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Development and validation of an epidermolysis bullosa family/parental burden score

H. Dufresne,[1] S. Hadj-Rabia,[1,2] C. Taieb[3] and C. Bodemer[1,2]

[1]Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), Institut Imagine, Hôpital Universitaire Necker-Enfants Malades, 149 Rue de Sèvres 75015, Paris, France
[2]NSERM U1163, Université Paris Descartes – Sorbonne Paris Cité, Institut Imagine, 149 Rue de Sèvres 75015, Paris, France
[3]Public Health and Quality of Life, Pierre Fabre, Paris, France

Summary

Background The notion of the individual burden associated with a disease has been introduced to determine 'disability' in the broadest sense: psychological, social, economic and physical. Subtypes of epidermolysis bullosa (EB) are rare, life-threatening, untreatable chronic genodermatoses.
Objectives To develop and validate a specific questionnaire assessing the burden on families of children with EB: Epidermolysis Bullosa Burden of Disease (EB-BoD).
Methods Items were generated by a verbatim report from parents of children with EB. Subsequently, a study was implemented for psychometric analysis. An epidermolysis bullosa burden-of-disease questionnaire was refined via item reduction according to inter-question correlations, consensus among experts and exploratory factor analysis. Internal consistency was determined by calculating Cronbach's α. Concurrent validity was determined by calculating the correlation between EB-BoD and the Short-Form 12 items (SF-12) questionnaire.
Results From a primary list of 30 items, EB-BoD was reduced to a 20-item questionnaire, covering four disease aspects based on the exploratory factor analysis. Construct validity was demonstrated and the EB-BoD questionnaire showed good internal consistency (Cronbach's $\alpha = 0{\cdot}9$). The resulting EB-BoD score was significantly correlated to the mental dimension of SF-12 ($r = -0{\cdot}61$), but it was not correlated to it's physical dimension ($r = 0{\cdot}04$). EB-BoD scores were significantly discriminating between EB subtypes.
Conclusions The EB-BoD questionnaire appears to be a useful assessment tool regarding medical and socioeconomic issues in patients with EB and their families. EB-BoD scores correlate well with the family/parental burden experienced by the families of patients with EB.

Correspondence
Hélène Dufresne.
E-mail: helene.dufresne@nck.aphp.fr

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What's already known about this topic?

- Inherited epidermolysis bullosa is a highly heterogeneous group of rare diseases characterized by fragility and blistering of skin and mucous membranes.
- The notion of 'burden' has been introduced to quantify the health of a population better and to determine the priorities of action in the public health field.

What does this study add?

- The validation of a specific tool, the EB Burden of Disease questionnaire, measuring a specific individual and family burden score in patients with epidermolysis bullosa.

Inherited epidermolysis bullosa (EB) is a heterogeneous group of rare genetic disorders characterized by mucosal and skin fragility. Three major types are described: EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB), according to the level of cleavage in the skin. Molecular testing is the most accurate diagnostic procedure for definition of the different EB subtypes.[1] Disease severity is variable according to the subtype, and extracutaneous manifestations and complications can lead to significant morbidity and mortality. The low incidence of EB and the phenotypic variability challenge the management of such patients, which is currently oriented on skin care and treatment of complications.[2–5] Recently, consensus recommendations have been published.[5]

The notion of 'burden' has been introduced by the World Health Organization to quantify better 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.[6]

To assess the individual burden of EB, a self-administered questionnaire would be the most convenient evaluation tool. So far, no validated questionnaire has been developed. Methodological consensus for developing this type of tool is lacking. The conception of HRQoL questionnaires follows a rigorous methodology that could be used to develop burden questionnaires. Recent publications were inspired by that method in the field of genetics and dermatology.[7,8]

The goal of this study was to determine the EB burden of disease in the families of patients with EB. We developed and validated the EB Burden of Disease (EB-BoD) questionnaire to obtain a specific and informative score.

Materials and methods

The self-administered EB-BoD questionnaire was set up using a three-phase methodology: conceptualization, development and validation.[9,10] The EB-BoD questionnaire was developed in a multidisciplinary approach including experts in questionnaire conception and quality-of-life indexes (C.T.), and management of patients with EB (H.D., S.H.R. and C.B.). The study was approved by the Commission Nationale de l'Informatique et des Libertés (the French data protection authority; authorization number 1690350).

Creation of the questionnaire

The first stage included the creation of a verbatim report based on a review of relevant literature and data collection, including the various complaints expressed by parents of patients during a one-to-one session with the same social worker who took the notes (H.D.). A French social assessment was used, inspired by a standardized methodology (available on request). Parents of patients with EB from those attending our department between 1 September 2013 and 25 February 2014 were successively included until complaints became redundant. Complaints were converted into individual items.

The EB-BoD questionnaire was created in a question-and-answer format. We used a six-point Likert scale (never, rarely, sometimes, often, very often, constantly) to limit missing data. 'Not applicable' was also included.[8,11] Statistical methods for psychometric validation are reported in Appendix S1 (see Supporting Information). Questions were retained when standardized regression coefficients ranged from 0·4 to 0·9. The final questionnaire was evaluated in native French-speaking subjects during individual, cognitive debriefing interviews to determine issues with question-and-answer wording (ambiguity, misunderstanding, acceptability). Pilot testing was performed by a specialized institution (Lionbridge, Dublin, Ireland).[8] Dimension scores were calculated by totalling individual item scores. A global score, the total of all individual item scores, was transformed into a 0–100 scale. A higher EB-BoD score reflects a higher EB burden.

Validation of the questionnaire

The pilot questionnaire was implemented in a reference centre for EB (Department of Dermatology, Necker-Enfants Malades Hospital, Paris). Subjects who fulfilled the following criteria were asked to complete a questionnaire: parents of a child with EB, fluent in the French language, with oral consent for participation. The diagnosis of EB was based on clinical and histopathological analysis and/or molecular tests. In the field of rare diseases, a group of 30 subjects is sufficient to validate a questionnaire.[12]

Psychometric properties were evaluated by assessing the internal consistency reliability, and the construct (concurrent and discriminative) validity of the EB-BoD questionnaire (Appendix S1). For internal consistency reliability, Cronbach's α coefficients of 0·6–0·69 are acceptable.[12] Concurrent validity was determined by calculating the Spearman coefficient (r) between EB-BoD and two standard quality-of-life questionnaires: the nonspecific Short-Form-12 (SF-12) and the Psychological General Well-Being Index (PGWI). The SF-12, a multipurpose questionnaire, has two subdimensions: a physical component summary and a mental component summary. The higher the score, the better the HRQoL.[13] A significance level of 0·05 was fixed for all tests.

Test–retest analysis, translation and cross-cultural adaptation

To assess the reproducibility of EB-BoD questionnaire, a test–retest analysis was conducted. Subjects were retested by the same social worker (H.D.) after at least 2 weeks to check daily variations. Following best practice, linguistic and cross-cultural adaptation was carried out by Lionbridge following a nine-step process for the English language (Table S1; see Supporting Information).[14]

Results

Creation of the questionnaire

The initial conceptual phase involved the 23 parents of a 12-patient group [four recessive DEB (RDEB), two dominant DEB (DDEB), four EBS and two JEB], who discussed their complaints and disabilities related to EB. The major identified concerns of parents were daily life, family life, child's life, disease, treatment, economic consequences and social impact. The original 54 items were turned into a 30-question form. Questions about the impact on parents' lives were highly correlated to each other ($r > 0{\cdot}7$), and nine questions were removed after consensus. Two redundant questions were turned into one.

The final version of the EB-BoD questionnaire, which was used in the psychometric analysis, consisted of 20 items. Standardized regression coefficients were all $> 0{\cdot}4$ (Table S2; see Supporting Information). According to standardized regression coefficients, each group of questions was assigned a dimension (each one consisting of at least three questions): family life (seven questions), child's life (three questions), disease and treatment (five questions) and economic and social impact (five questions).

Validation of the questionnaire

Among the 60 parents recruited, 56 sent their questionnaire back. One questionnaire was rejected due to incomplete data. The cohort ($n = 55$) included 24 girls (44%) and 31 boys (56%): 17 had EBS, 30 RDEB, three DDEB and five JEB (Table 1). Cronbach's α was 0·9, indicating good internal coherence. The coherence was confirmed in each dimension as follows: 0·87 for family life, 0·51 for child's life, 0·79 for disease and treatment and 0·81 for economic and social impact.

The physical dimension of SF-12 is not correlated to the total EB-BoD score and its various dimensions (Table 2). The mental dimension is negatively correlated to the EB-BoD score and mildly correlated to the family-life dimension. The PGWI is negatively correlated to the EB-BoD score and mildly correlated to the family-life dimension. Analysis of the SF-12 highlighted an alteration in the quality of life mostly of the parents in the mental HRQoL dimension ($38{\cdot}7 \pm 13{\cdot}4$), rather than the physical dimension ($48{\cdot}2 \pm 10{\cdot}3$). The mean EB-BoD score was $47{\cdot}5 \pm 17{\cdot}5$ (Table 3).

Comparison of EBS and RDEB groups showed a significant difference: $38{\cdot}6 \pm 16{\cdot}8$ and $51{\cdot}7 \pm 15{\cdot}0$, respectively (Tables 3, 4). The family-life dimension was more discriminative, while the disease and treatment dimension was not statistically significantly different (Tables 3).

The EB-BoD score was significantly higher ($52{\cdot}8 \pm 15{\cdot}8$) in patients > 7 years of age vs. patients < 7 years of age ($42{\cdot}7 \pm 18{\cdot}2$). The EB-BoD score was not correlated to the patients' sex. Families with incomes > €1700 per month had a mean EB-BoD score of $41{\cdot}5 \pm 16{\cdot}3$, while families with smaller income had an EB-BoD score of $56{\cdot}3 \pm 15{\cdot}9$. Among the four dimensions, only family life was impacted, with an EB-BoD score of 17·5 in the group with higher income vs. 9·43 in the lower-income group, showing a difference of 85%.

The intraclass correlation coefficient (ICC) was 0·97. The test–retest analysis confirmed that the questionnaire is reproducible. The ICC of each dimension was $> 0{\cdot}90$: family life (0·93), child's life (0·96), disease and treatment (0·97) and economic and social impact (0·94).

The original French version of the EB-BoD questionnaire has been translated and has undergone linguistic and cultural adaptation in to US English (Table 5).

Discussion

Disease burden is a social and economic challenge. Currently, disease burden is not redeemed in health policy decisions. It simultaneously takes into account the quality of life, integration within the community, organization of everyday life and the consumption of medical resources. A previous study has reported a negative impact on the quality of life of children with genodermatoses.[8,15–19] As far as paediatric patients are concerned, the burden is shared by the whole family, which is important not to overlook.

Table 1 Demographic and clinical characteristics of the 55 patients with epidermolysis bullosa (EB)

EB subtype	RDEB	DDEB	JEB	EBS	Total
Number of patients	30	3	5	17	55
Male/female, n (%)	16/14	2/1	5/0	8/9 (47/53)	31/24 (57/43)
Age (years), mean or mean ± SD (range)	9·2 (0·4–18)	7·7 (4–13)	5·4 (0–15)	6·8 ± 4·4 (2–17)	8·0 ± 4·9 (0–18)
Questionnaire filled by father/mother	5/25	0/3	0/5	0/17	5/50
Family history of EB, n (%)	10 (33)	3 (100)	4 (80)	9 (53)	26 (47)
Mode of inheritance (autosomal recessive/dominant)	30/0	0/3	5/0	1/16	36/19
Family situation: married or cohabiting, n (%)	29 (97)	2 (67)	5 (100)	16 (94)	52 (95)
Single child, n (%)	7 (30)	2 (67)	0	2 (12)	11 (20)

RDEB, recessive dystrophic EB; DDEB, dominant dystrophic EB; JEB, junctional EB; EBS, EB simplex.

Table 2 Correlation coefficients for the concurrent validation of the Epidermolysis Bullosa Burden of Disease (EB-BoD) questionnaire vs. the Short-Form-12 (SF-12) and Psychological General Well-Being Index (PGWI) questionnaires

	SF-12 MCS	SF-12 PCS	PGWI
Global EB-BoD score	0·61; P < 0·001	0·050; P = 0·79	0·65; P < 0·001
Family life	0·55; P = 0·0015	0·10; P = 0·58	0·55; P < 0·001
Child's life	0·31; P = 0·088	0·23; P = 0·22	0·42; P = 0·010
Economic and social impact	0·57; P < 0·001	0·098; P = 0·60	0·52; P = 0·0012
Disease and treatment	0·33; P = 0·072	0·072; P = 0·70	0·43; P = 0·0084
MCS_12	1·00		
PCS_12		1·00	
PGWI			1·00

MCS, mental component summary; PCS, physical component summary.

Table 3 Different dimensions of the Epidermolysis Bullosa Burden of Disease questionnaire in the different epidermolysis bullosa (EB) subtypes of the cohort

	Global	Family life	Child's life	Disease and treatment	Economic and social impact
RDEB	51·67 ± 15·01	14·81 ± 6·62	18·52 ± 5·62	8·41 ± 4·98	9·93 ± 2·51
DDEB	49·00 ± 13·00	10·33 ± 7·64	19·33 ± 5·51	9·33 ± 2·89	10·00 ± 1·00
JEB	49·80 ± 13·44	14·80 ± 4·21	18·20 ± 5·36	8·40 ± 5·32	8·40 ± 1·14
EBS	38·57 ± 16·78	10·57 ± 5·52	13·86 ± 6·89	6·50 ± 3·70	7·64 ± 3·15

Values are the mean ± SD. RDEB, recessive dystrophic EB; DDEB, dominant dystrophic EB; JEB, junctional EB; EBS, EB simplex.

Table 4 Correlation of the epidermolysis bullosa (EB) subtypes: P-values determined by Student's *t*-test

	RDEB	DDEB	JEB	EBS
RDEB	–	NS	NS	0·0075
DDEB	NS	–	NS	NS
JEB	NS	NS	–	NS
EBS	0·0075	NS	NS	–

RDEB, recessive dystrophic EB; DDEB, dominant dystrophic EB; JEB, junctional EB; EBS, EB simplex; NS, not significant.

Most of the time, the parents themselves perform daily dressing and care for their child with EB. The burden includes the financial costs of the treatment, the time spent away from work and the lack of social support from friends and family members. Daily dressing, which can take up to 2 h per day, is time consuming. These aspects highlight the importance of understanding and measuring the burden of the disease on the entire family.[5]

The EB-BoD questionnaire, leading to an EB-BoD score with quantified items, has been developed to address those issues. Considering the methodology, nondiscriminative items – such as pain, guilt and frustration – were removed because they were evoked by > 90% of the parents. The internal consistency reliability of the questionnaire was good ($\alpha = 0{\cdot}9$), and the EB-BoD score was correlated to the mental HRQoL dimension of the SF-12, confirming its concurrent validity.

As the EB-BoD questionnaire was designed for parents, the lack of correlation between the EB-BoD score and the SF-12 physical component summary seems to be natural. Those results were consistent with previous studies evaluating the quality of life among parents of children with genodermatoses or other chronic skin diseases.[7,15–19] Furthermore, known-group validity has been evaluated according to the EB subtype. A significant difference was found between parents whose child had EBS and those with RDEB ($P < 0{\cdot}001$). Interestingly, complications such as limitation of mobility and lassitude of daily care impacts the EB-BoD score in patients > 7 years of age. The small size of the JEB and DDEB groups might explain the absence of statistical difference of the EB-BoD score. Additional studies are mandatory to assess differences between EB subtypes. However, it should be kept in mind that EB is a rare disease, which makes it difficult to obtain convenient group sizes.

To assess the interpretability of the EB-BoD questionnaire, it would be necessary to evaluate the sensitivity of the questionnaire to identify clinically meaningful change in a prospective cohort study.

With a specific questionnaire such as EB-BoD, an evaluation of disability in the broadest sense caused by the disease is feasible, contrary to an HRQoL questionnaire. The EB-BoD questionnaire has a social and economic dimension at an individual level that appears essential for patients with EB and their families, who have unmet needs. The usefulness of a validated self-administrated specific EB-BoD questionnaire leading to a score with quantified items is therefore very important. It also represents a useful tool for assessing therapeutic education programmes. Further cross-cultural validation of the EB-BoD questionnaire will permit international perspectives.

Table 5 English-language and cross-cultural adaptation of the Epidermolysis Bullosa Burden of Disease questionnaire

The disease your child has is now well known. However, less known are the impact and consequences it will have on your daily life. For each statement below, you may choose from seven possible answers. There are no right or wrong answers. Answer as spontaneously as possible while thinking about your situation over the last 4 weeks	Always	Very often	Often	Sometimes	Rarely	Never	Not applicable
My child's skin disease caused us to want to move	☐	☐	☐	☐	☐	☐	☐
My child's skin disease led me to want to stop working	☐	☐	☐	☐	☐	☐	☐
I think about my child's skin disease all day long	☐	☐	☐	☐	☐	☐	☐
I try to protect my child because of his/her skin disease	☐	☐	☐	☐	☐	☐	☐
My child's skin disease prevents us from going on vacation	☐	☐	☐	☐	☐	☐	☐
My child requires more attention than others due to his/her skin disease	☐	☐	☐	☐	☐	☐	☐
Our child's skin disease forced us to question our future plans	☐	☐	☐	☐	☐	☐	☐
My child's skin disease prevents me from visiting my family	☐	☐	☐	☐	☐	☐	☐
My family does not come to see us because of my child's skin disease	☐	☐	☐	☐	☐	☐	☐
Our child's skin disease creates problems in our relationship	☐	☐	☐	☐	☐	☐	☐
The medical consultations for my child's skin disease often leave me feeling frustrated	☐	☐	☐	☐	☐	☐	☐
People's reactions to our child's skin disease are difficult to accept	☐	☐	☐	☐	☐	☐	☐
I struggle to accept our child's skin disease	☐	☐	☐	☐	☐	☐	☐
I have a hard time getting used to the odor produced by our child's skin disease	☐	☐	☐	☐	☐	☐	☐
I have great difficulty in finding child care for my child on account of his/her skin disease	☐	☐	☐	☐	☐	☐	☐
My child has great difficulty in school on account of his/her skin disease	☐	☐	☐	☐	☐	☐	☐
I am afraid for my child's future due to his/her skin disease	☐	☐	☐	☐	☐	☐	☐
The treatments are beginning to wear me down	☐	☐	☐	☐	☐	☐	☐
Each time I go to the hospital, I do not feel well the day before	☐	☐	☐	☐	☐	☐	☐
Each time I go to the hospital, I do not feel well the day after	☐	☐	☐	☐	☐	☐	☐

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Stages of the linguistic and cross-cultural validation.

Table S2. Standardized regression coefficients from the final rotated factor pattern.

Appendix S1. Statistical methods for psychometric validation.