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Systematic Review of Hematidrosis: Time for Clinicians to Recognize This Entity

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Abstract

BACKGROUND

Hematidrosis is a sporadic disease, to a point where its existence is still denied up to this day. It is also linked to stigmata, psychological roots, and religious beliefs, strengthening clinicians' disbelief around hematidrosis.

AIM

This systematic review aims to conduct a thorough review to classify the likelihood of hematidrosis in each case.

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 old. 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.

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 when 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 this day. The mythical perception surrounding hematidrosis create 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, specify in which journals the articles were published, and more importantly, do not define what constitutes a hematidrosis. Therefore, this study aims to 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 authors adhered to The Preferred Reporting Items for Systematic Review (PRISMA) 2020 guidance[8]. The protocol of this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database with a registration number CRD42021289372.

The population 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 be highly likely of hematidrosis if: (1) the bleeding episode was witnessed directly by medical professionals, (2) attempts are 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 be unlikely diagnosed with 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 6th December 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 can be seen 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 used to assess the quality of case reports and case series, 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 sent an inquiry email once.

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 2,955 articles, where 188 articles were immediately excluded as duplicates. After title and abstract screening, 2,692 articles were excluded. Out of the 75 articles assessed for eligibility, three articles did not provide the full papers[15-17], three articles were review articles[2, 3, 18], one article mentioned other causes of the bleeding[19], and four articles were purely hemolacria[20-23]. These articles were then excluded, resulting in 68 articles[7, 24-89]. We found another six articles through hand-searching and citation searching [90-95]. 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 present 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 present with 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 minutes (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%).

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. Amongst skin biopsies that have been done, abnormal findings include dilation of blood vessels with extravasation of blood[33, 56, 70, 71, 79], possible mild squamous hyperplasia and mild dermal fibrosis[76], papillary dermal edema[30, 46] with dermal melanophages[46], bloody exudate from areas that do not contain sweat glands[55, 84], a low number of gross cystic disease fluid protein 15-positive eccrine sweat glands[61], loosening areas caused by the separation of collagen fibres [55], and acanthosis of the epidermis with broadening of rete pegs along with hypergranulosis and marked hyperkeratosis[30].

The most common pharmacologic therapy used is beta-blockers (43.0%), with anxiolytic coming second (23.2%). Amongst 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 days (2-730 days), as well as an improvement of bleeding symptoms (41.1%) in 28 days (10-720 days).

Amongst all the 106 cases, the majority of cases belong to the "likely" group with 58 cases (54.7%), followed by being "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. Our results include 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[96]. Including the 76 cases from Holoubek and Holoubek's review[5] and our cases, there are currently 182 hematidrosis cases in the world.

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[84, 88], Russian[48, 89], French[34, 54, 68], Spanish[60], and Portuguese[32], the majority of the articles are written in the 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 between 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[41]. However, we do not argue 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[97]. Reflecting on the types of journal specialities, most cases are published in dermatology, pediatric, or internal medicine journal. Only 12.2% of the cases are published in a hematology journal. This point strengthens 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[98]. Lastly, publication bias may play a role in determining which cases get published[99]. 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 old, which is consistent with previous review findings of 9-15 years old[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[100-102] has been established and might explain the higher prevalence amongst these populations. In this study, the bleeding characteristics vary significantly. Some

patients experienced bleeding episodes during sleep[71], while others never experienced bleeding during sleeping[61, 75]. In some cases, patients usually bleed during the day or evening[24, 25]. 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[103-105].

The head is the most common bleeding site, while headaches are the most common prodrome symptom. Spontaneous extracranial hemorrhagic phenomena (SEHP) may be caused by trigemino-autonomic reflex and sterile neurogenic inflammation[106]. Neural activation may also explain the prodromes of dizziness, nausea and vomiting, tingling, pain, photophobia, and phonophobia. Epistaxis is a frequent accompanying bleeding manifestation and may result from activating the trigeminovascular system and subsequent vasodilation of Kiesselbach's plexus[107]. Abdominal pain is the second most common prodrome. While certainly, the cause of abdominal pain is a multitude of etiologies, there is a case that report in which bleeding from distant sites preceded by abdominal migraine[108]. Activation of selected nerves and release of neuropeptide and neurotransmitters may facilitate haemorrhage remote from the site of pain[109].

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[43, 62]. Multiple blood veins are 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[62, 83]. These pathways explain why patients who suffer from anxiety, high blood pressure, or elevated sympathetic nervous system tone suffer from hematidrosis more frequently[83]. However, none of the biopsy results mention any vasculitis and this pathophysiology needs to be revisited. The pathophysiology mentioned also does not explain the common co-occurrence of hemolacria, GI bleed, and hematuria. While there is a case with PF3 dysfunction[58],

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*[110]. One author also tests for the presence of these bacteria in their case report, although they did not find any chromogenic bacteria[71]. 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 occurs alone and is never witnessed by family members or general practitioners[111]. 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].

Analysis of the exudate is done to ensure that the reddish or pinkish liquid contains blood components[72]. Some authors add benzidine test[31, 32, 42, 46, 50, 64, 77, 79, 93, 112], hemochromogen test[79], chloride test[80], or blood group matching[67] 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[55]. 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[55]. This means that patients need to be admitted just for the biopsy procedures. Clinicians need to weigh in the unnecessary risks of hospitalization and added fear and stress against the need for a confirmatory procedure that may add little 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[61], inosine[84], aluminium chloride hexahydrate[113], and oxybutynin[81] 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[31, 76]. When a patient has underlying anxiety or fear, a psychiatrist should be consulted to conduct appropriate psychosocial therapy[114]. 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*[72] also attempt at establishing hematidrosis diagnostic criteria. We agree on health professionals witnessing the bleeding episode to exclude psychiatric causes. However, Shahgholi *et al* mentioned blood analysis as one of their criteria. We opt for skin biopsies as they are the "gold 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* 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[67]. 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 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 and screening 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[115]. 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. 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* performed electron microscopy and immunoperoxidase studies with normal results on both[55]. Salas-Alanis *et al* 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[70]. These examinations will help us in better understanding 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 summed up 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"[116].

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 around 13 years old. Bleeding occurs the 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.

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PRIMARY SOURCES

1	Emmanuel Favaloro, Giuseppe Lippi. "Commentary: Controversies in Thrombosis and Hemostasis Part 1—Hematidrosis: “Blood, Sweat and Fears” or A “Pigment of Fertile Imaginations?”", Seminars in Thrombosis and Hemostasis, 2017 Crossref	22 words — < 1%
2	docksci.com Internet	16 words — < 1%
3	Addie M Peretz, Yohannes W Woldeamanuel, Alan M Rapoport, Robert P Cowan. "Spontaneous extracranial hemorrhagic phenomena in primary headache disorders: A systematic review of published cases", Cephalalgia, 2016 Crossref	15 words — < 1%
4	Hiroyuki Murota, Yorihisa Kotobuki, Kosuke Yamaga, Yoshichika Yoshioka. "Female child with hematidrosis of the palm: Case report and published work review", The Journal of Dermatology, 2019 Crossref	14 words — < 1%

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