No significant deviation from this hypothesis was observed in the offspring of affected females or among the sons of affected males; however, among the daughters of the latter, 4 were apparently normal: of these, 2 were 2 and 4 years, respectively. Since the dental problems, the

hypotrichosis, and changes in the texture and distribution of hair generally have a late onset in the family, only post-pubertal examinations will give assurance that these individuals will remain normal. As for the other 2, 1 19-year-old girl presented an essentially normal sweat pore count, 507, and did not show any clinical symptom. The third molars had to be extracted because of mal-position but this, of course, could have occurred independently of her genotype for the condition under consideration. The other girl was 22 years of age at the time of the examination; she was also clinically normal, showing a very high sweat pore count (598); the only abnormality found was the ectopic growth, in the palate, of her right upper canine. The penetrance of this gene in female obligate carriers can, therefore, be estimated to be $14 \times 100/18 = 78\%$, or $14 \times 100/16 = 87.5\%$ if the 2 children are not considered.

Discussion

As already stressed, the symptoms shown by the affected persons in this family are mild and generally do not interfere in a significant way with their viability or fertility. The psychomotor development and intelligence, though not measured by special tests, seemed normal, contrary to what was observed by Halperin and Curtis (1942) and Bernard *et al* (1963) in patients with this syndrome. The

TABLE V
TEST OF HYPOTHESIS THAT SYNDROME IS
CONDITIONED BY DOMINANT, SEX-LINKED GENE

	Offspring of Affected Males			
	Males		Females	
	Normal	Affected	Normal	Affected
Observed	12	0	4	15
Expected	12	0	0	18
	Offspring of Affected Females			
	Males		Females	
	Normal	Affected	Normal	Affected
Observed	7	17	9	9
Expected	12	12	9	9

Deviation considering the expected ratio of 1:1 in the sons of affected females: χ^2 , 3.4; 1 d.f.; $P > 0.05$.

frequency of asthma and of allergy to food or drugs is not significantly different from that found in the controls, which again differs from the findings of other authors (Vanselow *et al*, 1970; Reed, Lopez, and Landing, 1970). Atrophic rhinitis or the typical facies observed by other investigators in these types of dysplasia were not found either. Among the affected men, however, we encountered an increased incidence of non-specific skin lesions, dyskeratosis, and eczema.

In accordance with previous reports we observed among the affected a high degree of hair loss which usually starts at adolescence, leading to precocious baldness among the men and to a variable amount of hypotrichosis among the women; no case of complete alopecia, however, was found. Observations with the light microscope and scanning electron microscope revealed a distinct, hitherto undescribed, abnormality of the hair shaft among men and women with the syndrome. It is characterized by longitudinal clefts resulting in a nodular deformity and occasional transverse fissuring of the hair shaft. In addition to this abnormality, which was called 'trichorrhexis fissurata', dystrophic cuticular cells with micropits and disorganized fibrils of the hair shaft were also observed (Porter, Aoyagi, and Salzano, 1974).

In relation to the dental findings, it is clear that the abnormal males of the family described here are less affected than those described in other kindreds with a similar pattern of inheritance (cf., for instance, Reed *et al*, 1970). But it should be pointed out that quantitative data are scanty in relation to persons with this syndrome and even more so for obligate female carriers.

It is difficult to compare our results concerning sweat pore counts with those of other investigators, since the methods used were different. But we did not find complete absence of pores as in the patients of Frias and Smith (1968) or in those from families showing a pattern of sex-linked inheritance reported by Crump and Danks (1971). In relation to the affected women or obligate carriers data again are scanty, but while we found a reduction of 40%, Frias and Smith (1968) observed a stronger effect of the gene (a decrease of about 75%, with 1 of the carriers showing no pores at all).

The pattern of inheritance of the gene conditioning hypodontia, hypotrichosis, and hypohidrosis (syndrome 1, 2, 4 in Freire-Maia's, 1971 classification) was partially dominant X-linked in seven other instances (Emery, 1964; Frias and Smith, 1968; Verbov, 1970; Reed *et al*, 1970; Katz and Penneys, 1971; Mochizuki, Teramura, and Kawai, 1971; Crump and Danks, 1971). It is time, there-

fore, to review the concept that anhidrotic ectodermal dysplasia is usually inherited through an X-linked recessive gene. Probably the opposite is true, the syndrome only rarely manifesting itself in this way. To establish this with assurance, however, many more detailed studies are needed, in which special attention should be given to the female carriers.

The high degree of asymmetry and high variance in sweat pore counts observed among the affected females is in good agreement with the Lyon hypothesis of random inactivation of one X chromosome (Lyon, 1962). We have not found, however, the mosaic distribution of sweat pores described by Passarge and Fries (1973) in other obligate heterozygotes with this condition.

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