Original articles

Clinical aspects of X-linked hypohidrotic ectodermal dysplasia

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SUMMARY Boys with X-linked hypohidrotic ectodermal dysplasia and their families were studied. Many suffered severe illness in early childhood and nearly 30% died; many had feeding problems, severe fever, atopic disease, and recurrent respiratory infections. Some infants failed to thrive. We found no consistent common endocrine or immunological abnormality, although most had abnormal immunoglobulin production. This may be related to the abnormal mucosa of the gastrointestinal and respiratory tracts which exacerbates the chronic obstructive airways disease found later in life in those who smoke. Mental handicap was not a feature, although convulsions sometimes occurred during fever.

Early diagnosis is important to avoid attacks of severe fever and so that rational management may be planned for other problems that arise. Dental advice should be sought before school age and genetic counselling may also be required. Many female carriers may be recognised at clinical examination: their affected sons can then be diagnosed more readily.

Hypohidrotic (anhidrotic) ectodermal dysplasia (HED) is characterised by the diminution or absence of eccrine sweat glands, by oligodontia and peg shaped teeth, and by hair that is sparse and thin. It is of interest to paediatricians because the substantial mortality and morbidity that are associated with it are manifest principally in young children. Early diagnosis—that is, before the condition becomes obvious—may also improve outcome.

The sex linked pattern of inheritance for HED was first described by Darwin in 1844.1 The gene locus is now known to be on the proximal part of the X chromosome long arm, and gene localisation using deoxyribonucleic acid (DNA) probes is now progressing rapidly.2 Male infants with HED are known to be at risk of severe fever and anecdotal reports have been published of cases who have been mentally retarded, possibly as a result of their high fevers.4 Their increased risk of chest infection and of atopic disease is also well recognised.5

This study reports the clinical findings from a survey of the disease that began in mid 1985. We have tried to determine the range of severity, in particular the mortality among affected male infants, and to pursue three lines of inquiry initiated by previous workers. The possibility of a primary immunological defect was investigated, the previous finding of low serum concentrations of parathyroid hormone was examined,6 and methods of identifying female carriers of the gene were evaluated.

Methods

Letters were sent to almost all hospital paediatricians, dermatologists, and clinical geneticists listed in the Medical Directory, and to many hospital dental surgeons. We asked them to notify us of any cases they knew of and for permission to contact the families concerned. We sought and obtained the consent of each family's general practitioner or dentist where appropriate, before contacting the index case. Families were visited at home, and the affected boys and possible carrier female subjects were examined. Measurements of height, weight, and head circumference were taken, and the chest, skin, and nails were examined.

Where possible, blood samples were taken for use in a concurrent genetic linkage study with DNA probes and for immunological and endocrinological investigations. Finger tip impressions were taken in Permelastic light body impression material (Sybron/Kerr) by spreading the mixed material on the subjects’ finger pads, immersing them in warm
water, and then peeling the impressions off with adhesive tape. These were stored on microscope slides in racks and subsequently examined under a dissecting microscope at a magnification of 10.

Sweat tests were performed on the backs of definite and possible carrier female subjects: iodine in spirit was painted over as large an area of the back as possible. This was allowed to dry and then covered with a layer of corn starch in oil applied as evenly as possible. The subject was then asked to sit near a fire until she became hot. The pattern of sweating shown on her back by black dots over the active sweat pores was then noted.

Immunoglobulins G, A, and M were measured by radial immunodiffusion, IgE by radioimmunoassay, and IgG subclasses by semiquantitative simple immunodiffusion. Antibodies to the commensals Escherichia coli and Candida albicans were detected by haemagglutination and immunofluorescence, respectively. Total classical and alternative pathways of complement, lymphocyte surface markers, and \( \alpha \)- and \( \gamma \)-interferon production by peripheral blood lymphocytes were measured as previously described. For neutrophil chemotaxis, an ‘underagarose’ method was used with N-formyl-L-methionyl-L-leucyl-L-phenylalanine as chemotaxin.

Serum parathyroid hormone was measured by a new immunochemiluminometric assay specific for the intact 1–84 peptide. With this assay all normal subjects have detectable circulating concentrations. The intact peptide corresponds to the circulating biologically active peptide and provides an assessment of parathyroid secretory activity that is probably superior to the conventional radioimmunoassay.

Prolactin was measured by a radioimmunoassay technique using Chelsea reagents provided by Keith Ferguson of the Chelsea Hospital for Women. Thyroid stimulating hormone was measured using a monoclonal tracer supplied by Serono, and antisera for the solid phase was supplied by the Scottish Antibody Production Unit and measured by the automated method of John and Jones. Free thyroxine (FT4) was measured by radioimmunoassay, using a commercial kit (Amerlex Free T4 Kit, Amersham).

**Results**

We contacted 56 families with some form of hypohidrotic ectodermal dysplasia. Of these families, 22 had more than one affected subject, and the inheritance in all the families was compatible with X-linkage. Another 12 families had only one affected subject, but there was firm evidence of sex linked inheritance because the mother of the affected subject showed several features of the condition and there were often several such related female carriers. The remaining cases, although some were probably examples of the X-linked form, were excluded from the study.

The phenotype of X-linked HED (fig 1) has been well described, and we have no new findings. The boys had sparse scalp and body hair, only a few teeth which were peg shaped (figs 2 and 3), and diminished or absent eccrine sweat pores. The mean number of erupted teeth of the deciduous and permanent dentitions in the male subjects was six. Over 30% had abnormalities of the breasts (absent, simple, or accessory nipples) and over 30% had ‘simple’ ears (bat ears, satyr ears, or absence of some folds). As others have reported, we commonly found wrinkling and pigmentation around the eyes.

Sweat pores were usually absent from the finger tips of most of the men in this series (fig 4), though several men in two families showed appreciable, although still subnormal, numbers of sweat pores. There was no doubt about the mode of inheritance in either family. Twenty seven of 50 infants (54%) suffered recurrent fevers; some boys were intolerant of cold, possibly related to their lack of subcutaneous fat.

**Severe Illness in Early Childhood**

The mortality in early childhood was assessed by

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*Fig. 1 Nine year old boy with hypohidrotic ectodermal dysplasia.*
considering the 22 families with more than one affected male subject. The family tree was drawn as far back as eye witnesses could distinctly recall, and male subjects were included if there was reliable information about their health in childhood. The index case in each family was excluded from this analysis. The table shows the mortality: nine of the 12 deaths occurred in infancy; two deaths in the second year; and one death at 2½ years. Neonatal deaths did occur, as in the two index cases. Of the 12 deaths, three occurred in the 1940s, three in the 1950s, one in 1960s, four in the 1970s, and three have occurred so far in the present decade. Notably eight of the deaths occurred in the elder of two affected brothers, and only two boys died who were the younger of two affected brothers. This shows...
Fig. 4  *Finger impressions of affected boy (a) and normal adult (b).*

that early diagnosis—whether by physician or by family improves the outcome for these boys.

If doubt is cast on these figures (in case the diagnosis in some cases was suspect) a similar conclusion can be reached by considering the infant mortality of the 88 male subjects born to the obligate carriers whom I met in this study; of these 88, 20 died in infancy. This gives a mortality varying from 23% (if affected boys are no more likely to die than their normal brothers) to 45% (on the assumption that all the normal boys survive).

The figures for severe illness in early childhood in the same table relate to all survivors about whom we had clear information concerning their childhood (whose parents were available for interview). These illnesses commonly comprised prolonged high fevers in infancy often accompanied by chest infections and failure to thrive. All these children were admitted to hospital and were given intravenous fluids. Many of them spent several months of the first year in hospital. In the table the data on mortality and illness are combined to give the risk of an affected boy having a severe illness, fatal or otherwise.

**NUTRITION AND GROWTH**

Thirty two of 47 boys (68%) had feeding problems and 19 had some degree of failure to thrive. The feeding problems comprised apparent lack of interest in feeding or a frank inability to feed despite good effort. Forty two of 53 infants (79%) had nasal obstruction caused by the accumulation of dried crusts in the nasopharynx and this may have prevented adequate sucking. A few infants required tube feeding for weeks or months. Sixteen of 49 boys (33%) had problems chewing specific foods such as nuts and tough meats when older even with dentures. Thirty one of 50 male subjects (62%) produced insufficient saliva and hence required fluid to swallow dry foods. Nine of 53 (17%) were also allergic to specific foods.

Affected male subjects tended to be of below average stature, weight, and head circumference, with about 10% being more than two standard deviations below the population mean for these

**Table Complications of HED in early childhood**

<table>
<thead>
<tr>
<th>Complication</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First year:</strong></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>9/43 (21)*</td>
</tr>
<tr>
<td>Severe non-fatal illness</td>
<td>14/49 (29)</td>
</tr>
<tr>
<td>Total with episodes of severe illness</td>
<td>25/58 (43)</td>
</tr>
<tr>
<td><strong>Years 0–3:</strong></td>
<td></td>
</tr>
<tr>
<td>Mortality in years 0–3</td>
<td>12/43 (28)*</td>
</tr>
<tr>
<td>Severe non-fatal illness</td>
<td>18/51 (35)</td>
</tr>
<tr>
<td>Total with episodes of severe illness</td>
<td>32/65 (49)</td>
</tr>
<tr>
<td><strong>Other complications in survivors:</strong></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>39/55 (71)</td>
</tr>
<tr>
<td>Asthma or recurrent wheezing</td>
<td>35/54 (65)</td>
</tr>
<tr>
<td>Nasal crusting</td>
<td>42/53 (79)</td>
</tr>
<tr>
<td>Recurrent fevers in infancy</td>
<td>27/50 (54)</td>
</tr>
<tr>
<td>Recurrent upper respiratory tract infections</td>
<td></td>
</tr>
<tr>
<td>in childhood</td>
<td>21/47 (44)</td>
</tr>
<tr>
<td>Feeding problems in infancy</td>
<td>32/47 (68)</td>
</tr>
<tr>
<td>Specific allergies (to foods or drugs)</td>
<td>14/53 (26)</td>
</tr>
</tbody>
</table>

*Mortality figures exclude index cases.
characteristics. This was most noticeable in the first few years, when general health was poorest. Four infants were below the third centile for weight at birth; the two who are now adult are above the twenty fifth centile for height and weight, and one of the boys, now aged 3, has caught up to near the tenth centile. The other boy remains below the third centile at 9 years; he had a Wilms' tumour removed and subsequent chemotherapy. A boy aged 14 remains below the third centile for weight for height at 3 and 15 months of age; only the elder boy had feeding problems.

ATOPY AND CHEST DISEASE

Thirty nine of 55 boys had eczema in childhood; this tended to become less severe with age. Thirty three of 54 also gave a history of recurrent wheezing typical of asthma, and a further two cases (included in the table) had audible wheezes on examination. This indicated a high incidence of atopy. The association of HED with chronic chest disease was noted by Beahrs et al, and is probably the result of deficient mucus production by the respiratory epithelia in the trachea and bronchi as well as in the nasopharynx. Three male subjects in the families described here died of chronic obstructive airways disease in their sixties, during the past 3 years. All three men were heavy smokers and had either lived or worked in areas with industrial dust pollution; one had died from pneumonia aged 28 years.

Assessment of humoral immunity was performed in 36 affected male subjects, 25 of whom had distinctly abnormal results and a further two of whom had marginally abnormal immunoglobulin concentrations; no consistent primary defect was identified, however. Ten of 36 had raised IgG concentrations, some as high as 48 g/l, and three subjects had low concentrations. IgM concentrations were raised in three cases and reduced in six, although the reduction was marginal in most of them. Eight subjects had definitely low IgA concentrations; and in one case it was marginally low. IgE was considerably raised in most, a few having concentrations of >1 g/l; in all, 19 of 28 tested had raised concentrations.

None of the patients lacked any IgG subclass. Normal titres of antibody to the commensals E coli and C albicans were present in all but one patient. This child, who lacked antibodies to C albicans, was almost 4 years of age when tested; the organism is widely distributed and antibodies to it are usually evident by the age of 6 months.

The complement system, both classical and alternative, was assessed by haemolytic assay and found to be normal in all seven patients tested. Peripheral blood leucocyte and lymphocyte counts were normal in 25 cases. Because of transport problems, tests of cellular immunity and neutrophil function had to be restricted to a smaller number of patients. T cell numbers were assessed in eight male subjects and subsets were normal in six. In two boys the T8 (suppressor) class was marginally raised compatible with a minor viral infection. All cases were clinically well when the blood was taken for leucocyte function tests. Alpha and γ interferon production was normal in the six cases tested. Neutrophil chemotaxis was measured in four cases and nitroblue tetrazolium reduction in eight, with normal results in all cases.

Thyroid function was measured in 25 cases and the free thyroxine concentration was normal in each case. The thyroid stimulating hormone concentration, however, was raised in two boys at 6-6 and 9-7, respectively. The prolactin concentration was normal in the first boy but was marginally raised (at 455 mU/l) in the second, raising the possibility of a more generalised hypothalamic dysfunction. Both these boys were above the fiftieth centile for height, weight, and head circumference and doing reasonably well at normal school. Prolactin assays were performed in 19 other cases and yielded normal results.

Parathyroid hormone assay measuring intact parathyroid hormone was performed on serum taken from 22 of the affected male subjects. Only one value was far from the normal adult range of 0-96–9-8 pmol/l, being 39-6. Excluding this case, for which we have no explanation at present, the mean, range, and standard deviation of the cases of HED were 2-58, 0-85–9-50, and 1-95 pmol/l, respectively. These do not differ significantly from (adult) normal values. A previous report mentioned a tendency for the parathyroid hormone concentration to be low in cases of HED, but the assay method was not specified and was probably a traditional radioimmunoassay for the C terminal of parathyroid hormone and not for the intact protein. Serum concentrations of calcium and phosphate, and alkaline phosphatase activity were normal in that report; we did not measure them in our cases.

CONVULSIONS AND DEVELOPMENT

Three of 50 boys had convulsions in childhood, and a further two boys may have done so. No adults had any such episodes. We outline the case histories as follows.

Case 1 had a prolonged high fever at 10 weeks of age, with multiple seizures and he developed a spastic cerebral palsy. Although his intellect was
difficult to assess, his mental development seemed to be less impaired than his physical defects initially suggested. His development before this illness was unremarkable.

Case 2 had a fever at 2 weeks of age, with two brief convulsions, then no further episodes. When last seen he was functioning well at a normal secondary school and had no apparent sequelae.

Case 3 had an isolated convolution when otherwise well during the investigation of polyuria at the age of 4 years. Such polydipsia and polyuria may be used as a mechanism for controlling body temperature during a severe episode of illness at 9 months.

Case 4 had high fevers and may have had a brief febrile fit.

Case 5 had a similar history to that of case 4, occurring at 2 months; neither had a convincing history of convulsions and neither child suffered adverse sequelae.

Of the 50 cases for whom we had adequate information about their childhood, in 10 some concern was expressed about the child's development. One child had cerebral palsy (case 7), and he attends a school for the physically and mentally handicapped. One child attends an ESN (M) class, and his development has been generally retarded. He suffered severe illness during his first 2 years, although he is not thought to have had convulsions. The other eight children all developed normally and did well in normal schools, but they had some early difficulty with speech or hearing, or both, which subsequently resolved. Another two boys received preschool speech therapy.

Seven of 38 boys had additional school problems; four were plagued by teasing at school. They were called names such as 'Dracula' or 'Fang'. This problem was worse in secondary schools than in primary schools, and could have assumed major proportions in adolescence. The three remaining boys had all missed substantial periods of school because of ill health and had work to do to catch up. In one case this necessitated temporary placement in a remedial class.

Of the adults seen, none was handicapped except by heat intolerance. The range of occupations undertaken by men with HED is wide, ranging from technical, managerial, and academic positions to manual labour. One labourer fainted in a heat spell, and several men have been unable to tolerate very hot industrial work. There are insufficient adults in this series to see if HED is significantly associated with any particular pattern of employment, but our strong impression is that the range of occupation is limited solely by heat intolerance. The ability to tolerate hot conditions varies among individuals, and the male subjects in certain families have few symptoms: they include those who have appreciable numbers of sweat pores.

FEMALE CARRIERS
Fifty seven obligate carrier female subjects in 22 families were interviewed and examined. Some displayed no features of the condition, a few resembled the affected male subjects, while most displayed a few of the features. Symptoms of hypohidrosis were generally not severe, but 26% complained of heat intolerance and 46% had noticed that they sweated less than normal. Some of the carriers had feeding difficulties similar to those of the boys in early childhood and had also had recurrent chest infections, but these were never as severe as in the men. Eighteen per cent described themselves as 'chesty' and nineteen (79%) of the 24 who tried to breast feed their infant(s) reported an insufficiency of milk.

The permanent teeth were examined by us or described by the woman herself in 46 cases, and 36 of these women (78%) had distinct dental abnormalities. These comprised absent permanent teeth, often associated with the persistence of deciduous teeth, small teeth resulting in gaps between the teeth, and peg shaped teeth. The deciduous teeth were described as having been abnormal in seven of the 15 women who could clearly recall their milk teeth with absent, peg shaped, or small teeth. This was borne out by examination of three young girls who were confirmed carriers, all of whom had some small or absent teeth. Thirty nine of 54 confirmed carriers (72%) described their hair as being sparse, or fine, or both. Their eyebrows were also often thin, sometimes being particularly sparse over the lateral third.

The sweat tests performed on 37 confirmed carriers were positive in all but one case (97%), showing distinct patches of anhidrosis. In a few cases only these followed the lines of Blaschko. It is important to be familiar with the appearance of the normal back when performing this test, so as not to overinterpret normal variation in the distribution of sweat pores. Sweat tests were also performed on the backs of 29 definite gene carriers whose teeth were unequivocally abnormal; the sweat test was positive in 28 cases.

Discussion
The natural history of HED varies among subjects
and perhaps between families, but it does follow a pattern. Most of the boys have problems as infants with difficulties in feeding or episodes of severe illness, or both, often of severe fever associated with infections such as pneumonia. As long as the boys are subject to ill health concern is expressed about their growth and development.

Those boys who are breast fed may receive inadequate milk from their mothers who will usually be carriers of the condition: these women are often unable to breast feed their infants, although some do so perfectly well. When advising the mother of a bottle fed infant it is useful to suggest that she does not heat up his bottle: heating can make it less palatable and contribute to his overheating.

At some stage from the age of 1 to 4 years most affected boys will abruptly, and for no obvious reason, show an improvement in their general condition. They are no longer subject to serious illness, they feed well, and they grow and develop normally. They may, however, remain susceptible to recurrent upper respiratory tract infections, bouts of fever, eczema, asthma, and food allergy. They may require water to drink with meals and need artificial tears because of inadequate salivary and lachrymal secretion. They will almost certainly require dental attention and artificial dentures. They may be bothered by teasing at school and self consciousness during adolescence. They are unlikely, however, to fall seriously ill. Heat intolerance does occur in older boys but can be dealt with by taking cool drinks and wearing wet T shirts.

Previous reports of mental retardation have exaggerated the problem, probably through a reporting bias; we found no evidence of mental retardation as a primary feature of the disease. The one child in our series with cerebral palsy was much less retarded mentally than he was physically, and his handicap was probably due to his fits at the age of 10 weeks. Only one other child had an appreciable educational problem and this did not constitute evidence of mental deficiency.

To what extent the abnormal conformation of the airway—the nose and the mouth with the oligodontia—may contribute to speech problems is not clear. It may be that artificial dentures have a role in assisting the boys' speech development; whether dentures help acoustically or serve to boost confidence among peers is not clear. Many boys are eager to wear dentures from the age of 3 or 4 years and this can be safely encouraged; upper dentures, at least, are often tolerated from this age. They may help with eating as well as boosting confidence and aiding speech.

Hearing may be mildly and transiently impaired by the crusts of dry wax that accumulate in the external auditory canal and perhaps by blockages in the eustachian tubes.

The results of immunological function tests showed a scatter of disorders, especially in humoral function, but no consistent anomaly. This pattern could be generated by secondary effects of the recognised defects in mucosal integrity and function. The respiratory and gastrointestinal tracts are defective in mucus production and may therefore permit the passage of excessive quantities of foreign material leading to dysregulation of the immune system. The defective mucus production in the respiratory tree probably contributes to the chronic obstructive airways disease that may develop in male subjects who smoke and who also work in a dusty atmosphere.

Immune function tests were only performed in survivors. The possibility therefore exists that those who succumb in early childhood do have a more severe immune disorder, perhaps a disorder of cell mediated immunity. We did not test delayed hypersensitivity reactions, and these have been shown to be impaired in some male subjects with HED.14 We also did not test enzymes in the pathways of DNA biosynthesis in phytohaemagglutinin stimulated lymphocytes, as has previously been done.15 The finding of reduced activities of these enzymes in patients with a diverse range of immune defects is difficult to interpret; only one patient with HED was tested. The comparison in that paper was with normal subjects rather than with cases of atopy or chronic sepsis, and similar findings were made in one patient with a high concentration of IgE. There is certainly no reason to suppose that the finding was related to the primary defect in HED.

Thyroid anomalies have been described in cases of hypohidrotic ectodermal dysplasia,16 although not necessarily in X-linked HED. It would seem prudent to monitor the growth of boys with HED and to investigate those with short stature so as to detect endocrine or other treatable causes of this problem. We did not confirm the previous report of low parathyroid hormone concentrations in these subjects.6

Most female carriers of HED are recognised by dental anomalies, and most of those whose teeth are normal may be recognised by their abnormal pattern of sweating. Asking for symptoms of HED and looking for sparse scalp hair were found to be too subjective to identify carriers accurately. The dental and sweating signs are useful because they can be applied to female relatives to modify the recurrence risk that is given to them after the birth of even one affected child in a family. It is hoped that DNA probe analysis of the gene will permit still more accurate counselling in the future. When an affected
infant is anticipated it may be that his early management is improved so that he is less likely to succumb to infection or severe fever.

After childhood the practical problems of living with HED steadily lessen. The subject with HED and his family, however, would be particularly foolish to smoke. He would also be well advised to avoid a hot or dusty atmosphere at his place of work.

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