Aus der Klinik und Poliklinik für Dermatologie und Allergologie
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Technischen
Universität München

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.) an der
Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Understanding the rare genodermatoses Darier's disease and Hailey-Hailey disease: lessons learned from the national registry MDHHgermany

vorgelegt von

Dr. Danielle Franziska Rogner

aus

Kapstadt, Südafrika

Jahr
2025

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

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List of Abbreviations

CME	**Continued medical education**
DD	**Darier's disease**
DLQI	**Dermatology life quality index**
HHD	**Hailey-Hailey disease**
MD	**Morbus Darier**
MDHHgermany	**Morbus Darier Hailey-Hailey germany**
NRS	**Numeric rating scale**
QoL	**Quality of life**
SWLS	**satisfaction with life score**
TUM	**Technical University of Munich**

Publication List

Rogner D, Heimerl L, Heyer S, Biedermann T, Sattler E, Zink A. Patients' perspective, quality of life and treatment goals in Hailey-Hailey disease: Lessons learned from the German National Registry. J Eur Acad Dermatol Venereol. 2023 Oct 20. doi: 10.1111/jdv.19583. Epub ahead of print. PMID: 37863661.

Rogner, D., Laura Heimerl, Biedermann, T., Sattler, E., & Zink, A. (2024). Unmet Needs in Darier's Disease from a Patient's Perspective: Lessons Learnt from the German Registry. *Acta Dermato-Venereologica*, *104*, adv19663. https://doi.org/10.2340/actadv.v104.19663

Appendix List

Rogner DF, Lammer J, Zink A, Hamm H. Morbus Darier und Morbus Hailey-Hailey: Stand 2021. J Dtsch Dermatol Ges. 2021 Oct;19(10):1478-1502. German. doi: 10.1111/ddg.14619_g. PMID: 34661362.

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3.	Prof. Henning Hamm	Writing of manuscript, collection of clinical images, revision of manuscript	
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Your contribution to the publications

I was fully responsible for the design and establishment of the MDHHgermany registry, as well as the conceptional design and programming of the instruments of the questionnaires in REDCAP[1]. I wrote an extensive study protocol, explaining all components of the registry meticulously. My supervisor PD Dr. Dr. Alexander Zink had very good ideas and additions to these, before the registry was initiated and patients were included. I reached an ethical approval for the registry, contacted dermatologists and included a vast number of patients myself- either because they were patients at our hospital or because they reached out to us after learning about the registry and did not have a physician who took care of their condition.

I coordinated all data collection with the help of my co-author Laura Heimerl.

Paper I: Patients‘ perspective, quality of life and treatment goals in Hailey-Hailey disease: Lessons learned from the German National Registry

I performed the writing of the manuscript, my co-author Laura Heimerl and I were responsible for the data analysis, data preparation as well as plausibility checks. All assessments were electronically documented using CE-certified software solutions (ESPRIO, Seracom Software Solutions GmbH, Stuttgart, Germany and REDCap, Research Electronic Data Capture; REDCap 8.5.28 ©2019 Vanderbilt University, Nashville, TN, USA). The entire analysis was based on descriptive statistics performed in R studio version 2023.3.0.386.

Lastly, all co-authors revised it and I submitted it after adapting all the comments and remarks.

Paper II: Unmet needs in Darier’s disease from a patient’s perspective: Lessons learnt from the German registry

I performed the writing of the manuscript, my co-author Laura Heimerl and I were responsible for the data analysis, data preparation as well as plausibility checks. All assessments were electronically documented using CE-certified software solutions (ESPRIO,

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Paper III (Appendix): Darier and Hailey-Hailey disease: Update 2021

Prof. Henning Hamm, a senior consultant at the dermatological department of the University of Würzburg, is one of the experts regarding Hailey-Hailey disease but also Darier's disease.

After having being invited by the Journal der deutschen dermatologischen Gesellschaft (JDDG) to write a CME article on DD and HHD, I contacted Prof. Hamm, as I knew that his expertise would vastly improve this article.

I wrote the first draft of the manuscript and did the literature research of over 100 published papers and he revised it and improved it vastly with his in-depth knowledge at experience in the field of these genodermatoses. After adaptation of his comments and remarks, I handed in the manuscript. As I was the corresponding author, I replied to many requests and questions regarding the manuscript and the treatment of affected individuals.

Doctoral Thesis: Introductory Summary

Darier‘s disease (DD, alternatively termed as follicular dyskeratosis) and Hailey-Hailey disease (HHD, also referred to as familial benign chronic pemphigus) are genetic skin disorders exhibiting an autosomal dominant inheritance pattern. The first documentation of Darier occurred in 1889 when Jean Darier of Paris and James Clark White of Harvard, Cambridge/Massachusetts, USA, independently documented the condition. In contrast, Hailey-Hailey disease was first described in 1939 by the siblings Howard and Hugh Hailey of Atlanta/Georgia, USA[2, 3].

Darier’s disease counts as an orphan disease (ORPHA: 218[4]).

Both conditions are defined by an impaired adhesion of epidermal keratinocytes. In DD this leads to aggregated reddish-brown plaques and papules which can cause large, macerated areas with a distinct body odour, first manifestation is usually in the second decade of life. In HHD the genetic mutation leads to papulovesicles and blisters, which mainly manifest in intertriginous areas. The first manifestation is also in early adulthood.

Clinical diagnosis for both diseases can be made clinically and is usually confirmed through dermatohistopathological methods. Due to the fact, that the severity varies vastly and therefore the clinical picture can also vary a lot, the diagnosis is often only made in delay[5, 6].

However, the major challenge lies in the treatment of these conditions, posing difficulties for both patients and dermatologists. Both diseases can cause major frustration and an impairment of the quality of life for affected individuals, as the pain, body odour, time consumation and stigma can lead to social isolation [3, 7, 8]. Furthermore, as the therapeutic armoury is very limited and this is also frustrating for treating doctors, many patients don’t feel treated adequately and feel like they are not being heard[7-9].

As there is a major unmet need in all aspects of these diseases: diagnosis, treatment and life overall of affected individuals, the Technical University of Munich initiated a nationwide registry called MDHHgermany end of 2019, with first patients being included beginning of 2020 [10]. The goal is to develop an evidence-based clinical registry and research framework for deeper insights into the medical care of patients with these diseases. With the help of various tools many aspects such as demographics (gender, age, affected family members, age at first diagnosis, disease duration, employment status, marital status etc.), the assessment of

subjective symptoms (e.g. pruritus, pain, burning sensation), evaluation of patient satisfaction with medical care, as well as past and current therapies (topical and systemic) were performed. Furthermore, a main focus was to assess the patient's perspective on the skin condition in view of the Quality of life (QoL), satisfaction with life and others, see table 1[10].

The overall idea is to analyse patients and their disease from their point of view, in order to figure out their therapeutic goals (for example "less itch would improve my life a lot"), their highest disease burden (for example "body odour is most bothersome to me") etc. and to integrate this knowledge into therapeutic decisions, hopefully improving the medical care and overall satisfaction of affected individuals. Furthermore, as many affected patients can enter their treatment options and the effectiveness of these within the questionnaires, we hope to figure out therapies which have helped others.

On the long run, the established platform can potentially also lead to further epidemiological, immunological and clinical studies, additionally improving the treatments of these suffering individuals.

The registry MDHHgermany recruits patients from both university and community hospitals, dermatology clinics, and self-help organisations. Participation is open to all dermatologists in Germany. Eligible participants are adults and minors (after consent of the person with legal custody) diagnosed with a clinically, and preferably histologically, confirmed disease. Additionally, individuals from self-help platforms are included, as some affected patients may lack a dedicated physician for their condition.

Enrolled patients undergo prospective follow-up for a minimum of twenty-four months. Throughout this time, both doctors and patients complete either questionnaires on paper or the preferred online version on REDCap (Research Electronic Data Capture; REDCap 12.2.2 - © 2022 Vanderbilt University). In cases where a questionnaire on paper is utilized, data was forwarded to the dermatological clinic of the Technical University of Munich (TUM) and entered via hand through REDCap [1].

Medical data (e.g. Physician's global assessment, Body surface area etc.) is recorded through doctor's study visits conducted at participants enrollment (Baseline/ Visit 1). After this the visits are annually, if there is a physician taking care of the patient, alternatively only the patient's questionnaire is filled out. Participant's study visits occur at patient enrollment (Visit

1), followed by visits on a 3-monthly basis as well as in response to exacerbations or as needed for alternative reasons.

Subsequently, the aim of this doctoral thesis was to further characterize individuals with DD or HHD and the mental burden of these diseases, treatment of their disease as well as their medical care. Furthermore, we want to shed light onto and emphasize the major unmet need of affected individuals, hoping for better treatment options in the future, as well as for better medical care and also better understanding for the patients by the treating physician.

Table 1: Structure of the questionnaire at V1 in the MDHHgermany registry (questionnaire can be downloaded here: https://redcap.link/al65m8c9*)*[8]

Baseline visit (V1)	
Demographics	• Sex • Age at inclusion and at disease onset • Weight • Height • Education status • Employment status and absence from work • Marital status • Parental status
Family and individual medical history	• primary diagnosis (year) • affection within family and disease severity (mild, moderate, severe) • disease severity progression throughout life • hospital stays within last 5 years • outpatient consultations within last 12 months • reason for doctor's visits • non-conventional practitioner visits
Severity of disease	• Self-evaluation of disease intensity, using scale from "no disease activity" to "severe manifestation."

	• Relevance 10 predefined subjective symptoms (for example pruritus, body odour, pain, sleep disturbance etc.) • satisfaction with treatment and medical care during past three months on a 10-point-scale (numeric rating scale) • evaluation of disease severity, pain, pruritus, burning of skin, sleep disturbance (on previous three days) on a 0- to 10-point-scale • reflection of disease control within last 12 months
Recent therapies and treatment goals	• relevance of 10 predefined treatment goals (e.g. leading a normal life, less pain, more self-confidence etc.) • inclusion in treatment decision-making • satisfaction with treating doctor • systemic and topical therapies as of primary diagnosis • Personal evaluation of the systemic and topical treatments that are most tolerable and effective.expenses per month in Euros, not covered by medical insurance
Mental burden	• QoL (measured with the DLQI) • subjective sense of well-being • Overall life satisfaction

Darier and Hailey-Hailey disease: Update 2021 (Appendix I)

As management of the two genodermatosis Darier's disease and Hailey-Hailey disease is often majorly challenging for the treating physicians and many physicians and dermatologists lack knowledge and therapeutic management of affected patients with DD or HHD, we decided to write a CME-article (continuing medical education) with all the therapeutic options which have ever been published in the literature, also taking into account all new and possible future

developments. This article was aimed at facilitating treatment of affected individuals, therefore improving the medical care of these[2, 7].

Additionally, the article was published in order to gain attention to the nationwide registry MDHHgermany and show patients and physicians, that affected individuals are not forgotten and improvement for their wellbeing is a goal.

Furthermore, the article was written generally to create more awareness for DD and HHD again, as many patients reported that a lot of physicians don't even know their disease, despite being able to treat it[10].

The article showed large acceptance and resonance amongst physicians and patients, reports showed that treatment could be improved in a number of affected individuals. Furthermore, many patients entered the registry after reading about it in the article and treating physicians also included many patients and approached us regarding therapeutical questions etc..

Patients' Perspective, Quality of Life and Treatment Goals in Hailey-Hailey Disease: lessons learned from the German National Registry (Publication I)

After three years after initiation of the registry MDHHgermany, the first interim analysis of the collected data on patients with HHD was performed. Patients who were included from June 2020 until 2023 were analysed.

One hundred and two patients with HHD were included, 90 of these were deemed eligible and subjected to analysis (mean age: 49.91 years, sex: 73.33% women, 26.67% men).

The analyses especially focused on the patients' perspective of the disease, their QoL and treatment goals.

Results were shocking, as 39.77% stated that their life is severely/very severely impacted by the disease. In addition, 56.92% of patients stated that no systemic therapy had been effective up to this date, 25.56% had not received one up to the point of inclusion into the registry. The contentment with medical management tended to be low and satisfaction with life (SWL) was mediocre. The most burdensome subjective symptom is a burning sensation (according to the 10-point-scale).

In general, the "real-life" data from this analyses state a significant disease burden that affects the quality of life of patients. with HHD, furthermore the limited treatment armoury leads to dissatisfying disease control.

Collectively, the findings emphasize the pressing need for enhanced medical care for those affected, aiming not only to ameliorate skin conditions but also to enhance the overall well-being and quality of life of HHD patients..

Unmet needs in Darier's disease from a patient's perspective: Lessons learnt from the German registry

As we had included the two genodermatoses DD and HHD, we also performed an analysis of baseline data of affected individuals from the registry MDHHgermany with Darier's disease. The analysis was performed on DD patients who had been recruited between June 2020 and 2023[11].

In total, fifty five Darier patients were included, of these fourty seven were analysed due to eligibility.

Other than in the analysis of HHD patients, where the emphasis was put on quality of life and overall satisfaction with life, the emphasis of this paper was on medical care, current and past treatments, subjective symptoms and therapy goals. The quality of life of DD patients had already been studied in the past and a significant impairment had been shown[12, 13].

Regarding the subjective symptoms, patients stated that pruritus was their most bothersome symptom. 42.6% of all DD patients had not received a systemic treatment so far and a large amount stated that the systemic therapies were ineffective. Patient satisfaction with medical care and treatment showed to be mediocre on the whole.

In summary, the results of this analyses showed an alarming unmet need regarding patients' satisfaction with their medical care and treatment, also underlined by the reported lack of disease control.

Additional studies and interventions are crucial to improve the therapeutical armoury for affected individuals.

Conclusion

With the work of these publications, the Ph.D. thesis and the establishment of the MDHHgermany registry, we could show in depth, how the two genodermatoses Darier's disease and Hailey-Hailey disease severely affect quality of life and many other aspects of life in affected patients. However, the extent of this impairment, had not been studied in such

detail before and the results of the analyses from included registry patients, does also upset and shock to a certain extent.

Next to the lack of disease control, the management of the diseases and the prescribed therapies still have a vast demand for improvement.

By publishing this work, we are hoping that physicians, who treat DD and HHD patients read these and use them as a guide for decision-making in the management of these patients. Furthermore, attracting attention towards these diseases again can help these often isolated patients to be heard again.

As part of the registry MDHHgermany and as this does also present a platform for clinical and immunological studies, we also performed microbiome and transcriptome analysis on fourteen patients with DD from the registry.

In summary, we could show a role of cutaneous dysbiosis, implicating that possibly an alteration of this microbiome e.g. by transplantation could improve the patients skin condition[14-16]. Without platforms like the MDHHgermany registry, studies like these would not have been possible.

The work of this registry is not finished with this doctoral thesis, but it is still continuously recruiting and the next step would be to analyse and correlate the patient's and physician's perspectives of the diseases.

Publication I: Patients' Perspective, Quality of Life and Treatment Goals in Hailey-Hailey Disease: lessons learned from the German National Registry

Rogner D, Heimerl L, Heyer S, Biedermann T, Sattler E, Zink A. Patients' perspective, quality of life and treatment goals in Hailey-Hailey disease: Lessons learned from the German National Registry. J Eur Acad Dermatol Venereol. 2024 Feb;38(2):419-429. doi: 10.1111/jdv.19583. Epub 2023 Nov 21. PMID: 37863661.

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ORIGINAL ARTICLE

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Patients' perspective, quality of life and treatment goals in Hailey–Hailey disease: Lessons learned from the German National Registry

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Abstract

Background: Hailey–Hailey disease (HHD) remains a difficult-to-treat dermatosis and little is known about the patient's perception of the disease activity, the treatment success and its impact on quality-of-life (QoL).

Objective: To obtain better understanding of HHD patients' needs regarding their medical condition, financial burden, QoL, subjective well-being and treatment thereof as well as satisfaction to evaluate common treatments' 'real-life' relevance.

Methods: With initiation of the national registry for Darier's disease (DD; Morbus Darier, MD) and Hailey–Hailey disease (HH) MDHHgermany, patients with HHD diagnosis were included starting June 2020. To assess subjective symptoms, patients filled out questionnaires such as the DLQI (dermatological life quality index), numeric rating scale (NRS) for itch, pain and burning sensation, as well as the SWLS (satisfaction with life scale) questionnaire to quantify overall satisfaction in life. Additionally, data on therapies were collected along with the patients' satisfaction of those and their medical care. Furthermore, patients assessed financial aspects and work ability.

Results: One hundred and two patients were recruited from dermatology clinics, office-based dermatologists and self-help platforms across Germany between June 2020 and February 2023, 90 were eligible and analysed (mean: 49.91 years, 73.33% females, 26.67% males). 39.77% stated according to the DLQI their life is severely/very severely affected. Satisfaction with life was mediocre. Burning sensation was most pronounced among subjective symptoms (NRS 5.85 ± 2.80). Systemic treatments were rated as ineffective according to 56.92%, 25.56% had never received one. Most prescribed systemic treatments were corticosteroids (73.8%), followed by low-dose naltrexone (LDN) (26.2%), retinoids (15.4%) and antibiotics (13.8%). Satisfaction with medical care was generally low.

Conclusion: Our 'real-life' data state a major disease burden and impact on the QoL for affected individuals, as well as limited disease control due to inadequate therapies. MDHHgermany can provide insights into improvement of healthcare support with this debilitating disease and improve QoL. In the long term, it aims to provide basis for further clinical trials, epidemiological studies and immunological investigations.

INTRODUCTION

Hailey–Hailey disease (HHD, *Syn.*: familial benign chronic pemphigus) is an autosomal dominant genodermatoses characterized by impaired adhesion of epidermal keratinocytes.[1] HHD was first described in 1939 by the brothers Howard and Hugh Hailey of Atlanta/Georgia, USA and despite a considerable amount of research to understand its aetiology, clinical features and management,[2,3] the exact prevalence can only be estimated at around 1/50,000, with differential interindividual disease severity.[2,4]

Hailey–Hailey disease still presents a difficult-to-treat disease and apart from published case reports and small cohorts,[2] data from routine care are necessary to evaluate the 'real-life' situation of health care for patients with HHD to obtain a better understanding of patients' needs. Furthermore, little has been formally investigated concerning happiness, subjective symptoms and the QoL in patients affected by this debilitating disease.[5,6]

To address this, the German national registry MDHHgermany was initiated in 2020 by the Department of Dermatology and Allergology at the Technical University of Munich.

The primary goal of MDHHgermany is to establish an evidence-based nationwide clinical registry and research network to (i) characterize the medical care and pharmaceutical therapies of patients suffering from DD or HHD, (ii) to record the patient's perspective on the disease regarding QoL, treatment goals and treatment satisfaction with a focus on treatment sequence and change in treatments and (iii) to evaluate the effectiveness, safety and tolerability of topical and systemic therapies.

Here we provide results from the first interim data analysis of the registry, focusing on baseline characteristics, QoL, satisfaction with medical care on the whole and prescribed treatments of HHD patients.

MATERIALS AND METHODS

MDHHgermany registry

MDHHgermany is a prospective observational cohort study in the form of a nationwide clinical (multicentre) registry. It is a patient-perspective based registry of affected individuals with DD or HHD which is supposed to capture the patient's perception of the medical condition, psychosocial impact, QoL and subjective well-being as well as satisfaction with received treatments and treatment goals.

Patients are recruited at university and non-university hospitals, dermatological practices as well as self-help platforms. All dermatologists in Germany may participate. Registry data provided in this interim analysis were compiled at baseline from patients included into the registry from June 2020 to February 2023.

Inclusion criteria/subjects

Adults suffering from a clinically and preferably histologically diagnosed HHD who are in- or outpatients at the participating clinics and able to understand the German version of the questionnaire are eligible to participate. Furthermore, we also include patients from the self-help platform, as a number of HHD patients do not have a physician taking care of their condition. All patients had to assess within the questionnaire, how their disease had been diagnosed.

Study variables, schedule of assessments and instruments in the registry

To evaluate the medical care, clinical outcomes, received treatments, satisfaction with treatments and QoL in addition to demographic data and the patient's perspective on HHD, enrolled patients are prospectively followed up for at least 24 months. During this period, physicians and patients fill in paper-based questionnaires or preferably the identical online version on REDCap[7] (Research Electronic Data Capture; REDCap 12.2.2 – © 2022 Vanderbilt University). If the paper-based version is used, data are sent to the dermatological department of the Technical University of Munich (TUM) and is manually entered via REDCap.

To record clinical data, physician study visits are performed at patient inclusion (baseline visit/V1) and subsequently once a year.

Patients' study visits are performed at patient inclusion (V1), hereinafter every 3 months and additionally upon flare-ups or if required for other reasons.

For this interim analysis, only baseline data were considered. At baseline, the patient was asked to fill in a questionnaire that comprises five sections including basic demographic data, familial and personal disease history, severity of the disease in general along with specific symptoms, recent therapies and treatment goals as well as the assessment of the psychosocial impact (Table 1).

Demographics

Patients were requested to fill out their gender, age, their marital status and parental status. Patients also stated their education and employment status and whether they were able to perform their job or were on sick leave. Additionally, the familial history was assessed, including affected relatives and their disease severity.

Disease history, symptoms and severity of disease

Up to date, there is no validated scoring system to evaluate the disease severity of patients suffering from HHD, such as the

TABLE 1 Five sections within the baseline questionnaire for the patient at V1.

V1 (baseline)	
Demographics	• Gender • Age • Weight • Height • Education • Occupation • Marital status
Familial and personal disease history	• Year of disease onset • Familial affection • Skin-related health status within last 12 months • Disease progression • In- and out-patient stays within last 5 years • Frequency, type and reason for physician visits • Alternative practitioners visits
Severity of disease	• Relevance of 10 defined symptoms in regard to disease burden • Satisfaction with medication and medical care • Personal assessment of disease severity, pain, pruritus, stinging sensation, sleep disturbance within the last 3 days • Reflection of disease control (well controlled vs. not controlled at all within last 12 weeks)
Recent therapies and treatment goals	• Relevance of 10 defined treatment goals • Participation in treatment decision • Satisfaction with treating physician • Received treatments since disease onset • Personal assessment of the most tolerable and effective systemic and topic treatment • Treatment goals from a patient's perspective • Expenses per month
Mental burden	• Quality of life (DLQI) • Subjective well-being • Overall satisfaction in life

SCORAD for atopic dermatitis.[8] Therefore patients were asked to assess their disease severity using the following tools:

- Assessment of the subjective symptoms: pain, itch, pruritus and sleeplessness within the last 3 days, using NRS (10-point-scale; 0 = no itch/pain/burning/sleep disturbance; 10 = unbearable itch/pain/burning/sleep disturbance).[9,10]
- Assessment of disease burden by choosing from a variety of symptoms (e.g. body odour, pain etc.).
- Personal assessment of disease severity on a scale ranging from 'no disease activity' to 'severe affection'.
- Number of affected months in the past year.

Recent therapies, treatment goals and satisfaction

Individuals were requested to assess subjective importance of therapy goals (e.g. normal body odour, relief of pain), effectiveness and tolerability of past and current treatments (topical/systemic), number of doctor's visits and reasons, inpatient visits with outcome and overall satisfaction with the treatment during the past 3 months (10-point-scale), including questions regarding the satisfaction with the medical care (e.g. 'Does your doctor include you in the decision making?').

Psychosocial impact and mental burden

Quality of life

The QoL was assessed via the validated German version of the DLQI,[11,12] which is a dermatology-specific health-related quality of life questionnaire that consists of 10 items, interrogating the impact of a skin disease on subjective symptoms, feelings, daily activities, choice of clothes, leisure and social interaction, sport, work or school, personal relationships, sexual difficulties and treatment within the last 7 days.[13] To obtain the DLQI, individual scores are summed, resulting in a minimum of 0 (no impairment) and a maximum of 30 (highest impairment) and subdivided into five categories as suggested by Hongbo et al.[11–13]

Subjective well-being and heuristic happiness

We used a composition of questionnaires which had been compiled by Schuster et al. to assess subjective well-being in a large sample of Psoriasis patients (recruited at the dermatological department of the Technical University of Munich), compared to healthy controls (recruited with the help of a recruitment service (TestingTime, Zurich, Switzerland)). Participants filled in validated scales measuring subjective well-being—operationalized as satisfaction with life (SWLS) and heuristic happiness.[14,15]

To assess the cognitive component of subjective well-being, the patient's overall life satisfaction was operationalized using the SWLS questionnaire.[16] It consists of five claims about the patient's satisfaction with life (e.g. 'The conditions of my life are excellent'.), which are rated on a 7-point-Likert-scale ranging from 1 ('Strongly Disagree') to 7 ('Strongly Agree'). The sum of the five individual scores vary in the range 5–35, with 35 being the highest satisfaction with life.[16]

Additionally, a single question adapted from the European Social Survey was included to measure heuristic happiness on an 100-point-scale ranging from 0 (extremely unhappy) to 100 (extremely happy): 'Taking all things together, how happy would you say you are?'.[17]

Data management and statistical analysis

All assessments mentioned above were electronically documented using CE-certified software solutions (ESPRIO,

Seracom Software Solutions GmbH and REDCap, Research Electronic Data Capture; REDCap 8.5.28 ©2019 Vanderbilt University). Upon request, the patient report could also be completed on paper. The pseudonymized data are sent and stored at the registry data centre at the dermatological department of the TUM.

All data obtained from HHD patients who were included into the registry until 12 February 2023 was interrogated. Prior to analysis, data were checked for plausibility and completeness, by thorough review of each questionnaire in person. Questionnaires in which only 75% or less of all questions were answered were considered incomplete and excluded. When the disease was not clearly stated in the questionnaire, all answers of this patient were dismissed. When a score was calculated, a single missing value in one question led to the exclusion of all answers for the score calculation. For the analysis of single questions within an assessment however, the patient's answer was still included. The entire analysis was based on descriptive statistics (including mean, standard deviation, frequencies and percentiles) performed in R studio version 2023.3.0.386.

RESULTS

Number of patients and patient characteristics

From June 2020 to February 2023, 102 patients with HHD were included in the registry, of these 90 were analysed, the remaining ($n = 12$) were excluded due to missing and/or not plausible data, see above. The study cohort showed a female preponderance (73.33% vs. 26.67%). The mean age of all respondents was 49.91 ± 10.92 years. Patient characteristics at time of enrolment are described in Table 2.

HHD was diagnosed at a mean age of 28.23 ± 10.54 and on average the patients were affected since 21.59 years ± 11.38 (Table 2) at baseline. 76.67% knew of an affected family member, on average these were 2.25.

Employment and ability to work

81.11% participants were employed, of which 52.06% worked full time and 46.58% part time. Among those who were currently not working, 47.06% were pensioners, 5.88% were unemployed and 11.76% were on long-term sick leave due to HHD. During the last 12 months prior to baseline, 24.72% of patients were not able to work for more than 10 days and 20.22% could not go to work on 0–10 days due to HHD (Table 3).

Subjective disease severity and symptoms of HHD

The highest values were reported for burning with a mean value of 5.85 ± 2.8, followed by itch (5.37 ± 2.82), pain (5.13 ± 2.56) and 5.00 ± 3.07 for sleep disturbance (Table 4). Patients chose from numerous subjective symptoms in regard to HHD, which are burdensome to them (Figure 1). Overall, 84.9% stated that the pain affects them a lot day-to-day, 83.7% assessed that pruritus is a troublesome symptom, 75.6% of patients stated that their relationship is troubled by HHD, whereas 41.9% find the daily treatment time-consuming (Figure 1). The personal assessment of disease activity ranging from 'no activity' to 'severe activity' showed that an equal percentage of participants perceived their disease as moderate or severe (41.18%, respectively), only 2.35% had no activity (Figure 2). Affected

TABLE 2 Patient characteristics and family history.

Mean age in years at V1 ($n = 90$)	49.91 (SD 10.92; min = 24 years, max = 84 years)	
Age of first diagnosis (mean) ($n = 90$), SD	28.23 (min: 8 years, max 59 years), 10.54	
Disease duration (in years) ($n = 90$), SD	21.59 (min: 1 year, max: 52 years), 11.38	
	N	**%**
Gender ($n = 90$)		
Female	66	73.33
Male	24	26.67
Level of education ($n = 88$)		
Without graduation	0	0.00
Certificate of secondary education	14	15.91
General certificate of secondary education	36	40.91
General qualification for university entrance	19	21.59
Graduate degree	19	21.59
Family history ($n = 90$)		
Number of siblings (average)	3	
Affected family member (more than one family member possible)		
No affected family member	21	23.33
Affected family members	69	76.67
Number of affected family members on average	2.25	
If a family member is affected by HHD, how severe would you say their disease is? ($n = 69$)		
Currently not present	22	31.9
Mild	10	14.5
Moderate	24	34.8
Severe	13	18.8
Marital status ($n = 89$)		
In a relationship	19	21.35
Married	46	51.69
Divorced	12	13.48
Widowed	1	1.12
Unmarried	11	12.36

individuals were asked to indicate on how many months their skin was affected within the past year. 16.67% were affected >6 months, 63.33% reported that their skin was affected permanently.

Regarding the disease severity of affected relatives, participants classified 31.9% with 'no disease activity', 34.8% indicated 'moderate activity'.

Quality of life, happiness and patient satisfaction—The psychosocial impact of Hailey–Hailey

Based on the DLQI, 97.73% of patients were affected by their disease with 38.55% reporting the highest possible impairment and the mean DLQI being 17.34 ± 7.96 out of 30 (Figure 3).

Overall, the questions 'Over the last week, how much has your skin influenced the clothes you wear', and 'Over the last week, how itchy, sore, painful or stinging has your skin been?' had the largest impact on QoL.

The mean total score for the SWLS questionnaire was 21.61 ± 7.17 out of 35 with a mean value of 4.35 ± 1.43 for single answers, indicating that the patients were slightly satisfied with their life overall (Tables 5 and 6, and Figure 4).[16]

Regarding heuristic happiness on a 0- to-100-point-scale, the overall mean value was 46.52 ± 27.05, which points towards mediocre happiness (Table 7).

TABLE 3 Employment and capacity to work, $n = 90$.

	N	%
Working ($n = 90$)		
Yes	73	81.11
No	17	18.89
Of those who are working ($n = 73$), these are		
Working full time	38	52.06
Working part time	34	46.58
Currently on leave	1	1.37
Of those who are currently not working ($n = 17$), these are		
Pensioners	8	47.06
Invalidity pensioner	4	23.53
Currently on sick leave due to HHD	2	11.76
Housewife	2	11.76
Apprentice	0	0
Unemployed	1	5.88
On how many days of the past 12 months were you not able to work due to HHD? ($n = 76$)		
On no day	36	40.45
0–10 days	18	20.22
>10 days	22	24.72
I do not work	13	14.61

TABLE 4 Subjective disease severity and symptoms of HHD.

Assessment	N	Mean ± SD
Patient's report on (in the past 3 days)		
Pruritus (0- to 10-point scale); 0: no itch; 10 = worst imaginable itch	87	5.37 ± 2.82
Pain (0- to 10-point scale); 0 = no pain; 10 = worst imaginable pain	87	5.13 ± 2.56
Burning sensation (0- to 10-point scale); 0 = no burning sensation; 10 = worst imaginable burning sensation	86	5.85 ± 2.8
Sleep disorder (0- to 10-point scale); 0 = no disturbance; 10 = worst disturbance	87	5.00 ± 3.08
Assessment	**N**	**%**
How severe would you classify your HH disease ($n = 85$)		
Currently not present	2	2.35
Mild	13	15.29
Moderate	35	41.18
Severe	35	41.18
On how many months was skin affected by HHD in past 12 months? ($n = 90$)		
<3 months	6	6.67
3–6 months	12	13.33
>6 months	15	16.67
Permanently	57	63.33

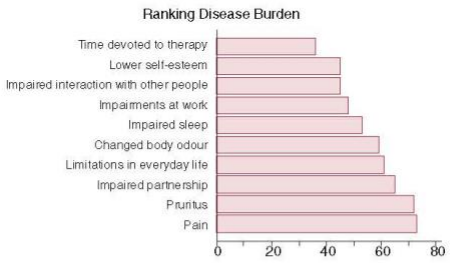

FIGURE 1 Display of symptoms, which affect patients the most ($n = 90$); x-axis = number of patients.

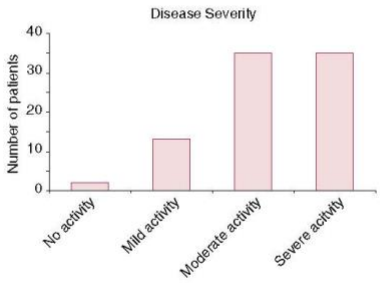

FIGURE 2 Display of own assessment of disease severity (displayed in %; $n = 85$).

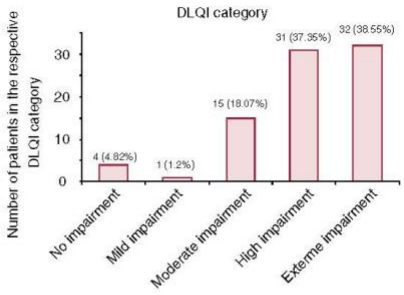

FIGURE 3 Dermatology Life Quality Index—overall analysis (DLQI questions 1 to 10).

TABLE 5 Display of descriptive statistics on SWLS (each question replied on a 7-point-Likert-scale; total score range 5–35).

Question	Mean ± SD	NA
For the most things, my life is close to my ideal	4.09 ± 1.59	4
The conditions of my life are excellent	4.15 ± 1.82	5
I am satisfied with my life	4.55 ± 1.64	5
So far, I have gotten the things that are important to me in life	4.94 ± 1.57	5
If I were born again, I would change almost nothing in my life	4.00 ± 1.77	5
Items averaged	4.35 ± 1.43	4
Total score	21.61 ± 7.17	7

TABLE 6 Display of grouping of SWLS scores into categories according to the total score.

SWLS category (total score)	*N*	%
Extremely dissatisfied (5–9)	8	9.64
Dissatisfied (10–14)	8	9.64
Slightly dissatisfied (15–19)	13	15.66
Slightly satisfied (20–24)	20	24.10
Satisfied (25–29)	22	26.51
Extremely satisfied (30–35)	12	14.46

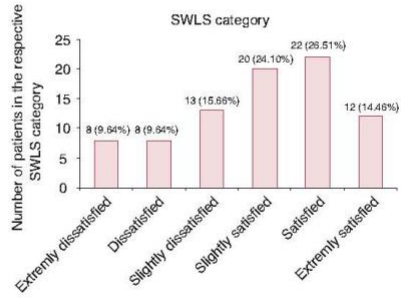

FIGURE 4 Display of grouping of SWLS into categories according to the total score; *y*-axis = number of patients.

TABLE 7 Descriptive statistics for the happiness measures (HHD, psoriasis and healthy controls).

	Satisfaction with life *n*, m ± SD	Heuristic happiness *n*, m ± SD
Hailey–Hailey disease	*N* = 83; 4.35 ± 1.43	*N* = 80, NA = 10; 46.52 ± 27.05
Psoriasis	*N* = 52; 5.02 ± 1.14	*N* = 50; 59.2 ± 28.1
Healthy control	*N* = 106; 4.82 ± 1.26	*N* = 106; 70.8 ± 20.6

TABLE 8 'Which systemic therapy have you received in the past?'—display of the systemic therapies received by HHD patients in the MDHHgermany registry; More than one reply possible.

Systemic therapy	*N*	%
Number of patients who received systemic treatment	65	72.22
Number of patients who did not receive systemic treatment up to date	23	25.56
Patients who did not reply to this question (NA)	2	2.22
Substance most commonly subscribed (*n* = 65)		
Corticosteroids	48	73.8
Low-dose naltrexone	17	26.2
Retinoid (isotretinoin, acitretin)	10	15.4
Antibiotics (not closer defined)	9	13.8
Others (alphabetical order)		
Cetirizin	1	1.5
Cladribin (received for multiple sclerosis)	1	1.5
Cyclosporine A	1	1.5
Dapsone	6	9.2
Dermabrasion	3	4.6
Fluconazole	1	1.5
Hydroxyzin	1	1.5
Laser	6	9.2
Magnesium	2	3.1
Meditation	1	1.5
MTX	6	9.2
Red light lamp	2	3.1
Vitamin C	2	3.1
Vitamin D	1	1.5
Vitamin K2	1	1.5

Treatment information

Systemic treatment

72.2% of all patients had received at least one systemic HHD treatment with corticosteroids (73.8%) representing the most prescribed treatment, followed by LDN (26.2%),[18] retinoids (15.4%) and antibiotics (13.8%). Additionally, various other therapies were subscribed (Table 8). 56.92% of all patients who had received a systemic therapy in the past stated that none was effective. Highest efficacy was reported for corticosteroids, LDN

and antibiotics. No patient stated that retinoids had been effective (Table 9).

Topical treatment

The most prescribed external therapy were topical corticosteroids with 98.86%, followed by antiseptic body wash (54.55%), cream containing urea 10% (23.59%) and topical calcineurin inhibitors (21.59%; Table 10). However, 26.14% stated that no topical therapy was effective. In general, topical steroids (40.1%) were assessed as most effective, followed by antiseptic lotions and creams (10.22%) and topical combinations including steroid and antibiotics (7.96%). Due to the difficult-to-treat nature, the patients have tried a large number of external therapies (Table 11).[2]

Disease activity, doctor's consultation and satisfaction with medical care

Regarding doctor's consultations, participants had 0.75 ± 1.49 inpatient stays within the last 5 years; however, 41.18% reported a worsening or an indifferent skin condition after discharge. Outpatient visits were required 5.48 ± 5.23 times within the last 12 months. The most approached doctors were dermatologists (88.1%), followed by general practitioners (56.0%). Most commonly the physician was consulted for prescription of medication (95.3%), followed by worsening of the skin (75.6%). A naturopath had been seen by 22.22% in the past 5 years.

In addition, patients were questioned whether the consulted doctor includes them and their therapeutic goals in decision making regarding therapy. 24.7% stated that this only slightly applies. Only 30.6% of the participants confirmed

TABLE 9 'Which systemic therapy has been the most effective so far?'—display of the most effective systemic therapies according to patients with HHD in the MDHHgermany registry; more than one reply possible.

Most effective systemic therapy ($N = 88$)	N	%
Corticosteroids	9	13.85
Antibiotics (not closer defined)	9	13.85
Low-dose naltrexone	7	10.77
Retinoid (isotretinoin, acitretin)	0	0
Others (alphabetical order)		
Cetirizin	1	1.54
Cladribin (received for multiple sclerosis)	1	1.54
Cyclosporine A	0	0
Dapsone	0	0
Fluconazole	1	1.54
Hydroxyzin	1	1.54
Magnesium	2	3.08
Meditation	1	1.54
MTX	0	0
Vitamin C	2	3.08
Vitamin D	1	1.54
Vitamin K2	1	1.54
No systemic therapy effective	37	56.92
NA	2	3.08

TABLE 10 'Which topical therapy has been prescribed so far?'—patients were requested to choose.

External therapy ($n = 88$)	N (%)	%
Topical corticosteroids (e.g. prednicarbat, advantan, mometasonfuroat)	87	98.86%
Topical calcineurin inhibitors (tacrolimus, pimecrolimus)	19	21.59%
Cream containing Urea 10%	21	23.86%
Shower gel with antisepsis (e.g. octenisan)	48	54.55%
Bath additions (e.g. potassium permanganate)	14	15.91%
Topical retinoids	7	7.95%

TABLE 11 'Which of the topical therapies have you found most effective so far?'—display of the most effective external therapies in patients with HHD from the MDHHgermany registry; More than one answer possible.

Which external therapy is most effective? ($n = 88$)	N	%
Substance		
Topical steroid	36	40.1
Antisepsis	9	10.22
Topical steroid + antibiotic	7	7.96
Cream containing Urea 10%	4	4.55
Topical antibiotic	3	3.41
Topical antifungal agent	2	2.27
Topical steroid + antisepsis	1	1.14
Others (alphabetical order)		
Basic salt bath	2	2.27
Crystal violet	1	1.14
Dead sea salt bath	1	1.14
Decoderm tri	1	1.14
Dimethyl sulfoxide (DMSO; naturopathic)	1	1.14
Foam bandage (Mepilex)	3	3.41
Healing spring bath	1	1.14
Natron	1	1.14
Silver cream	2	2.27
Sulphur	1	1.14
Tannolact	4	4.55
Topical steroid + antibiotic + antifungal	1	1.14
Traumeel cream	2	2.27
Vitamin D/calcipotriol	1	1.14
NA	2	2.27
No topical therapy has worked so far	23	26.14

that the doctor explains reasons for therapy recommendations and only 17.6% could participate in decision making. On average, patients stated that they spend 54.92 ± 58,64€ on their therapy which is not included in their health care (Table 12).

Furthermore, overall satisfaction with the medical care of the skin disease was interrogated on a 10-point scale (0 = very dissatisfied, 10 = very satisfied), the mean value was 3.54 ± 2.72, indicating that a vast majority is dissatisfied with their medical care. The treatment satisfaction was 3.44 ± 2.69 on average, pointing towards dissatisfaction (Table 12).

Treatment goals

Within the registry, patients were requested to assess their treatment goals. 84.1% desired to no longer experience pain and 79.6% stated that the easement of pruritus was an important goal. 76.1% wished to live a normal daily life and 67.1% found the goal of being able to engage in normal leisure activities important (Figure 5).

DISCUSSION

MDHHgermany was designed to establish an evidence-based nationwide clinical registry and research network to obtain a better understanding for HHD patients' needs, to characterize the 'real-life' medical care and the effectiveness and safety of available therapies.

Here, we demonstrated that the disease-related QoL and life overall in affected individuals is majorly impacted. HHD patients reported lower heuristic happiness compared to a healthy control group, and moreover a slightly lower SWL. Even when compared to affected individuals with Psoriasis, where a lower QoL and life satisfaction has consistently been demonstrated by previous studies,[19,20] HHD patients had a lower single-item score on the SWL and heuristic happiness[15] (Table 7), consequently indicating that HHD patients suffer to an even larger extent than psoriasis patients.[15,16,20]

The satisfaction with disease control and treatment was shown to be low and the evaluation of subjective symptoms (itch, pruritus, burning sensation and sleeplessness) revealed, that these were far from being well controlled. Moreover, the subjective assessment of disease activity demonstrated that a large proportion classified their HHD disease as moderate to severe and many stated that their skin was permanently affected. Apart from the subjective symptoms, our findings show that many patients had numerous affected relatives, which indicates, that the prevalence of this disease is most likely higher than stated in the literature.[21] However, as the participant's data are pseudonymized, we were unable to exclude participating relatives in the data analysis of affected family members, possibly leading to incorrect results.

TABLE 12 Disease activity, doctor's consultations and satisfaction with medical care.

Assessment	N	%
Looking back, how sure are you about the date of the first diagnosis? (*n* = 89)		
Very sure	45	50.56
Pretty sure	25	28.09
Slightly sure	14	15.73
Not sure	5	5.62
	Mean ± SD	
Doctor's consultation due to HHD		
Inpatient in last 5 years (median), *n* = 34	0.75 (0–7; SD: 1.49)	
Outpatient in last 12 months (median), *n* = 83	5.48 (0–30; SD: 5.23)	
	N	**%**
Specialization of consulted doctor (*n* = 84)		
Dermatologist	74	88.1
General practitioner	47	56.0
Internal medicine	7	8.3
Other	14	16.7
In case you had an inpatient stay due to HHD in the past 5 years, was the treatment successful? (*n* = 34)		
No, skin condition worsened	7	20.59
No, skin condition was unchanged at discharge	7	20.59
Yes, skin condition was slightly improved	9	26.47
Yes, skin condition was markedly improved	11	32.35
For what reason was a doctor consulted for HHD? More than one answer possible (*n* = 86)		
Prescription	82	95.3
Worsening of skin condition	65	75.6
Routine check up	33	38.4
Consultation of possible therapies	25	29.1
Distinct subjective symptoms (e.g. itch, sleeplessness, pain)	20	23.3
How many flare ups in past 12 months? (n = 90)		
1–2	10	11.11
3–6	15	16.67
>6	17	18.89
Skin was permanently affected	48	53.33
Looking back, would you say that your skin condition is worsening? (*n* = 51)		
1. Yes, very	19	37.25
2. Yes, a lot	21	41.18
3. Yes, slightly	8	15.69
4. No, not at all	3	5.88
Consulted doctor explains reasons for therapy recommendation (*n* = 85)		
Does not apply at all	15	17.6

TABLE 12 (Continued)

Assessment	N	%
Slightly applies	24	28.2
Applies partly	20	23.5
Applies	16	18.8
Fully applies	10	11.8
Consulted doctor includes me and my therapeutic goals in decisions ($n=85$)		
Does not apply at all	9	10.6
Slightly applies	21	24.7
Applies partly	18	21.2
Applies	22	25.9
Fully applies	15	17.6
Consulted doctor gives me a chance to participate in the decision in regards to the therapy ($n=85$)		
Does not apply at all	14	16.5
Slightly applies	17	20.0
Applies partly	18	21.2
Applies	21	24.7
Fully applies	15	17.6
Has a naturopath been seen for the disease? ($n=90$)		
Yes	20	22.22
No	70	77.78
How much money is spent on average per month (medication not covered by healthcare; in Euros)? ($n=76$; NA = 14)	54.92 (SD: 58.64; Min: 0; max: 300)	
How satisfied are you currently (last 3 months) with the medical care of your skin disease? (0 = very dissatisfied, 10 = very satisfied; 0- to 10-point scale; $n=85$)	85	3.54 ± 2.72
How satisfied are you currently (last 3 months) with the medical treatment of your skin disease? (0 = very dissatisfied, 10 = very satisfied; 0- to 10-point scale; $n=84$)	84	3.44 ± 2.69

FIGURE 5 Display of therapy goals assessed by the patients, more than one answer possible. *x*-axis = percentage of patients.

HHD patients mainly consult dermatologists and general practitioners frequently for various reasons. The occasional requirement for inpatient stays resulted in a deteriorated or unchanged skin condition. Regarding work ability, patients reported that they missed a considerable number of workdays due to their disease. This does not only reveal severe affection on an individual basis, but also imposes a considerable burden for the health system.

Due to the rarity of the disease, the reason of choice as well as evidence for the effectiveness of topical or systemic therapies is predominantly based on small cohorts and case reports. With this interim analysis however, we were able to provide an initial overview of the efficacy of currently used topical and systemic therapies based on a larger cohort. The overall treatment satisfaction and effectiveness of prescribed external and systemic therapies was notably low and was accompanied by a dissatisfaction of HHD patients with the available medical care in general. Furthermore, it is noteworthy that a considerable proportion of HHD patients in the registry had not received any systemic treatment, further emphasizing the challenges of HHD treatment.

Consequently, we present compelling evidence that the treatment of HHD remains a significant challenge, and thus we could not identify a single treatment regime, which benefits every individual, reflecting the literature analysis.[3,21,22]

Both the severe psychosocial impact as well as the perception of being inadequately treated were worrying phenomena. Up to this date, no research has shed light on the patient's perspective in such depth. However, Harris et al. showed among 66 HHD patients that the DLQI is majorly impacted, showing an average of the DLQI score of 6.06. This is lower than in our cohort (17.59), reasons for this could be that all patients were contacted via email, our cohort was largely included after seeking help at a physician, implicating a more severe course of disease.

Gisondi et al. also showed an impacted QoL in 22 affected HHD patients in 2005, using the Skindex-29 and the 12-item-general-health questionnaire.[5,6]

In summary, our results emphasize that HHD is far from being adequately controlled and therefore calls once again for a major improvement of the medical care of these patients.

Not only do we lack effective therapies, but patients are also troubled majorly by subjective symptoms and are largely dissatisfied with the medical care in general.

Collectively, these results strongly highlight the pressing requirement for improved medical management of HHD in order to not only improve the skin condition but also enhance the overall well-being of affected individuals.

However, it is important to acknowledge the limitation of this. Due to the rarity of HHD, only a small cohort of patients was assessed. Additionally, the subjective nature of the questionnaire and the timepoint of the study visit could have biased the results towards an overestimation of the disease

severity. It has to be noted, that mainly patients with a higher suffering might approach the doctor, thereby leading to a selection bias of included patients towards more severely affected individuals. On the other hand, HHD remains difficult-to-treat, which could explain why many patients are still majorly affected.

Furthermore, to date, no official scoring for HHD exist, hence the used questionnaires and assessments might lack accuracy for the investigated dermatosis. Amar et al. have suggested a scoring system for DD recently, which could possibly be implemented for HHD in the future.[23]

Lastly, as many patients stopped seeing a physician due to lack of treatment success, we also enrolled patients from online self-help platforms. Here we had to rely on the statement of the participant that the disease was diagnosed by a physician in compliance with the diagnostic standards.

CONCLUSION

'Real-life' patient's perspectives are essential in understanding a disease in more depth. With this analysis of our data, we present the first comprehensive overview of the patients' perspectives on the disease severity of HHD, treatments and its psychosocial impact.

The 'real-time' data from MDHHGermany demonstrated drastically, that there is still tremendous room for improvement of HHD disease control in many aspects including disease-related QoL, numerous subjective symptoms, disease severity, working ability, satisfaction with life and effective therapeutic options. Measures at optimizing treatment might contribute to filling the gaps between patients' perspectives, treatment goals and their 'real-life' implementation.

In the future, the MDHHgermany registry will provide a continuous valuable basis for clinical trials as well as immunological and epidemiological studies for the development of new disease-specific therapeutic strategies. This could include the particular focus on the unmet need for pain and itch control, possibly including other disciplines such as psychologists and wound managers.

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CONFLICT OF INTEREST STATEMENT

D.R. has received research grants, honoraria as lecturer and/or consultant and/or travel grants from Eli Lilly, Novartis and Pfizer. L.H., T.B., E.S., S.H. and A.Z. has no conflicts of interest to be noted.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

ETHICS STATEMENT

The registry has formally been approved by the local ethics committee of the Technical University of Munich (49/19 S-SR).

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Publication II: Unmet needs in Darier's disease from a patient's perspective: Lessons learnt from the German registry

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ORIGINAL REPORT

MJS PUBLISHING

Unmet Needs in Darier's Disease from a Patient's Perspective: Lessons Learnt from the German Registry

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The MDHHgermany registry was initiated to characterize the "real-life" situation of affected individuals with Darier's disease (DD; Morbus Darier, MD) and Hailey-Hailey disease (HH), including their treatment and healthcare. To gain deeper insights into medical care of patients with DD, various aspects such as demographics, subjective symptoms, patient satisfaction with medical care, past and current therapies were explored. Patients with diagnosed DD were included. Subjective symptoms such as itch, pain and burning sensation were assessed. Individual therapy goals were recorded and patients assessed previous/current therapies along with satisfaction of medical care and treatment. A total of 55 patients were recruited; 47 patients were eligible for the analysis. Pruritus was rated the most bothersome symptom. Some 42.6% had not received systemic treatment so far or systemic therapies were rated ineffective (32.6%). Most commonly oral retinoids were prescribed, followed by corticosteroids. Patient satisfaction with medical care and treatment proved to be mediocre. This "real-life" data show an alarming unmet need regarding patients' satisfaction with medical care and treatment, evidenced by the reported lack of disease control. Further studies and interventions are needed to improve the spectrum of available therapies. MDHHgermany provides a foundational platform for future clinical trials, epidemiological studies, and pathophysiological analyses.

Key words: Darier's disease; genodermatosis; orphan disease; disease burden; registry.

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Darier's disease (DD) is a rare genetic disorder characterized by skin lesions and nail abnormalities. The condition follows an autosomal dominant inheritance pattern, caused by mutations in the *ATP2A2* gene on chromosome 12q23-24.1, which encodes the sarcoplasmic and endoplasmic reticulum calcium ATPase type 2 (SERCA2) protein (1–4).

SIGNIFICANCE

Darier's disease is a rare, autosomal dominantly inherited, debilitating disease, which can lead to stigmatization and social isolation. Its management and therapies remain difficult, as therapeutic options are limited. Aim of our research was to shed light on the in-depth patient's perspective of the disease and medical care hereof, hopefully enhancing our overall understanding of DD and leading to an improvement of patient management on the whole.

The clinical presentation of DD varies in severity and may encompass various skin lesions such as keratotic papules and plaques, typically located on the trunk, scalp, and seborrheic areas. The lesions can coalesce to large papillomatous masses, often accompanied by pruritus and foul odour. In addition, nail abnormalities such as longitudinal striations, subungual hyperkeratosis, and V-shaped notches may be evident (5–7).

The characteristic skin lesions and nail abnormalities associated with the disease can result in physical discomfort, emotional distress, and social stigma, all contributing to a negative impact on patients' overall well-being (8). To date, 2 studies have demonstrated reduced health-related quality of life (HRQL) in 74 (8) and 133 DD patients (9), respectively. However, the patients' perspectives on satisfaction with the available medical care and treatments has not been described.

With initiation of the national registry for DD (Morbus Darier, MD) and Hailey-Hailey disease (HHD), MDHHgermany, we aimed to collect data to evaluate the "real-life" situation of healthcare for individuals affected by DD, along with its psychosocial impact (10). This study presents data obtained from an interim analysis on 47 patients with DD included in the registry from June 2020 to March 2023, emphasizing the baseline characteristics combined with the disease severity and the patients' satisfaction with medical care and treatment.

MATERIAL AND METHODS

MDHHgermany registry

MDHHgermany is a nationwide clinical registry, including patients with DD and HHD from dermatology clinics and office-based dermatologists in Germany (10,11). For objectives see Table SI.

Inclusion criteria for Darier's disease patients

Individuals who had been clinically and preferably histologically diagnosed with DD and who were either inpatients or outpatients at the selected centres were eligible to participate in the study, provided they were able to understand the German version of the questionnaire. Additionally, we incorporated patients from the self-help platform, as there are several individuals with DD who lack a physician managing their condition. Within the questionnaire, all patients were required to indicate how the diagnosis was made.

Schedule of assessments and study instruments for Darier's disease patients

Enrolled patients in the registry were followed up prospectively for a minimum of 24 months, throughout which paper-based questionnaires were filled out by both doctors and patients, or alternatively online using REDCap (Research Electronic Data Capture; REDCap 12.2.2, © 2022 Vanderbilt University) (12). For paper-based questionnaires, the data were manually entered into the REDCap system by the dermatology department of the Technical University of Munich.

Patient registry questionnaires were completed at inclusion (baseline visit; V1) and then ideally every 6 months using REDCap. Unscheduled visits were possible if required due to flare-ups or if desired by the patient for other reasons.

To achieve high acceptance and unbiased free-text answers, we incorporated innovative questionnaires in addition to validated questionnaires including the numeric rating scale (NRS) (13) and DLQI (see Table SII) (8). At baseline (V1), the patient was requested to complete a questionnaire encompassing 5 sections, covering basic demographic details, familial and personal medical history, the overall severity of the disease, specific symptoms, and recent therapies and treatment objectives, as well as questions regarding the psychosocial impact (Table SII).

To record clinical data in addition to subjective data and improve patient satisfaction, physician study visits were conducted at patient inclusion (V1) and ideally once a year or after any changes in treatment. These visits were not performed for patients who had participated via the self-help platform and include information on current and past therapies, reasons for treatment decisions made by the physician, as well as an assessment of the severity of DD (using the proposed "DD score" by Amar et al. in a recent publication) (14).

Data management and statistical analysis

All assessments were electronically documented using CE-certified software solutions (ESPRIO, Seracom Software Solutions GmbH, Stuttgart, Germany and REDCap, Research Electronic Data Capture; REDCap 8.5.28, ©2019 Vanderbilt University, Nashville, TN, USA). For this interim analysis, only baseline data included in the registry between 10 June 2020 and 15 March 2023 were considered. Prior to analysis, data were checked for plausibility and completeness. Incomplete questionnaires, in which less than 75% of all questions were answered, were deemed ineligible and excluded from the study. In cases where the disease was not explicitly specified in the questionnaire, all responses provided by that particular patient were disregarded. When calculating a score, the presence of a single missing value in any question resulted in the exclusion of all answers for the purpose of score calculation. However, when analysing individual questions within an assessment, the patient's response was still considered. The entire analysis was based on descriptive statistics performed in R studio version 2023.3.0.386 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and general patient characteristics

In total 55 patients with DD were enrolled in the registry, and 47 patients were analysed in this first data interim analysis. The remaining ($n = 8$) participants were excluded due to missing and/or implausible data. The patients' demographic data including family history, education, and working capability is described in **Table I**. At inclusion, the mean age of the study population was 49.4 ± 14.4 years, with females accounting for 67.4% of the cohort.

The majority (80.9%) of the study population were employed. Interestingly, 25.5% of all patients were on sick leave for 1–10 days throughout the past year due to DD.

Some 57.9% of DD patients knew of affected family members (on mean 2.5 ± 1.2 affected family members). It was assumed by the patients that the severity of the family members' disease ranged from moderate to severe for 39.3%.

Disease history, activity, and doctor's consultation before inclusion in the registry

The mean age at first diagnosis was 24.1 ± 12.1 with 21 being diagnosed before the age of 20 (**Fig. 1**), as commonly stated in the literature (1). The mean disease duration before registry inclusion was 25.1 ± 17.3 years (**Table II**).

When evaluating the intensity of their own condition (mild, moderate, or severe), 86.4% opted for the classifications of "moderate" or "severe" (**Fig. 2**) and the majority (58.7%) noted the presence of persistent DD lesions over the past year (see Table II).

In considering the requirement for healthcare of DD patients, it is noteworthy that, on average, the patients had 1.4 ± 2.4 inpatient stays in the past 5 years and 4.9 ± 4.4 outpatient stays in the past 12 months. Interestingly, 45.5% reported a slight improvement in the skin condition upon an inpatient stay, while 18.2% noted that the skin condition had worsened.

As expected, the most consulted specialist was a dermatologist (93.0%), followed by general practitioner (34.9%); 14.9% of the patients had seen a naturopath in the past 5 years.

The predominant reasons for consultations were the deterioration of DD (83.7%), prescription of medication (48.8%), and routine check-ups regarding DD (41.9%). Overall, patients stated having spent €49.7 ± 50.7 on their disease per month for non-healthcare plan medication (see Table II).

Subjective symptoms and disease burden regarding Darier's disease

Participants assessed pain, itch, burning sensation, and sleeplessness over the past 3 days on a numeric rating

Table I. Baseline patient characteristics

Age, years, mean±SD; range	49.4±14.4; 26–87
Gender, *n* (%)	*n* = 46, NA = 1
Female	31 (67.4)
Male	15 (32.6)
Level of education, *n* (%)	*n* = 45, NA = 2
Without graduation	0 (0)
Certificate of secondary education	16 (35.6)
General certificate of secondary education	10 (22.2)
General qualification for university entrance	14 (31.1)
University degree	5 (11.1)
Marital status, *n* (%)	*n* = 47, NA = 0
In a relationship	7 (14.9)
Married	26 (55.3)
Divorced	6 (12.8)
Widowed	1 (2.1)
Unmarried	7 (14.9)
Working, *n* (%)	*n* = 47, NA = 0
Yes	38 (80.9)
No	9 (19.1)
Of those who are working, these are:	*n* = 38
Working full time, *n* (%)	22 (57.9)
Working part time, *n* (%)	15 (39.5)
Currently on leave, *n* (%)	1 (2.6)
Of those who are currently not working, these are:	*n* = 9
Pensioners, *n* (%)	5 (55.6)
Invalidity pensioner, *n* (%)	1 (11.1)
Currently on sick leave, *n* (%)	1 (11.1)
Housewife, *n* (%)	0 (0.0)
Unemployed, *n* (%)	2 (22.2)
Scholars/students, *n* (%)	0 (0.0)
On how many days of the past 12 months were you not able to work due to your skin condition? *n* (%)	*n* = 47, NA = 0
On no day	19 (40.4)
0–10 days	12 (25.5)
> 10 days	7 (14.9)
I don't work	9 (19.1)
Family history	
Number of siblings (average; *n* = 38, NA/Excluded = 9)	1.78 (1.44)
Number of affected family members, mean ± SD	2.5 ± 1.2
If a family member is affected, how severe would you say their disease is? *n* (%)	*n* = 28, NA = 19
Currently not present	10 (35.7)
Mild	7 (25.0)
Moderate	7 (25.0)
Severe	4 (14.3)

SD: standard deviation; NA: not answered.

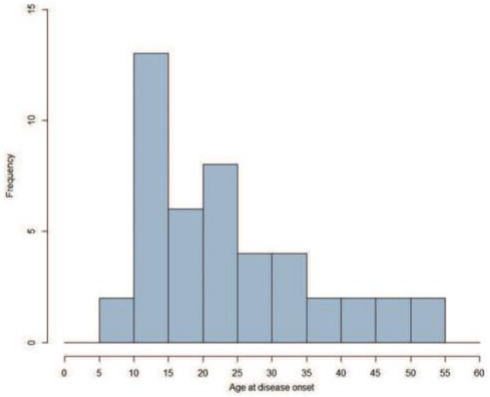

Fig. 1. Age at first diagnosis (*n* = 47) (min: 6 years, max: 53 years). x-axis: age in numbers.

scale ranging from 0–10, whereby 0 reflects not being troubled at all and 10 indicates being very troubled (13). Pruritus was rated with the highest value (5.6 ± 2.7), followed by burning sensation (3.9 ± 2.7), pain (3.6 ± 3.0), and sleep disorder (3.2 ± 3.2) (**Table III**, **Figs 3 and 4**). Accordingly, when patients were asked to select from a variety of aspects which pose the highest burden on them, pruritus was chosen by most patients (*n* = 37), followed by lower self-esteem and pain (**Fig. 5**).

Frequency and effectiveness of available therapies

Almost all included patients (*n* = 44) received topical therapy, while only 27 patients received systemic medi-

Table II. Disease history and activity before inclusion in the registry

Age at first diagnosis, mean ± SD, (*n* = 47)	24.1±12.1
Disease duration, in years since 2021, mean±SD; range, (*n* = 44, NA = 3)	25.1±17.3; 0–66)
Assessment, *n* (%)	
Looking back, how sure are you about the date of the first diagnosis? *n* (%)	*n* = 47, NA = 0
Very sure	16 (34.0)
Pretty sure	21 (44.7)
Slightly sure	4 (8.5)
Not sure	6 (12.8)
Looking back, would you say that your skin condition is worsening? (Question was added in 2021), *n* (%)	*n* = 20, NA = 27
1. Yes, very	4 (20.0)
2. Yes, a lot	10 (50.0)
3. Yes, slightly	5 (25.0)
4. No, not at all	1 (5.0)
How severe would you classify your disease as being, *n* (%)	*n* = 47, NA = 0
Currently not present	0 (0)
Mild	6 (13.6)
Moderate	26 (59.1)
Severe	12 (27.3)
On how many months was skin affected in past 12 months? *n* (%)	(*n* = 46, NA = 1
< 3 months	10 (21.7)
3–6 months	6 (13.0)
> 6 months	3 (6.5)
permanently	27 (58.70)
Doctor's consultation due to DD	
Inpatient in last 5 years, *n* = 41, NA = 5, excluded = 1, mean±SD: range	1.4±2.4; 0–10
Outpatient in last 12 months, *n* = 45, NA = 1, excluded = 1, mean±SD; range	4.87±4.4; 0–20
If you had an inpatient stay due to DD in the past 5 years, was the treatment successful? *n* (%)	*n* = 22)
No, skin condition worsened	4 (18.2)
No, skin condition was unchanged at discharge	2 (9.1)
Yes, skin condition was slightly improved	10 (45.5)
Yes, skin condition was markedly improved	6 (27.3)
Specialization of consulted doctor, *n* (%)	*n* = 43, NA = 4
Dermatologist	40 (93.0)
General practitioner	15 (34.9)
Internal medicine	1 (2.3)
Other	1 (2.3)
For what reason was a doctor consulted? More than one answer possible, *n* (%)	*n* = 43, NA = 4
Worsening of skin condition	36 (83.7)
Prescription	21 (48.8)
Routine checkup in regard to DD	18 (41.9)
Consultation of possible therapies	5 (11.6)
Distinct subjective symptoms (e.g., itch, sleeplessness, pain)	14 (32.6)
Has a naturopath been seen for the disease? *n* (%)	*n* = 47, NA = 0
Yes	7 (14.9)
No	40 (85.1)
How much money is spent on average per month (in Euros) on medication not included in your health plan? (*n* = 33, NA = 14, mean±SD; range	49.7±50.7; 0–250

SD: standard deviation; NA: not answered; DD: Darier's disease.

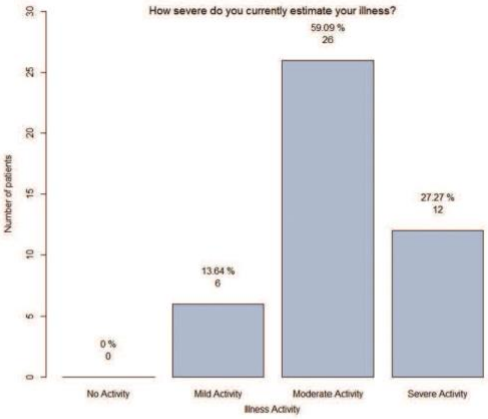

Fig. 2. Display of assessment of disease severity ($n = 44$). y-axis: number of patients.

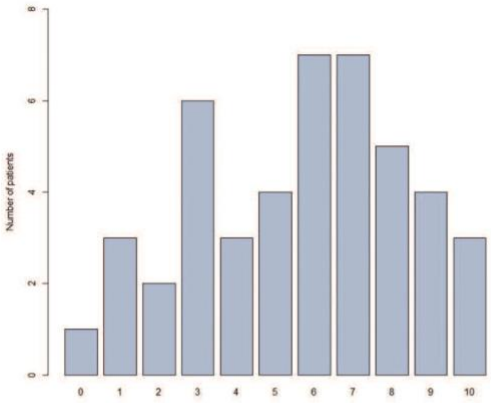

Fig. 3. Display of the symptom "itch" ($n = 45$) on a 10-point-scale, 0 = no itch, 10 = worst imaginable itch. x-axis: 0- to-10 point scale; y-axis: number of patients.

cation. Topical corticosteroids (97.7%) emerged as the primary prescribed topical medication, followed by topical retinoids (32.6%), whereas the most prescribed systemic medication was retinoids (66.7%), especially acitretin, followed by systemic corticosteroids (59.3%) (**Table IV**). Concerning effectiveness of topical therapy, 44.2% of patients rated topical steroids as the most efficacious. However, 32.6% reported ineffectiveness of any topical treatment (Table IV). In accordance, 29.6% rated retinoids the most effective systemic therapy, and 11 (40.7%) found no systemic therapy effective at all (Table IV).

Table III. Subjective symptoms, patient satisfaction, and treatment goals at baseline

Assessment	
Consulted doctor explains reasons for therapy recommendation, *n* (%)	*n* = 43, NA = 4
Doesn't apply at all	8 (18.6)
Applies slightly	4 (09.3)
Applies partly	13 (30.2)
Applies mostly	5 (11.6)
Applies fully	13 (30.2)
Consulted doctor includes me and my therapeutic goals in decisions, *n* (%)	*n* = 43, NA = 4
Doesn't apply at all	3 (7.0)
Applies slightly	10 (23.3)
Applies partly	10 (23.3)
Applies mostly	7 (16.3)
Applies fully	13 (30.2)
Consulted doctor gives me a chance to participate in the decision with regard to the therapy, *n* (%)	*n* = 42, NA = 5
Doesn't apply at all	5 (11.9)
Applies slightly	6 (14.3)
Applies partly	5 (11.9)
Applies mostly	13 (31.0)
Applies fully	13 (31.0)
Assessment	
How satisfied are you currently (last 3 months) with the medical care (caretaking by your physician etc.) of your skin disease?[a]	44, NA = 3
Mean ± SD	4.1 ± 3.2
How satisfied are you currently (last 3 months) with the medical treatment (systemic and topical therapies) of your skin disease?[a]	43, NA = 4
Mean ± SD	3.7 ± 3.1
Patient's report on (in the past 3 days)	45, NA = 2
Pruritus (0- to 10-point scale)[b], mean ± SD	5.6 ± 2.7
Pain (0- to 10-point scale)[b], mean ± SD	3.6 ± 3.0
Sleep disorder (0- to 10-point scale)[c], mean ± SD	3.2 ± 3.2
Burning sensation (0- to 10-point scale), mean ± SD[d]	3.9 ± 2.7

[a]0 = very dissatisfied, 10 = very satisfied; 0- to 10-point scale. [b]0 = no pain; 10 = worst imaginable pain. [c]0 = no disturbance; 10 = worst disturbance. [d]0 = no burning sensation; 10 = worst imaginable burning sensation.
SD: standard deviation; NA: . **[AQ3]**

Satisfaction with medical care and therapeutic goals

To assess the patients' perspectives on medical care, the questionnaire evaluated their inclusion in therapy decisions and satisfaction levels. Only 30.2% of patients described doctors having fully explained therapeutic recommendations, while 18.6% received no explanation. Accordingly, 30.2% experienced full inclusion in decision-making, 16.3% mostly, 23.3% partly, and 23.3% slightly. The remaining patients did not feel involved.

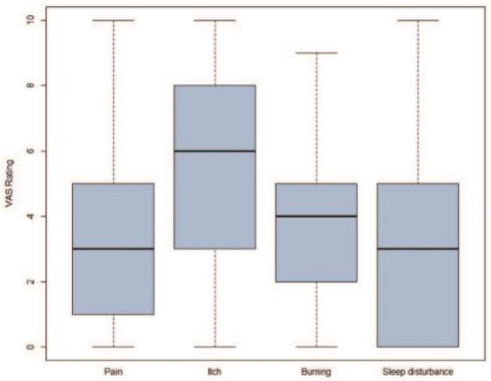

Fig. 4. Bar plot of subjective symptoms pain, itch, burning sensation, and sleep disturbance during the past 3 days ($n = 45$). y-axis: 0- to-10 point scale.

Fig. 5. Display of ranking of disease burden ($n=46$). x-axis: number of patients.

Table IV. "Which topical and systemic therapy have you received so far among the following? Which of the therapies have you found most effective so far?" Display of the most commonly prescribed topical and systemic therapies and rating of effectiveness. Most commonly prescribed percentage was calculated as percentage of those who had received therapy

Topical therapy	$n=46$; NA = 1
No external therapy, *n* (%)	3 (6.5)
Topical corticosteroids (e.g. prednicarbate, Advantan, mometasone furoate), *n* (%)	42 (97.7)
Topical retinoids, *n* (%)	14 (32.6)
Topical calcineurin inhibitors (tacrolimus, pimecrolimus), *n* (%)	6 (14.0)
Cream containing urea 10%, *n* (%)	21 (48.8)
Shower gel with antiseptics (e.g., Octenisan), *n* (%)	20 (46.5)
Bath additions (e.g., potassium permanganate), *n* (%)	7 (16.3)
Which topical therapy is most effective? (44 had received one), *n* (%)	
No topical treatment effective	14 (32.6)
Topical steroid	19 (44.2)
Topical steroid+antibiotic	0 (0.0)
Topical antibiotic	1 (2.3)
Topical antifungal agent	1 (2.3)
Topical steroid+antiseptics	1 (2.3)
Antiseptics	2 (4.7)
Cream containing urea 10%	3 (7.0)
Others (alphabetical order)	
Calcineurin inhibitors	1 (2.3)
Crystal violet	1 (2.3)
Natrium phosphoricum D6 cream (Schuessler salt)	1 (2.3)
Retinoid topical	1 (2.3)
Rose hydrolat	1 (2.3)
Tannolact	1 (2.3)
Vitamin D/calcipotriol	1 (2.3)
Zinc cream	2 (4.7)
Systemic therapy, n (%)	$n=46$; NA = 1
Patients who received systemic treatment, *n* (%)	27 (58.7)
Patients who did not receive systemic treatment, *n* (%)	19 (41.3)
Substance most commonly prescribed, *n* (%)	
Retinoid (acitretin [$n=17$], isotretinoin [$n=1$]), *n* (%)	18 (66.7)
Corticosteroids, *n* (%)	16 (59.3)
Low dose naltrexone, *n* (%)	5 (18.5)
Antibiotics (not closer defined), *n* (%)	0 (0.0)
Others (alphabetical order), *n* (%)	
MTX, *n* (%)	2 (7.4)
Otezla, *n* (%)	1 (3.7)
Weight reduction, *n* (%)	1 (3.7)
Most effective systemic therapy, *n* (%)	
Retinoid (mainly acitretin, $n=1$ isotretinoin), *n* (%)	8 (29.6)
Low dose naltrexone, *n* (%)	2 (7.4)
Corticosteroids, *n* (%)	2 (7.4)
Antibiotics (not further defined), *n* (%)	0 (0.0)
Others (alphabetical order), *n* (%)	
Weight reduction, *n* (%)	1 (3.7)
No systemic therapy effective	11 (40.7)

On a 0- to 10-point satisfaction scale (0 = dissatisfied, 10 = very satisfied) for medical care and treatment in the last 3 months, the mean values were 4.1 ± 3.2 and 3.7 ± 3.1, respectively, indicating mild to moderate dissatisfaction (see Table IV).

Concerning therapy goals (**Fig. 6**), a vast majority (80.4%) priorixtized ending pruritus, followed by achieving a normal daily life (58.7%) and eliminating pain (54.3%).

DISCUSSION

Darier's disease (DD) frequently proves to be a debilitating condition that significantly affects the quality of life and, to date, remains difficult to treat (9).

As already anticipated when this registry was started, our initial interim analysis supported 2 main observations: (a) individuals impacted by DD are not receiving adequate treatment, as evidenced by their dissatisfaction with medical care, and (b) the disease activity remains high, contributing to a moderate to severe disease burden, likely attributed to the reported lack of effective therapeutic options.

One of the most important findings was that the majority of patients rated the general satisfaction with medical care and treatment below mediocre. A considerable number of individuals reported ineffectiveness of both external and systemic therapies. In addition to the patients' personal perspective, the insufficient efficacy was also evident by the amount of in- and outpatient stays, potentially imposing a considerable burden on the health system.

The baseline characteristics could show that a special focus of future research should be brought to the burden inflicted by pruritus, which constantly emerged as the most distressing symptom across various tools. In accordance, its alleviation was ranked the primary therapeutic goal for patients in the MDHHregistry, indicating that available therapies are not sufficient to reduce itch. Unfortunately, despite a single successful case report in

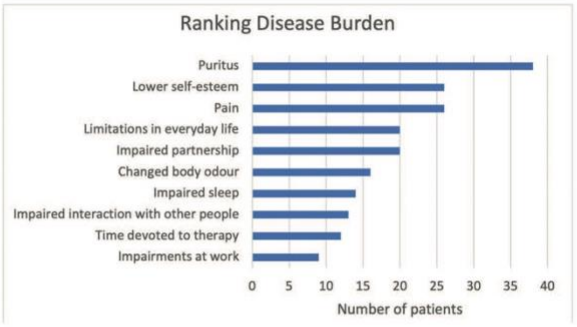

Fig. 6. Display of therapeutic goals, more than one answer possible ($n = 46$). x-axis: number of patients.

the literature, conventional antihistamines do not demonstrate a significant impact when used in the day-to-day clinical routine, altogether underlining the pressing need for efficient antipruritic treatments (15).

Apart from the relevance of pruritus and pain management, the registry also revealed that altered body odour affected the life of DD patients. It is noteworthy that a potential therapeutic strategy could emerge from novel findings by Amar et al. (14). The authors highlighted the role of dysbiosis in odour changes and demonstrated potential management through microbiome transplantation or targeted enhancement of beneficial bacteria. In particular, *S. hominis* and *C. acnes* could improve the disease activity by mitigating inflammation and body odours linked to exacerbations.

Our finding that most patients consistently experienced skin issues throughout the year, coupled with an alarming 86.4% who categorized their disease activity as "moderate" or "severe", further supports the notion that DD still requires more efficient therapies due to a lack of adequate disease control. Overall, we show that despite our progress in understanding the underlying pathophysiology of DD (1, 16, 17), the development of new therapies has not succeeded during the last decades. Strikingly, we still rely on the same therapies that were already employed 20 years ago. To that end, retinoids remain the most effective and commonly prescribed, even though the side effects and the teratogenicity often leave us with hands tied (18, 19). While the literature describes numerous case reports on various therapies (2,20), none has yet achieved the required breakthrough (2). In contrast, registries like MDHHgermany can provide the first step to explore unconventional therapy options that have proved successful in several patients, forming the basis for broader clinical trials of new treatment regimens and the improvement of existing therapies.

Limitations

Our data analysis comes with several limitations, above all the size of the study cohort, as numerous centres did not have capacity to undergo the time-consuming ethics process. Therefore, the majority of patients were recruited in Bavaria. Nevertheless, DD is a rare disease and affected patients have never been assessed this extensively. Furthermore, the subjective symptoms burn, pruritus, sleep, and burning were assessed only for the past 3 days, introducing a potential bias as patients tend to consult a doctor when the disease activity is at its peak. Consequently, we also faced a potential selection bias for severely affected and already diagnosed patients, as individuals who regularly visit in- or outpatient departments or actively searched for health information regarding DD were more likely to participate in the registry. Lastly, the assessment of current and past therapies did not differentiate between topical and systemic medication during a flare-up and medication when the skin is stable, which is, however, crucial in our everyday routine.

It is important to note that our analysis relies primarily on the patients' perspective, and assessments like disease severity were not validated by a direct comparison with a physician's clinical assessment. Additionally, some participants entered the registry without a physician (especially from the self-help platform), hence the diagnosis of DD is not entirely definite. However, the primary goal of this analysis was to assess the patients' perspective rather than objective clinical data. The correlation of patients' and physicians' assessments within MDHHgermany will be examined in the future.

Conclusion

In conclusion, these baseline characteristics offer valuable insights into the current healthcare landscape and treatment approaches for patients with DD in Germany. Our "real-life" data could demonstrate an alarming burden inflicted by the disease on the patients and reveal a critical shortage of efficient therapies, emphasizing the urgent need for additional agents to achieve a perceptible improvement of the disease activity in DD patients. We found that treatment strategies should aim at alleviating the most burdensome symptoms, especially pruritus, ideally tailored to the patient's individual needs and preferences.

We hope that this "real-life" data collection will enhance physicians' overall understanding of their DD patients, guide physicians' decision-making regarding therapeutic goals and contribute to improved management of these difficult-to-treat patients.

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Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Ethics statement: The registry has formally been approved by the local ethics committee of the Technical University of Munich (49/19 S-SR). All participating sites handed in the ethics at their local ethics committee.

Conflicts of interest: D.R. has received research grants, honoraria as lecturer and/or consultant, and/or travel grants from Eli Lilly, Novartis, and Pfizer. L.H. has no conflicts of interest to be noted. T.B. has no conflicts of interest to be noted. E.S. has no conflicts of interest to be noted. S.H. has no conflicts of interest to be noted. A.Z. has no conflicts of interest to be noted.

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Appendix I: Darier and Hailey-Hailey disease: Update 2021

Rogner DF, Lammer J, Zink A, Hamm H. Darier and Hailey-Hailey disease: update 2021. J Dtsch Dermatol Ges. 2021 Oct;19(10):1478-1502. German. doi: 10.1111/ddg.14619_g. PMID: 34661362.

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Darier and Hailey-Hailey disease: update 2021

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Summary

The autosomal-dominant genodermatoses Darier disease and Hailey-Hailey disease present special challenges to dermatologists. Despite their similar pathogenesis featuring impaired adhesion of suprabasal keratinocytes as a result of defective ATPases in epidermal calcium channels, the two diseases differ considerably in clinical presentation and therapeutic options. Darier disease is characterized by reddish brown, keratotic papules in seborrheic and intertriginous areas, which may coalesce into extensive lesions. Individuals affected with Hailey-Hailey disease primarily develop intertriginous papulovesicles and small blisters, which often evolve into erythematous plaques with erosions and painful fissures. Quality of life is significantly reduced because of complaints (itch, burning sensation, pain), body malodor and chronicity. Therapeutic options remain limited. Antiseptics and intermittent topical corticosteroids are a cornerstone of therapy, and systemic anti-infective treatment is often required in cases of superinfection. Ablative surgical interventions such as dermabrasion and CO_2 laser surgery can lead to long-term remissions in intertriginous Hailey-Hailey disease, while temporary relief may also be achieved by intralesional injections of botulinum toxin. Of the systemic medications available for Darier disease, acitretin, which is approved for this purpose, has the best supporting evidence. The efficacy of immunosuppressants and immune modulators is inconsistent. Low-dose naltrexone produces more satisfactory results in Hailey-Hailey than Darier disease. The present CME article summarizes current knowledge of the two dermatoses, taking recent developments into account.

Introduction

Both diseases are inherited via an autosomal dominant pattern.

Darier disease (*Syn.:* follicular dyskeratosis) and Hailey-Hailey disease (*Syn.:* familial benign chronic pemphigus) are genodermatoses with an autosomal dominant inheritance pattern. Both diseases are characterized by impaired adhesion of epidermal keratinocytes. Darier disease was first described in 1889 by Jean Darier of Paris and simultaneously by James Clark White of Harvard, Cambridge/Massachusetts, USA. Hailey-Hailey disease was first characterized only fifty years later (in 1939) by the brothers Howard and Hugh Hailey of Atlanta/Georgia, USA [1, 2].

Diagnosis of both diseases can often be made clinically, with a follow-up confirmation using dermatohistopathological methods. Treatment, on the other hand, remains a challenge for both patients and dermatologists. Much hope has been placed in more targeted, pathogenetically oriented treatments and novel gene therapeutic approaches for the improvement of patients' quality of life, in particular for severely affected individuals [1].

This CME article offers an overview on the pathogenesis, clinical presentation, and available therapeutic options for the two genodermatoses, and describes some approaches for novel and future treatments. Despite their similar pathogenesis,

these diseases differ significantly in many respects (see Table 1), thus warranting a separate discussion.

Darier disease

Epidemiology

The world-wide prevalence of Darier disease is 1 : 30 000–1 : 100 000 [2].

Pathogenesis

Darier disease is inherited in an autosomal-dominant pattern, with complete penetration and variable expression. Spontaneous mutations have been reported in up to 68 % of the patients investigated [3]. The disease is caused by pathogenic mutations in the *ATP2A2* gene, with more than 350 distinct mutations reported

Table 1 Comparison of the characteristics of Darier disease and Hailey-Hailey disease.

	Darier disease	Hailey-Hailey disease
Synonym	Dyskeratosis follicularis	Familial benign chronic pemphigus
Mutated gene	*ATP2A2*	*ATP2C1*
Calcium pump disorder	SERCA2 in the endoplasmatic reticulum	hSPCA1 in the Golgi apparatus
Age at first manifestation	Usually 2nd decade	Usually 3rd/4th decade
Clinical presentation	– Brownish-erythematous, occasionally confluent papules in seborrheic areas – Papillomatous plaques in the intertriginous areas, partly macerated	– Erythematous to erosive and suppurating plaques with fissures, mainly in the intertriginous areas
Histology	– 'Corps ronds' (dyskeratotic cells in the stratum spinosum) – 'Grains' (dyskeratotic cells in the stratum granulosum) – Suprabasal fissuring	– Pronounced suprabasal acantholysis – Occasional dyskeratoses
Topical treatment	– Antiseptic treatment – Topical corticosteroids – Topical calcineurin inhibitors if indicated – Topical retinoids – Botulinum toxin injections (axillar area)	– Antiseptic treatment – Topical corticosteroids – Topical calcineurin inhibitors – Botulinum toxin injections (axillar area)
Surgical treatment	In less extensive disease, where appropriate: – Dermabrasion – CO_2 laser therapy – Er:YAG laser therapy	– Dermabrasion – CO_2 laser therapy – Er: YAG laser therapy
Systemic treatment	– Antibiotics, aciclovir in cases of superinfection – Retinoids, especially acitretin – Corticosteroids (short-term)	– Antibiotics, aciclovir in cases of superinfection – Retinoids, especially acitretin – Naltrexone low-dose – Where appropriate: dapsone, methotrexate, ciclosporin, apremilast

to date [4, 5]. The gene encodes isoform 2 of the sarcoplasmic and endoplasmic reticulum calcium ATPase (SERCA2). The enzyme transports calcium across the membrane of these structures into the lumen of the endoplasmic reticulum (ER), thereby maintaining low cytosolic calcium levels [6]. Experimental studies have shown that blocking the SERCA pumps with thapsigargin disrupts the development and function of desmosomes and tight junctions [7]. This impairs the adhesion of adjacent suprabasal keratinocytes, histologically characterized as acantholysis, and results in anoikis (programmed cell death, a subtype of apoptosis) which causes the dyskeratoses visible in histology [6].

Darier disease is caused by mutation in the *ATP2A2* gene. This disrupts the SERCA2 pump and leads to impaired calcium homeostasis in the keratinocytes and decreased cell-cell adhesion.

Patterns of involvement and clinical manifestations of the disease vary widely among individuals. With the exception of the associated neuropsychiatric disorders mentioned below [8], there appears to be no correlation between genotype and phenotype, especially since clinical severity can vary greatly even within a family sharing the same mutation [5].

Clinical presentation

Darier disease usually appears in the second decade of life, often during puberty [2] and takes a chronic course. Male individuals frequently show a more severe form of the disease. UV exposure, heat, humidity, sweating, friction, and infections may provoke symptoms. Medication with interferons, azathioprine, lithium [9], and calcium antagonists [10] may aggravate the disease. Quality of life is often greatly impaired [11].

Clinically, Darier disease presents with isolated or aggregated reddish-brown papules and plaques with a keratotic surface, resulting in a 'grating' sensation on palpation (Figure 1). While the disease is also called "follicular dyskeratosis", in reality the interfollicular dermis is also affected. Predilection sites include seborrheic areas (scalp, forehead, nasolabial fold, chest, upper back) as well as intertriginous areas (axillary and inguinal folds, in women also the submammary region) (Figure 2). On the trunk, the papules may coalesce into large lesions, and in the intertriginous areas into macerated hypertrophic vegetations [12]. Affected individuals suffer from pruritus, burning sensations, and pain, and especially if the intertriginous areas are affected, they often emanate an unpleasant, musty body odor which can lead to social isolation.

Darier disease presents with brownish papules mainly in the seborrheic and intertriginous areas, with a keratotic surface. These may coalesce into macerated lesions.

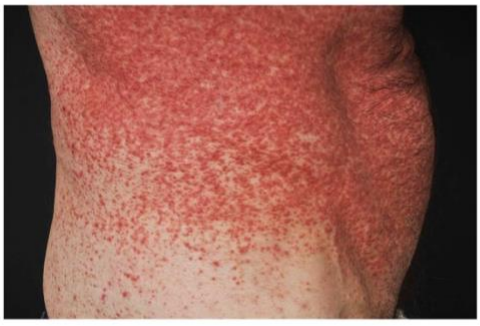

Figure 1 Darier disease: classical clinical picture featuring aggregated, inflammatory papules on the trunk.

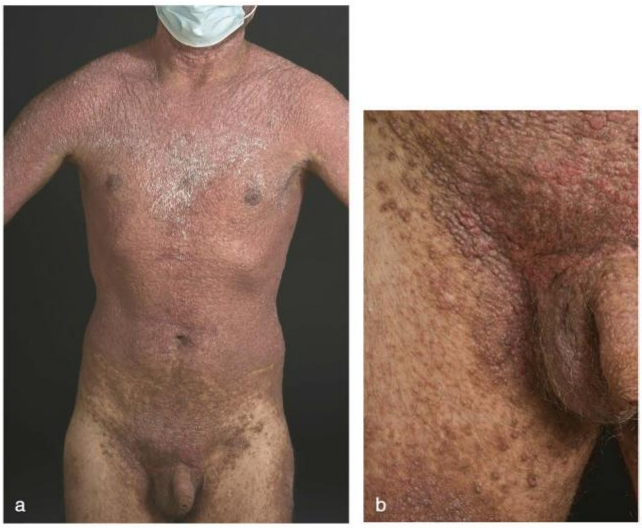

Figure 2 Darier disease: confluent inflammatory papules on the trunk (a) with massive involvement of the inguinal fold (b).

Palmoplantar findings often involve small, irregular depressions (pits) and yellowish-brown hyperkeratotic papules. The dermatoglyphs at the fingertips are interrupted [13]. Flat, wart-like papules on the dorsal aspects of the hands and feet may also occur as an isolated phenomenon, called acrokeratosis verruciformis Hopf. This is an allelic variant of Darier disease [14–16].

Typical affections of the nails (especially the fingernails) include red and white longitudinal streaks (longitudinal erythronychia or leukonychia) and grooves that end in a V-shaped notch in the free edge of the nail, with subungual hyperkeratosis

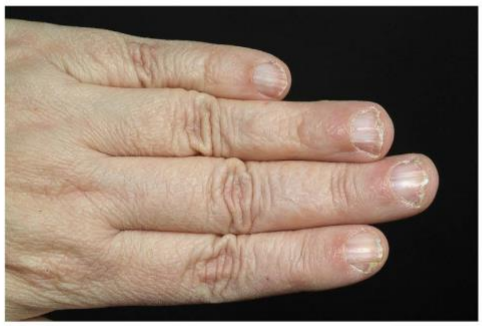

Figure 3 Nail involvement in Darier disease: longitudinal red and white streaks (erythronychia and leukonychia longitudinalis) with V-shaped notches at the free edges of the nails.

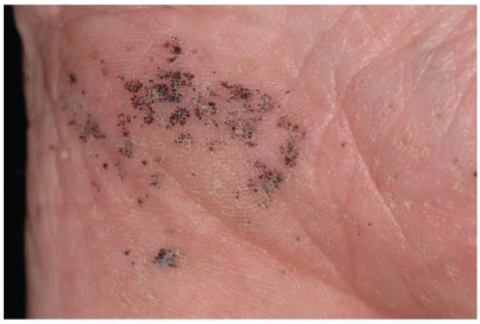

Figure 4 Acral-hemorrhagic Darier disease on a palm.

(Figure 3) [17]. In the area of the red stripes, the nails are thinner and prone to painful splitting [18].

The hard palate and the buccal mucosa may show 'cobblestone-like' papules and leukokeratosis. Gingival hyperplasia and macroglossia have also been described as possible affections of the oral mucous membranes [19]. Hyperkeratotic papules on the rims of the eyelids as well as chronic blepharitis may also occur [20].

In the bullous form of the disease, vesicles and blisters are frequently provoked by sweating and fever, showing intraepidermal fissures by histological examination [21]. The hemorrhagic form shows superficial hemorrhages in acral areas, caused by mechanical stress (Figure 4) [22]. Very rarely, a variant of Darier disease with prominent comedones occurs, always affecting the face but occasionally other areas as well. Typical keratotic papules and other clinical signs of the genodermatosis are not always present in these cases [23].

Typical nail changes in Darier disease include red and white longitudinal streaks ending in V-shaped notches at the free margin of the nail plates.

Linear/segmental Darier disease follows the Blaschko lines (Figure 5) and represents genetic mosaicism. This is usually type 1 segmental mosaicism (heterozygosity for a post-zygotic de novo mutation), but cases of type 2 segmental mosaicism (homozygosity or hemizygosity within the segment with heterozygosity

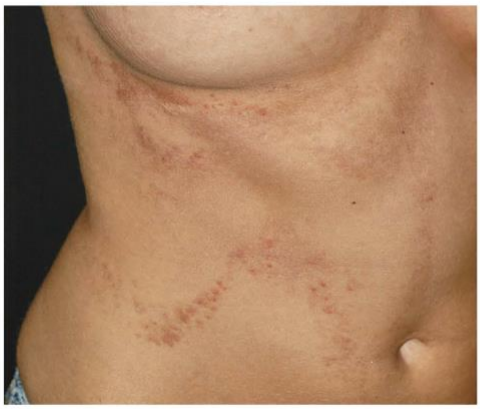

Figure 5 Linear Darier disease on the trunk.

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Acrokeratosis verruciformis as well as bullous, hemorrhagic, comedonic and linear/segmental types are clinical variants of Darier disease.

in the rest of the body) have also been reported [24–28]. The latter is characterized by unusually severe lesions in the affected segment superimposed on the common, diffuse phenotype. Molecular genetic evidence has been provided for both variants of mosaicism [26, 27].

Neuropsychiatric disease is more frequent in Darier patients than in the general population [9, 29]; apparently there is an association with 'loss of function' mutations [30]. Data from the Swedish national registry have shown that the risk of mental retardation is increased by factor 6, the risk of bipolar disorder by factor 4.3, and the risk of schizophrenia by factor 2.3 in patients with Darier disease [31, 32]. Out of 100 affected individuals in Britain, 50 % developed a psychiatric disorder within their life span, 30 % developed severe depression, 31 % reported suicidal thoughts, 4 % had bipolar disorder, and 3 % had epilepsy [8, 9, 33–37].

Darier disease is frequently associated with neuropsychiatric disorders.

Complications

Patients with Darier disease have a significantly increased risk of bacterial superinfection (mostly *Staphylococcus aureus*) and fungal infections (mostly candida species, more rarely dermatophytes) [38], especially in areas with macerated and erosive lesions. One dreaded complication is superinfection with herpes simplex virus, which may become life-threatening (Figure 6) [39]. Superinfections may lead to massive deterioration of the clinical status; they must be detected early and treated systemically. Development of squamous cell carcinomas based on Darier lesions is highly unusual [40].

Acute exacerbation may be caused by superinfection with *Staphylococcus aureus* or herpes simplex virus.

Diagnosis and differential diagnoses

Darier disease can often be diagnosed or suspected upon clinical examination. This is facilitated by noting the more subtle lesions on the oral mucous membranes, the hands, and particularly the very typical findings on the nails. The diagnosis should always be confirmed by histology. If the clinical and histological findings are unequivocal, molecular genetic diagnostics are not necessary [13].

Diagnosis is frequently delayed due to differential diagnoses and lack of experience with this rare disease. The most common differential diagnoses for Darier

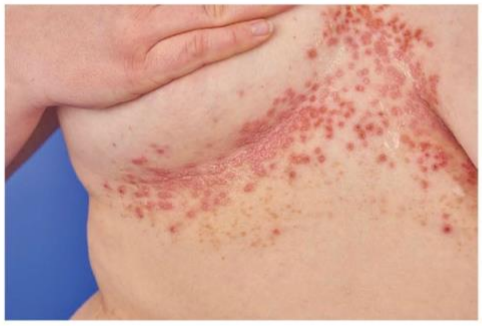

Figure 6 Herpes simplex virus infection on intermammary and submammary sites superimposing preexistent Darier disease.

Table 2 Clinical differential diagnosis of Darier disease.

Hailey-Hailey disease	– See article
Seborrheic dermatitis [123]	– Figurate erythemas with pronounced margin and pityriasis-like scaling in seborrheic areas – Severe forms in immunosuppressed individuals – Nails and mucous membranes not affected – Histology as for dermatitis, no dyskeratoses, no acantholysis
Grover's disease [124]	– Self-limiting, occasionally persisting dermatosis mainly on the trunk – Exacerbation due to UV rays, sweating, heat, friction – Occurrence after age 40 years, mainly in men – Disseminated, very pruritic, non-confluent keratotic papules and papulovesicles – Nails and mucous membranes not affected – Histology: acantholysis and dyskeratosis

disease include Hailey-Hailey disease, seborrheic dermatitis, and Grover's disease (Table 2).

Histology

Histological examination in Darier disease (Figure 7) shows moderate acanthosis with orthohyperkeratosis and columns of parakeratosis. Suprabasal fissuring and individual dyskeratotic cells are typical findings. These cells are keratinocytes that have lost contact with the adjacent cells, resulting in a rounded appearance. Their

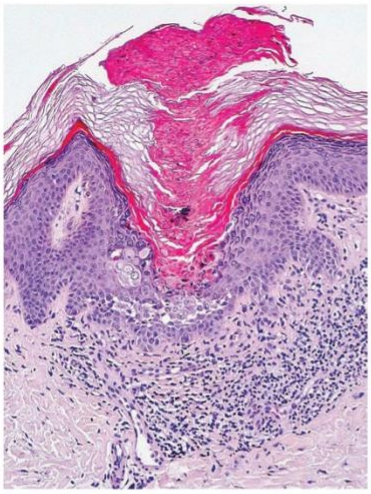

Figure 7 Photomicrograph of Darier disease. Hyperkeratosis with focal parakeratosis, mild acanthosis. Suprabasal cleft, single dyskeratotic keratinocytes in all layers of the epidermis (corps ronds, grains). Subepidermal lymphohistiocytic infiltrate (hematoxylin-eosin stain, bar: 100 µm) (photograph: Andreas Kerstan, MD, Department of Dermatology, Venereology and Allergology, University Hospital Würzburg).

Histology in Darier disease is characterized by pronounced dyskeratosis.

cytoplasm is hypereosinophilic, the nucleus is pycnotic and surrounded by a light halo. They are called *corps ronds* in the stratum spinosum and *grains* in the stratum granulosum and stratum corneum. Lymphohistiocytic infiltrations, especially in the perivascular areas, are found in the subepidermis [41]. Immunofluorescence investigations are negative.

General recommendations

Mechanical stress at the predilection sites, especially the intertriginous areas, should be decreased by wearing loose cotton clothing and through weight loss. Air-tight dressings should be avoided. Superinfections must be treated early. Psychiatric comorbidity needs to be considered, and if the patient so wishes and agrees, consultation with a psychiatrist should be arranged [2].

Topical treatment

Keratolysis as well as antiseptic treatment to avoid superinfection are essential. Topical corticosteroids are also used.

Keratolysis can be achieved by topical application of preparations with urea, glycerin, or lactic acid. Antiseptic treatment is essential, for example with antiseptic creams or shower gels containing octenidine or chlorhexidine. These decrease microbial colonization of the skin as a possible trigger factor, as well as the risk of superinfection.

In addition, topical corticosteroids of class II–III can be applied temporarily, and class IV can also be used for shorter periods of time. Success is variable, and there are no available studies on this type of treatment. In special areas like the face and intertrinigous regions, topical calcineurin inhibitors such as tacrolimus or pimecrolimus are preferable [42, 43]. Treatment with topical keratolytic and antiseptic preparations combined with temporary use of anti-inflammatory substances can maintain relatively unremarkable skin findings in many cases. Topical retinoids such as isotretinoin are also an option in cases of localized lesions and mild findings, but this may cause irritation [2, 44].

There are also individual case reports on topical treatment with the following substances:

- Vitamin-D3 analogs (calcipotriol and tacalcitol), in most cases however worsening of the skin [45]
- 5-Fluoruracil (1 % 1 x per day), inconsistent results [46]
- Diclofenac gel 3 %, good response in four patients [47, 48]
- Fusidinic acid [49]
- Gentamicin [50]

A fundamental problem of topical treatments is that long-term use would be required for sustained results, but in reality application is restricted to limited areas due to increased absorption and for some agents also possible irritation.

One other therapeutic option are intralesional injections of botulinum toxin A (50–100 IU per site) to eliminate sweat as a trigger factor. This is limited to moderate lesions in the axillar region; efficacy is sustained over a period of 3–8 months [51].

Systemic treatment

There is only a very limited number of effective systemic treatments, with no randomized, placebo-controlled trials. The largest body of evidence is available for systemic retinoids, in particular acitretin which is explicitly approved for treating

Among systemic treatments, the best body of data is available for acitretin.

Darier disease [52]. The initial recommended dose is 0.2–0.3 mg/kg body weight [BW]; this may if necessary be increased in steps until the individually effective dose, which may vary greatly, has been reached. Low doses of 10–15 mg per day are often said to be effective but we cannot confirm this from our experience. Under-dosing with side effects predominating over the intended effects should certainly be avoided. In cases of periodic exacerbation during the summer months, repeated application of retinoids over limited periods of time is also an option.

A non-controlled trial with isotretinoin (initially 0.5 mg/kg BW per day, subsequently dose adaptation depending on efficacy and tolerability) in 104 patients showed improvement of the skin findings in 95 % of cases [53]. Unfortunately, acitretin and isotretinoin are frequently discontinued despite yielding good results, due to mandatory monitoring of laboratory values and various side effects. These always include dehydration of the skin and mucous membranes, as well as typical retinoid side effects such as hair loss, headache, gastrointestinal complaints, myalgia, paronychia, increased liver enzymes, and dyslipidemia. In cases of long-term use, skeletal hyperostosis and extraossary calcification need to be considered. Depending on the daily and cumulative dosage, X-ray monitoring of the spine and feet are recommended, albeit at long intervals [54]. For female patients of reproductive age, one advantage of isotretinoin and also alitretinoin [55] as compared with acitretin is their significantly shorter biological half-life, which only requires strict contraception for the period of intake and one month after discontinuation. Alitretinoin also offers a better side effect profile, but there are only a few case reports as to its efficacy [56]. Dosage here varied between 10–30 mg per day.

In severe cases, treatment with oral corticosteroids over a limited period of time (prednisolone initially 0.5 mg/kg BW, tapering off over several weeks) may result in temporary improvement. Superinfection must always be excluded beforehand. Individual case reports have also described successful treatment with doxycycline (100 mg per day), taking advantage of its additional anti-inflammatory effect [57]. There are also some case reports on ciclosporin (about 3 mg/kg BW per day), albeit with inconsistent results [58].

Surgical and physical therapies

Apart from topical treatments, ablative therapies with dermabrasion, CO_2 laser, or Er:YAG laser may also be considered for less extensive lesions such as in linear Darier disease. In individual cases, the results have been very satisfactory [59–62], but not all patients respond sufficiently. Therefore, the effect should first be tested in a small area. As with some topical treatments, this option is limited by the fact that the genodermatosis is often widespread.

There are also individual case reports and smaller case series on successful topical photodynamic therapy, sometimes in combination with acitretin [63, 64].

Ablative therapies (dermabrasion, CO_2 laser, Er:YAG laser) are effective but limited by the size of the areas that can be treated.

In cases of hypertrophic, vegetating lesions in intertriginous areas, there is an option of last resort, in analogy to hidradenitis suppurativa: large-scale excision of affected lesions with subsequent secondary healing or split-skin grafting. This requires strict adherence by the patient, so the indication must be defined strictly [65].

Novel therapies

Based on satisfactory results in three patients with Hailey-Hailey disease [66] (see below), Boehmer et al. treated six Darier disease patients with oral low-dose naltrexone (5 mg per day). This was combined with oral magnesium substitution (200 mg per day) since it has been shown that magnesium inhibits plasma

membrane calcium ATPase and thus influences calcium efflux from the cells and intracellular calcium homeostasis [67]. The results were inconsistent: Patients with mild disease (few affected areas, hardly any maceration) showed a good response whereas patients with moderate to severe disease (macerated lesions, multiple affected areas) did not show any satisfactory improvement, with a deterioration of the skin in some cases [68].

Hailey-Hailey disease

Epidemiology

There are no exact data on the prevalence of Hailey-Hailey disease; it is estimated to be around 1 : 50 000 [1].

Pathogenesis

Hailey-Hailey disease is characterized by mutations in the *ATP2C1* gene which encodes the calcium pump hSPCA1. This decreases the calcium concentration within the Golgi apparatus and leads to impaired adhesion of epidermal keratinocytes.

Hailey-Hailey disease is inherited in an autosomal-dominant pattern with complete penetration and extremely varying expressivity [1]. More than 180 disease-causing mutations have been described for the *ATP2C1* gene [5, 69]. This gene encodes the ATPase hSPCA1, which transports calcium and magnesium into the Golgi apparatus of keratinocytes [1]. Apparently, decreased calcium concentrations within the Golgi apparatus result in faulty processing of desmosomes while adherens junctions remain intact. This leads to a loss of cell-cell contact in suprabasal keratinocytes with incomplete acantholysis [70, 71]. Deeper portions of the hair follicles and sweat glands do not appear to express the gene defect [41].

Clinical presentation

Hailey-Hailey disease mostly manifests in early adulthood, though occasionally later and in isolated cases already in childhood [72, 73].

The disease shows a chronic or chronic-relapsing course with exacerbations. Friction, heat, UV rays, humidity, sweating, infections, pregnancy, menstruation, and also additional or intercurrent dermatoses such as scabies are considered trigger factors. Hailey-Hailey disease can lead to a massive impairment of a patient's quality of life and to social isolation [74].

Erythema, papulovesicles and blisters develop especially in intertriginous areas and other regions exposed to increased friction. These lesions may coalesce, soon rupture, and result in erosions. The typical findings show rather clearly delineated, oozing, inflammatory plaques pervaded by irregular fissures (Figure 8). The latter are more easily detected by stretching the skin (accordion phenomenon). Predilection sites include areas with increased friction such as the retroauricular region, lateral parts of the neck, axillae, flexor sides of the elbows, navel, inguinal region, genital and perianal region, in women also the submammary region, and in obese individuals the abdominal folds (Figure 9). Patients with maximum affection may show extensive erosion and hypertrophic, encrusted vegetations in the intertriginous areas (Figure 10). More rarely, extensive lesions may occur on the trunk. Patients suffer from severe pain, burning sensations, and pruritus; a fetid body odor may also develop especially in cases of bacterial superinfection. Acute lesions may leave hyperpigmented or hypopigmented residues after healing [1]. In about 50 % of patients, the nails show narrow, whitish, longitudinal streaks (longitudinal leukonychia) (Figure 11) [18, 73]. The mucous membranes are not affected.

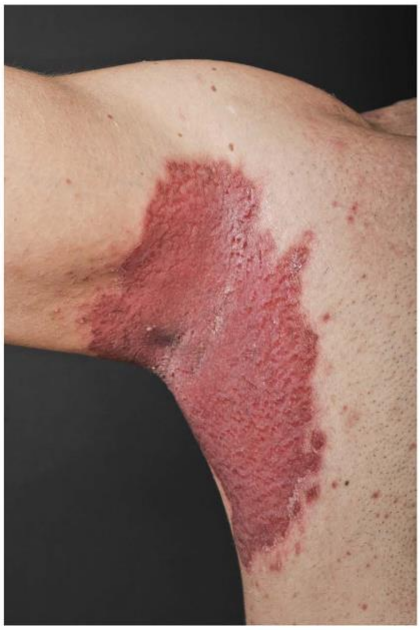

Figure 8 Hailey-Hailey disease: pronounced involvement of the armpit with multiple fissures.

Hailey-Hailey disease is characterized by inflammatory, oozing plaques in intertriginous regions, pervaded by fissures.

Rarely, linear manifestations of Hailey-Hailey disease following the Blaschko lines may occur, both as segmental type 1 and segmental type 2 variants. As in Darier disease, both types of mosaicism have been confirmed by molecular genetics [28, 75–77].

As opposed to Darier disease, there are no extracutaneous symptoms. This may be explained by compensatory mechanisms via other, non-skin-specific calcium pumps such as SERCA1 on the membranes of the Golgi apparatus [6].

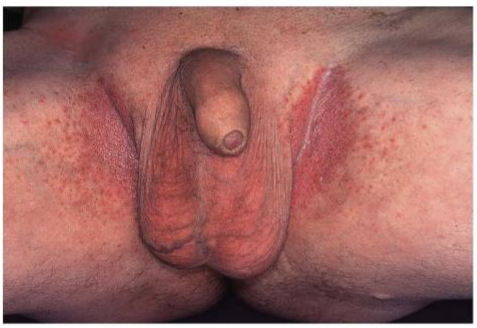

Figure 9 Hailey-Hailey disease: symmetrical involvement of the groins.

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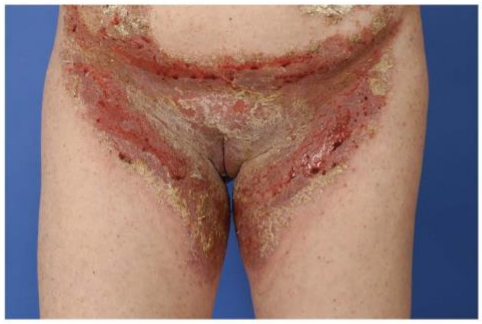

Figure 10 Hailey-Hailey disease: pronounced involvement of the abdominal fold and genitoinguinal region with large erosions.

Complications

Bacterial, fungal, and viral superinfection may lead to exacerbations in Hailey-Hailey disease.

Superinfection with bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), fungi (*Candida* species), and viruses (herpes simplex) may occur especially on erosive and macerated plaques [78], leading to significant exacerbation of the lesions. In a few cases, squamous cell carcinomas arising on chronic lesions have been reported, particularly in the genital region [79].

Diagnosis and differential diagnoses

Hailey-Hailey disease is diagnosed based on the often very typical clinical findings, with histological confirmation. Detection of a mutation in the *ATP2C1* gene using molecular biology techniques is not routinely required but is useful in unclear cases [80].

Differential diagnoses for Hailey-Hailey disease include, apart from Darier disease, other ptychotropic dermatoses such as pemphigus vegetans, acanthosis nigricans, erythrasma, intertrigo, intertriginous candidosis, and in the perianal region also dermatitis and genital warts (Table 3) [81]. Intertriginous (or papular)

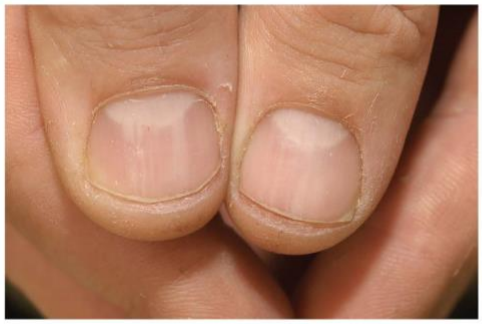

Figure 11 Nail involvement in Hailey-Hailey disease: longitudinal leukonychia in both thumb nails.

Table 3 Clinical differential diagnosis of Hailey-Hailey disease.

Darier disease	– See Table 2
Pemphigus vegetans [125]	– Rare variant of pemphigus vulgaris – Papillomatous vegetations in the intertriginous areas – Neumann type: initially vesicles and blisters, Hallopeau type: pustules – Histology: acantholysis – Direct immunofluorescence: autoantibodies to desmoglein 3, rarely also desmoglein 1, desmocollin 1 and 3
Inverse psoriasis [126]	– Variant of psoriasis vulgaris in the intertriginous areas – Clearly delineated, erythematous plaques, scant or absent scaling – Frequently pruritic – Histology: slight epidermal hyperplasia, less pronounced hyperkeratosis with exoserosis containing inflammatory cells
Erythrasma [127]	– Clearly delineated, slightly scaling, brownish-red lesions – No or only mild pruritus – Predilection sites: axillary and inguinal areas – Causative agent: *corynebacterium minutissimum* – Red fluorescence in Wood light
Intertrigo [128]	– Relatively clearly delineated, erythematous and partly macerated plaques in intertriginous areas – Superinfection by bacteria or *candida albicans* may occur
Intertriginous candidosis	– Rather clearly delineated erythema with peripheral scaling in intertriginous regions – Pustules and satellite lesions in the immediate vicinity
Genital warts (condylomata acuminata) [129]	– Skin-colored to reddish papillomas that tend to coalesce – Predilection sites: genitoanal region, inguinal area – Causative agent: human papillomaviruses, mainly HPV-6 and HPV-11

acantholytic dyskeratosis is an allelic variant of Hailey-Hailey disease where the clinical lesions are limited to the genital and inguinal area, the perineum and the perianal region [82].

Histology

Histology in Hailey-Hailey disease is characterized by acantholysis with acanthosis and occasional dyskeratoses.

Histological examination (Figure 12) in Hailey-Hailey disease shows pronounced but incomplete acantholysis that has been compared to a collapsing brick wall. In some cases, entire rete ridges are affected. Dyskeratoses are much less common than in Darier disease. The epidermis is covered by hyperparakeratosis with serum inclusions and is in part very hyperplastic. This needs to be considered when performing ablative treatments. The dermis shows perivascular to diffuse, lymphohistiocytic inflammatory infiltrates with added neutrophilic granulocytes, especially when at eroded sites [41, 83, 84].

Treatment and patient management

Treatment of Hailey-Hailey disease is often difficult. Therapeutic recommendations are mainly based on small case series, individual case reports, and the physician's personal experience. Systemic treatments are not regularly effective, and there are no randomized clinical studies or treatment guidelines. It is essential to inform the patient about this fact, to reduce disappointment in case of insufficient

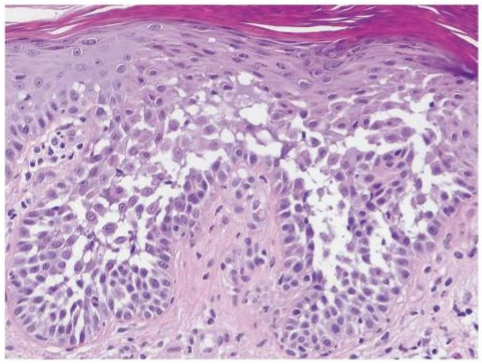

Figure 12 Photomicrograph of Hailey-Hailey disease. Acanthosis with prominent incomplete acantholysis. Mild lymphohistiocytic infiltrate in the upper dermis (hematoxylin-eosin stain, bar: 100 µm) (photograph: Andreas Kerstan, MD, Department of Dermatology, Venereology and Allergology, University Hospital Würzburg).

efficacy of the chosen treatment. Since the disease is often limited to circumscribed areas, ablative surgical treatment offers more benefit than in Darier disease.

General recommendations

Mechanical stress, heat, and sweating in the predilection areas should be decreased by wearing loose cotton clothing and by weight loss. Air-tight dressings and adhesive plasters should be strictly avoided since these may trigger exacerbations and new lesions. Superinfections must be treated early and appropriately [73].

Topical treatment

Zinc oxide shaking mixtures, or soft zinc paste, are recommended for basic care of the large body folds. To reduce microbial colonization and decrease the risk of superinfection, antiseptic cleansers (for example octenidine-containing solutions) and hydrophilic antiseptic emulsions or creams (for example with chlorhexidine) are recommended.

A combination of antiseptic and – for limited periods of time – anti-inflammatory topical preparations is effective in less pronounced cases of Hailey-Hailey disease.

Inflammatory lesions can be treated with class II–III topical corticosteroids [73, 85]. Especially in the intertriginous predilection areas, these should only be used for limited periods of time, or at intervals, so skin atrophy and striae may be avoided. Topical calcineurin inhibitors may be used successfully instead. One study showed that tacrolimus ointment (0.1 %) resulted in better responses than pimecrolimus cream (1 %) despite less suitable galenics [86]. In many less pronounced cases, a combination of topical antiseptics and anti-inflammatory treatment can stabilize the affected skin.

Apart from the abovementioned therapeutic options, there are individual case reports on the successful use of topical treatments with:

- 5-Fluorouracil [87]
- Calcitriol [88]
- Antibiotics such as gentamicin cream and clindamycin gel [89]
- Antifungals such as ketoconazol 2 %

The irritative potential of 5-fluoruracil and topical vitamin-D3 analogs must, however, be taken into account when treating this intrinsically irritable dermatosis.

One other therapeutic option is offered by intralesional injections of botulinum toxin A (50–100 IU per site) to decrease sweating as a trigger factor. This is used mainly in patients with mild to moderate axillar lesions [90].

Treatment of complications and superinfections

In cases of bacterial superinfection, suppurating areas should be dried out with antiseptic compresses and, where appropriate, with dyes (eosin solution). Topical antibiotics such as gentamicin and fusidinic acid may also be applied occasionally [89], but these should be used with caution due to possible development of resistances and contact allergy. In severe cases, systemic antibiotics such as flucloxacillin, first-generation cephalosporins, or clindamycin are indicated [1]. Superinfection with candida species can usually be managed with topical antifungals, while herpes simplex infections always require systemic treatment with acyclovir.

Systemic treatment

Superinfections with staphylococci or herpes simplex viruses should be treated systemically with antibiotics or acyclovir, respectively. Otherwise, the most comprehensive body of data is available for low-dosed acitretin.

Apart from anti-infectives for bacterial and viral superinfection, systemic therapies for Hailey-Hailey disease are of limited value. Randomized, placebo-controlled studies on individual substances are lacking. The best evidence is available for oral retinoids, in particular acitretin at low doses of 10–30 mg per day. Higher doses may increase acantholysis and cause clinical exacerbation [91–93]. Exacerbations can be managed with oral corticosteroids (such as prednisolone at an initial dose of 0.5 mg/kg BW per day) but rebound effects may occur after discontinuation. Systemic corticosteroids are not appropriate for long-term therapy.

There are also individual case reports on successful treatment with:

- Doxycycline (100 mg per day) [94]
- Methotrexate (7.5–15 mg per week) [95–97]
- Dapsone (initially 50–200 mg per day, with subsequent reduction to 50 mg) [98]
- Etanercept (one positive case report; 75 mg per week) [99]
- Azathioprine [100]
- Ciclosporin (2.5 mg/kg BW per day) [101, 102]
- Thalidomide (initially 100 mg 3 x per day, maintenance dose 50 mg per day) [103]
- Terbinafine (250 mg per day) [104]

Only dapsone is approved for the treatment of Hailey-Hailey disease – despite the lack of clinical studies.

Since it is known that the defective calcium pump is magnesium-dependent, some patients have been successfully treated with magnesium 300 mg per day [105, 106].

Of the drugs mentioned above, only dapsone is approved for the treatment of Hailey-Hailey disease – despite the lack of clinical studies.

Surgical and physical treatment

In a number of cases with extensive intertriginous lesions, ablative surgery such as dermabrasion [107] (Figure 13), CO_2 laser and Er:YAG laser treatment, and argon plasma coagulation [108] have shown remarkable success. When performed correctly, with sufficiently deep ablation of the affected skin areas down into the

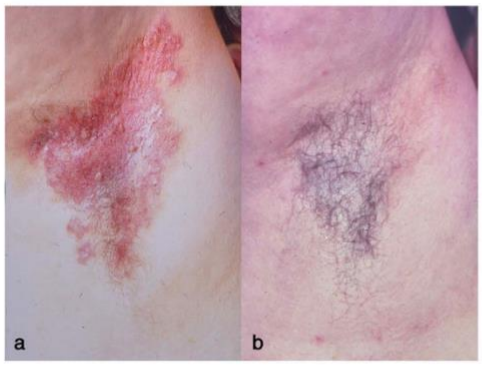

Figure 13 Involvement of the armpit in Hailey-Hailey disease (a). Result some months after successful dermabrasion (b).

dermis, long-term or even lifelong freedom from symptoms in the treated areas can be achieved (Figure 13). For larger areas such as the axillary and inguinal regions that can be stretched without folds either through tumescence local anesthesia or by tissue fixation by the surgical assistant, we consider dermabrasion to be superior to the other methods. Here, multiple punctate hemorrhages offer information on the required depth of ablation [107]. Sadly, high-speed dermabrasion is used less and less frequently since it is bloodier than laser treatments and requires operator experience with the procedure. Additionally, new devices are no longer manufactured. In the genital and perianal region, ablation is technically easier with CO_2 and Er:YAG lasers or argon plasma coagulation [109]. Long-term therapeutic success requires that the often severely acanthotic epidermis is completely removed. This can be confirmed after the procedure via histological examination of punch biopsies from the treated area. The ablation should exceed by about 1 cm the maximal extent of the dermatosis hitherto observed in this region. If the ablation has been performed at sufficient depth, re-epithelialization in regions with many skin appendages such as the axilla will take 7–14 days. This will originate from the keratinocytes of the hair follicles and sweat glands, which apparently lack the intrinsic defect in cell adhesion [84, 107]. The abraded areas will usually heal with minimum scarring or hypopigmentation without loss of function. Small marginal recurrences outside the treated areas cannot always be avoided, but on the other hand this proves the efficacy of the method. In ten patients, 38 out of 46 regions remained completely symptom-free for several years after dermabrasion [107]. Extensive excision of the affected skin with subsequent grafting of split-skin or full thickness skin, as occasionally recommended in the past, has become obsolete since the introduction of ablative therapies [110].

Dermabrasion, ablative laser therapies, and argon plasma coagulation are indicated for regional and especially intertriginous Hailey-Hailey lesions if conservative treatment options have failed.

Success has occasionally been achieved with topical photodynamic therapy, combined with medications such as acitretin [111, 112]. Individual cases of narrow-spectrum UVB light therapy with partial remission have been reported (82). It should, however, be noted that Hailey-Hailey disease may be triggered by UV radiation.

Novel therapies

After a serendipitous observation, Ibrahim et al. [66] in 2017 reported the successful use of low-dose naltrexone (LDN) (1.5–3.0 mg per day) in three patients

with Hailey-Hailey disease. Therapeutic success was subsequently confirmed by other authors in twelve additional patients, however with sometimes significantly higher oral doses of up to 12.5 mg per day [113–115]. Naltrexone is a long-acting opioid receptor antagonist which is used as an antidote for drug intoxication at a dose of 50 mg orally. The precise mechanism of action in Hailey-Hailey disease is currently unknown, though a beneficial effect on intracellular calcium homeostasis is suspected. Due to the low dose, LDN only binds to the keratinocyte μ1 receptor for 4–6 hours, resulting in a paradoxical increase of β endorphins and μ receptors [116]. LDN has additional anti-inflammatory and analgesic effects which have also led to experimental treatments of patients with chronic pruritus, lichen planopilaris, and systemic sclerosis [117].

Low-dosed naltrexone has been used successfully in some cases of Hailey-Hailey disease.

Kieffer et al. treated four patients with severe, treatment-refractory Hailey-Hailey disease with the phosphodiesterase inhibitor apremilast at a dose of 2 × 30 mg per day as used for psoriasis [118]. Moderate to marked improvement was noted in all patients after six months, although two patients had recurrences soon thereafter despite ongoing treatment.

Other individual case reports have been published, using high doses of vitamin D3 (8000 IU per day) [119] as well as the anticholinergics glycopyrrolate [120] and oxybutynin [121] for successful reduction of sweating.

Conclusion and outlook

Treatment of the genodermatoses Darier disease und Hailey-Hailey disease is still less than satisfying and requires patience. Basic recommendations include avoiding known triggers, consistent skin care and antiseptic treatments, and topical anti-inflammatories as necessary. Apart from the beneficial effects of retinoids in Darier disease and ablative therapies in Hailey-Hailey disease, systemic treatment is frequently a matter of trial and error until an effective option at a suitable dose is found.

Not only the efficacy of available treatment options, but also patients' views of their disease and the specific impairment of their quality of life are largely unknown. We also assume that there are many undetected milder cases. This is why the German national registry *MDHHgermany* was initiated in 2019 at the Department of Dermatology and Allergology am Biederstein at the Technical University of Munich, supported by the Eva Luise und Horst Köhler Foundation for Rare Diseases (https://www.derma-allergie.med.tum.de/fuer-patienten/darier-und-hailey-hailey.html). The aim of this registry is to collect clinical data on patients with Darier disease and Hailey-Hailey disease, as well as recruitment of a cohort for future clinical studies so patient management can be improved. Patients and doctors can contact the primary author of this publication for further information [122].

Thus far, 80 patients have been included in the registry. Evaluation of preliminary data shows that the quality of life in affected individuals is significantly impaired and that there is an immense and largely unmet need for effective treatment options. Less than 10 % of the currently included patients were satisfied with the success of their treatment.

The German national clinical registry MDHHgermany includes patients with confirmed Darier disease and Hailey-Hailey disease.

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