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Hypohidrotic ectodermal dysplasia

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Hypohidrotic ectodermal dysplasia (HED) is an uncommon X linked condition. The phenotype includes sparse scalp hair, largely absent body hair, deficiency of the eccrine sweat glands, and anodontia or oligodontia with conical teeth (figs 1 to 3). There is often a distinctive facies, with prominence of the forehead, a depressed nasal bridge, prominent lips, and periorbital wrinkling and pigmentation. Subcutaneous fat is often diminished or absent, as are the mucous glands in the respiratory tree and the gastrointestinal tract.

HED was first described in 1848 by Thurnam,[1] and later in the 19th century by Darwin.[2] It was assigned to the X chromosome in 1921 by Thadani,[3] who later reported that the carrier females could manifest signs of the condition.[4] The full significance of this was not appreciated until Mary Lyon hypothesised the random inactivation of one X chromosome in each female cell early in embryogenesis.[5]

Incidence

HED is found in all racial groups and in all areas of the world. The incidence at birth was estimated by Stevenson and Kerr,[6] based on the prevalence of HED in Oxfordshire: they suggested a rate of 1 per 100 000 births. Personal experience would support this estimate.

Clinical course

Infants may have dry, peeling skin at birth that makes them look dysmature. Some infants only present later with oligodontia, but many have feeding problems caused by crusts of nasal secretions that obstruct the nose. They may suffer from fevers in hot weather, from recurrent chest infections, and from eczema. Some infants with recurrent septicaemia may benefit from prophylaxis with antibiotics. Reports of a primary immune deficiency as a feature of HED have not been substantiated.[7–9]

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Clouston[10] and other authors[11 12] have pointed out that hypohidrosis could result in impaired thermoregulation leading to hyperpyrexia and apparent cot death. The recurrent episodes of hyperthermia or sepsis or both more usually resolve spontaneously and growth and development proceed normally.

Temperature control in older children can be helped by cool surroundings, drinking cool fluids, and taking cool showers or wearing wet T shirts (table). Some of the males also suffer in cold weather because of their reduced subcutaneous fat.

The growth of boys with HED should be monitored and short stature should not be regarded as being a natural consequence of HED: a few boys with HED may be subject to endocrine deficiencies.[13] Mental development is generally normal and suggestions of intellectual retardation are unfounded,[14] but some boys do have speech problems. These may be associated with difficulty in articulation caused by oligodontia and nasal obstruction, with hearing problems from wax in the auditory canal, and with a lack of social confidence resulting from the unusual facies. The early fitting of artificial dentures, before primary school age if the boy is willing, can help his speech and facial appearance as well as his nutrition.

Convulsions may occur in association with hyperpyrexia in early childhood, but are uncommon,

TABLE *Clinical approach to HED.*

Mortality in early childhood (higher in first affected sib; most deaths occur in infancy)	30%
Severe illness in early childhood (including deaths)	50%

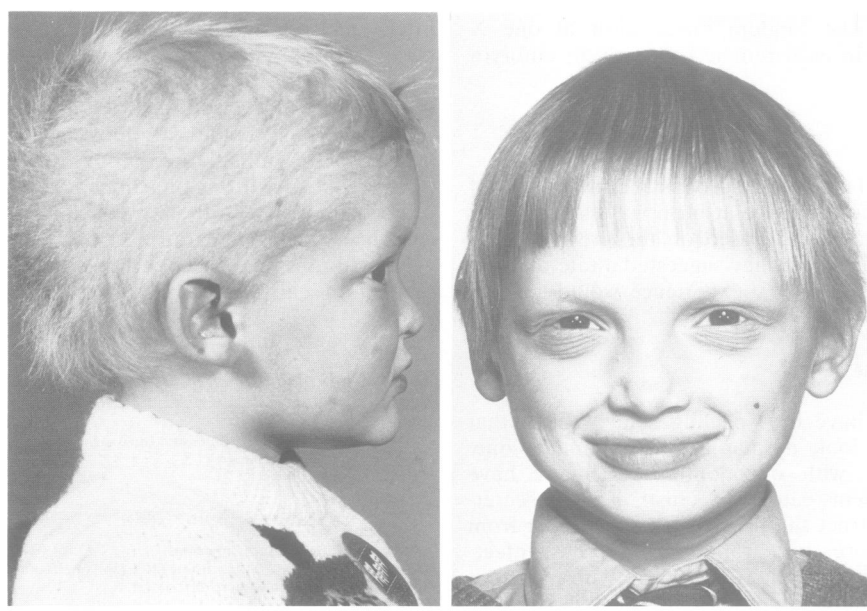
Control of body temperature: tepid sponging, showers, cold drinks, antipyretics, wet clothing.
Treatment and prophylaxis of infections.
Feeding problems (70%): nasal crusting (80%) will often contribute. Heated drinks and dry foods may cause difficulties.
Monitor growth: short stature is not inevitable and warrants full investigation.
Monitor speech and hearing: artificial dentures fitted before school may help speech, confidence, and nutrition.
Asthma (65%) and eczema (70%) require standard treatments.
Deficient lacrimal secretions require eye drops.
Genetic counselling and support.

occurring not very much more frequently than in the general population.

Deficiency of saliva may necessitate the drinking of water with food, and eye drops may remedy any deficiency of lacrimation. Inadequate salivation may also predispose to dental decay.

Adolescents are often very self-conscious, but can be reassured that men with HED lead entirely

(a)



(b) (c)

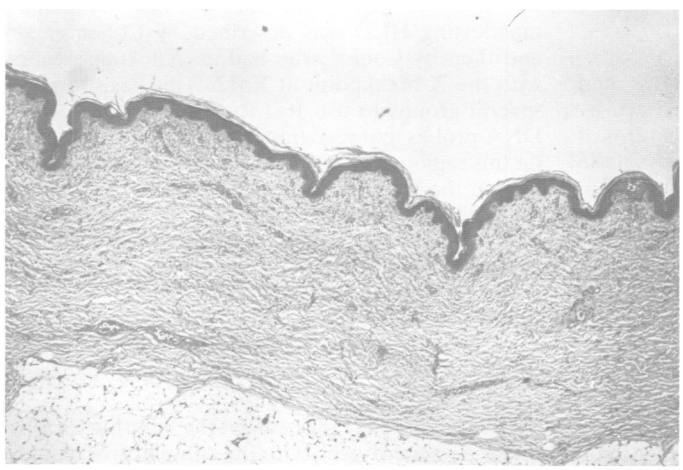
FIG 1 *(a, b, c) Three males with X linked HED. (Courtesy of the families, and of the Medical Photography Departments, Coventry and Warwickshire Hospital and University Hospital of Wales.) Fig 1 (c) is also reproduced by kind permission of the Editor, Archives of Disease in Childhood.*

normal social lives, although their occupation and leisure activities sometimes need to be modified if heat intolerance is a continuing problem. Once mixing in the world of adults, affected men generally find little problem with their appearance. They should be advised to avoid industrial work in a dusty atmosphere and not to smoke, because these factors may lead on to chronic obstructive airways disease.[15]

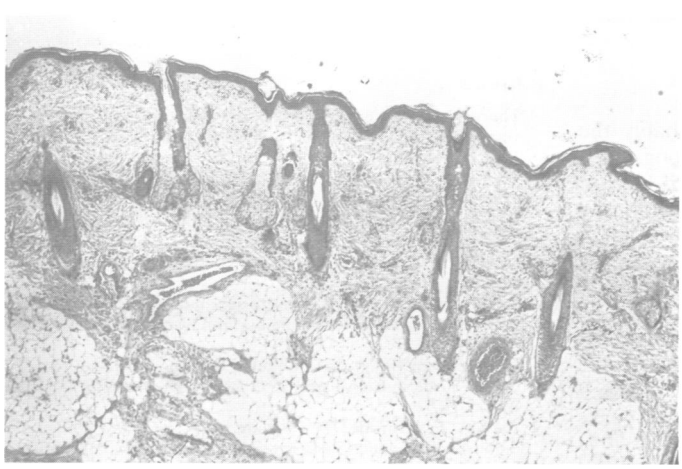
Differential diagnosis

In their recent compendium, Freire-Maia and Pinheiro[16] recognise 117 varieties of ectodermal dysplasia, but only a few are likely to cause confusion in diagnosis. The pedigree structure may distinguish the much less common, autosomal recessive variety of HED that cannot be distinguished clinically.[17] In the isolated case, a search should be made for manifesting female carriers. Other recessive conditions whose phenotypes overlap are distinguished by severe nail dystrophy and normal sweating (Fried's tooth and nail syndrome), by normal teeth (hypohidrotic ectodermal dysplasia with hypothyroidism), or by mottled pigmentation of the skin, mental retardation, and absence of hypohidrosis (Berlin's syndrome). The rare Rosselli-Gulienetti syndrome includes features of ectodermal dysplasia, as well as facial clefts and popliteal pterygia.

Dominant ectodermal disorders are also distinguished by pedigree structure or by atypical features



(a)



(b)

FIG 2 *Postmortem photomicrographs of skin from male infant (a) abdomen, (b) scalp. Note absence of sweat glands and paucity of hair. (Courtesy of Dr J R Read, Castle Hill Hospital, North Humberside.)*

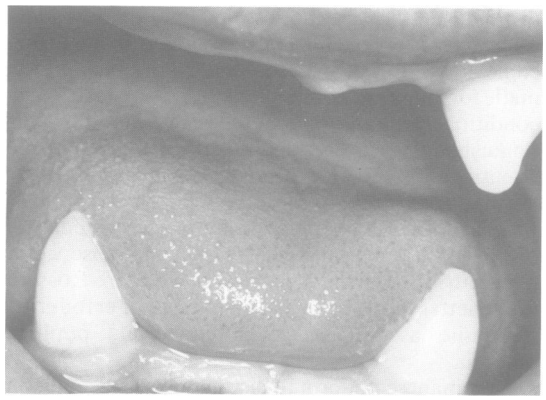


FIG 3 *Teeth of male with HED. (Courtesy of Mr P Crawford, Dental Hospital, University of Wales College of Medicine.)*

in the isolated case. Thus, the EEC, AEC, and Rapp-Hodgkin syndromes are characterised by facial clefts and other abnormalities. The features of Clouston's dominant hidrotic ectodermal dysplasia also include a severe nail dystrophy. The dominant Basan syndrome is characterised by severe nail dystrophy, simian creases, and absent dermatoglyphics, in addition to hypotrichosis, hypodontia, and hypohidrosis. The Zanier-Roubicek syndrome can be distinguished by the normal eyebrows and eyelashes, the transverse streaks in dental enamel, and the sparing of palmoplantar sweating. Koshiba's tricho-onychodental dysplasia has a distinct pattern of dental malformation and more severe nail dystrophy. The Lenz-Passarge HED is a condition almost identical to that under review, but said to be transmitted as an X linked dominant disorder with more severe manifestation in males.

Genetic aspects

The sex linked inheritance of HED, probably the commonest ectodermal dysplasia, has long been recognised. The molecular defect, however, has not been elucidated; the suggestion that low parathyroid hormone levels[9] may be a primary feature of the condition has not been substantiated. Another suggestion, of genetic heterogeneity with several X linked loci involved,[16] is also unsupported by evidence, although gene localisation for the Lenz-Passarge dysplasia has not been attempted. Clinical heterogeneity, however, does exist both within and between families.

Female carriers may be identified in at least 70% of cases by clinical examination.[18] Dental examination alone, in fact, will reveal this proportion of carriers[19] and more may be recognised by examination of sweat pores.[20 21] I have experienced considerable difficulty in interpreting the results of direct sweat pore counting (heavy housework can obliterate sweat pores) and prefer the whole back sweat test of Happle and Frosch[22] to reveal the pattern of Lyonisation as manifest in the lines of Blaschko. Even this test, however, is not invariably correct, and may leave some residual doubt.

Female heterozygotes may manifest patchiness of body or scalp hair, in addition to dental and sweating anomalies. Others suffer problems with heat intolerance, chest infections, and even failure to thrive in infancy; a very few have a facies reminiscent of the affected males. These findings can be largely explained in terms of Lyonisation.[23 24]

Classical linkage studies excluded close linkage to the loci for Xg[25] and for G6PD.[26] A female manifesting HED was described by Cohen *et al*[27] and then by Cook[28]; she had an X;9 translocation with the X breakpoint at Xq12. This has prompted several groups to use RFLP techniques to identify DNA probes that recognise closely linked sequences on this region of the X.[29–31] A consensus view would be that the HED locus lies close to the centromere, probably on proximal Xq; *DXYS1* (recognised by pDP34) lies distal at 10 cM and *DXS14* (recognised by probe 58–1) lies across the centromere on proximal Xp at 7 to 10 cM. These loci are probably too distant to be useful alone in prenatal diagnosis. The locus *DXS146* (recognised by the probe pTAK8) may lie closer to *HED*, but has been studied in only a few families.[31]

Homology of *HED* with the murine 'tabby' mutation accords well with the comparative maps of human and mouse X chromosomes,[32] and these conditions map close to the loci for Menkes' disease and PGK in both species.

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