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CASE REPORT

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Dermatology* (*WJD*, *World J Dermatol*) is to provide scholars and readers from various fields of dermatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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CASE REPORT

Generalized prurigo nodularis with dramatic response to dupilumab treatment: A case report

Cagdas Boyvadoglu, Huseyin Serhat Inaloz

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Abstract

BACKGROUND

Prurigo nodularis (PN) is a chronic condition characterized by a papulonodular pruriginous eruption of unknown aetiology. Currently, there are no medications for PN that the United States Food and Drug Administration has approved, which leads to very variable practices in the prescription of off-label treatments. Treatment of PN is based on clinical experience rather than controlled trials. We present our case of generalized PN, in which we had a dramatic response with dupilumab.

CASE SUMMARY

A 58-year-old female patient was admitted to our clinic with severe itchy, erythematous nodular lesions that were widespread all over her body, especially on the legs and back. It was learned that the patient's complaints started 4 years ago, and there was a significant increase in the lesions in the last period. Dermatological examination revealed diffuse firm erythematous excoriated nodular lesions all over the body. In the blood tests of the patient, serum Immunoglobulin E (IgE) was measured at 9330 IU/mL. The patient was diagnosed with generalized prurigo nodularis together with clinical and histopathological findings. Due to severe clinical findings and the presence of comorbidities, dupilumab treatment was planned for the patient. In the follow-up 4 mo later, it was observed that all nodular lesions healed with postinflammatory hypopigmentation. The IgE value decreased to 1500 IU/mL after 4 mo of dupilumab treatment.

CONCLUSION

Dupilumab treatment stands out as an effective and safe systemic treatment agent among existing systemic treatments.

Key Words: Dupilumab; Prurigo nodularis; Pruritus; Immunoglobulin E; Atopic dermatitis; Case report

Core Tip: Prurigo nodularis (PN) is a difficult disease to treat and causes frustration to both the patient and the treating doctor. Treatment of PN is based on clinical experience rather than controlled trials. PN is a disease that negatively affects the quality of life of patients due to severe itching. Patients often receive limited benefit from first-line treatments and require systemic therapy. Dupilumab treatment stands out as an effective and safe systemic treatment agent among existing systemic treatments. In this case, we show how effective and well tolerated treatment with dupilumab is in the treatment of recalcitrant PN.

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INTRODUCTION

Prurigo nodularis (PN) is a chronic condition characterized by a papulonodular pruriginous eruption of unknown aetiology. PN is a difficult disease to treat and causes frustration for both the physician and the patient. Previously, it was reported that there is an association between various systemic diseases and PN. The classic lesion in PN is a firm pruritic nodule that is hyperkeratotic, numbers from a few to hundreds, and ranges from several millimetres to 2 cm in diameter[1]. PN most frequently affects middle-aged adults and tends to be observed more often in women compared with men. PN is related to psychiatric, cardiovascular, renal, and endocrine disorders, besides malignancy and the human immunodeficiency virus (HIV). The burden of systemic comorbidities in PN frequently exceeds that of other inflammatory skin disorders (*i.e.*, psoriasis or atopic dermatitis)[2].

Immune and neural dysregulation are important in the pathogenesis of PN. Neuropeptides and immune cells are implicated in cutaneous inflammation. Interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides are only a few of the mediators that immune cells in the skin release to cause a significant inflammatory reaction and severe itching. That immune reaction is critical to the pathogenesis of PN. Additionally, eosinophils play an important role in the cutaneous inflammation and itching related to PN. Eosinophil infiltration is observed in the dermis of PN patients' lesional skin. It is believed that the pathophysiology of PN is a cutaneous reaction pattern brought on by recurrent cycles of chronic itching and scratching[3].

Therapy for PN is based on topical, intralesional, and systemic neuroimmune modulatory treatments to split a short-circuited itch-scratch cycle. A personalized therapy plan, centered on the comorbidities, patient's age, disease severity, and side effect profile of treatments, is needed[3].

Dupilumab is a human monoclonal antibody; it blocks interleukin-4 and interleukin-13. Dupilumab has shown efficacy in asthma patients with high eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)–mediated inflammation could benefit the therapy of Th2-associated diseases, including atopic dermatitis[4]. Guttman-Yassky *et al*[5] showed that dupilumab rapidly and effectively inhibited cellular and molecular cutaneous mediators of inflammation, reversed related epidermal abnormalities, and improved disease severity scores and symptoms in patients with AD. Dupilumab remarkably inhibited systemic type 2 inflammatory mediators, including the chemokines, periostin, and total and allergen-specific Immunoglobulin E (IgE).

Dupilumab treatment has been demonstrated to be an efficacious therapy for PN. Compared to atopic dermatitis, the treatment response to dupilumab therapy initiates later. Two months of treatment are needed until the pruritus is relieved. Complete remission is uncommonly observed before 4 mo of treatment. Atopic dermatitis-related PN patients need longer therapy than non-atopic dermatitis-related PN patients[6].

Our patient had persistent and severe generalized PN. In our patient, for whom we started dupilumab treatment, a complete response was obtained in a short time. We present this case to emphasize that dupilumab therapy should be an important treatment agent that should be considered in the treatment of severe generalized PN.

CASE PRESENTATION

Chief complaints

A 58-year-old female patient was admitted to our clinic with severe itchy, erythematous nodular lesions

that were widespread all over her body, especially on her legs and back.

History of present illness

It was learned that the patient's complaints started 4 years ago, and there was a significant increase in the lesions in the last period. She had previously used systemic corticosteroid and oral antihistamine treatments for these itchy lesions, but there was no improvement. Then she was treated with omalizumab 300 mg every 4 wk for 19 mo, but did not benefit and there was a significant increase in nodular lesions, especially in the last period.

History of past illness

She had diabetes, hypertension, and coronary artery disease. She was using sitagliptin, metformin, insulin, telmisartan, acetylsalicylic acid, and trimetazidine for these diseases.

Personal and family history

The patient and her family had a known history of atopy.

Physical examination

Dermatological examination revealed diffuse firm erythematous excoriated nodular lesions all over the body, especially on the anterior surfaces of the tibia (Figure 1A) and back (Figure 1B).

Laboratory examinations

In the blood tests of the patient, serum IgE 9330 IU/mL (normal range: 0-100 IU/mL), white blood cell 14.8 × 10^3/μL (normal range: 3.39-8.86 × 10^3/μL), eosinophil 7.6% (1.13 × 10^3/μL (normal range: 0.03-0.27 × 10^3/μL)), lymphocyte 16.10% (2.38 × 10^3/μL), neutrophil 69.30% (10.25 × 10^3/μL (normal range: 1.5-5 × 10^3/μL)), hemoglobin 10.2 g/dL (normal range: 11.1-14.7 g/dL), hematocrit 32.4% (normal range: 36.9%-49.1%) , mean corpuscular volume 74.5 fL (normal range: 87-102.2 fL), platelet 542 × 10^3/μL (normal range: 158-374 × 10^3/μL), iron 17 ug/dL (normal range: 70-180 ug/dL), total iron binding capacity 421 ug/dL, C-reactive protein 7 mg/L (normal range: 0-5 mg/L), erythrocyte sedimentation rate 67 mm/h (normal range: 1-30 mm/h), glucose 151 mg/dL (normal range: 74-106 mg/dL), vitamin B12 83 ng/L (normal range: 180-914 ng/L), anti-HIV (-), anti- hepatitis C virus (-), hepatitis B surface antigen (-) were measured.

Imaging examinations

Biopsy taken from the nodular lesion on the patient's back: "Focal keratotic, prominent granular layer, and large area of the epidermis with parakeratotic and psoriasiform hyperplasia containing fibrin and neutrophils was observed; increased vascularity in the upper dermis; infiltration consisting of perivascular condensed lymphocytes, plasmacytes, and eosinophil polymorphs." reported as. It was observed as “IgG, IgA, IgM, complement C3, and complement component 1q negative” in immunofluorescence microscopy.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was consulted to internal medicine with blood results. No malignancy was found in the further examinations.

FINAL DIAGNOSIS

The patient was diagnosed with generalized prurigo nodularis together with clinical and histopathological findings. The patient was evaluated as having atopic dermatitis related PN because of the pruritus, xerosis, atopy history, and high IgE values. The peak pruritus numerical rating scale was 9 before treatment.

TREATMENT

Oral iron replacement therapy was given to the patient by the internal medicine department, but clinical findings did not improve. Cyclosporine and other immunosuppressive treatment options could not be planned for the patient due to concomitant hypertension and other systemic diseases. Due to severe clinical findings and the presence of comorbidities, dupilumab treatment was planned for the patient. Dupilumab therapy was administered at the standard dose: An initial induction dose of 600 mg followed by 300 mg every 14 d.

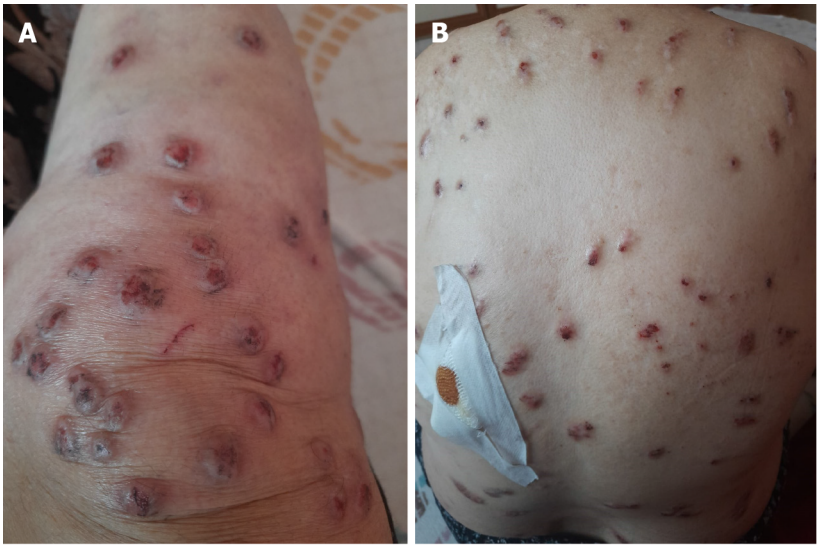

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Figure 1 Firm erythematous excoriated nodular lesions. A: Anterior surfaces of the tibia; B: Back.

OUTCOME AND FOLLOW-UP

In the follow-up 4 mo later, it was observed that all nodular lesions healed with postinflammatory hypopigmentation (Figure 2) in the patient whose itching complaint completely resolved in a short time. The IgE value decreased to 1500 IU/mL after 4 mo of dupilumab treatment. The peak pruritus numerical rating scale was 0 after 4 mo of dupilumab treatment.

DISCUSSION

The mechanisms underlying the development of PN are still not fully known. The pathogenesis of PN involves T cells and their cytokines, particularly IL-31. IL-31 is mainly produced by activated Th2 cells, cluster of differentiation 45R0 cutaneous lymphocyte antigen T cells, and mast cells. IL-31 has a significant role in the induction of chronic cutaneous inflammation. It has been shown to have an important role in the etiology of atopic dermatitis and has been accepted as a major dermal pruritogen [7,8]. In comparison to healthy skin, messenger RNA for IL-31 is found more frequently in PN lesional skin[3]. IL-31 and its receptor have become potential therapeutic targets for a range of pruritic diseases, including PN[9].

Lesional biopsies have shown that IL-4 and IL-13 have critical roles in the development of PN. Hence, there are similarities between PN and atopic dermatitis in terms of the involvement of Th2 activation and the signal transducers and activators of transcription pathway[10]. Therefore, it has been suggested that blocking IL-4/13 with dupilumab could help manage skin inflammation, which leads to itch[11].

Currently, there are no medications for PN that the United States Food and Drug Administration has approved, which leads to very variable practices in the prescription of off-label treatments. Treatment of PN is based on clinical experience rather than controlled trials. Studies are limited to case reports and case series. Thus, larger studies with a homogeneous design are required. However, corticosteroids, pimecrolimus, and calcipotriol can be used as topical treatments for PN. However, they have limited efficacy. Phototherapy is recommended as a second-line treatment agent. Phototherapy is an especially useful option for medically complex patients who have comorbidities and drug interactions with other medications. PN patients most commonly need treatment with systemic therapies because many patients are refractory to the therapies. Systemic neuromodulating drugs like gabapentin, pregabalin, aprepitant, naltrexone, butorphanol, duloxetine, paroxetine, fluvoxamine, and thalidomide, as well as systemic immunomodulating drugs like methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, and dupilumab, can be used[1,3].

A literature review revealed that all 11 patients with recalcitrant prurigo nodularis treated with dupilumab had a good or perfect response to treatment and tolerated treatment well. Dupilumab seems to be a safe but costly alternative for the therapy of refractory PN patients[12]. In our patient, a complete response to dupilumab treatment was obtained within 4 mo, which is consistent with the patients previously reported in the literature.

It has been shown that patients with atopic dermatitis-related PN respond more slowly to treatment than patients with non-atopic dermatitis-related PN[6]. Although our patient had atopic dermatitis-

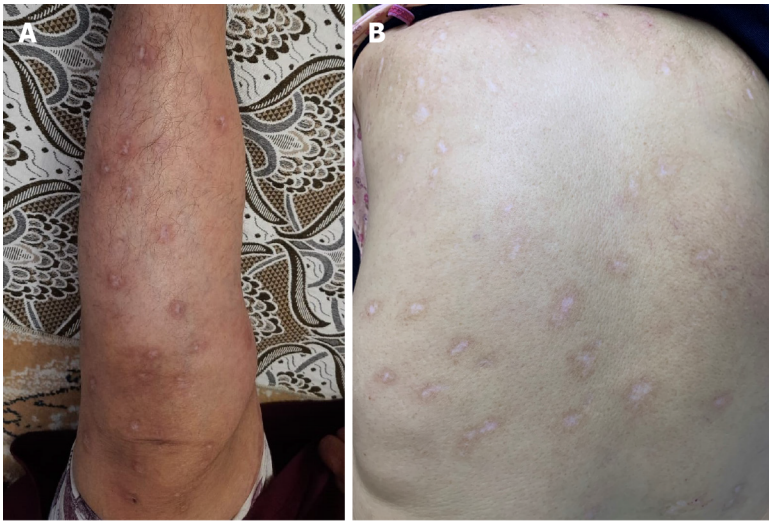

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Figure 2 Nodular lesions healed with postinflammatory hypopigmentation. A: Anterior surfaces of the tibia; B: Back.

related PN, she responded very well to the treatment in a short period of 4 mo, along with a significant decrease in very high IgE values. It was not possible to comment on whether the dramatic decrease in IgE values was due to dupilumab treatment or whether it was due to the discontinuation of omalizumab treatment.

As a result, complete remission was observed in our patient in a short time after dupilumab treatment. No side effects were observed in the follow-up of dupilumab treatment. No itching was observed in the patient's follow-up. Significant improvements in sleep and quality of life were observed. Based on our case, it can be predicted that dupilumab treatment is an effective and safe treatment for patients with refractory generalized PN.

CONCLUSION

PN is a disease that negatively affects the quality of life of patients due to severe itching. Patients often receive limited benefit from first-line treatments such as topical treatments and phototherapy and require systemic therapy. Dupilumab treatment stands out as an effective and safe systemic treatment agent among existing systemic treatments. There are few cases of PN treated with dupilumab in the literature, so more studies are needed to evaluate its efficacy. We present our case of generalized PN, in which we had a dramatic response with dupilumab.

FOOTNOTES

Author contributions: Boyvadoglu C and Inaloz HS contributed equally to this work; Boyvadoglu C and Inaloz HS designed the report; Boyvadoglu C wrote the manuscript; All authors have read and approve the final manuscript.

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SYSTEMATIC REVIEWS

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WJD mainly publishes articles reporting research results and findings obtained in the field of dermatology and covering a wide range of topics including acneiform eruptions, acute generalized exanthematous pustulosis, angiolymphoid hyperplasia with eosinophilia, breast diseases, cutaneous fistula, dermatitis, dermatomyositis, erythema, exanthema, facial dermatoses, foot diseases, hair diseases, hand dermatoses, keratoacanthoma, keratosis, leg dermatoses, lipomatosis, lupus erythematosus, mastocytosis, morgellons disease, nail diseases *etc.*

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SYSTEMATIC REVIEWS

Systematic review of hematidrosis: Time for clinicians to recognize this entity

Gilbert Sterling Octavius, Fellisa Meliani, Rivaldo Steven Heriyanto, Theo Audi Yanto

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Abstract

BACKGROUND

Hematidrosis is a sporadic disease, to a point where its existence is still denied up to date. It is also linked to stigmata, psychological roots, and religious beliefs, whih has strengthened clinicians' disbelief in hematidrosis.

AIM

To conduct a thorough review to classify the likelihood of hematidrosis cases.

METHODS

We searched PubMed, Science Direct, Medline, and Google Scholar, as well as four different preprint databases, including Medrxiv, Research Square, SSRN, and Biorxiv. We included studies from 1996 onwards, with no limitation on language. Hematidrosis was classified as "unlikely", "likely", and "highly likely".

RESULTS

There are 74 articles with 106 hematidrosis cases. India (n = 40) and China (n = 11) report the most cases. Patients are mostly female (76.5%) with a median age of 13 years. The head region is the most common bleeding site (n = 168/254). Headaches (26.9%) and abdominal pain (16.4%) are the most common prodromes. Beta-blockers (43%) and anxiolytic (23.2%) are the most commonly prescribed pharmacotherapy. Psychotherapy (37.5%) and counseling (32.5%) are the most utilized non-pharmacotherapy measures. Only 41.1% and 19.8% of all cases reach complete resolution and are highly likely to be hematidrosis, respectively.

CONCLUSION

Although hematidrosis is rare and the pathophysiology is still largely unknown, that does not mean hematidrosis does not exist. It is important to note that the most frequent trigger factors are either anxiety, fear, or excessive stress. Clinicians need to exclude other diagnoses and search for stressors to alleviate the bleeding.

Key Words: Hematidrosis; Bloody sweat; Stigmata; Blood

Core Tip: This is a systematic review on hematidrosis, an entity that is still mostly unknown, even to the experts. While this is not a guide to diagnose hematidrosis, this systematic review will help clinicians understand hematidrosis, the clinical pictures, the current available treatment, as well as the next steps in hematidrosis research.

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INTRODUCTION

The first case of hematidrosis dates back to the 3rd century B.C., where the first two treatizes by Aristotle contained sweat mixed with blood[1]. In the Bible, it is mentioned that these symptoms were written during Jesus Christ's sufferings in the garden of Gethsemane (Luke 22:44)[2,3]. Hematidrosis is an eccrine sweat disorder where sweat mixed with blood appear spontaneously without any visible trauma to the skin appendages. It is a diagnosis of exclusion[3]. Under International Classification of Disease 10 (ICD 10) in 2016, hematidrosis is given a diagnosis code of L74.8 under "other eccrine sweat disorders". However, this disease entity is still not widely accepted as a "true pathological disease" for various reasons[2,3].

Initially, the very existence of hematidrosis is questioned up to date. The mythical perception about hematidrosis creates a stigma where the bleeding is more related to pious beliefs than a genuine medical condition[4]. Another contributing factor is that a previous review on hematidrosis was done by Holoubek and Holoubek in 1996, encompassing 76 hematidrosis cases[5]. However, this review has been criticized for reporting the cases without laboratory confirmation[3,5]. Lastly, Favaloro & Lippi[6] mention some factors contributing to the plausible deniability of hematidrosis. Those explanations include the rarity of the disease, the possibility of Munchausen's syndrome (or Munchausen's by proxy), stress and its consequence on self-inflicted injuries, little scientific evidence that hematidrosis is an entity, and most reports are from older literature, in a foreign language, published in non-haematology journals, and there is a lack of publications in high-quality journals[6].

Several authors have attempted to conduct a literature review or systematic review on this topic[2,3,7]. However, the reviews do not present a comprehensive search, do not specify in which journals the articles were published, and more importantly, do not define what constitutes a hematidrosis. Therefore, we conduct a more thorough systematic review about hematidrosis, with a classification of the likelihood of hematidrosis cases in each journal. This review shall guide clinicians in identifying what hematidrosis is, how it presents, the necessary laboratory or radiology tests needed, as well as the treatments.

MATERIALS AND METHODS

Eligibility criteria

The Preferred Reporting Items for Systematic Review (PRISMA) 2020 guidance was used[8]. The protocol of this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database with a registration number CRD42021289372.

The subjects studied were all patients diagnosed with hematidrosis without any age limitations. The diagnosis of hematidrosis is determined by the respective authors, and we classified the diagnosis as "unlikely", "likely", or "highly likely". A patient was considered to have “highly likely” hematidrosis if: (1) The bleeding episode was witnessed directly by medical professionals, (2) attempts were made to exclude other possible diagnoses, (3) skin biopsies and bleeding analysis were done and found to be normal or inconclusive, and (4) bleeding photos were included in the article; while a patient was determined to have “unlikely” hematidrosis if: (1) The bleeding episode was not witnessed by medical professionals or from family members, (2) minimal or no tests were done to exclude hematidrosis (only routine blood work was done), (3) other disorders possibly explain the bleeding, and (4) no bleeding photos were provided. Lastly, a hematidrosis case was classified as “likely” if it did not satisfy all the highly likely or unlikely criteria.

This review's inclusion criteria are any original articles published after 1996 without any restrictions in language. We restricted the year for literature search to ensure that studies that had been reviewed by Holoubek & Holoubek were not included[5]. We also included grey literature such as conference abstracts, thesis, or dissertations. The exclusion criteria of this study are reviews, opinion-based articles (letter to the editors or commentary), bleeding caused by other disorders, pure hemolacria, and animal studies. Citations from review studies were combed to ensure literature saturation. In order to guarantee that all available studies were included, we conducted citation and hand searches manually and *via* Research Gate.

Search strategy and study selection

The literature search started on December 6, 2021 and ended on the same day. We searched four different academic databases, including PubMed, Science Direct, Medline, and Google Scholar, and four different preprint databases, including Medrxiv, Research Square, SSRN, and Biorxiv. The keywords used were "hematidrosis", "hematohidrosis", and "bloody sweat". The Medical Subject Heading (MeSH) terms for each database are listed in Table 1. All records were imported into the Rayyan software, where duplicates were detected automatically and screened manually[9]. This software also allowed authors to collaborate in selecting the relevant studies. Two independent authors conducted the initial search (GSO and RSH), importing all the findings into Rayyan software. Another author (FM) cross-checked the initial searches. These three authors independently screened all available studies. Conflicts were resolved by discussion with the expert (TAY). In the case of studies with overlapping publications (abstracts later published into a full paper), we chose studies that provided more data.

Data extraction and quality assessment

Data extraction was carried out independently by two authors (FM and RSH), then reviewed by another author (GSO) to ensure accuracy. We extracted relevant information such as study identification (author and year of publication), study characteristics (location and article type), and patients' characteristics (number of patients, age, sex, underlying conditions, characteristics of bleeding, laboratory and radiological examinations, therapies, and outcome).

The Joanna Briggs Institute (JBI) checklist for case reports and case series were used to assess their quality, respectively[10]. Three reviewers (GSO, FM, and RSH) independently assessed the scale, and any discrepancies were sorted with the expert (TAY) until a consensus was attained. If any missing data or further data were needed, corresponding authors were contacted *via* an inquiry email.

Data synthesis

To incorporate all of the data in this review, pooled descriptive tests were employed. The mean and standard deviation of data reported in median and range (or interquartile range) were calculated[11-13]. The means and standard deviations were then combined into a single value using the Cochrane method[14].

RESULTS

The initial search yielded 2955 articles, where 188 articles were immediately excluded as duplicates. After title and abstract screening, 2692 articles were excluded. Out of the 75 articles assessed for eligibility, three articles did not have full texts[15-17], three articles were review articles[18], one article mentioned other causes of the bleeding[19], and four articles were purely hemolacria[20-22]. These articles were then excluded, resulting in 68 articles[7,23-28]. We found another six articles through hand-searching and citation searching[29-34]. In total, there are 74 articles included in this review, with a total of 106 patients (Figure 1 and Table 1).

Most of the cases are heavily concentrated in Asia, particularly India (n = 40/106) and China (n = 11/106). Australia only reports one case of hematidrosis, the least among other continents (Figure 2). Patients presented with the disease as early as an hour or as late as seven years before consulting to doctors. Anxiety, stress, and fear are the most common trigger for bleeding, while psychiatric disorders are the most common comorbidities in most patients. Notably, 36 cases (34%) do not have any obvious bleeding triggers. Besides bleeding from the skin, patients may also present with hematuria, gastrointestinal (GI) bleed (hematemesis, melena, hematochezia or rectal bleed), or epistaxis. Patients may bleed as frequently as more than 35 times a day or as rare as two times in two years. Most bleeding episodes subside in a few seconds to a few minutes, although in one case, the bleeding stops after 30 min (Table 2).

The majority of the patients are females (76.5%), with a median age of 13 (0.17-72) years old (Table 3). When patients experience prodrome(s) before the bleed, they mostly report headache (26.9%) or abdominal pain (16.4%). Most articles were published in 2019 (n = 15/74), followed by 2021 (n = 10/74) (Figure 3). When analyzed by the category of the journals, most hematidrosis cases are published in dermatology journals (25.7%), followed by internal medicine journals (23.0%) and pediatric journals (20.3%).

Table 1 Medical subject heading terms used in each database

Database	Medical subject heading	Number of studies found
PubMed	"hematidrosis"[All Fields] OR ("haematohidrosis"[All Fields] OR "hematohidrosis"[All Fields]) OR ("bloody"[All Fields] AND ("tearings"[All Fields] OR "tears"[MeSH Terms] OR "tears"[All Fields] OR "tearing"[All Fields] OR "lacrimal apparatus diseases"[MeSH Terms] OR ("lacrimal"[All Fields] AND "apparatus"[All Fields] AND "diseases"[All Fields]) OR "lacrimal apparatus diseases"[All Fields] OR "lacerations"[MeSH Terms] OR "lacerations"[All Fields])) OR ("bloody"[All Fields] AND ("sweat"[MeSH Terms] OR "sweat"[All Fields] OR "sweating"[MeSH Terms] OR "sweating"[All Fields] OR "sweats"[All Fields] OR "sweatings"[All Fields])) OR "hemolacria"[All Fields]	203
Medline	((hemathidrosis) OR haematohidrosis) OR bloody sweat	1057
Google Scholar	allintitle: hematidrosis OR haematohidrosis OR bloody sweat	55
Science Direct	(Hematidrosis) OR (haematohidrosis) OR (bloody sweat)	200
MedRxiv	(Hematidrosis) OR (haematohidrosis) OR (bloody sweat)	367
BioRxiv	(Hematidrosis) OR (haematohidrosis) OR (bloody sweat)	839
SSRN	(Hematidrosis) OR (haematohidrosis) OR (bloody sweat)	0
Research Square	(Hematidrosis) OR (haematohidrosis) OR (bloody sweat)	134

Out of all the body regions, the head region is the most commonly affected (n = 168/254), especially around the ears or earlobes (n = 46), forehead (n = 24), and nose (n = 23). The next most common site is in the upper limbs (n = 31/254), with the arms being the most common site of bleeding in this region (n = 14). Although most cases do not state the laterality of bleeding (n = 81), more cases are bilateral (n = 15), as compared to being unilateral bleeding (n = 10) (Figure 4).

The bleeding episodes are mostly witnessed by healthcare professionals (65.1%). In the case of family members witnessing the bleeding episode, 50 cases (47.2%) are witnessed directly, and another 50 cases (47.2%) are not explicitly mentioned. The majority of the cases provide bleeding pictures (80.2%). Laboratory tests and radiologic or other tests are done in 94.3% and 38.7% cases, respectively, resulting in a normal result in 86.8% of the cases. An analysis of the bleed is done in 67.0% of cases, generally resulting in the discovery of peripheral blood components. There are many doctors from different specialities involved in the care of hematidrosis patients, with paediatricians (20.5%), psychiatrists (19.3%), dermatologists, and otolaryngologists (both at 16.6%) being the most common specialities consulted.

Skin biopsies, the "best reference standard", is only done in 28.3% of cases, with 63.3% of them being normal or non-specific. Among skin biopsies that have been done, abnormal findings include dilation of blood vessels with extravasation of blood[35-39], possible mild squamous hyperplasia and mild dermal fibrosis[40], papillary dermal edema[41,42] with dermal melanophages[41], bloody exudate from areas that do not contain sweat glands[43,44], a low number of gross cystic disease fluid protein 15-positive eccrine sweat glands[45], loosening areas caused by the separation of collagen fibres[43], and acanthosis of the epidermis with broadening of rete pegs along with hypergranulosis and marked hyperkeratosis [42].

The most common pharmacologic therapy used is beta-blockers (43.0%), with anxiolytic the second (23.2%). Among the non-pharmacologic modality, psychotherapy (37.5%) and counseling (32.5%) are the most common therapies prescribed. Most patients experienced complete resolution (41.1%) in 60 d (2-730 d), as well as an improvement of bleeding symptoms (41.1%) in 28 d (10-720 d).

Among all the 106 cases, the majority of cases belong to the "likely" group with 58 cases (54.7%), followed by "unlikely" with 27 cases (25.5%). Only 21 cases (19.8%) are considered "highly likely" to be hematidrosis.

DISCUSSION

This systematic review contains 74 articles with 106 hematidrosis cases. We included more articles and cases compared to the other reviews and adjusting to their search timeline[2,3,7]. Hand-searching, citation searching, and including grey literature in our reviews certainly add more cases to our study. Although there has been some scepticism in including grey literature into a review, a proper systematic review shall be thorough during article searching, including finding grey literature[46]. Including the 76 cases from Holoubek and Holoubek's review[5] and our cases, there are currently 182 hematidrosis cases in the world.

Table 2 Characteristics of hematidrosis patients

Ref.	Patient No.	Time from onset to consultation	Triggers of bleeding	Other kinds of bleeding	Comorbidities	Bleeding frequency	Bleeding duration	Other Bleeding characteristics
Octavius *et al* [70], 2021	#1	One month	Not mentioned	Not mentioned	Not mentioned	Three times per day	Stopped immediately	Not mentioned
	#2	One month	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Bhattacharya *et al*[42], 2013	#1	One month	Not mentioned	Not mentioned	Not mentioned	> 10 times per day	Not mentioned	Not mentioned
Manonukul *et al* [43], 2008	#1	1.5 yr ago	Not mentioned	Not mentioned	Not mentioned	Recurrent episodes	Not mentioned	Not mentioned
Murota *et al*[45], 2020	#1	A few months	Excess pressure exerted while playing on the metal bar	Not mentioned	Not mentioned	Not mentioned	Not mentioned	It did not occur during sleeping
Das *et al*[89], 2020	#1	Two weeks	Head trauma	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	#2	One hour	Anxiety symptoms		Anxiety			
Matsuoka *et al* [36], 2020	#1	Two years	Not mentioned	Not mentioned	Dissociative disorder and self-harming	Few times per week	Not mentioned	Bloody sweat-like fluid secretion
Chabchoub *et al* [49], 2013	#1	6 mau	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Shafique *et al* [38], 2021	#1	3 mo	Not mentioned	Rectal bleed	Significant psychosocial stress due to parental separation	3-35 times per day	Not mentioned	Occurred during sleep and wakefulness
Carvalho *et al* [35], 2008	#1	November 2004	Physical exertion, increase in room temperature	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Ceased spontaneously
Rossio *et al*[32], 2014	#1	Not mentioned	His family was experiencing an extremely stressful time, and his mother had just passed away	Not mentioned	Not mentioned	Not mentioned	1-2 min	No predetermined time for recurrence
Gayal *et al*[90], 2020	#1	Six months	Hearing voices and anxiety	Not mentioned	Schizophrenia	1-2 or 10-15 times per day	Not mentioned	Depending on the intensity of psychotic symptoms
Dragan *et al*[91], 2017	#1	Not mentioned	Not mentioned	Epistaxis, hemoptysis	Tonsillectomy, benign hypertension	Not mentioned	Not mentioned	Not mentioned
Alsermani *et al* [23], 2018	#1	Five months	Bullying in schools	Not mentioned	Celiac disease	Twice weekly	1-2 min	Self-limited, usually in the evening
Jayaraman *et al* [92], 2017	#1	Seven days	Scolding from parents due to academic performance	Not mentioned	Mixed anxiety & depressive disorders, nocturnal enuresis	1-2 a day	3-5 min	Appears when punished or stressed
Jibbawi *et al*[33], 2021	#1	Not mentioned	Emotional stress	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Appears during stress and self-limited

Arakkal *et al* [24], 2016	#1	5 mau	Extreme physical exertion	Not mentioned	Not mentioned	Not mentioned	2-3 min	Bleeding when waking up, extreme physical activities, self-limited
Corrà *et al*[93], 2020	#1	Five years	Stress, anxious situation, exercise	Not mentioned	The peripheral visual deficit, non-hemorrhagic chronic gastritis, severe intestinal subocclusion	Five times daily	Few minutes	Self-limited
Mishra[72], 2009	#1	Not mentioned	Minor trauma	Hematuria, gastrointestinal bleed, epistaxis	Platelet function (PF3) dysfunction	Not mentioned	Not mentioned	Not mentioned
Mutanabbi *et al* [29], 2021	#1	4 mau	Stress	Hematemesis, hematuria, epistaxis	Not mentioned	1-2 a week	3-5 min	Ceased spontaneously, precipitated by upcoming stress & family issues
Soliman *et al* [61], 2019	#1	Six months	Not mentioned	Not mentioned	Hypotension, tachycardia, syncope	Not mentioned	30 seconds	Never at sleep and self-remitting
Tshifularo[94], 2013	#1	Not mentioned	Severe mental stresses at work, study, and home	Not mentioned	Not mentioned	2-3 a week every 3-4 mo	15-20 min	2-5 ml blood-stained non-clotting discharge
	#2	Two years	Severe stress			Four times in 2 years (2009-2010)	Not mentioned	Blood-stained sweaty discharge, not clotting and watery
	#3	Not mentioned	Stress			Two times in 2 years (2010-2011)	Not mentioned	Painless blood-stained sweat-like discharge
	#4	Not mentioned	Severe stress at school and home			1st episode at July 2013	Not mentioned	Not mentioned
Meyer *et al*[95], 2019	#1	Two days	Stumbled and fell on an iron toy train (trauma)	Not mentioned	Not mentioned	Almost daily	N/A	Self-limiting, episodic. Bleeding occurred from apparently healthy and undamaged skin; no superficial injuries
Techasatian *et al* [81], 2016	#1	April 2014	Not mentioned	Not mentioned	Not mentioned	> 10 times	10-30 seconds	The time of the bleeding episode was unpredictable, not related to exertion or triggers
Yeşilova *et al* [96], 2016	#1	2 d	Move from cold to a warm environment, fallen out of bed (trauma) one day before	Not mentioned	Not mentioned	20 times in 2 d	Not mentioned	Not mentioned
Quentric *et al* [97], 2019	#1	Not mentioned	General anxiety related to school	Epistaxis, nipple bleed	Not mentioned	3-4 times a day	Not mentioned	Spontaneously, mostly at night
Mora *et al*[98], 2013	#1	6 mo	Stress	Not mentioned	Not mentioned	Several times a day	Not mentioned	Spontaneous, self-limited, >30 episodes during hospitalization
Praveen *et al* [99], 2012	#1	3 mo	Stress (She had witnessed her elder sister being kidnapped nine months ago)	Epistaxis	Not mentioned	2-3 times every week and had two episodes on the same day on four occasions	Not mentioned	Not mentioned
Hansson *et al*[7], 2019	#1	Four weeks	Not mentioned	Not mentioned	Not mentioned	20 episodes in 4 weeks	Not mentioned	Not mentioned

Wang *et al*[44], 2014	#1	One month	Not mentioned	Not mentioned	Not mentioned	2-3 times a day	Not mentioned	The bleed is described as a fresh, small amount of blood
Jerajani *et al*[41], 2009	#1	Two months	Continuous mental stress	Not mentioned	Depressive disorder	Not mentioned	Not mentioned	Not mentioned
Lipsitt *et al*[100], 2018	#1	9 mo	Extreme emotional stress, excitement, or physical exertion	Not mentioned	Depression, anxiety, PTSD, non-epileptiform seizure	Seven times a day	Not mentioned	Progressive, episodic
Bhagwat *et al* [101], 2009	#1	Two years	Trauma (witnessing a woman beheaded), Feeling anxious	None	Severe depression	1-2 a day	15-20 min	Episodic
Sue Tin *et al*[40], 2015	#1	Three weeks	No obvious trigger	Not mentioned	Not mentioned	20 times a day	Not mentioned	Spontaneous, worse during warmer months
Pari[102], 2018	#1	Five days	Without any provoking factor	Not mentioned	Not mentioned	2-3 a day	30 min	Not mentioned
Patel *et al*[79], 2010	#1	Sincmaury 2007	Not mentioned	Not mentioned	Not mentioned	Once-daily	1 minute	Spontaenous, during school hours 9-11 am
Biswas *et al*[76], 2013	#1	Two years	Not mentioned	Not mentioned	An intelligent quotient (IQ) of 60-70 with a loss of insight	1-2x daily	10-15 min	Episodic, more frequent when waking up in the morning
Jafar *et al*[69], 2016	#1	Two weeks	Not mentioned	Epistaxis	Repeated faint attacks two years ago	Not mentioned	10-20 min	It was spontaneous, unpredictable, and intermittent, with no specific patterns, and it stopped spontaneously.
Wang *et al*[103], 2010	#1	3 yr	Emotional excitement	Not mentioned	Not mentioned	> 20 times during hospit-alization	Not mentioned	It always occurred during the middle of the day, never when sleeping at night
Thigarajan[83], 2019	#1	Three days	Stress fr'm father's demand on academics	Not mentioned	Primary enuresis, head tonsure, and trivial head trauma in a different location to the bleed	Not mentioned	Few seconds to a few minutes	Self-limited
Khalid *et al*[82], 2013	#1	Five years	Emotional stress	None	None	Not mentioned	Not mentioned	Not mentioned
Maglie *et al* [104], 2017	#1	Three years	Not mentioned	Not mentioned	Major depressive disorder and panic disorder	Not mentioned	1-5 min	Could occur in sleep or during physical activity & more intense bleeding occurs during emotional stress
Uber *et al*[71], 2015	#1	6 yr	Not mentioned	Not mentioned	Conversion, dissociative, and generalized anxiety disorder, high peak blood pressure	Not mentioned	Few minutes	Spontaneous, sometimes occur during sleep, coincidental with high blood pressure peak
Salas-Alanis *et al* [37], 2021	#1	Not mentioned	Acute emotional distress	Not mentioned	Not mentioned	Numerous	3-25 min	From 6 years old, all following emotional distress
Talwar *et al*[80], 2021	#1	One year	Separation from his aunt	Epistaxis, hematuria, hematochezia	Adjustment disorder	Once per week	A few minutes	It can occur during sleep
Chowdhury *et al* [105], 2019	#1	Two years	Migraine	Epistaxis, previous cesarean scar,	Migraine	Not mentioned	Not mentioned	Associated with headache, her son also had hematidrosis

				menorrhagia				
Das *et al*[89], 2016	#1	5 mo	Not mentioned	None	Otitis externa	Not mentioned	Not mentioned	More frequent on 06:00 A.M.
Hossain *et al*[77], 2018	#1	One and a half years	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	#2	Last two months	Not mentioned	Not mentioned	Repeated episodes of stiffening of limbs with associated self-muttering	Not mentioned	Not mentioned	Not mentioned
	#3	Six months	Not mentioned	Not mentioned	Acute anxiety state, repeated episodes of unresponsiveness and conduct disorder	Not mentioned	Not mentioned	Not mentioned
Thao *et al*[39], 2019	#1	One month	Marriage	Not mentioned	Continuous mental stress	Not mentioned	Not mentioned	Not mentioned
Récher[31], 2021	#1	Not mentioned	COVID-19 containment induced stress	Not mentioned	Not mentioned	Not mentioned	Not mentioned	A vascular pathway remains after 24 hours of bleeding
Omar[30], 2018	#1	Not mentioned	Stress	Not mentioned	Not mentioned	Occured in bouts	Not mentioned	Not mentioned
Tirthani *et al*[86], 2021	#1	Three months	Loss of parents	Not mentioned	Recurrent panic attacks with tachycardia	Not mentioned	2-3 min	Not mentioned
Ricci *et al*[106], 2018	#1	Three months	Major stressful event from an earthquake	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Bezner *et al*[25], 2013	#1	Two years	Not mentioned	Hematuria	Heavy and irregular menstrual bleed	Up to 20 daily	Not mentioned	The bleeding episodesreportedly decreased during her menstrual period, which typically lasted for approximately ten days
Mahamat Abderraman *et al*[50], 2019	#1	Five years ago	Not mentioned	History of hematuria, epistaxis,	Moderate anxiety-depressive disorder, acute urine retention, seizure, genu flexum	Not mentioned	10 min	Not mentioned
Rharrabti *et al*[51], 2016	#1	Not mentioned	Family abuse, parental conflicts	Vulvar bleeding	Conversion disorder. primary enuresis	Not mentioned	Not mentioned	Mostly at day, worsening during parental conflicts
Morillo *et al*[52], 2019	#1	Seven months	Not mentioned	Not mentioned	Bronchial asthma, previous history of abortion	Not mentioned	Not mentioned	Not mentioned
Kumar *et al*[78], 2021	#1	Not mentioned	Afraid, stress (during exams), anxiety	Not mentioned	High-grade anxiety	Not mentioned	Not mentioned	Spontaneous and recurrent (4-5 times in three days)
Camargo *et al*[53], 2020	#1	Four years	Stress and anxiety	Hematuria	Not mentioned	2-3 times a week	Not mentioned	Sporadic occurrence
Shen *et al*[107], 2015	#1	Six months	Not mentioned	Not mentioned	Tonic seizures	1x every few days	1-2 min	Spontaneous, transient, self-limited
Shahriari *et al*[108], 2020	#1	Six months	Going to the toilet or feeling lonely	Not mentioned	Not mentioned	Every two weeks	Not mentioned	Not mentioned

	#2	Not mentioned	Not mentioned	Epistaxis	Not mentioned	Every three weeks	Not mentioned	Not mentioned
	#3	Not mentioned	Fighting with her younger sister without any skin damage	Not mentioned	A history of aggression	Not mentioned	Not mentioned	Not mentioned
Badry *et al*[27], 2020	#1	One month	Stress	Hematemesis	Depression	3-5 per week	A few minutes	Not mentioned
Hoover *et al*[54], 2019	#1	Almost more than seven years	Illness (malaria) or distress	Hematemesis, hematochezia, hematuria	Previous history of treated malaria, human immunodeficiency virus(HIV) and hepatitis B due to blood transfusions	Not mentioned	Not mentioned	Not mentioned
	#2	Not mentioned	Irritability and crying	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Latorre Martinez *et al*[109], 2012	#1	One year	Stress	Not mentioned	Not mentioned	Not mentioned	A few minutes	Not mentioned
Kleymenova *et al* [47], 2020[1]	#1	Not mentioned	Weather, stress	Epistaxis	Menstruation problems	Not mentioned	Not mentioned	Not mentioned
Rani *et al*[84], 2018	#1	Not mentioned	Autonomic dysfunction	Hematuria	Autonomic dysfunction	Not mentioned	Not mentioned	Not mentioned
	#2		Autonomic dysfunction	Not mentioned	Spontaneous skin breaches resembling incision			
	#3		Emotional & Psychological stressors	Not mentioned	Not mentioned			
	#4		Emotional & Psychological stressors	Not mentioned	Not mentioned			
	#5		Emotional & Psychological stressors	Not mentioned	Not mentioned			
	#6		Emotional & Psychological stressors	Not mentioned	Not mentioned			
Wang *et al*[110], 2021	#1	One year	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	#2	Four months	Not mentioned	Hematemesis	Not mentioned	Once every few days to dozens of times a day	Several minutes	Not mentioned
	#3	Five months	Carsickness	Hematuria	Canker sores	Up to 60 times a day	Several minutes	Not mentioned
	#4	Nine months	Anxiety or nervousness, hemolacria induced by intense light	Hematemesis, hematuria	Tonic-clonic seizures	Once every few days to dozens of times a day	Several minutes	Not mentioned
	#5	Two months	Not mentioned	Not mentioned	Not mentioned	Once every few days to dozens of times a day	Several minutes	Not mentioned
	#6	Four years	Military training, minor	Not mentioned	Not mentioned	Once every few days to	Several	Not mentioned

			emotional stress, or even during studying			dozens of times a day	minutes	
	#7	Six months	Not mentioned	Not mentioned	Not mentioned	Once every few days to dozens of times a day	Several minutes	Not mentioned
Malik *et al*[34], 2019	#1	6-8 yr	Emotional stress	History of hemolacria	Gestational hypertension (after lost to follow up)	Not mentioned	Not mentioned	Bleeding started 6-8 years ago
	#2	Not mentioned	Periods of rage and stress	Epistaxis	Not mentioned	Not mentioned	Not mentioned	Unprovoked, self-limited, and not triggered
Shahgholi[75], 2018	#1	Several months	Extreme physical or emotional stress	Hematemesis	Not mentioned	Once or twice a day	10-15 min	Sometimes occurred spontaneously during sleep, subsided as soon as it is wiped
	#2	Not mentioned	Upcoming exam, playing a computer game, watching fiction TV movies or when parents not satisfying his demands	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	#3	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	5 min	Spontaneous, unpredictable, and intermittent
Jagannathan *et al* [111], 2016	#1	Not mentioned	Mental stress	Epistaxis	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	#2			Not mentioned				
	#3			Not mentioned				
	#4			Not mentioned				
	#5			Not mentioned				
	#6			Not mentioned				
	#7			Not mentioned				
	#8			Hematemesis				
Agarwal *et al* [28], 2017	#1	One month	Not mentioned	Not mentioned	Not mentioned	Not mentioned	10 seconds	Self-limited, during the day
Deshpande *et al* [112], 2014	#1	Since February 2013 (around more than one year ago)	Upcoming exams, fight with parents, and parents not satisfying his demands	Hemoptysis, hematuria, epistaxis, hematochezia, hematemesis	Oppositional defiant disorder	Not mentioned	Not mentioned	Not mentioned
Zhang *et al*[16], 2004	#1	Four months	Not mentioned	Hematemesis	A previous diagnosis of Henoch-schonlein purpura	Several times a day or once every 3-5 d	Lasts seconds	The bleeding can occur during sleep
Kumar *et al*[78], 2019	#1	One year ago	Suspected fear and anxiety of his lecturer	Not mentioned	Not mentioned	Three episodes per day to 20 episodes per month	Not mentioned	Not mentioned
	#2	Three months ago	Fearful dreams	Not mentioned	Not mentioned	> 5 episodes per day	Not mentioned	Episodes are not coinciding with dreams

								but occur after the event at night without any triggering factor in the day times as observed by parents at home and the hospital
Karpukhina *et al* [48], 2020	#1	One month ago	Not mentioned	Epistaxis	High anxiety, neurotic behaviour, and depression	Not mentioned	A few minutes	Not mentioned

[1]There are two cases presented in this literature. However, the second case is purely a hemolacria, so we excluded it.

Favaloro & Lippi's[6] arguments that most cases are outdated and presented in a foreign language are not valid anymore. Although some articles are written in Chinese[16,44] Russian[47,48], French[49-51], Spanish[52], and Portuguese[53], the majority of the articles are written in English language. Since the publications are mostly less than ten years old, we argue that the cases presented here are quite recent. Almost half of the articles were published in the years of 2019-2021. There is one study where the article was published in 2019, but on the website, the article is presented as if it was published in 2021. Therefore, we classify the study as published in 2019[54]. However, we believe that there is still a significant number of cases not published in a "high-quality journal" and thus may affect clinicians' perspectives on the eligibility of these cases[55]. Reflecting on the types of journal specialities, most cases are published in dermatology, pediatric, or internal medicine journals. Only 12.2% of the cases are published in a hematology journal. This point supports Favalaro & Lippi's argument about lacking publication in a high-profile hematology journal[6].

Most of the cases originate from China and India, the top two most populous countries globally. Although it seems convenient to link the connection between the majority of the cases belonging to the top two countries with the most population, the United States of America (USA) only reports three cases. Therefore, genetic, socio-cultural, race or environmental factors might play a role[56]. Lastly, publication bias may play a role in determining which cases get published[57]. Due to the rarity of the cases, many clinicians, even the most senior ones, may not encounter a hematidrosis case. Therefore, there is a lack of quality peer-reviewers who understand this case. This problem is confounded because many clinicians still doubt this disease entity[6].

The median age of patients with hematidrosis is 13 years, which is consistent with previous review findings of 9-15 years[3]. In this systematic review, 76.5% of the patients are females, while the most common trigger for hematidrosis is anxiety, fear, or mental illness. The connection between mental illnesses being more common in females[58-60] has been established and might explain the higher prevalence among these populations. In this study, the bleeding characteristics vary significantly. Some patients experienced bleeding episodes during sleep[38], while others never experienced bleeding during sleeping[45,61]. In some cases, patients usually bleed during the day or evening[23,28]. These patterns may reflect the physiological state of sympathetic nervous systems and hormonal fluctuations and their impacts on blood vessels and the pathophysiology of hematidrosis[62-64].

The head is the most common bleeding site, while headaches are the most common prodrome symptom. Spontaneous extracranial hemorrhagic phenomena may be caused by trigemino-autonomic reflex and sterile neurogenic inflammation[65]. Neural activation may also explain the prodromes of dizziness, nausea and vomiting, tingling, pain, photophobia, and phonophobia. Epistaxis is a frequent

Table 3 Demographics of patients with hematidrosis

Variables	N (%)
Sex (n = 102)	
Male	24 (23.5)
Female	78 (76.5)
Age in years (n = 94) (Median - range)	13 (0.17-72)
Prodromes[1]	
Headache	18 (26.9)
Dizziness	3 (4.5)
Abdominal pain	11 (16.4)
Nausea	4 (6.0)
Vomiting	4 (6.0)
Tingling	5 (7.5)
Photophobia	2 (3.0)
Phonophobia	2 (3.0)
Pain	3 (4.5)
Soreness	4 (6.0)
Asthenia	3 (4.5)
Easily irritable	2 (3.0)
Others	6 (8.7)
Presence of hemolacria	34 (32.1)
Types of journals	
Case report	4 (5.4)
Dermatology	19 (25.7)
Otorhinolaryngology	4 (5.4)
General or internal medicine	17 (23.0)
Hematology and oncology	9 (12.2)
Pediatric (including pediatric hematology and oncology)	15 (20.3)
Pharmacy	1 (1.3)
Preprint (Research Square)	1 (1.3)
Psychiatry	3 (4.1)
Reproductive health	1 (1.3)
Healthcare professionals witness the bleeding episodes	
Yes	69 (65.1)
No	25 (23.6)
Not explicitly mentioned	12 (11.3)
Family members witness the bleeding episodes	
Yes	50 (47.2)
No	6 (5.6)
Not explicitly mentioned	50 (47.2)
Provided bleeding pictures	85 (80.2)
Laboratory tests done	100 (94.3)
Radiologic and/or other tests done	41 (38.7)

Normal results from all the diagnostic tests done	92 (86.8)
Skin biopsies done	30 (28.3)
Normal or non-specific	19 (63.3)
Analyzed the blood from the bleeding site	71 (67.0)
Doctors involved in the case[1]	
Otolaryngologist	25 (16.6)
Ophthalmologist	6 (4)
Obstetrics and gynaecologist	3 (2)
Psychiatrist	29 (19.3)
Primary care	4 (2.7)
Pediatrics	31 (20.5)
Internal medicine	19 (12.8)
Dermatologist	25 (16.6)
Vascular surgeon	1 (0.7)
Neurologist	7 (4.8)
Tried to exclude other diagnoses	90 (84.9)
Pharmacotherapy[2]	
Beta-blockers	65 (43.0)
Anxiolytic	35 (23.2)
Antidepressants	10 (6.6)
Atropine patches	2 (1.3)
Drops of adrenaline with gauze	1 (0.7)
Ascorbic acids	6 (4.0)
Antifibrinolytic agents	2 (1.3)
Antihistamine receptor blockers	6 (4.0)
Hemostatics	2 (1.3)
Others	22 (14.6)
Psychosocial therapy[2]	
Psychotherapy	15 (37.5)
Behavioural therapy	6 (15)
Relaxation technique	6 (15)
Counseling	13 (32.5)
Outcome (n = 90)	
Complete resolution	37 (41.1)
Time taken for complete resolution in days (median) (n = 26)	60 (2-730)
Improvement of symptoms	37 (41.1)
Time taken for improvement of symptoms in days (median) (n = 19)	28 (10-720)
Relapse	8 (8.9)
Time taken for relapse in days (mean) (n = 6)	60 (53.4)
Spontaneous resolution	4 (4.4)
The patient is still under follow up	1 (1.1)
Loss to follow up	3 (3.3)
Possibilities of hematidrosis	

Highly likely	21 (19.8)
Likely	58 (54.7)
Unlikely	27 (25.5)

[1]One patient can be referred to multiple specialities or have multiple prodromes.
[2]One patient can receive more than one modality of treatment and more than one drug.

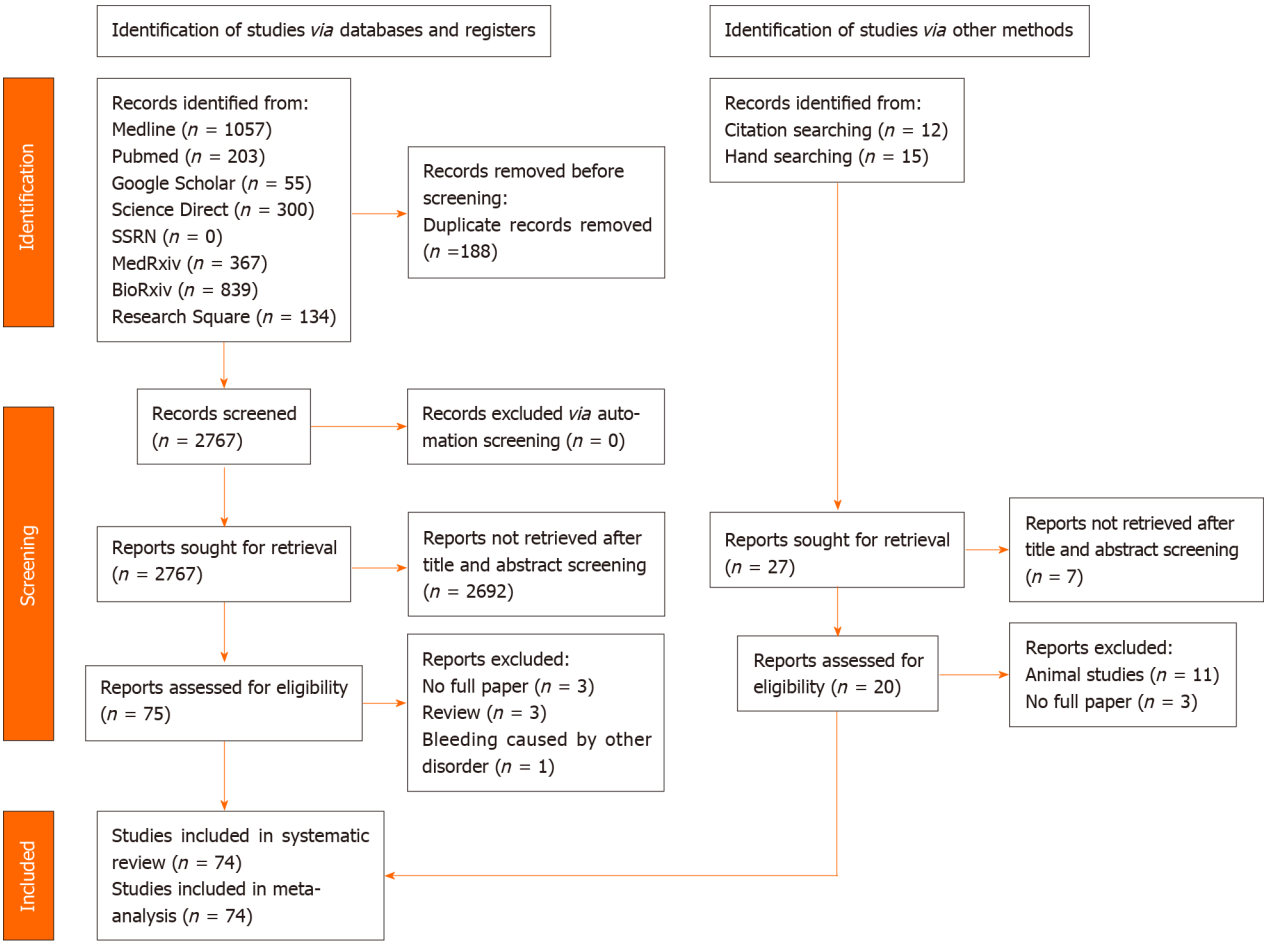

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Figure 1 PRISMA flowchart for selection of included studies.

accompanying bleeding manifestation and may result from activating the trigeminovascular system and subsequent vasodilation of Kiesselbach's plexus[66]. Abdominal pain is the second most common prodrome. While certainly, the cause of abdominal pain is a multitude of etiologies, a case was reported in which bleeding from distant sites preceded by abdominal migraine[67]. Activation of selected nerves and release of neuropeptide and neurotransmitters may facilitate haemorrhage remote from the site of pain[68].

The pathophysiology of bleeding in other areas is still unknown. The blood seeps into the sweat ducts due to vasculopathies in the dermal vasculature and enhanced sympathetic activation due to acute stress and anxiety, resulting in periglandular vascular constriction and subsequent expansion[69,70]. Multiple blood veins arranged in a net-like structure surrounding the sweat glands. These vessels are thought to contract and then widen to the point of rupture when they are under much stress. The blood now travels to the sweat glands, which are pushed to the surface and manifested as blood droplets mixed with sweat[70,71]. These pathways explain why patients who suffer from anxiety, high blood pressure, or elevated sympathetic nervous system tone suffer from hematidrosis more frequently[71]. However, none of the biopsy results mention any vasculitis and this pathophysiology needs to be confirmed. The pathophysiology mentioned also does not explain the common co-occurrence of hemolacria, GI bleed, and hematuria. While there is a case of PF3 dysfunction[72], other patients do not have any hematological abnormalities after extensive workups. In the past, hematidrosis was thought to be caused by infections such as *Chromobacterium prodigiosum* and *Micrococcus castellani*[73]. One author

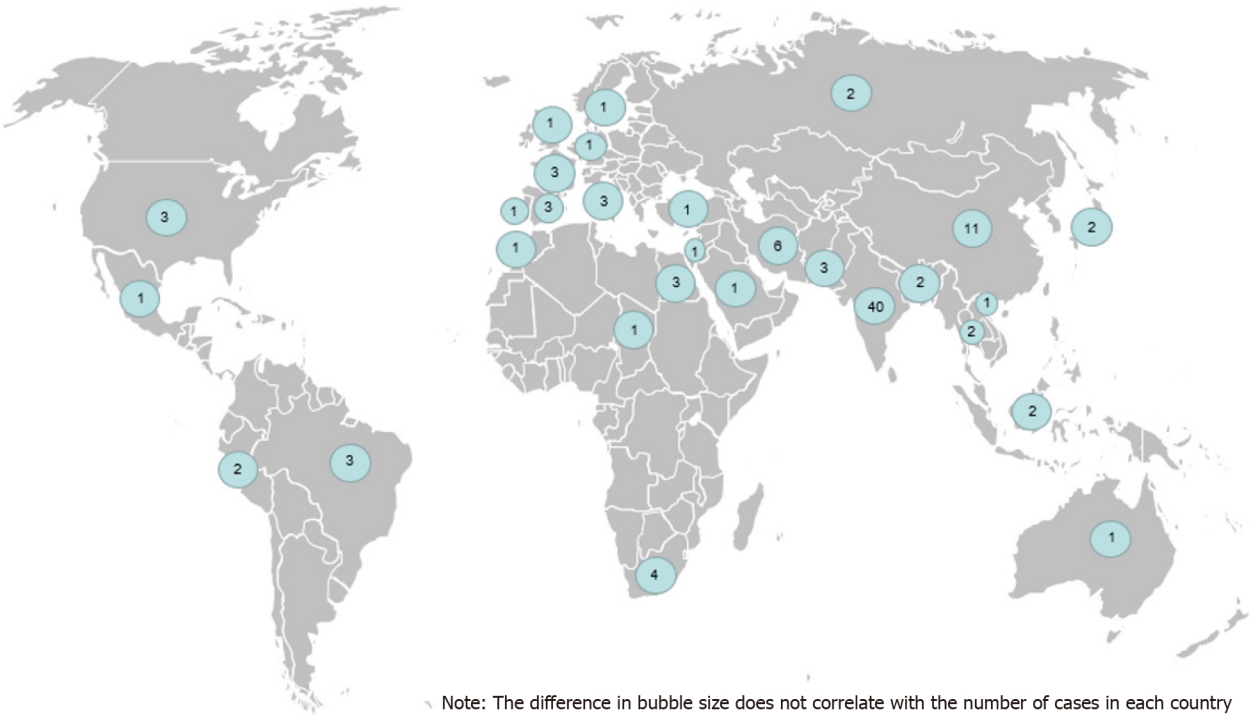

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Figure 2 Worldwide distribution of 106 hematidrosis cases from 74 articles.

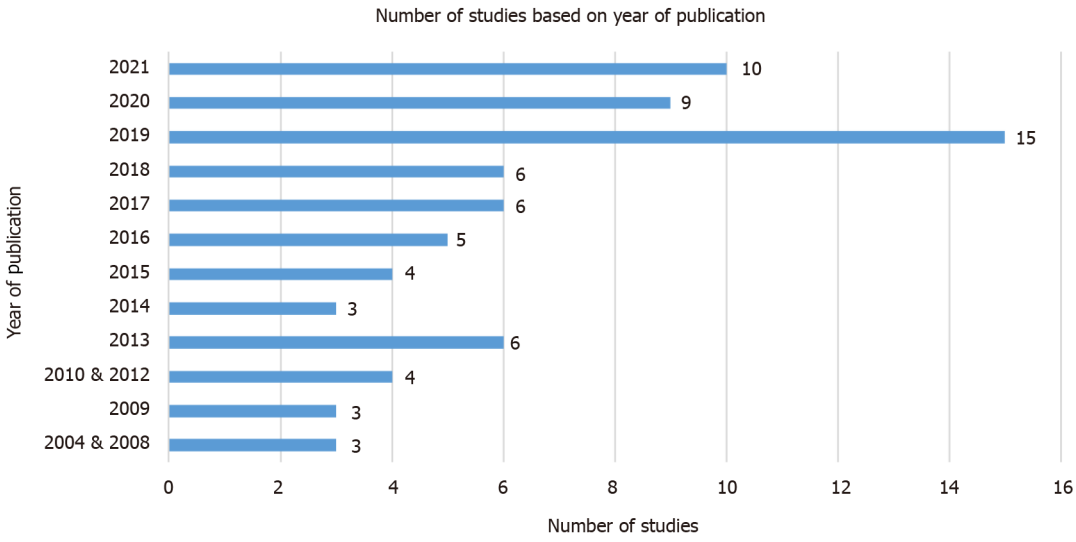

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Figure 3 The number of cases is based on the year of publication. Note that no studies were found to be published between 2005-2007 and 2011. There is one study published in 2004 and two studies in 2010.

also tested for the presence of these bacteria in their case report, although they did not find any chromogenic bacteria[38]. Figure 5 presents a complete postulated pathophysiological pathway of hematidrosis.

Cutaneous manifestation of Munchausen syndrome or other factitious bleeding related to stigmata usually presents in areas within reach of the arms of the patients (legs, arms, anterior part of the body, and face). These episodes always occur alone and is never witnessed by family members or general practitioners[74]. Therefore, when 34.9% and 52.8% of cases are not witnessed or explicitly mentioned to be witnessed by healthcare professionals and family members, respectively, the diagnosis of hematidrosis becomes weaker. It is important to note that family members as a witness have a lower strength of proof compared to being directly witnessed by healthcare professionals such as doctors, nurses, or residents. Munchausen syndrome cases by proxy where the parents smear their blood to their children to mimic hematidrosis[18].

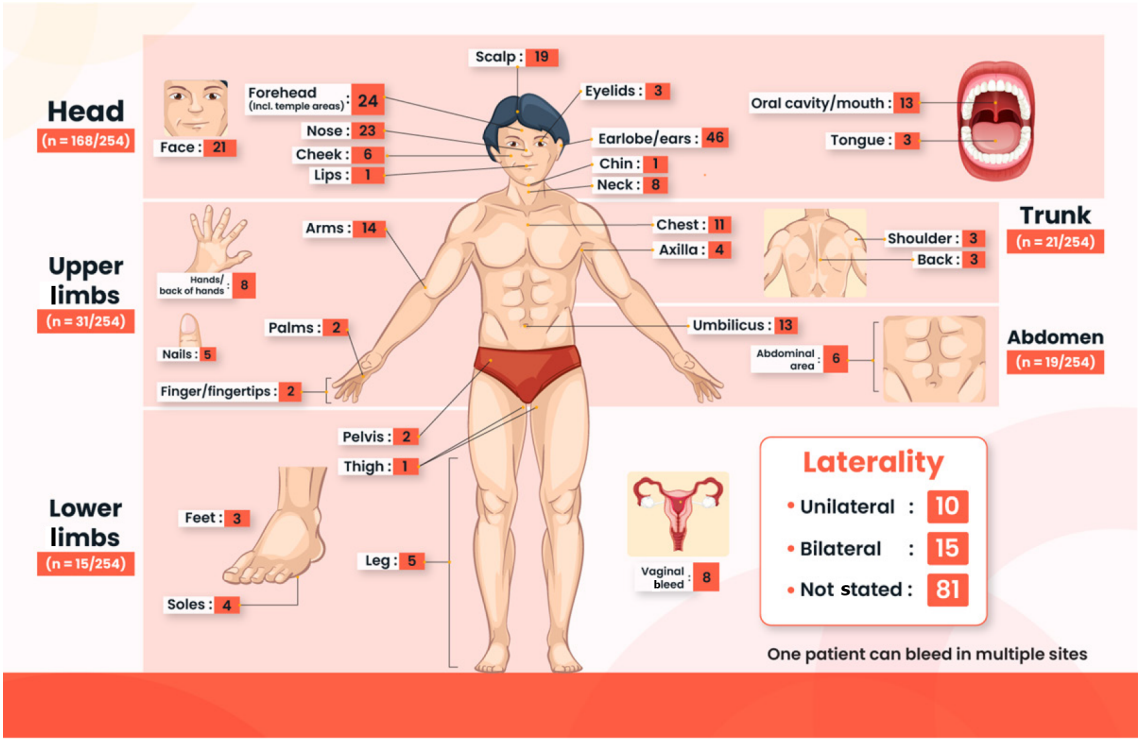

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Figure 4 Characteristics of bleeding sites. The head region is the most commonly affected (*n* = 168/254), especially around the ears or earlobes (*n* = 46), forehead (*n* = 24), and nose (*n* = 23). The next most common site is in the upper limbs (*n* = 31/254), with the arms being the most common site of bleeding in this region (*n* = 14). Although most cases do not state the laterality of bleeding (*n* = 81), more cases are bilateral (*n* = 15), as compared to being unilateral bleeding (*n* = 10).

Analysis of the exudate is done to ensure that the reddish or pinkish liquid contains blood components[75]. Some authors add benzidine test[32,41,53,76-82], hemochromogen test[39], chloride test[83], or blood group matching[84] in order to ensure that the blood is likely from the patient. However, as stated above, even though the presence of blood is confirmed *via* observation of red blood cells and other peripheral blood components under the microscope, the blood does not necessarily belong to the patient, even when matched by their blood group. Therefore, we propose that a skin biopsy needs further studies to be the "gold standard" to exclude other skin pathologies before safely confirming that a patient has hematidrosis[43]. However, a biopsy needs to be taken immediately during or after bleeding episodes. When the biopsy is taken any later, the results may be insignificant or even normal[43]. This means that patients need to be admitted just for the biopsy procedures. Clinicians need to weigh the unnecessary risks of hospitalization and added fear and stress against the need for a confirmatory procedure that may add little value to the diagnosis.

The wide involvement of specialists indicates that clinicians are initially perplexed by this condition. Multicollaboration among specialists is needed to exclude other causes of bleeding before diagnosing a patient with hematidrosis. The majority of the cases presented in this review tried to exclude other diagnoses before jumping into diagnosing hematidrosis. The full differential diagnosis of hematidrosis is presented in Table 4.

The most effective treatment seems to be a combination of pharmacologic and non-pharmacologic therapies. Beta-blockers and anxiolytics are the most commonly used pharmacotherapies in concordance with the postulated pathophysiology. However, other therapeutic modalities such as tap-water iontophoresis[45], inosine[44], aluminium chloride hexahydrate[85], and oxybutynin[86] are also used with mixed results. The wide range of therapies indicates that the optimal route, timing, and dosage of therapy is still largely unknown. For example, while atropine transdermal patches may be an effective treatment, certain bleeding locations such as the eyes or vaginal bleeding will exclude this treatment modality[40,76]. When a patient has underlying anxiety or fear, a psychiatrist should be consulted to give appropriate psychosocial therapy[87]. Only 41.1% of patients are fully resolved from bleeding episodes. This emphasizes that the current treatment is still not effective in managing hematidrosis. Clinicians are encouraged to educate and communicate about the aetiology and nature of the disease, emphasizing that this is not a stigma or a "shame" to suffer from hematidrosis. Underlying psychiatric disorders need to be addressed as well.

Shahgholi *et al*[75] also attempt at establishing hematidrosis diagnostic criteria. We agree on health professionals witnessing the bleeding episode to exclude psychiatric causes. However, Shahgholi *et al* [75] mentioned blood analysis as one of their criteria. We opt for skin biopsies as they are the "gold

Table 4 Differential diagnosis of hematidrosis

Hematologic disorders (Bezner *et al*[25], 2013; Peretz *et al*[68], 2016)
Acquired disorder of hemostatic mechanism
A hereditary disorder of hemostatic mechanism
Infection (Jirka, 1968; Peretz *et al*[68], 2016)
Chromobacterium prodigiosum
Micrococcus castellani
Disorders of vascular integrity (Bezner *et al*[25], 2013; Peretz *et al*[68], 2016)
Vasculitis
Amyloidosis
Connective tissue disorders
Gynecologic disorders (Bezner *et al*[25], 2013)
Ectopic endometriosis
Pathologic processes causing an acute increase in intracranial pressure
Cerebral venous thrombosis
Subarachnoid hemorrhage
Valsalva maneuver
Drugs (Girolami *et al*[74], 2014; Peretz *et al*[68], 2016)
Antiplatelets such as non-steroidal anti-inflammatory drugs
Anticoagulants
Glucocorticoids
Antidepressants (*e.g.* selective serotonin reuptake inhibitors)
Antiepiletics (*e.g.* topiramate)
Antibiotics
Chemotherapeutic agents
Intoxication with lysergic acid diethylamide (LSD)
Herbal supplement (*e.g.* Gingko Biloba)
Trauma (Meyer *et al*[95], 2019; Peretz *et al*[68], 2016; Rani *et al*[84], 2018; Yeşilova *et al*[96], 2017; Zhang *et al*[16], 2004)
Sleep disorders (parasomnia) (Peretz *et al*[68], 2016)
Psychiatric disorders (Bezner *et al*[25], 2013; Karpukhina *et al*[48], 2020; Peretz *et al*[68], 2016)
Factitious disorder/factitious disorder by proxy
Psychogenic purpura
"Artistic bleeding"
Religious stigmata or culture-bound phenomenon (Bezner *et al*[25], 2013; Girolami *et al*[74], 2014)
Sweat gland disorders (*e.g.* chromhidrosis) (Jerajani *et al*[41], 2009)

standard" for diagnosis, however more confirmatory studies need to be done before skin biopsies can be considered the "gold standard" for hematidrosis. Blood analysis can be plagued by some issues mentioned above. The last criteria by Shahgholi *et al*[75] are summarised in our criteria as the authors tried to exclude other possible diagnoses. This is imperative as hematidrosis is currently a diagnosis of exclusion. However, to be categorized as "highly likely" as hematidrosis, we also encouraged authors to include the bleeding pictures in the publication. This criterion is usually unable to be met by abstract or poster publications[84]. Our criteria serve only as guidance to consider hematidrosis as a plausible diagnosis and not as a confirmatory guideline.

Our review has some limitations. We could not confirm the true nature of hematidrosis in each case due to limited presentations in some of the articles. Therefore, we judged each case with the best available information. None of the contacted authors replied. Secondly, we could only postulate some

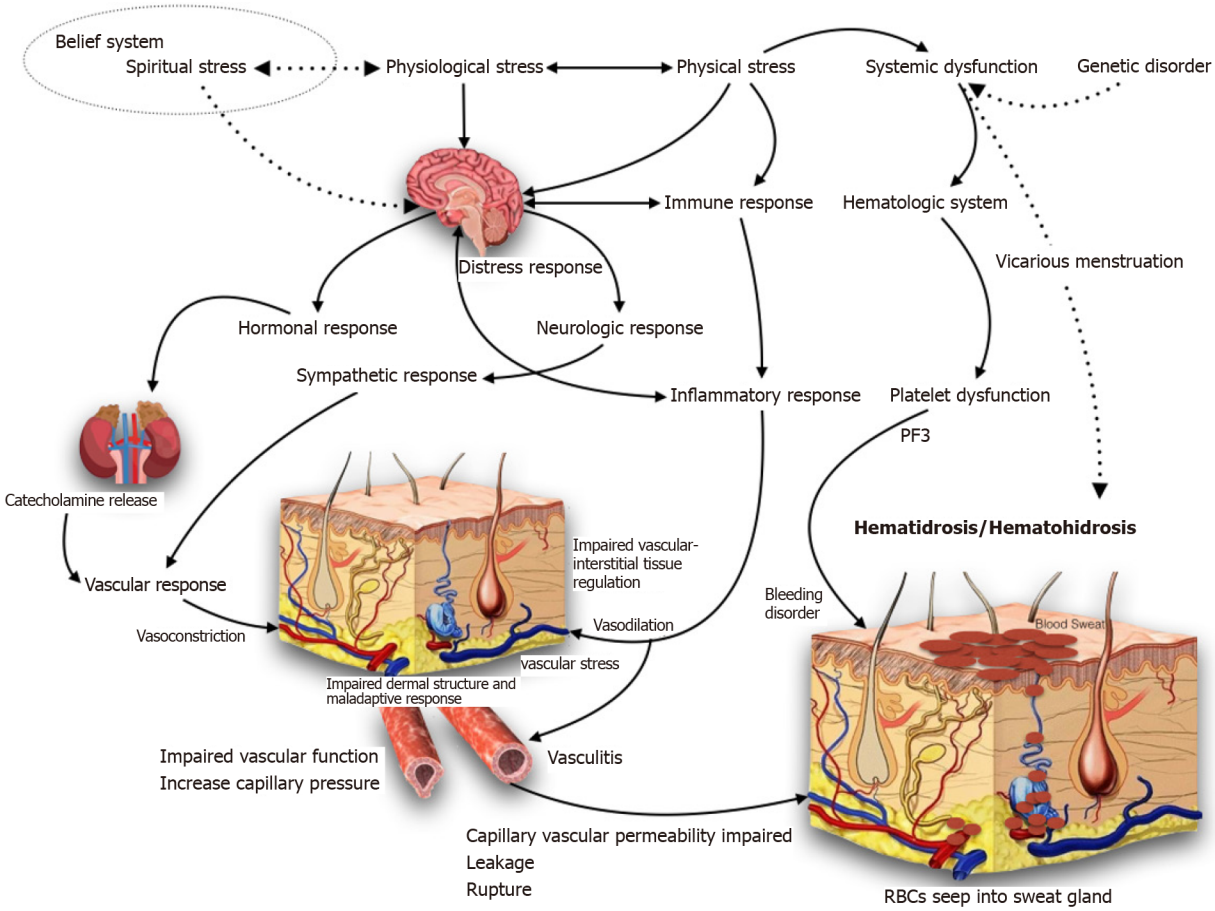

Figure 5 Postulated pathophysiology of hematidrosis. There are several hypotheses in hematidrosis pathophysiology. The vasculitis in the dermal vessels, exacerbated by sympathetic activation related to extreme stress and anxiety, leads to periglandular vessel constriction, and subsequent expansion, allowing the blood content to seep into the sweat ducts. Another theory states that multiple blood vessels around the sweat glands are arranged in a net-like form. It is believed that under tremendous stress, the vessels contract. Once anxiety passes, the blood vessels dilate to the point of rupture. The blood, at this point, goes into the sweat glands, which push the blood to the surface and manifests as droplets of blood mixed with sweat. RBCs: Red blood cells.

associations, theories, and hypotheses between each finding without any causal confirmation. A cohort study with a standardized protocol will help determine the nature, progression, and treatment of hematidrosis. The exclusion of three articles without access to the full article is another limitation. However, those three articles are from China screened from their abstracts, they are unlikely to alter our review's findings significantly. Lastly, we do not include pure hemolacria cases in our review because pure hemolacria has its own sets of causes[88]. Therefore, including pure hemolacria in this review will cause heterogeneity.

Despite the limitations, our review is the most up-to-date with the most comprehensive literature search compared to other reviews[7,16,23-25,27-39,40-45,47,48,49-54,61,69-72,75-78,79-84,86,89-112]. Including articles in any language, combined with grey literature, citation searching, and hand searching, ensured that all available articles were included. We present clinical, diagnostic, and other socio-demographic findings that will help clinicians identify hematidrosis.

The future direction in diagnosing hematidrosis is currently evolving. Manonukul *et al*[43] performed electron microscopy and immunoperoxidase studies with normal results on both. Salas-Alanis *et al*[37] performed a genetic analysis and found that 91.5% of the variants are missense variants. The pathogenic variants were found in genes related to the extracellular matrix. These examinations will help us better understand the pathophysiology of hematidrosis.

CONCLUSION

Hematidrosis is a rare disorder with an increasing number of cases. This disease is more common in Asia and young females with underlying anxiety, fear, stress, or depression. The head region is the most common bleeding site, and some patients may experience prodromal symptoms such as headache and abdominal pain. An important note to take is that hematidrosis might be accompanied by other kinds of

bleeding episodes such as hemolacria, GI bleeding, and epistaxis. The diagnosis is primarily on exclusion after ensuring that all the other diagnostic tests are normal. The most common treatment modality is a combination of pharmacologic (beta-blockers and anxiolytics) and non-pharmacologic (psychotherapy and counselling).

Although hematidrosis is rare and the pathophysiology is still largely unknown, that does not mean hematidrosis does not exist. It can bring severe panic towards parents or family members who care for these patients. Communication about the disease entity is imperative. A statement by Chambers perfectly surmmarized the rarity of hematidrosis "And as a rule, too, the more common the ailment, the more useful it is for you to hear about it"[113].

ARTICLE HIGHLIGHTS

Research background

Hematidrosis is a largely unknown entity, even to professional doctors.

Research motivation

In order to bridge the underlying knowledge deficit about hematidrosis, an updated systematic review is conducted.

Research objectives

We aim to conduct a systematic review of hematidrosis and identify the clinical characteristics, laboratory findings, as well as treatments given so far.

Research methods

We conducted a systematic search on eight different databases with no restrictions on the timeline using the English language.

Research results

There are 74 articles with 106 hematidrosis cases with India and China contributing the most cases. Patients are mostly females aged around 13 years. Bleeding occur most in the head region while beta-blockers and anxiolytics are the most frequent treatment given.

Research conclusions

Hematidrosis exists, and it is up to clinical researchers to further dissect this entity so that physicians can give better treatment in the future.

Research perspectives

More controlled skin biopsies and genetic studies with prospective follow-up or case-control studies may be needed to elucidate further and deepen our understanding of the pathophysiology and treatment of this disease.

FOOTNOTES

Author contributions: Octavius GS and Yanto TA did the conception of this research; Data collections and selections are done by Octavius GS, Heriyanto RS, and Meliani F; Octavius GS, Heriyanto RS, and Meliani F drafted the article while Yanto TA did critical revision of the article; Final approval of the version to be published was granted by all authors.

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