Hematidrosis: Pathophysiology and Therapeutic Strategy

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Abstract

Background: Hematidrosis is an extremely rare and mysterious disorder. The etiology and pathophysiology of this disorder remain mostly unknown, and there is no specific therapeutic strategy available up to now.

Methods: The clinical features, hemostatic and other laboratory tests, and bloody exudates of seven patients were investigated, and histologic examination of the affected skin was performed. They were treated with a new therapeutic regimen.

Results: The bleeding episodes could appear under different conditions, but often following physical or emotional stress, with some prodromes. The frequency and amount of bleeding varied with each individual. The effluent bloody samples showed all the components of the peripheral blood, mingled with a few epithelial cells. Histologic examination of the affected skin showed normal sweat glands containing no blood. Each of patients was treated individually, and a multi-drug "cocktail therapy" regimen mainly consisting of beta-receptor blocker, anxiolytic, and histamine H1/H2 receptor antagonists proved successful. Although most patients could relapse within 6 to 12 months, the treatment was still effective and they were finally cured.

Conclusion: nervous system-hypothalamus-autonomic nervous system pathway in association with histaminergic activation. A multi-drug "cocktail therapy" in accordance to this hypothesis would become a new effective regimen.

Introduction

Hematidrosis (ICD 10 2016 diagnosis code L74.8) was, at the outset, considered religious stigmata appearing in saints and priests[1], similar to the ones inflicted on the Christ during his crucifixion (New Testament. Luke 22:44). This disorder, also named "bloody sweat", is an extremely rare and mysterious. Up to 2016, only about 100 cases have been found in the literature[2,3]. After that a few additional cases were also described. There was generally only one case described in each report, except for a series of three children[4], and other four patients discovered by separated ENT specialists from South Africa[5]. Some medical professionals even doubt whether it is a real entity[6]. Hematidrosis is characterized by spontaneous and intermittent blood oozing from various parts of intact skin and/or mucous membranes. This fascinating phenomenon is mostly seen during adolescence, with more girls than boys affected. They generally have no medical or family history. Skin biopsy performed is normal or shows only minimal inconsistent changes³. Possible triggering factors could be identified in more than half of the cases, including stressful situations, psychiatric illness and organic triggering factors³. The etiology and pathophysiology of this disorder remain mostly unknown, and there is no specific therapeutic strategy available up to now. Here we reported seven cases of hematidrosis, and investigated their clinical features and responses to therapies. On this basis, we postulated the pathogenesis of hematidrosis, and

explored appropriate therapeutic methods in accordance to individual differences, which were used for treating these patients, and proved highly effective.

Case Series

This study was approved by our institutional ethical committee, and the informed consent was obtained from the parents of the patients in accordance with the Declaration of Helsinki.

The common clinical features shared by all the seven patients were shown in the Table. Their physical and mental developments were normal without bleeding diathesis.

The spontaneous bleeding episodes happened frequently, from once every few days to dozens of times a day, each lasting for one through several minutes, which were witnessed by our physicians. Bleeding could happen in a single area, or simultaneously occur in many parts of the body. The color of the oozing blood from the skin surface was different, from reddish, scarlet to dark red. The site, amount, duration and color of blood exudation might change in each patient and in each time (Fig 1 and Fig S1 in the Supplementary Appendix). No lesion or inflicted trace could be observed after wiping the affected area. The samples of the oozing fluid contained all components of the peripheral blood cells mingled with a few epithelial cells, the latter never exist in the circulating blood (Fig 2). The results of the hemostatic and other laboratory tests (complete blood count, blood biochemistry, platelet aggregation, bleeding time, coagulation screening tests, various coagulation factors, and von Willebrand factor) were within normal ranges (data not shown). The specific clinical features of each patient are as follows:

Case 1 denied any triggering factors, but her bleeding episodes were preceded by slight tingling sensation, and often accompanied by significant abdominal pain and vomiting. She was treated with beta-receptor blocker (propranolol 10 mg, twice daily) and anxiolytic drug (perphenazine 2 mg, twice daily), which were only partially effective, then she was given a multi-drug “cocktail therapy” consisting of propranolol, perphenazine, histamine H1 receptor inhibitor (chlorpheniramine maleate 2 mg, three times daily) and H2 receptor inhibitor (ranitidine 150 mg, twice daily). The frequency and severity of her episodes and related symptoms gradually improved, but relapsed after 5 months. After 1-year follow-up, she completely recovered.

Case 2 presented with recurrent multiple bleeding discharge from various parts of the body such as left eyebrow, eyes, ENT, forehead, and extremities, often preceded by tension like chest pain and dyspnea, as well as occasional transient disturbance of consciousness. Continuous video-electroencephalographic (EEG) monitoring did not find any epileptic discharge. In addition, she suffered from hematemesis three times, which was associated with left epigastralgia. The upper endoscopy showed superficial gastritis and duodenitis. The patient had been treated with beta blocker and anxiolytic drugs without improvement. Therefore, we tried to give her a therapy of “cocktail of drugs”, and occasionally adding raceanisodamine (a cholinceptor blocking drug) when she had abdominal problems. Her bleeding events were gradually reduced during a period of one month, but repeatedly relapsed, and did not more respond to the previous therapy. Although her EEG examination was normal, addition of antiepileptic drug

(levetiracetam 5 mg, twice daily) was given as a trial therapy. That led to a gradual relief, and then a complete remission during 2 months of period. Since then, all the medical intervention was discontinued, and she did not experience any new episode.

In case 3, blood oozing was severe, and visible hematuria appeared once. The prodromal symptoms were not obvious except for painful canker sores in the mouth and rare abdominal pain. The episodes occurred quite frequently, at most 60 times a day. There were no significant triggers for the bleeding, but it easily happened after carsickness. Biopsy of the oozing areas of skin showed no histopathological findings (Fig. 3A). She responded neither to β blocker nor anxiolytics. Then she was treated with the “cocktail of drugs”. All her bleeding and physical/emotional stress phenomena were disappeared in a month, but she suffered from repeated relapse. After 6 months treatment, she completely recovered.

In case 4, bleeding on various parts of the body was often associated with nervousness or anxiety, and bleeding out of the corner of eyes could even be stirred up by intense light. She also had gastrointestinal bleeding accompanying abdominal pain. The upper endoscopy showed superficial gastritis. A small volume of visible hematuria was also occasionally noted. In addition, she had once a tonic seizure, became unresponsive for half an hour, while the result of continuous video-EEG monitoring was normal. The management with the multi-drug “cocktail therapy” was efficient. The patient recovered two month after, without any medical intervention.

Case 5 first presented with an onset of hemolacria of her right eye, and then bleeding appeared mainly on the face. There was neither prodrome nor obvious triggers for the bleeding. Histologic analysis from the bleeding skin area was normal without any sweat gland changes (Fig. 3B). She was treated with the multi-drug “cocktail therapy”. The frequency of episodes reduced and gradually ceased during three months period. Since then, her scalp and face bleeding recurred several times.

Case 6 first appeared bleeding during a military training, which recurred in minor emotional stress or even during studying. The attacks were often preceded by symptoms of dizziness and nausea. His bleeding symptoms were relatively less severe. He was first treated with propranol which showed no significant improvement. He was then given the drugs of the “cocktail therapy” and raceanisodamine. During 6 months of follow-up, the frequency and severity of his episodes disappeared, except seldom minor bleeding trigged in emotional stress.

Case 7 first presented with frequently bloody discharge from the left ear. The cranial CT scan was normal, and ENT specialists found a mild narrowing of his left external ear canal and a normal tympanic membrane. He underwent canaloplasty of external and auditory meatus, but the problem of bloody otorrhea was not solved. Instead, spontaneous and frequent bleeding appeared on his face, extremities, and umbilicus. He had once been treated with hemostatics and plasma transfusion without any efficiency. He was then given the drugs of the “cocktail therapy”. After three months treatment, he did not experience any new episode and was cured.

Discussion

The diagnosis of hematidrosis could be made by recurrent, spontaneous and self-limited bleeding which is witnessed by medical personnel, and by identifying all blood components in the bleeding samples leaking from intact skin and mucous membrane without any lesion observed[4]. Hematidrosis affects more females than males, usually with an onset in adolescence[1,3]. Our series case was consistent with this depiction. The bleeding could occur on various parts of the body with occasional digestive or urinary bleeding[7,8], which was also observed in our case 2 and case 4. The episodes occur rather frequently. In case 3, the highest frequency even reached up to 60 times a day. In general, episodes last for 2 to 20 minutes with amount of each bleeding being several milliliters. Patients had no prior medical or psychological illness, and their family histories were normal, except for a boy and his half-sister who were born to a same mother, suggesting their possible genetic predisposition. However, whole genome sequencing was not performed to search its doubtful gene mutation[8].

It is of note that the spontaneous bleeding phenomena are distinctive, but not definitive criteria for hematidrosis. Other conditions such as vascular disorders, hematologic dyscrasias, infections, influence of drugs, vicarious menstruation, and self-inflicted lesion should be excluded in the differential diagnosis[2,3,9,10].

In the literature many triggering factors have been identified in most patients such as substantial physical or emotional stress and fear, and the bleeding episodes are often accompanied by many symptoms including headache, abdominal pain, nausea and vomiting[3,6], which were also presented in our case series. We found that the bleeding could be stirred up by minor events such as carsickness (case 3) and intense light (case 4). On the other hand, it might occur in association with psychotic symptoms (cases 2 and 4). All these phenomena strongly indicate a functional disturbance of the central nervous system-autonomic nervous system. Autonomic nervous system is controlled by the central nervous system mainly via the hypothalamus, and is involved in homeostasis, emotional processing, and all bodily functions. It has been found that seizure discharges commonly spread into autonomic pathways which are mediated through the cortical, limbic, and hypothalamic systems[11]. Therefore, it would be possible that activation of nerves and the release of neuropeptides as well as neurotransmitters would facilitate the appearance of hematidrosis under some unknown conditions. On the other hand, histamine, although mainly released by mast cells, is also localized in many tissues including brain, sympathetic ganglion and nerve fibers where it functions as a neurotransmitter involving in the regulation of peripheral sympathetic activity[12,13]. Moreover, histamine receptors H1R and H2R are coexpressed in most cell types, such as neurons and some ganglions, endothelial and epithelial cells, and they may function in a crossregulation manner[14]. H1R and H2R inhibitors are mainly used for the treatment of allergic and gastric acid-related conditions. It is well known that histamine can also dilate vasculature and increase blood flow via activation of H1R and H2R located in blood vessel[15], and disrupt endothelial barrier formation of venula indicated by changes in vascular endothelial cadherin localization at endothelial cell junction, and then increase vascular permeability, which could be abolished by histamine H1 receptor antagonists[16,17].

The pathophysiology of hematohidrosis remains unclear. Several hypotheses have been proposed including abnormal constriction and then dilation of capillary vessels to the point of rupture, dermal vasculitis, and stromal weakness due to defects in the dermis[4,6]. From our investigation, we could postulate that the basic pathogenesis of hematohidrosis might be perplexing regulation disturbance of central nervous system-hypothalamus-autonomic nervous system pathway in association with histaminergic activation. This disorder could be considered as an exceptive kind of mental and nervous illness rather than an organic disease.

It is generally believed that hematidrosis is due to blood leakage from ruptured skin capillaries to neighboring sweat glands[3,18]. However, the skin biopsy studies, including ours, never revealed any abnormalities apparent in sweat glands. On the other hand, blood oozing is not accompanied by sweating, and it could appear on the tongue and mucous membrane, and from subungual area where there are no sweat glands. Therefore, we believed that the term hematidrosis or "bloody sweat" is not accurately correct[19]. However, it is still an enigma how blood could spontaneously exude from intact skin and mucous membrane without leaving any trace of petechia, ecchymosis, or lesion. The mostly puzzling enigma is that we previously found a girl with hemotidrosis whose bloody exudate was shown to contain all the components of peripheral blood, while she occasionally discharged white frothy fluid from the tongue and the umbilicus, containing only white cells but no red cells[20]. Such oddity was described only in an Indian girl with hemotidrosis[21].

Up to date, there is no specific treatment regimen available for hematidrosis. Management with vitamin C, hemostatic drugs, corticosteroids or plasma products have been proven to be valueless. Some extensive therapeutic intervention treatments could cause dangerous risk. A patient had been reported to be infected with human immunodeficiency virus and hepatitis B virus, presumably acquired via blood transfusions[8].

Anxiolytics and atropine have respectively been reported effective in single case[21,22]. We first successfully treated a patient with β -receptor blocker propranolol, as we speculated that sympathetic nerve activation might play a role in her episodes[18]. This treatment method has been used by many other researchers, but its efficiency could be limited, and relapses occurred in some cases after the drug withdrawal[1,3,8,23]. Again our seven patients did not completely response to propranolol. According to the possible pathogenesis described above, we tried to form a mixture of multi-drug "*cocktail therapy*" consisting of anxiolytics, propranolol, and histamine H_{1/2} receptor antagonists in order to manage the related tricky problems. Following this therapeutic regimen, both frequency and severity of bleeding episodes gradually disappeared during 2-6 months period. According to our experience, the drug withdrawal should be gradually tapered, and most of our patients finally discontinued treatment. We previously reported a girl with hematidrosis whose bleeding onset was triggered by epilepsy, who was not responsive to propranolol or general therapy, but made a complete recovery after being treated with an anti-epileptic drug, oxcarbazepine[20]. Case 2 got a temporary remission following a therapy of "cocktail of drugs", but then repeatedly relapsed. Because she sometimes had transient disturbance of consciousness before bleeding onset, addition of another antiepileptic drug levetiracetam was given, and

she finally got a complete remission. According to our experience, each patient needs to be treated individually in light of different situations. It was noted that the relapse occurred in most patients. The treatment should be continued for 6 to 12 months after the initial episode was disappeared. Meanwhile ensuring a compassionate approach by physicians was important, as the patients always felt down and discriminated.

Hematidrosis is an extremely rare disorder with only about 100 cases reported worldwide from ancient time to nowadays[2,3]. It is amazing that we have found 9 patients (including two published elsewhere[19,20]) in our single institute during the past 10 years. That is perhaps because of the largest population in China, and our department of hematology is among the list of the most influential services in our country. On the other hand, this fact could indicate that hematidrosis is certainly not as scarce as originally thought.

Conclusions

We hypothesized that its pathogenesis might be related to regulation disturbance of central-autonomic nervous system pathway, and suggested a multi-drug "cocktail therapy" regimen, which has been proven to be a successful and even curable approach in this study, and could become a new effective regimen for management of hematidrosis.

Abbreviations

ENT: ear, nose, and throat; EEG: electroencephalographic; CT: Computed Tomography; H1R and H2R: histamine receptors.

Declarations

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Authors' contributions

Zhaoyue Wang, Jie Yin and Ziqiang Yu conceived and designed the study. Zhaoyue Wang and Jie Yin did data analysis and wrote the draft. Yue Han revised the manuscript and acted as the guarantor of the study. Danqing Kong, Chengyuan Gu and Xinyou Zhang collected the clinical data. Lijuan Cao and Xia Bai did laboratory work. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of our hospital. All subjects participating in the study gave written informed consent.

Consent for publication

All authors agreed on the manuscript.

Competing interest

The authors declare that they have no conflict of interest.

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Table

Table 1

The common clinical characteristics of the seven patients with hematidrosis

<i>Case number</i>	<i>sex</i>	<i>Age</i>	<i>Time of duration</i>	<i>Main sites of bleeding</i>	<i>severity of bleeding</i>
1. Z.Y.	F	12	1 y	Face, arms	++
2. Y.H.	F	18	4 m	Eyes, ENT, body	+++
3. C.W.	F	13	5 m	Mouth, ENT, face	+++
4. Y.H.	F	10	9 m	Eyes, face, neck	+++
5. S.Y.	F	12	2 m	Eyes, face	++
6. L.C.	m	16	4 y	Ear, face, umbilicus	+++
7. C.Z.	m	12	6 m	face	++

Figures

Figure 1

Representational bloody oozing from different parts of the body of the patients, which shows different colour. A. face. the colour of penetrated blood is reddish. B. face. the colour of penetrated blood is scarlet. C. eye and mouth. the colour of penetrated blood is dark red. D. bloody oozing from the umbilicus. E. simultaneous bloody oozing from the palm and knee. F. bloody oozing from the sole.

A

B

Figure 2

Blood films examined by microscope, A. The Smear from 'bloody sweat' containing red blood cells, mingled with a few epithelial cells. B. Smear from 'bloody sweat' containing red blood cells, neutrophils, and lymphocytes, mingled with a few epithelial cells. (Wright stain, magnification $\times 1000$).

Figure 3

Biopsies of the skin from the bleeding area A. normal structure of the skin tissue showing sweat gland containing no blood inside. B. normal structure of the skin tissue. (hematoxylin and eosin stain, magnification $\times 100$).

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