ORIGINAL ARTICLE

The Ectodermal Dysplasias-Burden of Disease Score: Development and Validation of an Ectodermal Dysplasia Family/Parental Burden Score

Hélène DUFRESNE[1,2], Oriane MAINCENT[1], Charles TAIEB[1], Christine BODEMER[1,3,4] and Smail HADJ-RABIA[1,3,4]
[1]Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), Filière Maladies Rares Dermatologiques (FIMARAD), ERN-Skin and [2]Pediatric Social Services, Hôpital Universitaire Necker–Enfants Malades, Assistance Publique – Hôpitaux de Paris-Centre (AP-HP5), Paris, [3]Institut Imagine and [4]University of University of Paris-Cité, Paris, France

Ectodermal dysplasias are genetic conditions affecting the development and/or homeostasis of 2 or more ectodermal derivatives, including hair, teeth, nails, and certain glands. No tool is available to assess the burden of ectodermal dysplasias and its multidimensional impact on patients and their families. This study developed and validated a familial/parental 19-item burden questionnaire designed specifically for ectodermal dysplasias. Each group of questions was linked to 1 of the following dimensions: (*i*) Impact of the disease on social life and hobbies; (*ii*) Future prospects; (*iii*) Restraint of the disease on outdoor activities; (*iv*) Financial burden of the disease; (*v*) Acceptance of the disease. Cronbach's alpha was 0.91 for the entire Ectodermal Dysplasias-Burden of Disease (ED-BD) scale, confirming excellent internal coherence. Intradimensional coherences all demonstrated excellent reliability ($\alpha > 0.76$). The ED-BD questionnaire was highly correlated with the Short Form-12 and Psychological General Well Being Index validated questionnaires. Cultural and linguistic validation in US English was conducted. Development and validation of the questionnaire was based on data from patients with the 2 main ectodermal dysplasias subtypes. This ED-BD questionnaire represents the first specific assessment tool for evaluating the familial/parental burden of ectodermal dysplasias.

Key words: ectodermal dysplasias; burden; questionnaire; quality of life; parents; genodermatoses.

Accepted May 17, 2023; Published Aug 30, 2023

Acta Derm Venereol 2023; 103: adv5203.

DOI: 10.2340/actadv.v103.5203

Corr: Smail Hadj-Rabia, Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), Filière Maladies Rares Dermatologiques (FIMARAD), ERN-Skin, Hôpital Universitaire Necker– Enfants Malades, Assistance Publique – Hôpitaux de Paris-Centre (AP-HP5), 149 rue de Sèvres, FR-75015, Paris, France. E-mail: smail.hadj@inserm.fr

SIGNIFICANCE

Ectodermal dysplasias are conditions affecting the development of ectodermal derivatives. Tooth anomalies and hypohidrosis have negative impact on quality of life. The "burden" assesses disability, social integration, home life and the use of medical resources. This study developed and validated a family/parental burden questionnaire for the parents and families of young patients with ectodermal dysplasia.

Ectodermal dysplasias (ED) are genetic conditions affecting the development and/or homeostasis of 2 or more ectodermal derivatives, including hair, teeth, nails, and certain glands (1). Among the 100 reported subtypes, hypohidrotic ED (HED) and P63-related ED account for approximately 60% of patients. For HED, the most common symptoms, ranging from mild to severe, are hypohidrosis or anhidrosis, hypotrichosis (sparse scalp and body hair) and teeth abnormalities (such as hypodontia, cone-shaped teeth or microdontia) (2), while for P63-related ED, oro-facial anomalies (clefting, hearing loss, scalp erosions) remain major features (2, 3). There are autosomal dominant and recessive forms of HED, and the most frequent transmission mode is X-linked (4). P63-related ED are autosomal dominant disorders (3). Previous studies have shown that HED and, more specifically, tooth abnormalities related to them, had a negative impact on health-related quality of life (HRQoL) (5, 6). Nevertheless, there is no specific tool to evaluate the quality of life and the impact of the disease on these patients and their family. Such a tool would be useful for clinicians, enabling a description of the caretaker's and patient's own perception and its evolution throughout the patient's care.

The notion of "burden" was introduced by the World Health Organization (WHO) to better quantify the health of a population and to determine the priorities of action in the public health field. The "burden of disease" concept now distinguishes between: (*i*) the overall burden, by measuring the economic impact on society, and (*ii*) the individual burden. The individual burden, for each patient and their family, assesses disability (e.g. "health-related quality of life" (HRQoL)), social integration, home life, and the use of medical resources including care, whether psychological, social, economic, or physical (7, 8).

Recently, burden questionnaires have been designed for several rare skin diseases, allowing for a better understanding of the global impact (psychological, socio-economic and physical) of these conditions on patients and their families (9–12). We propose here a validated, self-administered family/parental burden questionnaire designed for parents and families of young patients with ED.

MATERIALS AND METHODS

The self-administered questionnaire was developed in 3 phases (conceptualization, development, and validation) using: (*i*) standard methodology for the building of a multiple ability self-report questionnaire and of HRQoL claims, and (*ii*) a method for designing a patient burden questionnaire in dermatology (13–15). Items were verified against the COSMIN risk of bias checklist (16). The multidisciplinary working group consisted of 2 dermatologists, a social worker, an expert in questionnaire development, and 2 patients with ED. The project for the construction of the questionnaire obtained approval from the Committee for the Protection of Persons (CPP Ouest V, Rennes, France (CPP17/042-3)) on 31 July 2017. The responses were anonymized; at no time did the authors of the project or the persons in charge of the analgesia statistics know the identity of the responders. A cover letter including the contact details of 1 of the project authors was provided along with the consent form. This note also clearly explained the purpose of the project and guaranteed the anonymity of respondents.

Conceptual phase

The first step consisted of gathering a list of complaints and disabilities related to ED. These were expressed during 15 semi-structured face-to-face interviews with parents of young patients with ED (conducted from January to June 2018 by HD), and during a meeting of the French Association of ED patients (AFDE). The items were collected and rephrased for better comprehensibility. Redundant items were regrouped for conciseness.

Development phase

A questionnaire was created in a question and answer format based on the information collected. As frequently found in quality of life questionnaires, the responses, determined in agreement with the working group, were in the form of a 5-point Likert scale: "never" (0), "rarely" (1), "sometimes" (2), "often" (3), "very often" (4) "all the time" (5) and "not applicable".

After oral consent, the questionnaire was given to a random sample of French-speaking parents of children with ED (under 18 years). The diagnosis of ED was confirmed by clinical and/or molecular analysis. An exploratory factor analysis was performed in order to reveal latent constructs, assigning each item to its respective domain or dimension. Principal component analysis with varimax orthogonal rotation was then performed in order to determine to which domain or dimension each question belonged. Whenever questions could be linked to several dimensions, the questions were allocated to the dimension deemed by the expert working group to be the most semantically relevant.

Validation phase

Cronbach's alpha coefficient was used to test the homogeneity of the items in each field and hence evaluate the internal consistency (17). This coefficient varies from 0 to 1 and corresponds to a degree of homogeneity. A coefficient of 0.7 or higher shows good internal reliability.

To prove the unidimensionality of the questionnaire, a higher order factor analysis is required (confirmatory analysis). It consists of showing that the dimensions can be grouped into a single general dimension, represented by a single score.

Moreover, during this phase each question was tested on its own dimension. If the results were not significant, the question could be removed. The goodness of fit was rated by a Bentler comparative fit index greater than 0.9 and a Bentler-Bonett non-normed fit index greater than 0.9 (18). The root mean square error approximation (RMSEA) had to be approximately 0.05, or at least lower than 0.08 with a confidence interval of 0.05.

To ensure external validity, the participants were asked to answer validated self-administered questionnaires: the Short Form 12 (SF12) quality of life questionnaire and the Psychological General Well Being Index (PGWBI). Concurrent validity was calculated between the ED questionnaire and these standard questionnaires using Spearman's coefficient (r) (19).

The SF12 questionnaire (short version of the SF36) is a basic quality of life tool used to measure the health condition of the general population. It has 2 subsections (physical and mental health) that can be calculated with 12 questions. Higher scores on the SF12 indicate a better quality of life in terms of physical and mental health (20).

The PGWBI scale has been widely used among medical specialties and in numerous countries (21–25). It consists of 22 items, with a high score showing psychological wellness. Six emotional states are studied: anxiety, depressed mood, positive well-being, self-control, general health and vitality.

The concurrent validity between the ED questionnaire and the validated scores (PGWBI and SF12) was established by calculating the Pearson correlation. SAS Software version 9.4 (SAS institute, Cary, NC, USA) was used to analyse the data, with a significance threshold of 0.05 for all tests.

Translation and cross-cultural adaptation

Translation and cross-cultural adaptation were permitted due to a rigorous, validated methodology, which enabled the creation of a US English language version. This process consists of 9 specific steps that refine the translation while taking into account subtle nuances in the source document (26).

RESULTS

Conceptual phase

The major issues reported in the initial verbatim report concerned daily life, family life, the child's life, economic consequences, and social impact (Table SI). When necessary, questions were reformulated for better comprehensibility. At this point, an initial 49-item questionnaire was drafted.

Development phase

The initial 49 items were cut down into a 20-item questionnaire. Questions about the impact on social life were highly correlated with each other ($r > 0.7$), and 15 questions were removed after consensus. The information gathered by 16 questions was redundant and thus grouped into 3 questions. Fifty-one parents of ED children completed the 20-item questionnaire: 48 parents of 60 HED patients (43 *EDA* mutated patients (34 boys); 5 *EDAR* mutated patients (5 females); 2 *WNT10A* patients (1 boy); and 5 without molecular confirmation (3 girls)), and 3 parents of 3 P63-related ED (2 females).

Internal validity

Principal component factor exploratory analysis was conducted on the 20-item questionnaire answered by 51 participants. Each group of questions was allocated to a dimension and a total of 6 dimensions were identified (Table SII).

Since the sixth dimension had only 1 variable, the item associated with it was withdrawn: "the sickness of our child makes it difficult to maintain his/her relationship with his/her siblings''. Moreover, the item "my child needs more care depending on the season" was correlated with the second and fourth dimensions, with a slightly stronger correlation for the fourth. It was nevertheless decided to associate this item with the second dimension, because of the temporal aspect.

Therefore 5 dimensions were obtained in a 19-question form (Table SIII): (*i*) Impact of the disease on social life (7 questions); (*ii*) Future prospects (5 questions); (*iii*) Restraint of the disease on outdoor activities (3 questions); (*iv*) Financial burden of the disease (2 questions); and (*v*) Acceptance of the disease (2 questions).

Confirmatory analysis

A higher order factor analysis was conducted on the same patients as for the principal component factor exploratory analysis. The factors with a variant lower than 0.5 are not considered dependable. This confirmed that all items were significant, and none were withdrawn.

Cronbach's alpha coefficient was measured at 0.91 for the global questionnaire, showing excellent internal coherence. This was also confirmed in each dimension with coefficients greater than 0.76 (Table SIV).

Concurrent validity

The concurrent validity was tested by calculating the Pearson's correlation coefficient between the ED score and the PGWBI score, as well as the physical and mental score of the SF12. The PGWBI score was negatively correlated with the ED score (–0.441) and its 5 dimensions (from –0.23 and –0.42). Every correlation was significantly different from zero apart from the 5th dimension. The physical score of the SF12 was negatively correlated with the ED score. However, none of these correlations were significantly different from zero. The mental score of the SF12 was negatively correlated with the ED score (–0.53) and its dimensions (from –0.32 and –0.46), all correlations were statistically different (Table SV).

Translation and cross-cultural adaptation

A US English language version of the Ectodermal Dysplasias-Burden of Disease (ED-BD) questionnaire was created (**Table I**).

Table I. English-language and cross-cultural adaptation of the Ectodermal Dysplasias Burden of Disease (ED-BD) questionnaire

1- I/We give up on certain leisure activities because of my/our child's illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
2- My/Our child's illness makes eating out complicated (restaurant, family)					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
3- My/Our child's eating difficulties affect my/our social life					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
4- I/We choose where to go on vacation based on my/our child's illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
5- My/Our child's dental problems force me/us to exclude certain foods					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
6- My/Our child's illness has made me/us want to quit my/our job(s)					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
7- I/We fear for my/our child's future because of his/her illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
8- Complications related to our child's illness worry me/us					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
9- I/We feel lost when faced with the symptoms of my/our child's illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
10- My/Our child's illness has disrupted my/our life					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
11- My/Our child's future career worries me/us					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
12-Each time I/we go to the hospital, I/we don't feel good the next day					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
13-Each time I/we go to the hospital, I/we don't feel good the day before					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
14-It takes a long time to get my/our child ready each morning because of his/her illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
15-I/We allocate part of my/our household budget to my/our child's care					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
16-I/We have less money to spend because of the non-reimbursed costs associated with my/our child's illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
17-My/Our child needs more attention than other children depending on the season					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
18-It is hard to get my/our child to accept dental care related to his/her illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable
19-It is hard for me/us to see my/our child being teased because of his/her illness					
□ never	□ rarely	□ sometimes	□ often	□ all the time	□ not applicable

DISCUSSION

The concept of disease burden encompasses many social and economic issues. Nevertheless, it is only rarely used to inform health policy decisions. It simultaneously takes into account the quality of life, relationships within the community, daily life organization, and the use of medical resources. In the health domain, burden is increasingly reported for chronic diseases; especially skin diseases (8). EDs represent a group of rare and chronic diseases with a wide range of symptoms. Therefore, they have a multidimensional impact on the quality of life of patients, making it difficult to evaluate using the more general questionnaires currently available.

Previous studies have shown the negative impact that genodermatoses can have on the quality of life of patients (9–12).

The psychological distress of ED patients with oligodontia, and the negative impact of oligodontia on their quality of life, has been underlined. The influence of hypohidrosis was also suggested (6). Inability to sweat and the accompanying intolerance to heat can be a serious impediment on a daily basis: discomfort and fatigue in the early afternoon are frequently reported by patients with ED. However, in both of these previous studies, generic methods were applied to determine the quality of life. Hyposalivation and prostheses may also have an impact on a social life that includes shared meals. To take these specificities into account, we believe that a specific evaluation tool is needed for healthcare professionals to objectively assess the burden of ED.

Given the paediatric population of patients with ED, the disease burden is often shared by the entire family (26–29). Parents are affected by the different dimensions of the disease in helping with the daily care of their child, and in organizing necessary appointments with various specialists. As a chronic disease, it deeply impacts the quality of life for family members who have to assimilate the diagnosis and the lack of curative treatments. This burden includes economic (costs of the dental treatment, work leave), physical, psychological, and social (lack of support, specific difficulties related to the season period and the tooth agenesis) aspects, emphasizing the need to measure the burden of the disease on the whole family. The ED-BD questionnaire was developed to better qualify these issues, as a better understanding of disease burden leads to more appropriate patient care and, ultimately, to health improvement.

The ED-BD questionnaire proved to have a good internal consistency (Cronbach's alpha = 0.91) and was correlated with both the mental dimension of the SF12 and the PGWBI, attesting to its concurrent validity. There was nonetheless no significant correlation with the physical dimension of the SF12 of carers. These results are not unexpected, since the ED-BD questionnaire was designed for parents. Indeed, the results are coherent with previous studies on the quality of life among parents of children with genodermatoses (10, 12).

The specificity of the ED-BD questionnaire allows for a global evaluation of familial disabilities and difficulties that was previously not possible with a standard QoL questionnaire.

To our knowledge, this is the first burden questionnaire specifically intended for relatives of patients with ED. The format is short (19 questions with 5 possible answers), easy to use, and understandable. This study is representative of the French population, since patients followed at the centre for rare cutaneous diseases (MAGEC) come from all over France, from a wide range of social and cultural classes. Questionnaires were administered through the French association of ED patients (AFDE). The usefulness of a validated self-administrated specific ED-BD questionnaire leading to a score with quantified items represents a useful tool for assessing therapeutic education programmes. It may help in the development and the evaluation of new patient management approaches and the improvement in existing patients' healthcare.

The main limitation of the current study is the relatively small sample size of 51 parents. However, as ED are rare diseases, a small sample size is not surprising. Moreover, 48 of them were parents of a child with HED, the main subtype of ED. Therefore, specific issues related to other ED subtypes, such as P63- related ED, was probably not captured.

The English translation was made using a specific 9-step methodology, providing a culturally and linguistically validated questionnaire. This process could be used to create linguistically-validated and cross-culturally adapted versions of the questionnaire in other languages, such as German or Spanish.

ACKNOWLEDGEMENTS

The authors acknowledge the patients, their families and the French association of ED patients (Association Française des Dysplasies Ectodermiques).

The authors have no conflicts of interest to declare.

REFERENCES

1. Peschel N, Wright JT, Koster MI, Clarke AJ, Tadini G, Fete M, et al. Molecular pathway-based classification of ectodermal dysplasias: first five-yearly update. Genes (Basel) 2022; 13: 2327.
2. Wohlfart S, Meiller R, Hammersen J, Park J, Menzel-Severing J, Melichar VO, et al. Natural history of X-linked hypohidrotic ectodermal dysplasia: a 5-year follow-up study. Orphanet J Rare Dis 2020; 15: 7.
3. Maillard A, Alby C, Gabison E, Doan S, Caux F, Bodemer C, et al. P63-related disorders: Dermatological characteristics in 22 patients. Exp Dermatol 2019; 28: 1190–1195.
4. Trzeciak WH, Koczorowski R. Molecular basis of hypohidrotic ectodermal dysplasia: an update. J Appl Genet 2016; 57: 51–61.

5. Saltnes SS, Jensen JL, Sæves R, Nordgarden H, Geirdal AØ. Associations between ectodermal dysplasia, psychological distress and quality of life in a group of adults with oligodontia. Acta Odontol Scand 2017; 75: 564–572.
6. Pavlis MB, Rice ZP, Veledar E Bradley BR, Spraker MK, Chen SC. Quality of life of cutaneous disease in the ectodermal dysplasias. Pediatr Dermatol 2010; 27: 260–265.
7. WHO | About the Global Burden of Disease (GBD) project. WHO. [Accessed March 6, 2020] Available from https://www.who.int/healthinfo/global_burden_disease/about/en/.
8. Chren MM, Weinstock MA. Conceptual issues in measuring the burden of skin diseases. J Investig Dermatol Symp Proc 2004; 9: 97–100.
9. Dufresne H, Hadj-Rabia S, Taieb C, Bodemer C. Development and validation of an epidermolysis bullosa family/parental burden score. Br J Dermatol 2015; 173: 1405–1410.
10. Dufresne H, Hadj-Rabia S, Méni C, Sibaud V, Bodemer C, Taïeb C. Family burden in inherited ichthyosis: creation of a specific questionnaire. Orphanet J Rare Dis 2013; 8: 28.
11. Morice-Picard F, Taïeb C, Marti A, Gliksohn A, Bennani M, Bodemer C, et al. Burden of albinism: development and validation of a burden assessment tool. Orphanet J Rare Dis 2018; 13: 162.
12. Taieb C, Hadj-Rabia S, Monnet J, Bennani M, Bodemer C. Incontinentia pigmenti burden scale: designing a family burden questionnaire. Orphanet J Rare Dis 2019; 14: 271.
13. Seidenberg M, Haltiner A, Taylor MA, Hermann BB, Wyler A. Development and validation of a Multiple Ability Self-Report Questionnaire. J Clin Exp Neuropsychol 1994; 16: 93–104.
14. Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. Value Health 1999; 2: 113–127.
15. Ezzedine K, Bennani M, Shourick J, Taieb C. A Method for Designing a Patient Burden Questionnaire in Dermatology. Clin Cosmet Investig Dermatol 2020; 13: 521–528
16. Mokkink LB, de Vet HCW, Prinsen CAC, Patrick DL, Alonso J, Bouter LM, et al. COSMIN risk of bias checklist for systematic reviews of patient-reported outcome measures. Qual Life Res 2018; 27: 1171–1179.
17. Cronbach LJ, Warrington WG. Time-limit tests: Estimating their reliability and degree of speeding. Psychometrika 1951; 16: 167–188.
18. Bentler PM. Comparative fit indexes in structural models. Psychol Bull 1990; 107: 238–246.
19. Lim LL, Fisher JD. Use of the 12-item short-form (SF-12) Health Survey in an Australian heart and stroke population. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 1999; 8: 1–8.
20. Lundberg L, Johannesson M, Isacson DG, Borgquist L. The relationship between health-state utilities and the SF-12 in a general population. Med Decis Making 1999; 19: 128–140.
21. Gaston JE, Vogl L. Psychometric properties of the General Well-Being Index. Qual Life Res 2005; 14: 71–75.
22. Wiklund I, Karlberg J. Evaluation of quality of life in clinical trials. Selecting quality-of-life measures. Control Clin Trials 1991; 12: 204S–216S.
23. Wenger NK, Mattson ME, Furberg CD, Elinson J. Assessment of quality of life in clinical trials of cardiovascular therapies. Am J Cardiol 1984; 54: 908–913.
24. Namjoshi MA, Buesching DP. A review of the health-related quality of life literature in bipolar disorder. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2001; 10: 105–115.
25. Lundgren-Nilsson Å, Jonsdottir IH, Ahlborg G, Tennant A. Construct validity of the Psychological General Well Being Index (PGWBI) in a sample of patients undergoing treatment for stress-related exhaustion: a Rasch analysis. Health Qual Life Outcomes 2013; 11: 2.
26. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2005; 8: 94–104.
27. Sampogna F, Finlay AY, Salek SS, Chernyshov P, Dalgard FJ, Evers AWM, et al. Measuring the impact of dermatological conditions on family and caregivers: a review of dermatology-specific instruments. J Eur Acad Dermatol Venereol 2017; 31: 1429–1439.
28. Rees J, O'Boyle C, MacDonagh R. Quality of life: impact of chronic illness on the partner. J R Soc Med 2001; 94: 563–566.
29. Basra MKA, Sue-Ho R, Finlay AY. The Family Dermatology Life Quality Index: measuring the secondary impact of skin disease. Br J Dermatol 2007; 156: 528–538.