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INVESTIGATIVE REPORT

A Retrospective Study of Clinical and Mutational Findings in 45 Danish Families with Ectodermal Dysplasia

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Ectodermal dysplasias form a complex, nosologic group of diseases with defects in at least 2 ectodermal structures. A retrospective study of patients with ectodermal dysplasia seen at our department over a period of 19 years (1994–2013) was performed. The study population consisted of 67 patients covering 17 different diagnoses. Forty-five families were identified of which 26 were sporadic cases with no affected family members. In 27 tested families a disease-causing mutation was identified in 23 families. Eleven mutations were novel mutations. To our knowledge, we present the first large ectodermal dysplasia cohort focusing on clinical manifestations in combination with mutational analysis. We recommend a nationwide study to estimate the prevalence of the ectodermal dysplasia and to ensure relevant molecular genetic testing which may form the basis of a national ectodermal dysplasia database. ***Key words: ectodermal dysplasia; retrospective study; mutations; clinical findings.***

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The ectodermal dysplasias form a large heterogeneous group of more than 200 different inherited disorders that have in common developmental abnormalities of 2 or more structures derived from embryonic ectoderm. In 1848, Thurmann was the first to describe ectodermal dysplasia. Later, several clinical classifications of the ectodermal dysplasias have been proposed. Pinheiro & Freire-Maia (1) reviewed 154 different forms of ectodermal dysplasias and classified these according to clinical conditions including defects in 2 or more "classic" ectodermal derivatives – hair, teeth, nails, sweat glands (group A) or defect in one of the above mentioned structures plus at least one other ectodermal defect (group B). The anomalies affecting the epidermis and epidermal appendages are highly variable. Ectodermal dysplasias could also be subgrouped in 11 different entities based on an arbitrary clinic-mnemonic classification. However, in a clinical classification the variable expression of the same entity may be misleading when making a diagnosis.

Over the last decades, more than 1/3 of the causative genes in ectodermal dysplasias have been identified (2). The classification has developed from a clinical, descriptive one (1, 3, 4) to newer classifications, which attempt to integrate molecular genetics and corresponding clinical findings. An example of the latter was published by Priolo & Laganá in 2001 (5) and refined by Priolo in 2009 (6). This classification divided ectodermal dysplasias into 2 different groups, based on 2 different pathogenetic mechanisms. The first group included ectodermal dysplasias with defects in epithelial-mesenchymal interaction. Two different functional patterns of regulation in the first group were identified. The first pattern involved mutations in the EDA /EDAR/EDAR-ADD signalling pathway (i.e. hypohidrotic ectodermal dysplasia, HED). The second pattern involved mutations in the IKBKG regulation pathway (i.e. incontinentia pigmenti, IP). The second group included disorders in which an abnormal function of structural proteins were found, such as the connexin gene family (i.e. keratitis–ichthyosis–deafness syndrome, KID) as well as genes encoding keratins (pachyonychia congenita, PC). Not all ectodermal dysplasias can be classified according to the classification by Priolo (5). Another classification was proposed by Lamartine (7) based on molecular and biochemical factors dividing patients into 4 subgroups – group A: cell-cell communication and signalling (i.e. HED and IP), group B: adhesion (i.e. ankyloplepharon-ectodermal dysplasia-clefting syndrome, AEC), group C: development (i.e. Witkop syndrome), and group D: others (i.e. poikiloderma congenitale) (8).

In our opinion the definition of ectodermal dysplasias suggested by Priolo continues to be appropriate as it imposes clear limits for the conditions.

The aim of the current study was to identify patients with ectodermal dysplasias seen at the Department of Dermatology and Allergy Centre at Odense University Hospital during a 19-year period. We present a descriptive Table (Table SI[1]), with all clinical and mutational findings in the 45 families included in this study.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1799

METHODS

A retrospective chart review was conducted at our department between January 1994 and January 2013. Inclusion criteria were the following ICD-10 diagnoses: Q82.3 incontinentia pigmenti, Q82.4A dysplasia ectodermalis anhidrotica, Q82.4B dysplasia ectodermalis hidrotica, Q82.4C dysplasia ectodermalis hypohidrotica, Q82.8F dyskeratosis congenita, Q84.1B monilethrix, Q87.8H Papillon-Lefèvre syndrome, Q84.5D pachyonychia congenita, Q87.8E Goltz syndrome, and Q87.8I Rothmund-Thomson syndrome. Patients were identified with one of these diagnoses at referral or after first evaluation and their medical records including clinical photos were reviewed. Data obtained included age, gender, clinical characteristics, family history, modes of inheritance, and results of molecular genetic investigations.

RESULTS

Sixty-seven patients fulfilled the clinical or mutational criteria for ectodermal dysplasia in concordance to Pinheiro (1), with 28 males and 39 females belonging to 45 families. A total of 422 patients were excluded due to a final diagnosis different from ectodermal dysplasia, as the diagnosis had been waived during the diagnostic process. The median age at time of referral was 10 years, with a range of 2–90 years. The mean age of the cohort was 21 years, with a range of 2–92 years. Seventeen different diagnoses were found. Forty-one patients from 19 different families had affected relatives while 26 patients were sporadic cases. Twenty-seven families were genetically tested. A disease-causing mutation was identified in 23 families. Eleven mutations were novel mutations; see Table SI[1] for further details. Four families had been tested without finding a disease-causing mutation. Families, diagnoses, modes of inheritance, age and sex distribution, mutational and clinical findings are seen in Table SI[1]. Four families have previously been published as case reports, family number 11 (8), family number 33 (9), family number 41 (10), and family number 42 (11).

HED accounted for the largest number of patients ($n = 20$) belonging to 12 families. An example of a third-generation family with autosomal dominant HED is illustrated in Fig. 1. Clouston syndrome was the second most common condition ($n = 10$) with 4 affected families. For details regarding the individual families of our study, see Table SI[1].

DISCUSSION

Ectodermal dysplasia constitutes a diverse group of diseases, as seen in our cohort. The diseases are rare and we identified 45 families over a 19-year period at our hospital serving a background population of today 1.2 million inhabitants. In the beginning of the inclusion period the disease-causing genes for the ectodermal dysplasias were unknown. This may explain why not all families were molecular genetically tested. In general, HED is the most common form of ectodermal dysplasia, in accordance with our series. We found that trichodysplasia accounted for the most frequent clinical ectodermal defect followed by dental defects, onychodysplasia, and dyshidrosis, respectively. This is in accordance to findings by Pinheiro & Freire-Maia (1).

Mutations in the *EDA* gene encoding Ectodysplasin A were found in 3 families and mutations in the *EDAR* gene were found in 2 families. We found no families with mutations in *EDARADD* or *WNT10A*, which have previously been reported to cause HED (12). In our study, patients with autosomal recessive (AR) and dominant (AD) HED were clinically indistinguishable, as described by Munoz (13). X-linked inherited hypohidrotic ectodermal dysplasia (XLHED) was the most frequent in our group. According to Nguyen-Nielsen et

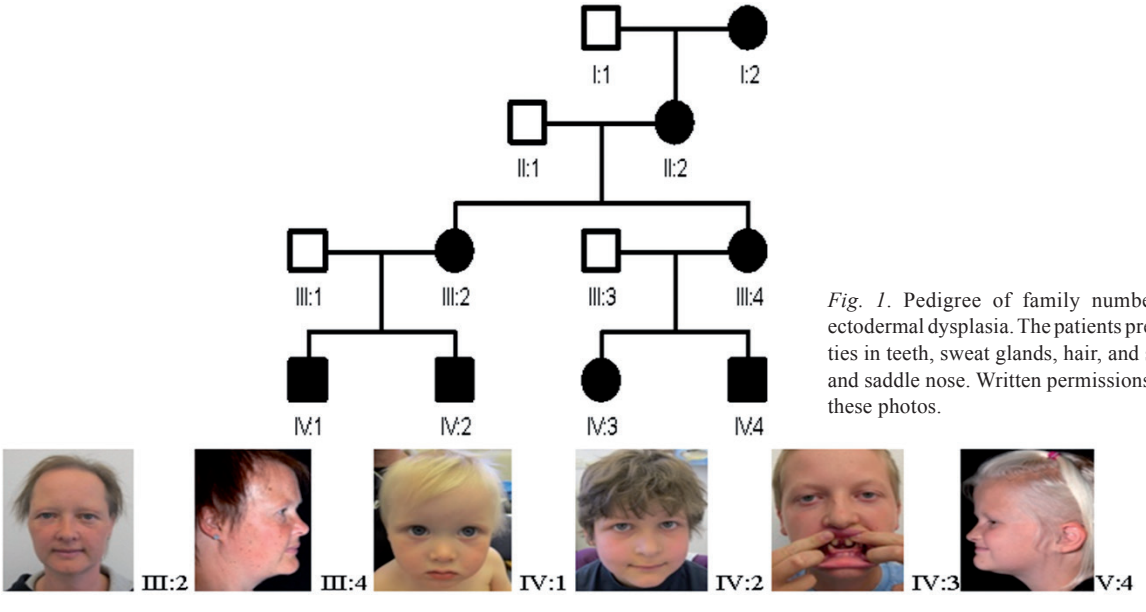

Fig. 1. Pedigree of family number 14. Hypohidrotic ectodermal dysplasia. The patients present with abnormalities in teeth, sweat glands, hair, and skin, frontal bossing, and saddle nose. Written permissions are given to publish these photos.

al. (14) XLHED is the most common HED in Denmark, with an estimated prevalence (clinically or molecularly diagnosed) of 4.2/100.000. Lexner et al. (15) have described the Danish XLHED patient cohort in detail.

Since 1968, all Danes have been provided with a personal identification number. This is an ideal basis to perform register studies. However, the outcome of a retrospective chart to identify patients with ectodermal dysplasias depends on correct registration of diagnoses. Some patients may have been incorrectly registered and therefore not included in our cohort. The former ICD-8 registration (used in Denmark from 1978 until 1993) included only 3 ectodermal dysplasia diagnoses and was insufficient, making it difficult to include patients seen at our Department before 1994. The present ICD-10 registration including 10 ED diagnoses is still inadequate to cover more than 200 distinct ED diagnoses. The lack of a sufficient diagnosis registration system is a potential pitfall when performing a retrospective study.

The median age at the time of referral was 10 years. Patients with ectodermal dysplasia present with visible ectodermal abnormalities, and we assume that a better knowledge of this disease group may reduce the diagnostic delay. Some patients show discrete phenotypic abnormalities however, and some patients are familiar with their disease due to affected family members and do not seek medical counselling. Patients may not know about the possibilities of molecular genetic testing. Patient associations provide a possibility for patients to access information and we recommend a close cooperation with these. The dermatologist plays a central role in coordinating the diagnostic and therapeutic process between different specialist departments (often including odontologist, paediatrician, oto-rhino-laryngologist, clinical geneticist, neurologist, ophthalmologist, orthopaedic surgeon, radiologist, plastic surgeon and others).

Over the last decades, knowledge about molecular genetic background for ectodermal dysplasia has emerged by the identification of several disease-causing genes. Further research in this area may reveal a genetic overlap between different clinical diagnoses and hopefully decrease the number of ectodermal dysplasias. A future classification of ectodermal dysplasias must include both phenotype and genotype.

In total we identified 17 families who had not been genetically elucidated, mainly because this was not an option when the patient was diagnosed. Four families had been tested without finding a disease-causing mutation. These families could be offered a new dermatological consultation to clarify the phenotype and offering referral to the department of clinical genetics to verify the diagnosis. Prenatal diagnostics will be possible if the underlying mutation can be detected.

A nationwide retrospective study of ectodermal dysplasia can form the basis of a central register for ectodermal dysplasia in Denmark, which would facilitate future studies.

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