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Rapp-Hodgkin hypohidrotic ectodermal dysplasia syndrome

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Four members in three generations of a family had Rapp-Hodgkin hypohidrotic ectodermal dysplasia syndrome with variable involvement of teeth, hair, nails and palate, characteristic facies and mild heat tolerance problems. In addition, the proband had a high sweat sodium, hypogenitalism, hypothelia and marked cicatricial scalp atrophy and scarring. Inheritance of the condition was consistent with an autosomal dominant mode and the manifestations are described to delineate further this rare phenotype.

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More than 200 clinically or genetically distinct forms of ectodermal dysplasia are known. A number of these occur as part of ectodermal dysplasia malformation syndromes which may include cleft lip and palate (Freire-Maia & Pinheiro 1984). It is possible that the ectodermal dysplasia/clefting syndromes form a distinct sub-group which are aetiologically heterogeneous (Pinheiro & Freire-Maia 1980).

Case Reports

The proband, C.P. IV-3 (Fig. 1 & 2) was the second live-born female child of a 25-year-old mother and 29-year-old unrelated father. Pregnancy and labour were normal and the infant's condition was satisfactory following a normal delivery. She was noted at birth to have curly, black, soft, woolly hair, a prominent forehead, hypoplastic nails and a low nasal bridge.

At age 2 months, she was seen because of difficulty with feeding, poor weight gain and episodes of cyanosis with nasal regurgitation. She had a short palate and sub-mucous cleft with a large velo-pharyngeal space and inefficient closure. The dome of the scalp was desquamated, with loss of brittle hair and secondary infection, and there was epiphora and chronic conjunctivitis with sparse eyelashes and brows. The nails were narrow and brittle and had never required cutting. The breast nipples were mildly swollen and inflamed, and later became retracted, scarred and shiny. The facies showed a high broad forehead with a narrow, pinched nose, small mouth and jaw and mid-facial hypoplasia. The external genitalia were hypoplastic with fused labia; a genitogram and cystogram showed normal uro-genital anatomy. Other normal investigations included urea and electrolytes, high-resolution chromosomal studies, plasma and urine aminoacid chromatography, and immune function. A biopsy of the skin from the plantar surface of the foot was

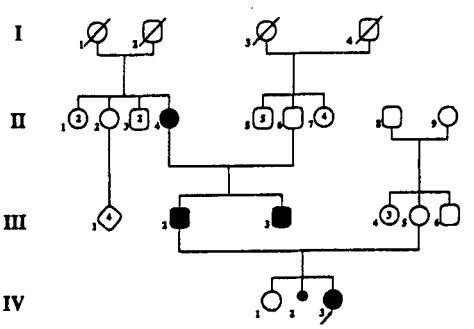

Fig. 1. The pedigree of the affected kindred.

reported as showing no specific abnormality on light or electron microscopy. Electron microscopy of the hair showed longitudinal spiralling, grooving and some mid-shaft flattening, typical of pili torti.

CP when recently seen (Fig. 3), now aged 10, was of normal stature and had cicatricial scalp lesions in association with disfiguring pustular folliculitis. Recurrent labial fusion required topical dienoestriol applications. She had mild heat intolerance, and dentition appeared small crowded and worn, with stippled enamel. An orthopantomograph x-ray showed all dentition apart from wisdom teeth to be present, and rolling of the anterior gingival tissues adjacent to the upper incisors was observed. Nails appeared irregular and dysplastic although sections were normal on microscopy, and numerous cultures for fungi proved negative. Plastic surgery had achieved satisfactory palatal competence.

A.P. III-2 (Fig. 1), the father of IV-3, was of normal physique and intellect and had significant problems with palatal insufficiency, a bifid uvula, rhinitis and multiple ear infections in childhood. These difficulties became less significant in adult life, but there was persisting conjunctivitis and epiphora. Despite reasonable dental attention, his teeth were said to have been reduced in number with pegging, and he was edentulous by the age of 17 years. His hair had always been brittle, unruly, dry and sparse. When examined, he had baldness extending from the wide frontal area to the crown and, apart from pubic hair, other body hair appeared thin. His facial features were similar to but less marked than IV-3. He thought he sweated less than other individuals, but had no subjective discomfort in hotter environments.

Fig. 2. The proband, (C.P., IV-3), aged 1 year. Features of Rapp-Hodgkin ED syndrome to note are the high forehead, the pinched nose with hypoplastic mid-face, small carp-shaped mouth, sparse short eye-lashes and brows which are thin laterally. The scalp hair is thin, short, coarse and wiry.

M.P. III-3 (Fig. 1), the proband's paternal uncle, was of low normal intellect, and had generally good health. He had a short palate with insufficiency, which caused significant symptoms of regurgitation, palatal speech,

Fig. 3. The proband (C.P. IV-3), aged 8 years, showing the thin, unruly, brittle, wiry scalp hair with a large chronic central cicatricial lesion.

rhinitis, conjunctivitis and epiphora. Scalp hair was brittle and sparse with extensive balding and less severe cicatricial scalp lesions than the proband, and loss of body hair, eyelashes and eyebrows. He was edentulous by the age of 13 years and had dysplastic nails. He did not experience significant heat intolerance. Electron microscopy of hair shafts showed typical pili torti (Fig. 4), as in the proband.

The mother of III-2 and III-3 was of normal physique, had a submucous cleft palate and became edentulous early in the second decade of life. She had severe hypotrichosis with sparse eye-lashes and eye-brows, and alopecia necessitated wearing a wig from the age of 24 years. She had chronic conjunctivitis with epiphora, and her nails were narrow and broke easily. She was aware of increasing discomfort with raised environmental temperatures, and complained of reduced sweating ability.

Investigation of Hypohidrosis

In order to document the degree of hypohidrosis in the affected individuals III-2 and IV-3, sweat pore counts were performed according to the method of Crump & Danks (1971), and sweating was induced by standardised iontophoresis (Passarge & Fries 1977).

IV-3 had 34.3 sweat pores per cm of epidermal ridge (normal range for age being 33 to 41.25); III–2 had 22.3 (normal range for age being 21 to 29.3); III–5 had 28.2 (normal range for age 27.5 to 30) and IV-2 had 36.1 (normal range for age being 30 to 38.25).

IV-3 produced 0.214 g and 0.219 g of sweat on separate analyses, and the sodium levels were elevated at 78 mmol/l and 156 mmol/l, respectively. III-2 produced 0.149 g of sweat with a sodium level of 49 mmol/l, III-5 0.122 g of sweat and a sodium level of 34 mmol/l, and IV-2 0.368 g of sweat with a sodium level of 30 mmol/l; these levels were all within the normal range on repeated study.

Discussion

Classification of the ectodermal dysplasias has become more complex as the number of specific syndromes expands (Freire-Maia & Pinheiro 1984). Delineation of the ectodermal dysplasias is based on the extent, nature and severity of ectodermal involvement, as well as the presence of associated malformations and the mode of inheritance. Rapp & Hodgkin (1968) described a specific entity, similar to hypohidrotic ectodermal dysplasia, which could be differentiated by the finding of palatal clefts. The classical features of hypohidrotic ectodermal dys-

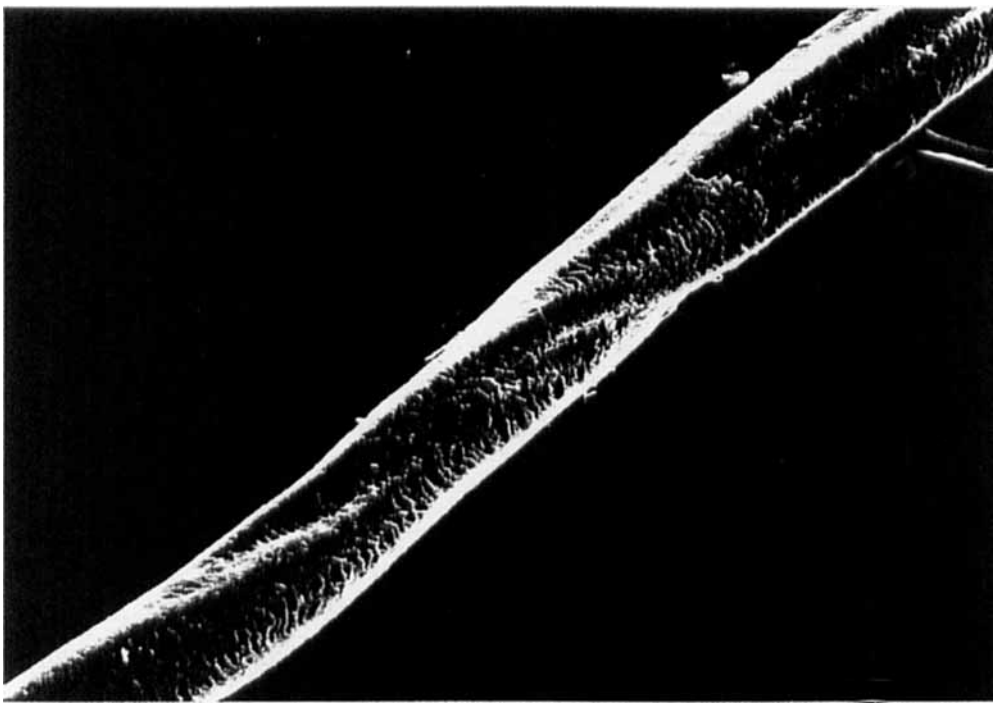

Fig. 4. Scanning EM of hairshaft (M.P. III-3) shows some mild flattening of the shaft with 180° longitudinal twist as seen in pili torti. There is also longitudinal grooving.

plasia, such as the narrow, pinched nose, microstomia and high broad forehead, shallow mid face, hypotrichosis and abnormalities of teeth with dysplastic nails are constant features of the Rapp-Hodgkin type. The distinctive features of Rapp-Hodgkin ectodermal dysplasia syndrome include palatal clefting, with or without lip involvement, palatal incompetence, abnormalities of the uvula with associated conjunctivitis, epiphora, rhinitis and chronic ear infections. Breathy voice changes have been described (Peterson-Falzone et al. 1981) and the genital abnormalities of hypospadias and/or hypogenitalism and minor syndactyly of the toes are less frequent associations (Stasiowska et al. 1981). Families reported with this condition indicate autosomal dominant inheritance, and male-to-male transmission has been described (Montes-G & Salinas 1986).

The patients reported in this paper have sufficient features to diagnose Rapp-Hodgkin ectodermal dysplasia syndrome and are compared with previous descriptions (Table 1). In addition, both the proband and her uncle had chronic, atrophic cicatricial scalp lesions and alopecia, which was aggravated by warmer temperatures. Electronmicroscopy of hair showed those changes previously described by Silengo et al. (1982). The proband also had labial hypoplasia and persistent labial adhesions. Bowen & Armstrong (1976) described an ectodermal dysplasia syndrome in 3 female siblings, 2 of whom had marked atrophic cicatricial scalp lesions, genital hypoplasia in association with cleft lip and palate, hypodontia, skin

Table 1

Summary of published reports of Rapp-Hodgkin ectodermal dysplasia syndrome[1]

Clinical features	Rapp & Hodgkin[2]	Summitt & Hiatt	Stasiowska et al.[3]	Schroeder & Sybert	Walpole & Goldblatt	Total
No. of individuals	3	1	2	2	4	12
1. FACE	2F 1M	1M	2F	1F 1M	2F 2M	7F 5M
Prominent forehead	3	1	2	1	4	11/12
Hypoplastic mid-face	NR	1	2	2	4	9/9
Pinched nose/short collumela	1(2NR)	1	2	2	4	10/12
Small mouth	3	1	1	1	3	9/12
2. HAIR						
General hypotrichosis	3	1	NR	NR	4	8/8
Scalp alopecia	3	1	1	2	4	11/12
Sparse eyebrows	3	1	2	2	4	12/12
Eye lashes sparse	3	1	2	2	4	12/12
3. CLEFT LIP/PALATE						
Absent uvula/palatal dysfunction	3	1	2	2	4	12/12
4. HEAT INTOLERANCE	1	1(?)	–	–	2	4/12
5. TEETH						
Hypodontia	3	1	2	2	3	11/12
Misshapen/poor enamel	3	1	2	2	4	12/12
6. NAILS						
Dystrophic/hypoplastic	3	1	2	2	4	12/2
7. EYE						
Epiphora	NR	1	1(NR)	–	2	4/7
Conjunctivitis	1	1	1	1	2	6/12
8. SHORT STATURE	–	1	–	–	–	1/12
9. HYPOGENITALISM						
(including hypospadias)	1	1	–	–	1	3/12
10. SYNDACTYLY – 2nd &3rd toes	NR	1	2	–	–	3/9

1. Does not include the brief abstract of Montes-G & Salinas (1986). 2. Additional report by Wannarchue et al. (1972). 3. Additional report by Silengo et al. (1981). NR: Not reported.

abnormalities and normal sweating. This condition could be differentiated from Rapp-Hodgkin ectodermal dysplasia syndrome in that all 3 sibs and significant intellectual handicap and cutaneous syndactyly of toes, and the mode of inheritance was most likely recessive.

Sweating and heat tolerance were reduced to a variable extent in this kindred in accordance with previous reports (Rapp & Hodgkin 1968, Stasiowska et al. 1981, Schroeder & Sybert 1987). Patients IV-6 and IV-4 reported some discomfort in higher environmental temperatures but not to the degree originally described by Rapp & Hodgkin (1968). Sweat pore counts have been used for heterozygote detection in X-linked and autosomal recessive forms of hypohidrotic ectodermal dysplasia (Crump & Danks 1971). In X-linked hypohidrotic ectodermal dysplasia, interpretation of the test is compounded by the significant variation in counts in normal individuals. Members of this family, in whom sweat pore counts could be obtained, had sweat gland levels in the lower normal range (Crump & Danks 1971, Passarge & Fries 1977, Frias & Smith 1968). The elevated sweat sodium in the female proband is of interest, as a similar finding has previously been reported by Robinson et al. (1962) in a family with hypohidrotic ectodermal dysplasia, sensori-neural hearing loss, polydactyly and syndactyly.

The proband's mammary complications of hypothelia were unusual, but athelia has been previously reported in a female with anhidrotic ectodermal dysplasia by Burck & Held (1981). Her nipple area became

smooth with loss of obvious nipple punctate characteristics following a prolonged period of inflammation. Ectodermal dysplasia in a female with athelia and hypogonadism has been described in association with a pericentric inversion of chromosome 9 (Moreno Fuenmayor et al. 1981), but our patient had a normal karyotype.

Dental abnormalities are a consistent though variable feature of Rapp-Hodgkin ectodermal dysplasia syndrome and in our proband consisted only of microdontia, enamel pitting and caries. Two of the patients, now edentulous, were said to have had characteristic pegging of their teeth and one had no secondary dentition. Nail changes were similar to, but less florid than those described and depicted by Schroeder & Sybert (1987).

This paper details the clinical manifestations of Rapp-Hodgkin ectodermal dysplasia syndrome in 3 generations of an affected kindred in order to delineate further this rare phenotype. The high sweat sodium in the proband is particularly interesting and warrants further investigation in the light of recent discoveries of underlying mechanisms in cystic fibrosis. The segregation pattern in this 3-generation family supports the evidence for autosomal dominant inheritance of Rapp-Hodgkin ectodermal dysplasia syndrome.

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