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Clinical Report

Hypothelia, Syndactyly, and Ear Malformation—A Variant of the Scalp-Ear-Nipple Syndrome ?: Case Report and Review of the Literature

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The scalp-ear-nipple syndrome is a rare autosomal dominant condition that involves lesions of the scalp, malformed external ears, and absence of rudimentary nipples and breasts. We report a case of a woman with hypothelia, bilateral mildly malformed ears, and syndactyly of the hands and feet, and review the literature on the hypothelia/athelia phenotype. This case may represent a mild phenotype of the scalp-ear-nipple syndrome or a newly recognized entity. © 2005 Wiley-Liss, Inc.

KEY WORDS: hypothelia; athelia; syndactyly; ear malformation

INTRODUCTION

Cases of hypothelia or athelia are rare, and are divided into two main sub-groups: Absence of breast and nipples (OMIM 113700) and scalp-ear-nipple syndrome (OMIM 181270). Scalp-ear-nipple syndrome was first described by Finlay and Marks [1978] in a family with 10 affected individuals over 5 generations. All of them had firm, bald nodules over the posterior aspect of their scalps that were raw at birth, but healed during their childhood years. The tragus, antitragus, and lobules of their ears were small and poorly formed with the superior edges of their helices 'folded over' to an exceptional degree. Nipples were either rudimentary or absent. Secondary sexual hair was scant.

CLINICAL REPORT

We report a 30-year-old woman who was born at term to a then 27-year-old mother who had been treated prenatally with medroxyprogesterone because of two previous miscarriages. The pregnancy was otherwise unremarkable, with no exposure to known teratogens. Birth weight was 3,430 g (50th centile) and length was 49.5 cm (50th centile). Developmental milestones were normal. She failed to develop any breast tissues, but did develop other secondary sexual characteristics, and menstruated at the end of her 8th grade. Although she had recurrent ear infections during her early childhood, her hearing and vision screens were normal.

On physical examination, low-set rudimentary nipples were noted on her mammary line, 7 cm below the expected nipple site under her reconstructed breasts. Both ears were normal in size. Her right ear was over-folded and mildly posteriorly rotated. Mild cutaneous syndactyly of the second, third, and fourth digits in both hands and feet was noted (Figs. 1 and 2). She did not have the typical findings of ectodermal dysplasia on examination of her hair, teeth, nails, or palms, and she had no lesions on her scalp. Karyotype was normal (46,XX).

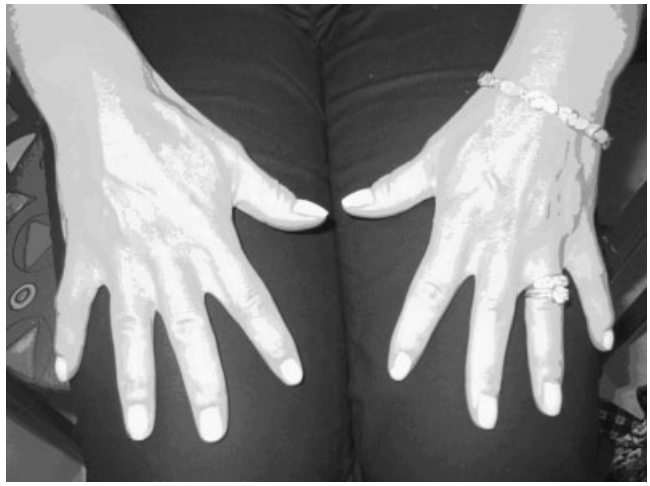

Fig. 1. Syndactyly of the fingers.

DISCUSSION

The findings in our patient suggest either a mild variant of the scalp-ear-nipple syndrome or a newly recognized entity. The following review is pertinent.

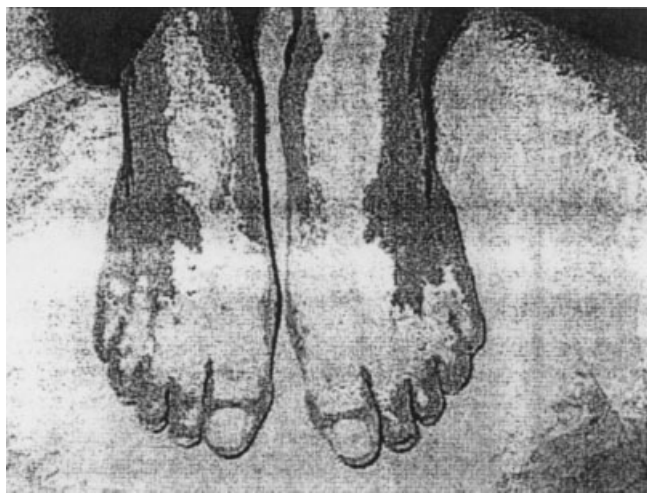

Fig. 2. Syndactyly of the toes.

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TABLE I. Hypothelia/Athelia Cases Previously Reported in the Literature

Reference	Our Case	Wylie [1888]	Batchelor [1888]	cited in Trier [1965]	Kowlessar and Orti [1968]	Kiskadden et al. [1949]	Trier [1965]	Dumic et al. [2002]	Tsakalakos et al. [1986]	Greenberg [1987]	Goldenring and Crelin [1961]	Lin et al. [2000]	cited in Trier [1965]	Wilson et al. [1972]	cited in Trier [1965]	Burck and Held [1981]	Wilson et al. [1998]	Al-Gazali et al. [2002]	Tuffli and Laxova [1983]	Finlay and Marks [1978]	Le Merrer et al. [1991]	Edwards et al. [1994]	Plessis et al. [1997]	Picard et al. [1999]
No. of Patients	1	1	1	7	2	1	1	1	2	1	2	2	2	7	7	4	1	2	2	10	1	7	1	2
"Syndromic"	+	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Assoc. syn[a]															ECD	ECD	ECD	ECD	ECD	SEN	SEN	SEN	SEN	SEN
Anhidrosis									–						+	–			+					
Inheritance[b]	S	S	S	AD	AR	S	S	S	S	S	AD	AD	AD Pen-	AD/ XLD	XLR	S	S	AR	AD	AD	AD	AD	AD	AD
Developm. Delay								speech		+							+	+						
FIT								+		+								+						
microcephaly								+													+			
Scalp defect	–													+					+	+	+	+	+	+
Scant hair									+	foc					+	+							Thin	
Scant eyelash and eyebrow									1/2							+								1/2
Scant sex. hair									+		+					+				+		3/7		
Dysplastic nails									+										+	+		+	1/2	
Dysplastic teeth									+			+			+	+			1/2			+	+	
Syndactyly	+												1/2							+		7/7		1/2
Malform. ears	+						+									+		+		+	+	+	+	+
Hearing impair								+	+	+		+					Mild	+						
Choanal atresia/ stenosis								+		+		1/2					+	+						
Limb anomalies						+							1/2			+	+				+			1/2
Renal Anomaly												1/2									+		+	+
Dysmorphic facies							+	+	+	+	+				+		+	+			+		+	+
Dacryocystitis								+		+								+						
Coloboma																							+	
Cataract																		+				1/7	+	
Cloft/high palate						+	+				+			alv		+								
Branchial fistula								+				1/2												
Hypothyroidism																	No	1/2						
Cong. heart defect																		1/2						
Cryptorchidism																		1/2						
Exposures in pregnancy					Pipamazine					Methimazole propranolol							Methimazole							

foc, focal; alv, alveolar ridge.

[a]Associated syndrome: SEN, scalp-ear-nipple syndrome; ECD, Ectodermal dysplasia.

[b]Mode of inheritance: S, sporadic; AD, autosomal dominant; AD pen-, AD with decreased penetrance; AR, autosomal recessive; XLD, X-linked dominant; XLR, X-linked recessive.

Although strictly speaking, athelia refers to the absence of nipples, and amastia refers to the absence of mammary tissue, these terms have been used interchangeably. However, we did not find any cases of amastia with normal nipples. This is consistent with the embryology of the breasts in which the development of the mammary gland precedes that of the nipples [Trier, 1965].

Syndromes associated with the absence of breast and nipples include ectodermal dysplasia with hidrosis [Burck and Held, 1981], ectodermal dysplasia with anhidrosis [Tuffli and Laxova, 1983; Trier, 1965], ectodermal euhidrotic dysplasia with hearing loss [Tsakalakos et al., 1986], and the scalp-ear-nipple syndrome [Finlay and Marks, 1978]. A summary of the major clinical features seen in these syndromic cases as well as in the isolated cases of athelia and amastia are listed in Table I.

At least 11 cases of isolated athelia or amastia have been reported. These patients were not known to have any other associated anomalies, and many of them inherited the trait in an autosomal dominant fashion.

The features in our patient include rudimentary nipples, bilaterally posteriorly rotated ears, over-folded pinna of the right ear, and syndactyly of the fingers and toes. This constellation of features resembles the scalp-ear-nipple syndrome [Finlay and Marks, 1978]. Scalp-ear-nipple syndrome is characterized by scalp abnormalities resembling that of aplasia cutis congenita, malformed ears, rudimentary or absent nipples, and scanty secondary sexual hair.

Syndactyly has been reported in nine cases of the scalp-ear-nipple syndrome, all of whom had dysplastic nails [Finlay and Marks, 1978; Edwards et al., 1994; Picard et al., 1999]. Also found were cutaneous syndactyly of the second and third toes, and partial syndactyly of the third and fourth fingers.

Renal involvement has been reported in at least four cases of scalp-ear-nipple syndrome, including a 23-year-old woman with unilateral congenital cataract and bilateral renal hypoplasia [Plessis et al., 1997] as well as a father who has left renal agenesis and syndactyly of the second and third toes, and his daughter who has right pyelo-ureteral duplication and bilateral camptodactyly of the fifth fingers [Picard et al., 1999].

Although a structural external ear abnormality is an important component of the scalp-ear-nipple syndrome, none of those patients had any hearing impairments. In contrast, of the six cases of athelia/amastia associated with hearing impairments, only one of them had an associated ear malformation.

There seems to be some overlap in the phenotype of the scalp-ear-nipple syndrome and ectodermal dysplasia. From an embryological perspective, this would not be surprising since abnormalities in the ectodermal tissue appears to be the underlying etiology behind both disorders. In fact, in the cases described by Tuffli and Laxova [1983], the clinical features were strongly suggestive of ectodermal dysplasia, associated with a midline scalp defect as well as hypothelia and hypomastia, but the ears appeared to be normal. Nevertheless, other authors have suggested that those two patients might have the scalp-ear-nipple syndrome [Edwards et al., 1994].

As indicated in Table I, the scalp-ear-nipple syndrome appears to be inherited as an autosomal dominant trait. In contrast, other "syndromic" and isolated forms of amastia and athelia may be sporadic occurrences, or be inherited mainly in either an autosomal dominant or autosomal recessive pattern.

van Steensel et al. [1999] suggested that lymphoid enhancer factor-1 (Lef-1) might be a potential candidate gene for the scalp-ear-nipple syndrome. Lef-1 is an HMG-domain DNA-binding protein expressed in the pre-B- and T-lymphocytes of adult mice and in the neural crest, mesencephalon, tooth germs, and other sites during embryogenesis [van Genderen et al., 1994]. Homozygous mutant mice lack teeth, mammary glands, whiskers, hair, and the mesencephalic nucleus of the trigeminal nerve, but show no defects in lymphoid cells. Although the phenotype is lethal in mice and nodules of the skin were not described, the lack of hair, absence of teeth, and aplasia of breast tissue suggest that Lef-1 may be a candidate gene for scalp-ear-nipple syndrome.

REFERENCES

Al-Gazali LI, Hamid Z, Hertecant J, Bakir M, Nath D, Kakadekar A. 2002. An autosomal recessive syndrome of choanal atresia, hypothelia/athelia and thyroid gland anomalies overlapping bamforth syndrome, another syndrome and methimazole embryopathy. Clin Dysmorphol 11:79–85.

Batchelor HT. 1888. Absence of mammae in a woman. Br Med J 2:876.

Burck U, Held KR. 1981. Athelia in a female infant-heterozygous for anhidrotic ectodermal dysplasia. Clin Genet 19:117–121.

Dumic M, Cvitanovic M, Saric B, Spehar A, Batinica S. 2002. Choanal stenosis, hypothelia, deafness, recurrent dacryocystitis, neck fistulas, short stature, and microcephaly: Report of a case. Am J Med Genet 113:295–297.

Edwards MJ, McDonald D, Moore P, Rae J. 1994. Scalp-ear-nipple syndrome: Additional manifestations. Am J Med Genet 50:247–250.

Finlay AY, Marks R. 1978. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. Br J Dermatol 99:423–430.

Goldenring H, Crelin ES. 1961. Mother and daughter with bilateral congenital amastia. Yale J Biol Med 33:466–467.

Greenberg F. 1987. Choanal atresia and athelia: Methimazole teratogenicity or a new syndrome? Am J Med Genet 28:931–934.

Kiskadden WS, Schechtman AM, Brock C. 1949. Theories of the etiology of congenital deformities. Int Abstr Surg 88:1–14.

Kowlessar M, Orti E. 1968. Complete breast absence in siblings. Am J Dis Child 115:91–92.

Le Merrer M, Renier D, Briard ML. 1991. Scalp defect, nipples absence and ear abnormalities: Another case of Finlay syndrome. Genet Couns 4:233–236.

Lin KY, Nguyen DB, Williams RM. 2000. Complete breast absence revisited. Plast Reconstr Surg 106:98–101.

Picard C, Couderc S, Skojaei T, Salomon R, de Lonlay P, Le Merrer M, Munnich A, Lyonnet S, Amiel J. 1999. Scalp-ear-nipple (Finlay-Marks) syndrome: A familial case with renal involvement. Clin Genet 56:170–172.

Plessis G, Le Treust M, Le Merrer M. 1997. Scalp defect, absence of nipples, ear anomalies, renal hypoplasia: Another case of Finlay-Marks syndrome. Clin Genet 52:231–234.

Trier WC. 1965. Complete breast absence. Case report and review of the literature. Plast Reconstr Surg 36:431–439.

Tsakalakos N, Jordaan FH, Taljaard JJ, Hough SF. 1986. A previously undescribed ectodermal dysplasia of the tricho-odonto-onychial subgroup in a family. Arch Dermatol 122:1047–1053.

Tuffli GA, Laxova R. 1983. Brief clinical report: New, autosomal dominant form of ectodermal dysplasia. Am J Med Genet 14:381–384.

van Genderen C, Okamura RM, Farinas I, Quo RG, Parslow TG, Bruhn L, Grosschedl R. 1994. Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice. Genes Dev 8:2691–2703.

van Steensel MA, Celli J, van Bokhoven JH, Brunner HG. 1999. Probing the gene expression database for candidate genes. Eur J Hum Genet 7:910–919.

Wilson MG, Hall EB, Ebbin AJ. 1972. Dominant inheritance of absence of the breast. Humangenetik 15:268–270.

Wilson LC, Kerr BA, Wilkinson R, Fossard C, Donnai D. 1998. Choanal atresia and hypothelia following methimazole exposure in utero: A second report. Am J Med Genet 75:220–222.

Wylie W. 1888. Case of entire absence of both mammae in a female aged 21 years. Br Med J 2:235.