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EVIDENCETHAT AEC SÍNDROME AND BOWEN-ARMSTRONG SYNDROME ARE VARIABLE EXPRESSIONS OF THE SAME DISEAS

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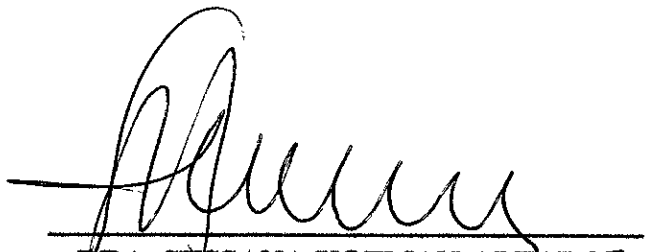

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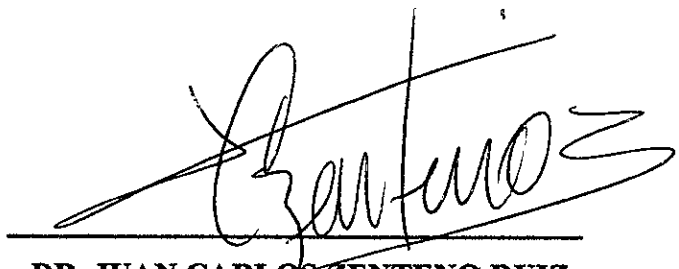

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Evidence that AEC Syndrome and Bowen–Armstrong Syndrome Are Variable Expressions of the Same Disease

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Abstract: Several clinical disorders combine ectodermal dysplasia (ED) and cleft lip and/or palate (CL/P). These conditions have been recognized as a group of diseases with a narrow phenotypic spectrum and multiple points of overlap. We report a patient with a clinical diagnosis of AEC syndrome (ankyloblepharon, ectodermal defects, and CL/P) who additionally has some features observed in a different ED-CL/P disorder, Bowen–Armstrong syndrome. Because of this clinical overlap, we suggest that AEC syndrome and Bowen–Armstrong syndrome may be variable manifestations of the same pathologic entity.

The association of ectodermal dysplasia (ED) and clefting of the lip and/or palate (CL/P) has been recognized in a number of clinical entities. The three most commonly diagnosed of these are EEC syndrome, characterized by ED, ectrodactyly (a malformation characterized by the absence or deficiency of one or more central digits of the hand or foot) and CL/P (1–7); Rapp–Hodgkin syndrome, consisting of ED, CL/P, and midfacial hypoplasia (8–15); and AEC syndrome, defined by ankyloblepharon, ectodermal defects, and CL/P (16).

The AEC or Hay–Wells syndrome was first described in 1976 (16) and more than 20 patients have been reported to date (16–21). This disorder has an autosomal dominant mode of inheritance with a high degree of penetrance and variable clinical expressivity (16,19). Ankyloblepharon (abnormal tissue strands between the eyelids) is a pathognomonic feature of the AEC syndrome that allows its differentiation from other ED-CL/P entities (22). This eyelid abnormality may result from either incomplete separation or abnormal fusion of the eyelid margins and is predominantly composed of vascularized connective tissue rather than persistent epithelial sheets, supporting the fusion theory (23,24). Other clinical findings in the AEC syndrome include coarse, sparse, wiry hair, mild hypohidrosis, scalp dermatitis, recurrent scalp infections, lacrimal duct atresia, otitis media, oligodontia, maxillary hypoplasia, CL/P, and dystrophic nails. Micropenis, hypospadias, and vaginal erosions are occasionally found (21). Although the AEC syndrome appears to be a specific disease, it was recently suggested that, due to its clinical overlap with Rapp–Hodgkin syndrome, these two disorders are probably the same clinical entity (15,25).

There are other rare syndromes that also combine ED and CL/P, but since there are very few reports of these conditions, it is not clear if some are phenotypic variants of single disorders (26–36). In 1976, Bowen and Armstrong (37) described three sisters with an ED-CL/P syndrome who also had variable mental retardation and mottled hyperpigmentation of inguinal and axillar areas. In two of the patients (1 and 3) ankyloblepharon was present at birth, while hypoplasia of the labia minora

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with absence of the normal vaginal opening was also observed in patient 1. In these patients the diagnosis of AEC syndrome was excluded (27), and the family is currently referred to in the literature as having Bowen–Armstrong syndrome (19,38–40).

We describe a patient with AEC syndrome who, in addition to the classic clinical features, had genital hypoplasia with absence of the vaginal opening and diffuse mottled hyperpigmentation. These latter anomalies are identical to those described in patients with Bowen–Armstrong syndrome, suggesting that this disorder and AEC syndrome are probably the same clinical entity.

CASE REPORT

The patient, a 2-year-old girl, was the product of the third pregnancy of a young nonconsanguineous couple. The family history was negative for congenital malformations and genetic diseases. She was born by normal delivery after a full-term, uncomplicated pregnancy. Birthweight was 2900 g and length was 49 cm. Immediately after birth it was noted that the patient's eyelids were partially fused by abnormal tissue strands. A cleft lip/palate was also present. These connecting strands were surgically removed when she was 3 days old and the CL/P was repaired at the age of 11 months. Psychomotor development was normal. When evaluated at 2 years of age she had normal stature and a normal head circumference. She had hypopigmented, coarse, sparse hair, and a peculiar facies characterized by sparse eyebrows and eyelashes, bilateral inner epicanthal folds, bilateral lower lid ectropion, broad and depressed nasal bridge, relatively short philtrum, thin upper lip, downturned corners of the mouth, and dysplastic posteriorly rotated auricles (Fig. 1). Anodontia, absent uvula, and a short neck were also present. Distal hypoplasia of the fingernails and toenails was also noted (Fig. 2). In addition, hypoplastic external genitalia with fusion of the labia, absence of the normal vaginal opening (Fig. 3), and diffuse mottled hyperpigmentation on the trunk and extremities (Fig. 4) were observed.

Chromosome analysis with GTG banding showed a normal 46,XX karyotype. Renal and pelvic ultrasonographs did not find malformations, and ophthalmologic evaluation found only bilateral ectropion with normal placement of the lacrimal puncta.

DISCUSSION

The ED-CL/P syndromes are recognized as a group of entities that exhibit a narrow clinical spectrum with multiple overlapping features (11). These characteristics make differential diagnosis difficult. In fact, several authors have proposed that some ED-CL/P syndromes are phenotypic variants of a single genetic defect (15,25).

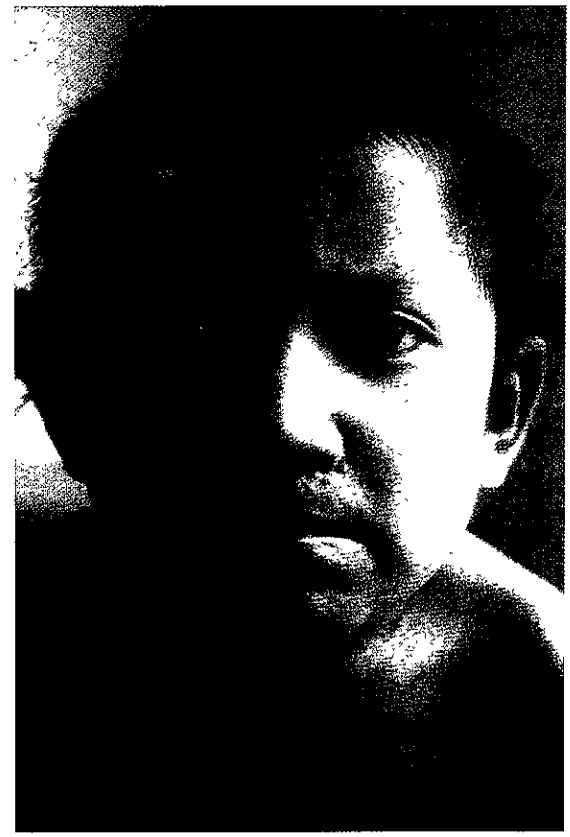

Figure 1. Facial appearance of the patient at 2 years of age.

In addition to the classic clinical traits of AEC syndrome, our patient showed other findings not previously described: hypoplastic external genitalia with fusion of the labia and diffuse mottled hyperpigmentation of the trunk and extremities. Of interest, these latter abnormalities are identical to those observed in Bowen–Armstrong syndrome, described only in three sisters who also had variable mental retardation (37). Although some authors have suggested that these patients have AEC syndrome (38–42), others have questioned this diagnosis (27), and the family remains in the literature as having Bowen–Armstrong syndrome.

We propose that the phenotypic overlap between the patients described by Bowen and Armstrong (37) and our patient with AEC syndrome may indicate that these two disorders are the same clinical entity, as was suggested previously for AEC and Rapp–Hodgkin syndrome (15,25). Although our patient was not mentally retarded like the patients of Bowen and Armstrong, such a discrepancy may be explained by the variable clinical expression seen in the ED-CL/P disorders. Furthermore, the mild mental retardation observed in one of the Bo-

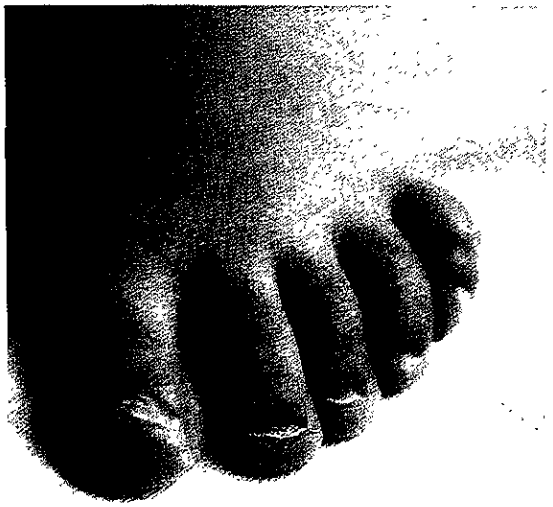

Figure 2. Patient's left foot shows distal hypoplasia of the toenails.

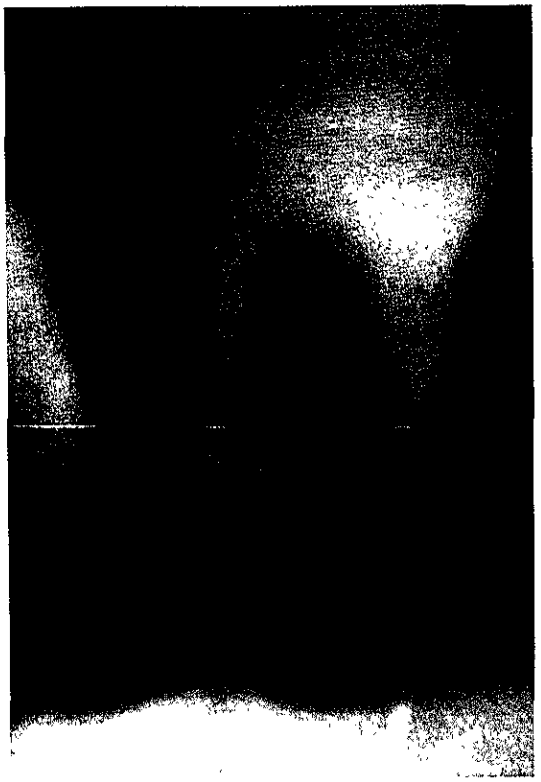

Figure 3. Hypoplastic external genitalia with fusion of the labia.

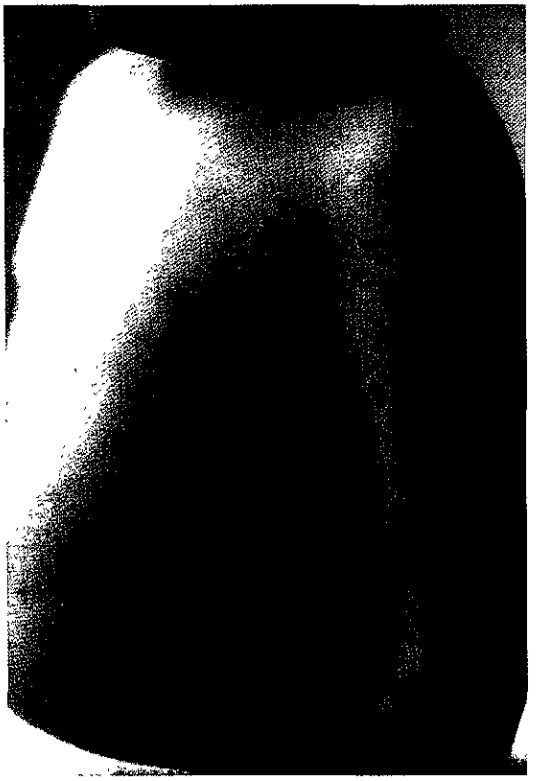

Figure 4. Mottled hyperpigmentation on the trunk and extremities.

wen–Armstrong patients was attributed to the lack of intellectual stimulation during prolonged periods of institutional care.

Of interest, the occurrence of Rapp–Hodgkin syndrome in a mother and EEC syndrome in her child was recently documented (42). This child also had ankyloblepharon, a cardinal feature of AEC syndrome. According to these data, we believe that EEC, Rapp–Hodgkin, AEC, and Bowen–Armstrong syndromes may be variable manifestations of mutations in the same gene. Thus allelic heterogeneity at a single locus may explain the great clinical overlap between these conditions (Table 1). Until the precise genetic defect(s) causing this group of diseases can be identified, however, clinical features must be used for their recognition and differentiation. Of interest, ankyloblepharon and labial fusion involve abnormal embryonic fusion processes that may be caused by mutation in a putative ED-CL/P gene.

In several patients with EEC syndrome, chromosomal rearrangements involving chromosome 7 were recognized and a candidate locus for this entity was subsequently identified in 7q21.3 (43). More recently, a second locus (EEC2) for syndromic ED and ectrodactyly has been located in chromosome 19 in a large Dutch family (44). In addition, homeobox-containing genes,

TABLE 1. *Primary Features of Related ED-CL/P Syndromes*

	EEC (EEC1)	Rapp–Hodgkin	AEC (Hay–Wells)	Bowen–Armstrong
Hair dystrophy	++	++	++	++
Dental dysplasia	++	++	++	++
Nail dystrophy	++	++	++	++
Sweat gland dysplasia	+	++	++	−
Lacrimal duct anomalies	++	++	++	−
Ankyloblepharon	+[a]	−	++	++
Cleft lip and/or palate	++	++	++	++
Hypoplastic maxilla	+	++	++	+
Ectrodactyly	++	−	−	−
Syndactyly	+	+	+	++
Urinary malformations	+	+	+	−
Abnormal external genitalia	+	+	+	+
Scalp dermatitis	−	+	++	+
Hearing loss	+	+	+	−
Mental retardation	+	−	−	++
Skin pigmentation anomalies	+	−	−	++

+ = feature found in up to 50% of cases; ++ = feature found in more than 50% of cases
− = feature not found.
[a] This feature has been described in only one EEC patient (42).

particularly MSX1 and MSX2, which are expressed in palate, teeth, and developing limbs, have been proposed as candidate genes for some ED-CL/P syndromes (45,46). These data suggest that mutations in closely related genes might offer another possible explanation for the clinical similarities observed in the ED-CL/P syndromes.

In conclusion, this patient is another example of the striking phenotypic overlap among the ED-CL/P syndromes. This observation stresses the importance of a detailed clinical examination of patients with ED-CL/P conditions until the molecular basis of this group of diseases can be determined.

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