Ectodermal dysplasia, primary hypothyroidism, and agenesis of the corpus callosum: variable expression of a single syndrome?

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Abstract

We present two unrelated children, a male and a female, with signs of ectodermal dysplasia, mental retardation, agenesis/dysgenesis of the corpus callosum, and primary hypothyroidism. Reports of ectodermal dysplasia with CNS malformations or hypothyroidism or both are rare. We suggest that the condition we describe is a distinct entity within the large group of ectodermal dysplasia syndromes and that it has a variable clinical spectrum. As both males and females are affected and in a few reports some parents show minimal signs, the inheritance is likely to be autosomal dominant.

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Keywords: mental retardation; hypothyroidism; ectodermal dysplasia; CNS malformation

Case reports

PATIENT 1

The proband is the 9 month old only son of healthy, non-consanguineous parents. The mother's brother has unspecified mental retardation. The pregnancy was complicated by bleeding during the first trimester. Delivery was accomplished by vacuum extraction and the cord was short. Apgar score was 4 at one minute. Birth weight was 3150 g, length 49 cm, and head circumference 36 cm. On neonatal screening, a TSH value of 32 mU/ml was found and a thyroid scintigram with technetium 99 showed absence of normal thyroid gland tissue and the presence of an ectopic goitre at the base of the tongue. A diagnosis of primary hypothyroidism was made and substitution therapy was started. Clinical examination at 9 months of age showed macrocephaly (OFC 48.5 cm) with frontal bossing, small and upturned nose, long philtrum, low set ears, fragile, dry, and slow growing scalp hair, sparse eyebrows, and a bifid uvula (fig 1). A partial cutaneous syndactyly of fingers 3-4 was observed. The nails are normal and teeth have not yet erupted. The child acquired head control by 6 months but does not sit without support. Microscopic examination of the scalp hair showed trichorrhexis nodosa (fig 2). Sweating is present and the sweat test was unremarkable. Because of lack of cooperation from the patient, the recommended tests for objective testing of sweat production, such as counting of sweat pores, could not be done.

A CT scan of the brain showed agenesis of the corpus callosum. The blood karyotype is normal, 46,XY.

PATIENT 2

The proband is a 16 month old female. Both parents are healthy and consanguinity is denied. A 6 year old sister has normal physical and mental development. The family history is negative for mental retardation or congenital malformations. She was the product of an uncomplicated pregnancy and delivery. Birth weight was 3350 g, but length and head circumference were not recorded. By 5 months of age, failure to thrive and developmental retardation were evident.

Dentition was abnormal in that the teeth were hypoplastic with a conical shape. The scalp hair was sparse and depigmented. She experienced frequent bouts of unexplained fever, mostly in the summer, and recurrent diarrhoea. At 5 months of age, a CT scan of the brain showed agenesis of the posterior portion of the corpus callosum. Physical examination at 16 months showed weight 7 kg (below the 3rd centile), height 73 cm (below the 3rd centile),

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Figure 1 Case 1: craniofacial dysmorphism.

Figure 2 Case 1: microscopic examination of the scalp hair showing trichorrhexis nodosa.

Figure 3 Case 2: clinical features.

and head circumference 48.5 cm (97th centile). She had macrocephaly, frontal bossing, sparse and depigmented scalp hair, sparse eyebrows and eyelashes, depressed nasal bridge with anteverted nostrils, a high arched palate, and conical teeth (fig 3). The patient was hypotonic and severely mentally retarded. The skin was dry and light with reduced sweating. The skin biopsy was consistent with a diagnosis of hypohidrotic ectodermal dysplasia. Echocardiography was performed because of the presence of cardiomegaly on chest x rays and showed a left ventricular hypertrophy. Primary hypothyroidism was first documented at 16 months by measurements of T3, T4, and TSH and by reduced uptake of technetium 99 on thyroid scintigram. Neonatal TSH screening was unremarkable. The blood karyotype was normal, 46,XX.

Discussion

We present two unrelated patients, a male and a female, with mental retardation, distinct craniofacial dysmorphism, agenesis of the corpus callosum, primary hypothyroidism, and signs of ectodermal dysplasia. The features are identical to those observed by Fryns *et al*¹ in a boy who also had cardiomegaly with biventricular trabecular hypertrophy, a finding present in our case 2. Reports of ectodermal

dyplasia with CNS malformation are rare. In 1992, Soekarman and Fryns² reported a boy with severe mental retardation, cerebellar hypoplasia with internal hydrocephalus, ectodermal dysplasia, and cleft palate, a feature also present in our first case. Devriendt *et al*³ described another patient with mental retardation, agenesis of the corpus callosum, distinct craniofacial dysmorphism, and mild signs of ectodermal dysplasia. The child's mother had similar but milder features and the authors suggested X linked or autosomal dominant inheritance for this distinct MCA/MR syndrome.

Silengo *et al*⁴ reported a retarded girl who had signs of hidrotic ectodermal dysplasia, including trichorrhexis nodosa of the scalp hair, cleft palate with lip pits, and a Dandy-Walker-like malformation of the brain. Her mother had milder features and autosomal dominant inheritance was suggested. None of the patients reported by Soekarman and Fryns,² Devriendt *et al*,³ or Silengo *et al*⁴ had primary hypothyroidism as a feature. The concurrence of primary hypothyroidism and ectodermal dysplasia has been observed in two brothers by Pabst *et al*⁵ and in a female by Pike *et al*.⁶ None of the three patients had mental retardation; imaging studies of the CNS were not performed. The available information suggests that a distinct type of ectodermal dysplasia with CNS malformation, ranging from agenesis of the corpus callosum to cerebellar hypoplasia, might exist. The clinical variability of the condition appears to be very wide and includes primary hypothyroidism resulting from hypoplastic or ectopic thyroid, cleft palate, and hypertrophic cardiomyopathy. The ectodermal involvement is variable as both hypohidrotic and hidrotic changes are observed. The degree of mental retardation is also variable. As both males and females are affected and some parents have similar, albeit milder, features, the inheritance is likely to be autosomal dominant.

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