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The Sabinas Syndrome

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SUMMARY

We have defined a new autosomal recessive disorder in patients stemming from a small community in northern Mexico. Diagnosable at birth, its major symptoms include brittle hair, mental retardation, and nail dysplasia. Structural hair abnormalities are seen by both light and electron microscopy. Hair cystine content is reduced while the copper/zinc ratio in hair is increased.

INTRODUCTION

As stated in our preliminary report [1], subsequent careful evaluation of the proband and her brother revealed no diagnostic biochemical abnormalities. There was increased copper and zinc in their scalp hair as determined by semiquantitative X-ray fluorescence, and reduced content of sulfur amino acids in their hair. Also of significance, both children were documented to be mildly retarded. Morphologic hair abnormalities under both light and scanning electron microscopy were dramatic.

Subsequently, because of the unique condition of these patients and the probable hereditary nature of their complaint, arrangements were made to study other involved families in Sabinas (fig. 1). Eleven more patients were located and studied by means of complete histories and physical examinations, analyses of serum trace metals, ceruloplasmin concentration, urine and serum amino acids, and routine metabolic urine screens [2]. In addition, serum and urine luteinizing hormone

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FIG. 1.—Map of Mexico indicating the relative location of Sabinas in relation to several other major Mexican cities.

(LH) and follicle-stimulating hormone (FSH) values were determined on four patients, and these were interpreted in conjunction with total plasma estrogen, estradiol, and testosterone levels [3]. All biochemical sampling of patients and other local persons were done in Sabinas. Samples were frozen and returned directly to Houston by private plane within hours of collection. Also, radiographic skeletal surveys and psychometric examinations in Spanish were performed on available patients.

CLINICAL FINDINGS

All affected individuals manifested a similar general appearance (fig. 2). The family pedigrees of 12 patients (fig. 3) show cousin marriages, normal parents, and equal sexes affected. These findings are consistent with an autosomal recessive inheritance. Each newborn patient could be readily identified clinically on the basis of persistent congenital scalp hypotrichosis. Pressure points near the temporal areas and at the occiput were most severely affected and were usually devoid of hair. Male-pattern baldness effect on scalp roots was evident in two older male patients from family 5 (fig. 3). In postpubertal patients, virtually no axillary or pubic hair was present, although a few sparse otic hairs and some vibrissae could be seen. One adult male patient had a moustache. None of the patients had ever required a haircut. For cosmetic purposes, those patients having some visible scalp hair used large amounts of tonsorial products for manageability. Others used skin oil for this purpose. On close examination, the scalp hairs were very brittle, coarse, wiry in texture, and broke off quite easily with mechanical trauma such as comb-

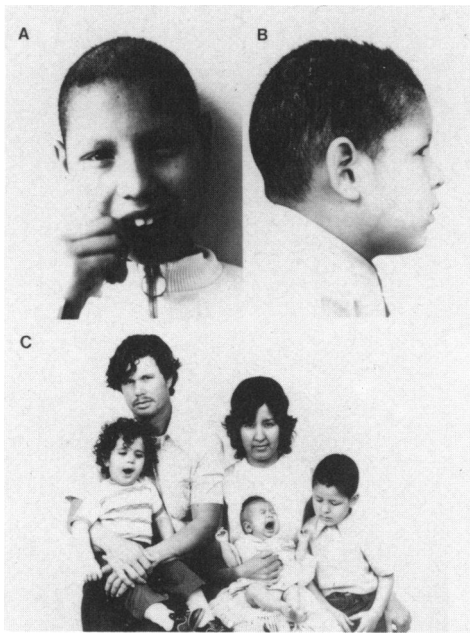

FIG. 2.—*A*, Female patient with short, brittle hair and marked reductions in eyebrows and eyelashes. *B*, Patient R. G., an affected male in the G. family. He has never had a haircut, and his hair is short and abnormal in appearance. *C*, The G. family, the index family in our study of the Sabinas syndrome. The parents and unaffected child on the *left* have abundant, normal hair, whereas the infant and child on the *right* have short, brittle hair.

ing and brushing. Some hairs could be visualized in their follicles, which were broken off at the skin line. Most patients had accompanying hyperkeratosis of moderate degree on exposed surfaces.

The most dramatic finding, the hair abnormality, was impressive under the light microscope (fig. 4*A* and 4*B*). Scanning electron microscopic photographs of hair from these persons and control subjects are seen in figures 5*A–D*.

All patients had moderate to significant nail dystrophies, with splitting and cracking proximally. Sections of the entire nail could be broken away in some severe instances (figures 6*A* and 6*B*). There was significant pigmentary retinopathy present in one of our patients, and by history in his sister as well (family 5, generation IV). One of the patients (family II) had unilateral congenital tortuosity of the retinal vessels. Other patients from other families manifested pale optic discs, without other associated ocular or visual abnormalities.

Maxillary hypoplasia was significant in many patients. The brittle, short hair, reduced eyelashes, crowded teeth, and dull appearance created a characteristic facial appearance (fig. 2). Post-pubertal patients had development of secondary sexual characteristics consistent with their age, except for sparse pubic escutcheons.

Of the older patients (family 1, 17-year-old female; family 3, 20-year-old female; family 5, 39-year-old male, 35-year-old female, and 25-year-old male), two females were married and had no offspring.

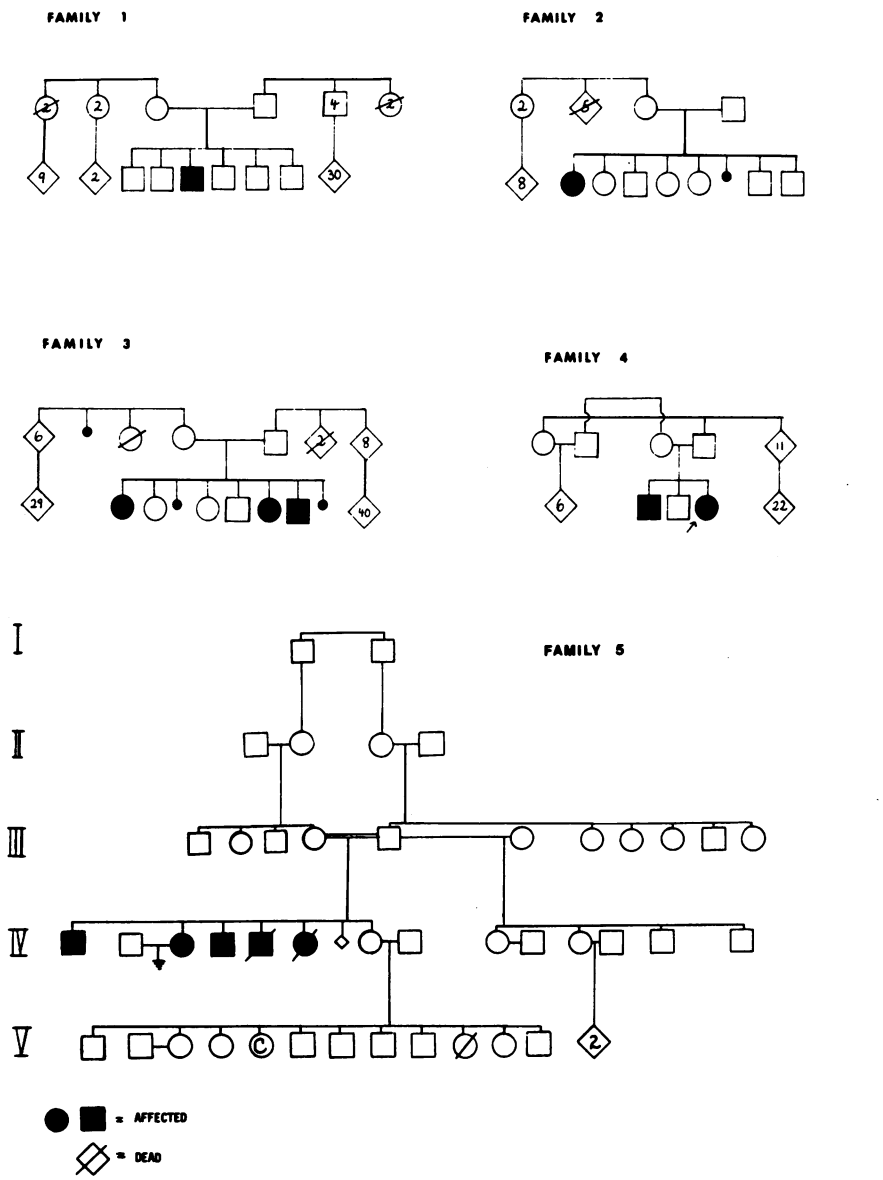

FIG. 3.—Pedigrees from five families with affected patients with Sabinas syndrome. Note that there are both male and female affected offspring born to normal parents. In family 5, there is consanguinity in the parents.

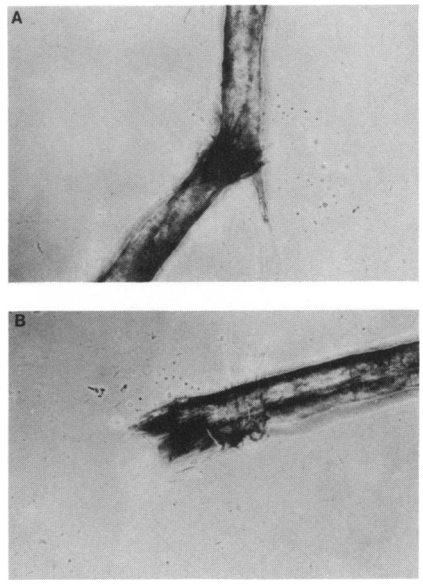

FIG. 4.—*A* and *B*, Light microscopic views of affected hair demonstrating general irregular structure and breaks within the hair as well as marked fraying of the ends where previously broken.

PSYCHOLOGICAL TESTING

In-depth psychometric testing was carried out on six patients by an experienced examiner who regularly works in the Sabinas area of Nuevo Leon. All cases studied demonstrated some degree of mental deficiency; I.Q.'s ranged between 50–60. A deficiency in eye-hand coordination was noted. Only one of the patients

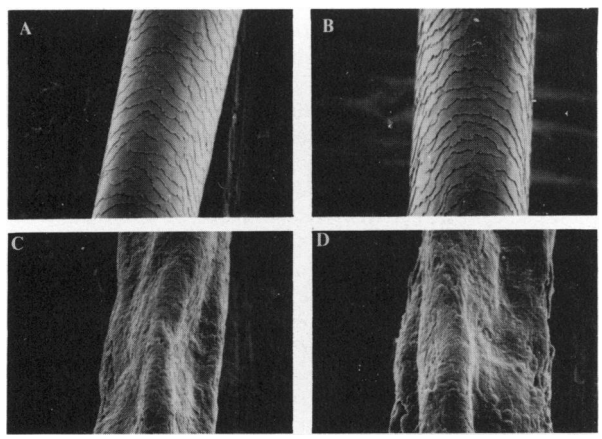

FIG. 5.—*A* and *B*, Scanning electron photomicrographs of normal hair showing very regular structure and usual barklike cuticle. *C* and *D*, Scanning electron photomicrographs of hair from Sabinas syndrome patients. When compared with normal (*A* and *B*), there is marked irregularity and absence of the usual scalelike surface.

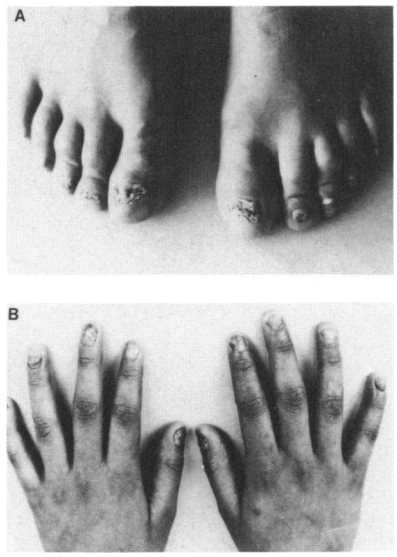

FIG. 6.—*A* and *B*, Onychodysplasia

initially appeared normal. On testing, however, he was clearly functioning in the mentally deficient range.

MATERIALS AND METHODS

Serum and amino acid analyses were done utilizing quantitative ion-exchange chromatography and a modified Beckman 121 analyzer directly interfaced with a computerized identification, and quantification programs as previously described [4].

Amino acid analysis of all patients and ethnically matched control samples were within normal limits. Red cell antigen, enzyme, and serum protein typing of involved individuals, known carriers, and controls were carried out for purposes of linkage analysis. Unfortunately, no clear-cut linkage ascertainment could be made on the basis of these studies.

Quantitative urinary carbohydrate studies carried out on two patients and appropriate controls were within normal limits. Quantitative amino acids serum from all patients was normal. Studies on matched controls from Sabinas gave values similar to Houston controls. Quantitative analysis of uv-absorbing compounds on one family (R. G., B. G., parents, and siblings) were normal. This method quantitates purines, pyrimidines, and a variety of other compounds of biologic significance that absorb in the uv spectrum.

Routine blood chemistries on a group of six patients with Sabinas syndrome showed no abnormalities when compared to Houston normals or a group of local Sabinas controls.

Quantitative amino acid analyses on the hair hydrolysates were performed using the following methods. One to 6 mg of dried hair was mixed with 2 ml of 6 molar HCl per mg of hair. Containers were flushed with nitrogen and sealed in order to minimize oxidation of the cystine and other labile acids during hydrolysis. Oxidation of cystine or cysteine results in the formation of cysteic acid among others. Thus, cysteic acid is a measure of the degradation and loss of cystine. Hydrolysis was continued for 24 hrs at 100°C. This timing gives reproducible and complete hydrolysis of the peptide linkages [5].

Sulphur, copper, zinc, and iron were analyzed in hair strands utilizing X-ray fluorescence spectroscopy. The hair strands were air-dried and placed on slides prior to analysis. Each hair sample produced a spectrum in the area of the individual peaks and were calculated to

adjust for different masses of hair presented to the X-ray beam. The scattered peaks of all samples were normalized, and a metal area to match peak area of ratio was calculated.

Sulphur, copper, zinc, and iron were thus analyzed and a copper-zinc ratio calculated. The *F* test for significance was performed to show any difference in the variance between the affected and the nonaffected individuals.

Chromosomal analyses of leukocytes from the propositus (R. G.) showed no abnormalities using banding techniques. Skin fibroblasts were cultured from control and affected patients utilizing skin biopsies obtained from the upper deltoid area. The technique and maintenance of the cultures were carried out as we described in [6]. The zinc and copper contents of cultured skin fibroblasts from individuals with the Sabinas syndrome and unaffected controls were determined using atomic absorption spectrophotometry and microsampling techniques. Previous studies of this type have been described from this laboratory [7].

RESULTS AND DISCUSSION

Amino acid analyses of control hair when compared with those of patients with the Sabinas syndrome showed very striking differences with regard to content of sulphur amino acids. Table 1 shows that control hair contains more than twice as much cystine per gram hair than does the affected hair in Sabinas syndrome. As in previous descriptions of amino acid abnormalities in the trichorrhexis nodosa of arginosuccinicaciduria, there were increases in lysine, aspartic acid, alanine, leucine, isoleucine, and tyrosine.

TABLE 1

HAIR AMINO ACID COMPOSITION (μmol/g)

AMINO ACID	CONTROL (NO. = 10)		ABNORMAL (NO. = 3) (SABINAS)			
	$\bar{X}$	SEM	$\bar{X}$	SEM	t	*P*
Aspartic acid	388.2	18.0	552.5	31.2	4.435	.005
Threonine	593.5	29.0	396.9	25.2	3.514	.005
Serine	946.3	51.1	719.2	38.5	...	...
Glutamic acid	938.9	43.1	1053.6	49.5	...	...
Proline	678.4	46.2	843.8	205.6	...	...
Glycine	474.4	28.3	485.2	26.7	...	...
Alanine	369.8	16.5	508.4	24.3	4.174	.005
Citrulline	13.2	5.2	8.4	4.4	...	...
Valine	442.6	21.6	435.6	22.0	...	...
Cystine	548.2	38.4	151.4	8.8	5.479	.001
Methionine	30.3	1.8	40.2	5.0	...	...
Isoleucine	199.2	10.6	297.4	40.0	3.534	.005
Leucine	503.4	23.3	719.6	20.4	4.800	.001
Tyrosine	173.4	11.2	255.7	17.6	3.626	.005
Phenylalanine	137.5	10.8	177.9	18.5	...	...
Ornithine	10.0	3.6	10.5	7.8	...	...
Lysine	162.3	12.0	258.0	10.2	4.136	.005
Histidine	49.2	4.3	52.8	1.5	...	...
Arginine	511.9	49.8	402.4	14.3	...	...

X-ray fluorescent studies of the hair demonstrated iron and copper concentrations that were significantly greater than in control hair. The zinc content of the hair samples, however, was not significantly different between affected and nonaffected controls (table 2).

Concentrations of zinc and copper in the cultivated skin fibroblasts from patients and their relatives were all within normal limits. Serum ceruloplasmin concentrations in both patients and carriers for this condition were also within normal limits.

Light and scanning electron microscopy of hairs taken from affected patients and control patients demonstrated striking differences. There was a noticeable loss of cuticle in the affected hair, and considerable disorganization in the surface of the hair (fig. 5*A–D*). The findings were identical with the original patient report from this laboratory [1]. In addition to the deficient cuticle cell formation, trichorrhexis nodosa was seen by light microscopy (fig. 4*A* and 4*B*). X-ray fluorescent studies did not demonstrate contamination with toxic trace metals such as thallium that would have been detected by this technique. Light microscopy examination of the hair did not demonstrate any evidence of monilethrix, pili torti, or other structural abnormalities.

These laboratory and family studies of patients with Sabinas syndrome have further enabled clear delineation of this disorder as being autosomal recessive. This can best be seen in figure 3, family 5, in which the parents of the affected offspring are consanguineous and unaffected. The siblings and half-siblings of the affected are not clinically involved, and there is no sign of the disorder in preceding or subsequent generations. A further test of the autosomal recessive postulate for this disorder cannot be performed on the basis of accumulated pedigree data because reproductive potential appears to be reduced in all affected patients. Because of the apparent decrease in fertility among affected patients, screening

TABLE 2

TRACE METAL CONTENT OF HAIR (SABINAS PATIENTS AND CONTROLS)

	Fe	Cu	Zn	Cu/Zn
Affected:				
Mean value	.020	.011	.039	.390
SD	.013	.007	.028	.229
SEM	.006	.003	.014	.114
No. subjects	3	3	3	3
Nonaffected:				
Mean value	.008	.007	.055	.141
SD	.005	.004	.041	.039
SEM	.001	.001	.013	.013
No. subjects	8	8	8	8
P test	6.693	3.732	.479	34.415
Significance	.05	.10	N.S.*	.001

* N.S. = not significant.

tests were performed on four of the younger post-pubertal patients. Sex steroid levels were appropriate for their menstrual phase and pubertal level (table 3). Only one of the three girls studied (I. C.) was more than 2 years post menarche. Her menses were normal and regular. Gonadotropin levels were not elevated, indicating no evidence of primary gonadal failure. All were slightly delayed but not pathologically late in entering puberty. The one male examined (C. C.) had normal testicular size (3.2 × 1.8 cm) and consistency for his stage of development. In the group that underwent endocrine studies, all but patient I. C. were still actively growing at the time of this examination. Although the number of patients studied and the information obtainable was limited, a nonendocrine cause is suggested for the decreased number of offspring among affected adults.

All the examined families have either originated from or currently live in Sabinas Hidalgo. We feel therefore that a founder effect is likely to be present in this small, remote, northern Mexican village.

Despite laboratory investigations, a specific biochemical basis in this autosomal recessive entity has not been ascertained. Serum ceruloplasmins were normal. Quantitative studies of urinary carbohydrate excretion analyzed by ion-exchange chromatography were within normal limits. Usual blood chemistries were normal.

The differential diagnosis of this syndrome includes a wide variety of related congenital hair abnormalities ([8–19] and table 4). Each of these clinical syndromes shares several characteristics with the Sabinas disorder, and should be thoughtfully considered in the differential diagnosis. Many share low hair sulfur content. We feel that virtually all these conditions can be separated from Sabinas syndrome if careful investigations are made. For example, the alopecia congenita of Stevanovic [15] can be ruled out on the basis of (1) its significant hyperkeratotic

TABLE 3

ENDOCRINE STUDIES ON SABINAS PATIENTS

	PATIENT			
	M. R.	B. C. G.	I. C.	C. C.
Age	14½	15	21¼	14⅚
Sex	Female	Female	Female	Male
Age at menarche	14¼	About 13½	14	...
Tanner stage (estimated)*	3	4	5	3
Menstrual phase	Follicular	Follicular	Follicular	...
Estradiol (μl, day 1–10, 25–70 pg/ml)	27	53.7	46.3	...
Testosterone (nl adult, 300–1200 ng/dl)	...	...	...	97
Serum LH (nl adult male, 3–12 ml μ/ml; premenopausal female, 2–25 ml μ/ml)	10.5	8.2	10.7	2.5
Serum FSH (ml adult male, 3–12 mIU/ml; premenopausal female, 3–30 mIU/ml)	7.7	5.5	6.4	2.8
Urine LH IU/hr†	0.055	0.11	0.29	0.14
Urine FSH IU/hr†	0.12	0.12	0.21	0.014

* Based on breast and genital development since it was not possible to define hair quality and distribution.

† Calculated from 4-hr urine collections. Only patient C. C. had values in the normal adult range for the published method [3].

TABLE 4

DIFFERENTIAL DIAGNOSIS OF SABINAS SYNDROME

Reference	Similar features	Dissimilar features	Genetics
Sabinas syndrome—this report	Alopecia, brittle hair, oligophrenia, and onychodysplasia	...	Autosomal recessive
Roselli and Gulienetti [16]	Alopecia, some with oligophrenia	Few teeth, hypohydrosis	X-linked
Weiss et al. [8]	Hypotrichosis	Multiple other somatic anomalies, including cleft lip, webbed knees	Autosomal recessive
Gorlin and Cervenka [17]	Hypotrichosis	Hypohydrosis, few teeth	Autosomal recessive
Gorlin and Cervenka [17]	Alopecia universalis	Amelogenesis imperfecta	?
Crandall et al. [18]	Alopecia with pili torti, oligophrenia	Endocrine abnormalities, deafness	Autosomal recessive
Shih [19]	Trichorrhexis nodosa and mental retardation	Arginosuccinic acid in blood and urine	Autosomal recessive

component and (2) its Mendelian dominant inheritance; another closely related entity, hidrotic ectodermal dysplasia of Clouston [20], can be differentiated by hyperpigmentation of the skin and also by its dominant mode of inheritance. Other familiar disorders summarized in table 4 can also readily be differentiated from Sabinas syndrome when careful attention is paid to their dissimilar features.

A very similar disorder in Monterrey, Mexico, has been reported by Cantu et al. [13, 14]. Unlike their patients, white cell counts were normal in our first two patients but not studied in our last patients. Their patients have not had the extensive biochemical studies that would permit their direct comparison with Sabinas syndrome.

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