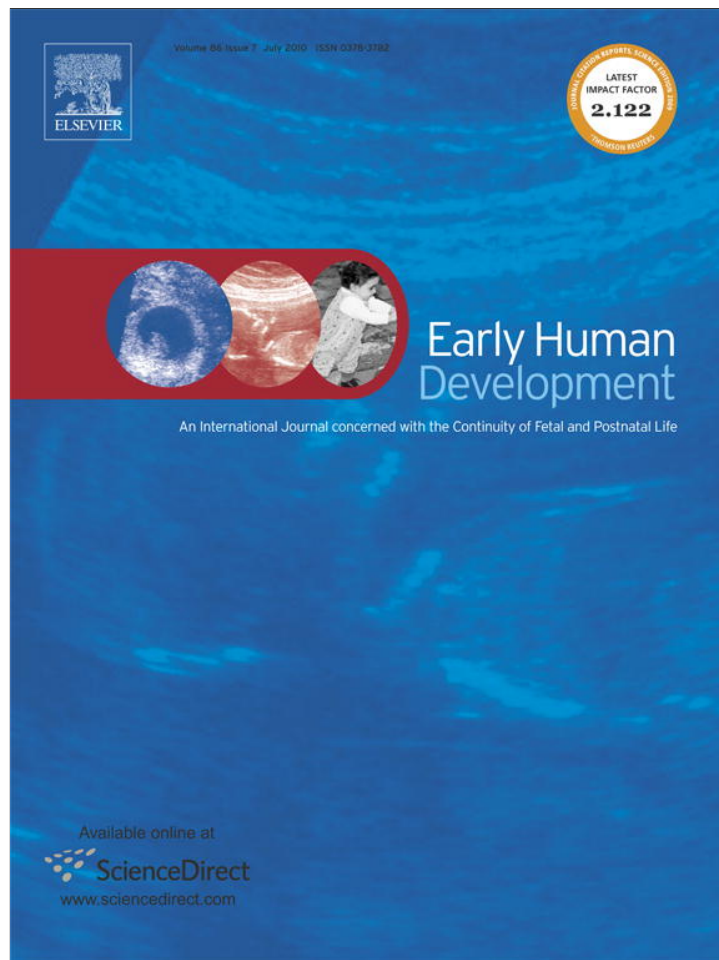


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy

Gert Blüschke^a, Kai-Dietrich Nüsken^b, Holm Schneider^{a,b,*}^a Department of Pediatrics, Section of Neonatology, Neuropediatrics and Metabolic Diseases, Medical University of Innsbruck, Austria^b Department of Pediatrics, University Hospital Erlangen, Germany

ARTICLE INFO

Article history:

Received 5 March 2010

Received in revised form 8 April 2010

Accepted 29 April 2010

Keywords:

Ectodermal dysplasia

Hyperthermia

Febrile seizure

Sudden infant death

ABSTRACT

Objective: To re-evaluate the mortality of hypohidrotic ectodermal dysplasia (HED) and the prevalence of hyperpyrexia and possible neurological sequelae in affected infants.

Study design: A cross-sectional postal survey was conducted among parents of 100 children with ectodermal dysplasia who had been registered with the German–Swiss–Austrian patient support group at any time point within the past 10 years. Detailed questionnaires referring to the first year of life were evaluated statistically. **Results:** 63% of parents returned completed surveys, identifying 57% of children as patients with X-linked HED and 20% as patients with autosomal HED or HED of unknown origin. Of those two groups, 17 infants had been placed in an incubator after birth, where body temperature recording proved to be of utmost importance. In 94% of all HED patients, episodes of unexplained fever were observed during the first year of life. X-linked HED was associated with frequent airway infections. Febrile seizures occurred in 5.9% of infants with X-linked HED and in 17% of the other HED patients. Developmental retardation was reported for 15% and 25%, respectively. Prognosis depended on the type of genetic defect and the time point of diagnosis. Except for one all patients survived infancy. Early recognition of the disease was aided by vigilant neonatal care and consulting a dermatologist or geneticist. Adequate instruction of the parents and networking with patient support groups also reduced the risks associated with HED.

Conclusions: Today, mortality of HED and the risk of hyperthermic brain damage are still increased, but lower than reported previously.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

The ectodermal dysplasias are a large, heterogeneous group of hereditary disorders characterized by defective formation of tissues derived from embryonic ectoderm. Mutations that affect the epithelial morphogen ectodysplasin A or its signalling pathway result in hypohidrotic ectodermal dysplasia (HED) [1], where a lack of sweat glands may lead to recurrent severe overheating. This rare condition was first described by Thurman [2] and also documented by Charles Darwin [3] who had received correspondence from India depicting a family in which 10 men had sparse hair, abnormal teeth and unexpected dryness of the skin during hot weather. Absence of sweating was understood as a major hazard when working out in the fields. However, the mortality of HED was found to be highest during the first year of life [4]. Although it has been widely accepted that children with HED are at substantial risk of sudden death in infancy due to fatal hyperpyrexia, few studies have investigated this issue

[4,5], indicating a mortality in early childhood of almost 30% [5]. In addition, there are anecdotal reports of HED cases with mental retardation, possibly as a result of repeated severe hyperthermia [6,7]. Impressions of frequent mental retardation in persons with HED and claims that their intelligence is different from that of the general population were difficult to dispute and may have been affected by biases against physically unattractive individuals.

However, there have been significant improvements in pediatric care over the past two decades. To complement the information published more than 20 years ago and to assess the prevalence of hyperpyrexia and possible neurological sequelae in affected infants today, patients' neonatal records were reviewed and a cross-sectional postal survey was conducted among parents of children with ectodermal dysplasia.

In our analysis, we distinguished between patients with clearly X-linked HED caused by a defect in the ectodysplasin A gene (EDA) and other HED patients, either carrying a mutation in the autosomal genes EDAR or EDARADD which encode the ectodysplasin A1 receptor or an intracellular signal mediator named EDAR-associated death domain [8], respectively, or suffering from HED of unknown origin. Thus, only the first group represents a well-defined homogeneous cohort, whereas the latter one is a heterogeneous group which may include also individuals with still undetected EDA mutations.

* Corresponding author. Department of Pediatrics, University Hospital Erlangen, Loschgestr. 15, 91054 Erlangen, Germany. Tel.: +49 9131 8533775; fax: +49 9131 8533013.

E-mail address: holm.schneider@uk-erlangen.de (H. Schneider).

2. Methods

2.1. Data collection

Neonatal records of 3 HED patients referred to the Department of Pediatrics of Innsbruck Medical University were reviewed to compile a detailed retrospective questionnaire (75 specific questions) addressing perinatal variables and family characteristics, distinctive features of the patient and parental observations during his first year of life as well as typical diagnostic procedures (Supplementary table). This questionnaire was sent out to the parents of 100 children who had been registered with the German–Swiss–Austrian ectodermal dysplasia patient support group at any time point between January 1999 and June 2008. In 8 cases, follow-up telephone interviews were conducted with the parents to add missing information or to resolve a possible misunderstanding. Only patients with hypohidrotic (anhidrotic) ectodermal dysplasia were included in the statistical analysis.

The study was approved by the ethics committee of Innsbruck Medical University, Austria, and conducted in compliance with Austrian and German legal requirements. Written informed consent was obtained from the parents or guardians of all children who served as subjects of the investigation.

2.2. Statistical analysis

Statistical analysis was performed using the chi-square test. Unless otherwise indicated the level of significance was set at 5%.

3. Results

Overall, 63% of parents (57/91) returned completed surveys on a total of 62 ectodermal dysplasia patients. However, two questionnaires could not be evaluated because of a lack of specific data. The 60 complete data sets identified 23% of affected children as individuals without hypohidrosis and 57% (34/60) as patients with clearly X-linked HED, while the remaining 20% (12/60) were classified as HED of autosomal or unknown origin (Table 1). Considering that autosomal mutations usually underlie one tenth of HED cases only, the latter group most likely also includes individuals with still undetected or spontaneous EDA mutations. Of the two groups of HED infants, 17% (8/46) had been born preterm, and 37% (17/46) had been placed in an incubator after birth. In all cases of a known family history of HED (14 children), body temperature of the newborn baby was monitored. In 7 neonates a provisional diagnosis was made on the basis of fever in connection with the incubator (Fig. 1), and further hyperpyrexia could then be avoided. Thus, body temperature monitoring proved to be of utmost importance in the neonatal management of the condition. In three cases, clinical diagnosis of HED could be confirmed by DNA analysis already within the first 2 months of life.

Table 1
Distribution of ectodermal dysplasia subtypes among the patients.

Diagnosis	Defective gene	Number of patients	Male	Female
X-linked HED ^a	EDA	34	34	0
HED of autosomal or unknown origin	EDAR, EDARADD, or unknown	12	5	7
Ectodermal dysplasia without hypohidrosis	Various	14	10	4

^a As evident from the reported molecular genetic findings, family tree and specific clinical anomalies of the mother. Only this group represents a well-defined HED cohort, whereas the second one is a heterogeneous group which may also include individuals with still undetected or spontaneous EDA mutations.

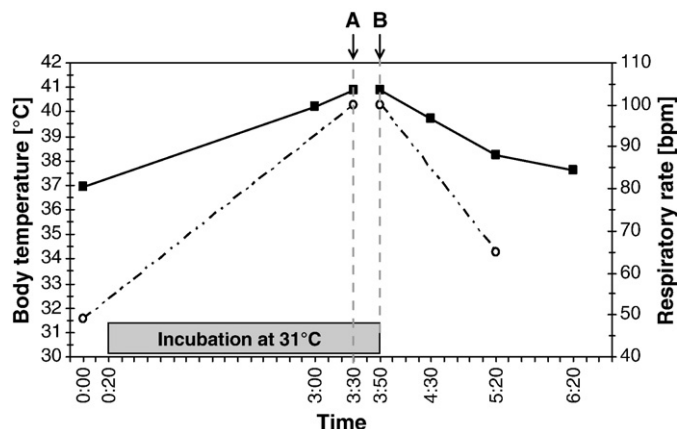


Fig. 1. Episode of unexplained fever in a two-day-old boy leading to early diagnosis of HED. Approximately 2 h after placing a male neonate in an incubator set at 31 °C, the boy started crying incessantly at night, demanding attention of the nurse. Courses of body temperature (filled squares) and respiratory rate (open circles) are shown. C-reactive protein concentration was not elevated. Following administration of a paracetamol suppository (A) and removal from the incubator (B) the child's temperature and respiratory rate declined to normal values.

For 94% of all patients with HED, episodes of unexplained fever during the first year of life were reported. As expected paracetamol suppositories were less effective than physical cooling. Fever was often associated with warm clothing (Table 2). Febrile seizures had been observed in 5.9% of infants with X-linked HED, which is significantly more frequent than in the normal population with an incidence of 0.82% during the first year of life [9] ($p = 0.027$), but even in 17% of patients with autosomal HED/HED of unknown origin ($p < 0.0001$). Long-term abnormality of EEG patterns was found only in one patient. However, the parents reported mental and/or motor developmental retardation for 15% and 25% of children with X-linked HED and autosomal HED/HED of unknown origin, respectively. Individual prognosis depended on several factors, including type and location of the genetic defect, the total number of febrile seizures and the time point of diagnosis. All patients with severe mental and/or motor retardation had experienced febrile seizures during their first year of life without diagnostic attribution. Except for one child, all patients of our cohort survived infancy.

Table 2
Family history of HED, hyperpyrexia during the first year of life and its possible consequences.

	X-linked HED	Autosomal HED/HED of unknown origin
Known family history of HED	14/34 (41.2%)	0/12 (0%)
Child was placed in an incubator after birth	11/34 (32.4%)	6/12 (50%)
Fever in connection with the incubator	5/11 (45.5%)	2/6 (33.3%)
Episodes of fever during the first year of life	33/34 (97.1%)	10/12 (83.3%)
Fever associated with warm clothing	19/34 (55.9%)	5/12 (41.7%)
Febrile seizures in the first year of life	2/34 (5.9%)	2/12 (16.7%)
Sudden death in infancy	1/34 (2.9%)	0/12 (0%)
Long-term abnormality of EEG patterns	0/34 (0%)	1/12 (8.3%)
Mental and/or motor developmental retardation	5/34 (14.7%) ^a	3/12 (25%) ^a
Delayed speech development	3/34 (8.8%)	3/12 (25%)

^a The criterion for mental and/or motor developmental retardation was parental affirmation of specific developmental abnormalities when comparing the affected child with other children of the same age (delay of cognitive skill markers and/or gross motor developmental milestones such as crawling or walking, impaired movement, lack of coordination). This was based on several independent questions to answer.

Table 3
Further early symptoms of HED.

Symptoms observed in the first year of life	X-linked HED	Autosomal HED/HED of unknown origin
Dry, scaly skin	33/34 (97.1%)	10/12 (83.3%)
Delayed teething (after 9 months of age)	33/34 (97.1%)	11/12 (91.7%)
Ceruminal clots	23/34 (67.6%)	4/12 (33.3%)
Recurrent respiratory tract infections	25/34 (73.5%)	4/12 (33.3%)

The significant differences between X-linked HED and autosomal HED/HED of unknown origin may in part be due to the greater percentage of preterm deliveries in the latter group (12% vs. 33%), although none of the patients was born before the 34th week of gestation.

Apart from hyperthermia, commonly reported HED-associated symptoms during the first year of life included a dry, scaly skin and delayed teething (Table 3), whereas recurrent airway infections were observed in most patients with X-linked HED, but only in one third of the infants with autosomal HED/HED of unknown origin. Interestingly, a similar difference was seen for ceruminal clots, another early symptom of HED.

The available medical records and the parents' reports showed that early recognition of the disease was aided by vigilant neonatal care as well as by consulting a pediatric dermatologist or geneticist and undertaking DNA analysis without delay. Interdisciplinary management, adequate instruction of the parents, particularly about temperature control and cooling procedures, and deliberate networking with patient support groups served as effective measures to avoid hyperpyrexia and other complications of HED.

4. Discussion

Eccrine sweating is an extremely important function in human thermoregulation. Problems affecting either the control of sweating activity or the glands themselves can lead to fatal hyperpyrexia. This applies in particular to the early childhood. Therefore, despite worldwide improvements in pediatric care, the reduced number of sweat glands in HED patients is still assumed to have a strong impact on mortality. An earlier study by Clarke et al. [4] revealed a higher mortality in the first affected male within a sibship than in the later born affected males. This previous finding also applied to the one family that reported a fatality in our study, as the boy who died was the older of two affected brothers. However, because of the small size of modern families the issue has become more difficult to explore. In addition, our study showed that at-risk infants today are much more likely to be identified prior to life-threatening events than a few decades ago. In most neonatal care units body temperature is monitored closely. Hyperthermia is recognized as an emergency and can be managed in a timely manner. There is no doubt about the great importance of temperature control in neonatal management, particularly if a child needs to be placed in an incubator. In a relevant number of cases, monitoring of body temperature allowed early clinical diagnosis of HED. Subsequent to that diagnosis awareness of the hazards related to the rare disease proved most helpful in preventing avoidable calamities. This applied in particular to families with prior knowledge of the disorder. Although heat intolerance persists throughout life, later it can be dealt with, e.g. by taking refuge to cooler places, moistening the T-shirt, using portable ventilators or taking cool drinks. Most other problems of living with HED also lessen as the child grows up.

In further pregnancies, midwives and doctors should always be informed about a family history of HED to accelerate the diagnostic process postnatally. If the family's mutation is known, genetic testing may be arranged immediately after birth. Any child born to a female carrier should be watched carefully until a definite diagnosis is made.

Nevertheless, our patient cohort evinced an increased prevalence of febrile seizures, mental and motor retardation in comparison with healthy infants. Approximately one-fifth of patients suffered distinct sequelae. The differences between X-linked and autosomal HED/HED of unknown origin require further investigation. However, death after febrile seizures is very rare, even in high-risk children [10], and 80% of HED patients appear to develop normally today with respect to severe complications of hyperthermia.

The accuracy of our findings may be limited by an ascertainment bias introduced into our study by sending the questionnaire to previous or current members of a patient support group. To evaluate the outcome and to compare it with older data for a very rare disease in a representative number of patients, this study design was the most feasible. However, it is likely that some parents of infants who died from HED have never become members of the respective patient support group. As national or international ED patients' registries have not been established yet, those families are extremely difficult to identify.

Our study indicates a mortality of 2.1% in the first year of life, which is higher than in healthy infants but tenfold lower than estimated by Clarke et al. [4] more than 20 years ago. Considering the ascertainment bias and statistical shortcomings due to the limited sample size or response rate to our survey, the real mortality of HED in infancy may lie between 2% and 20%, depending on the speed of diagnosis and the standard of medical care.

If the 5 main diagnostic criteria identified in this study (recurrent episodes of unexplained hyperthermia, dry and scaly skin, delayed teething, ceruminal clots and recurrent airway infections) complement the cardinal findings generally utilized (thin, lightly pigmented scalp hair and decreased sweating), it should be possible to diagnose the majority of HED cases within the first year of life. With such key findings clinicians can put a patient in a syndrome family. Specification can then be done by molecular analysis [11].

Although HED will remain a life-threatening disease, our study shows that its prognosis has improved over the last decades, probably as a result of more rapid recognition and adequate management of the disturbed thermoregulation – particularly during the first year of life.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgements

This study was supported by a grant from the German–Swiss–Austrian ectodermal dysplasia patient support group (to H. S.). The authors wish to thank all families who participated in the survey.

References

- [1] Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet* 2004;131C:45–51.
- [2] Thurman J. Two cases in which skin, hair and teeth were very imperfectly developed. *Proc R Med Chir Soc* 1848;31:71–82.
- [3] Darwin C. The variations of animals and plants under domestication, 2nd ed, Vol. II. London: John Murray; 1885. p. 319–20.
- [4] Clarke A, Phillips DI, Brown R, Harper PS. Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. *Arch Dis Child* 1987;62:989–96.
- [5] Salisbury DM, Stothers JK. Hypohidrotic ectodermal dysplasia and sudden infant death. *Lancet* 1981;1:153–4.
- [6] Halperin SL, Curtis GM. Anhidrotic ectodermal dysplasia associated with mental deficiency. *Am J Ment Defic* 1942;46:459–63.
- [7] Tanner BA. Psychological aspects of hypohidrotic ectodermal dysplasia. *Birth Defects Orig Artic Ser* 1988;24:263–75.
- [8] Mikkola ML. Molecular aspects of hypohidrotic ectodermal dysplasia. *Am J Med Genet A* 2009;149A:2031–6.
- [9] Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile convulsions. *Acta Paediatr Scand* 1990;79:550–7.
- [10] Vestergaard M, Pedersen MG, Ostergaard JR, Pedersen CB, Olsen J, Christensen J. Death in children with febrile seizures: a population-based cohort study. *Lancet* 2008;372:457–63.
- [11] Itin PH. Rationale and background as basis for a new classification of the ectodermal dysplasias. *Am J Med Genet A* 2009;149A:1973–6.