Migraine induced recurrent bloody otorrhea: A spontaneous extra-cranial hemorrhagic phenomena: Case series

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Keywords: Heamatohidrosis; Spontanious extra cranial hemorrhagic phenomenon; Primary headache; ; Migraine varient headache; Epilepsy

1. Introduction

Headaches are a common complaint, with 64% of people reporting at least one headache during their lifetime, and with 46% of people having at least one headache a year [1], [2], [3]. Headache is the main feature of primary headache disorders (PHDs), including migraine, tension-type headaches and trigeminal autonomic cephalgias (TAC) [4]. The headaches may be associated with autonomic and vasomotor features such as lacrimation and conjunctival injection. Cranial autonomic symptoms (CAS) are thought to be caused by activation of the trigemino-autonomic reflex, when the nociceptive stimuli triggers parasympathetic ganglia, resulting in parasympathetic overflow to the head and cranial vasculature [5]. In PHDs, CAS are present in 14–100% of cases [5], [6], [7], [8], [9], [10]. Almost 49% of patients with migraine report CAS [8], [10]. Cranial autonomic symptoms are characteristic of TACs but specific CASs may vary [1].

As a feature of PHDs, spontaneous extracranial haemorrhagic phenomena (SEHP) are poorly characterized and rarely recognized [11]. Bleeding may occur through the nasal mucosa termed epistaxis [12], subcutaneous tissue (termed ecchymosis when the lesions are >1 cm) [13], [14] and through sweet glands in hematohidrosis [15]. Little is known about the incidence of haemorrhagic phenomena in PHDs because epidemiological studies are scarce [1]. Few cases of SEHP have been reported in association with PHDs, suggesting that SEHP are rare. Only 105 cases have been reported over 120 years; 58 cases of epistaxis, 41 cases of ecchymosis, 5 cases of hematohidrosis and 1 case of haemorrhaging [1].

In the international classification of headache disorders (ICHD), 83% of PHDs are migraines, 18% of PHDs are TAC, with a few other tension-type headaches [4]. Epistaxis affects 67% of migraine patients and 13% of patients with TACs. Ecchymosis was seen in 87% of patients with TACs and 33% of patients with migraine. Headache type is seldom classified in patients with hematohidrosis. In patients with hematohidrosis, 80% of patients have episodic headaches and 20% of patients reports chronic headaches.

2. Hematohidrosis

2.1. Case report

We describe a case of a 23 year old, female Caucasian presenting with viral infection (URTI) and migraine headaches, with associated spontaneous bloody otorrhea – (hematohidrosis) and sometimes with nose bleeding. In this case, migraine headaches are triggered by flu-like infections and stress without an aura. The migraines meet the ICHD diagnostic criteria. The

patient always presented, and still presents, with a viral URTI, with a throbbing headache. The headaches are always unilateral, associated with nausea, vomiting, and spontaneous, painless unilateral (ipsilateral) bloody otorrhea with photophobia, tiredness, fainting spells and convulsions with confusion. The patient's symptoms usually last for a week, after which she recovers. The patient does not have any bleeding tendencies, trauma, drugs or middle ear infection and SARS-CoV-2 tests have been negative. An ENT examination revealed an intact, normal eardrum with a bloody discharge oozing from the skin of the external ear canal, akin to sweat (Fig. 1a, b).

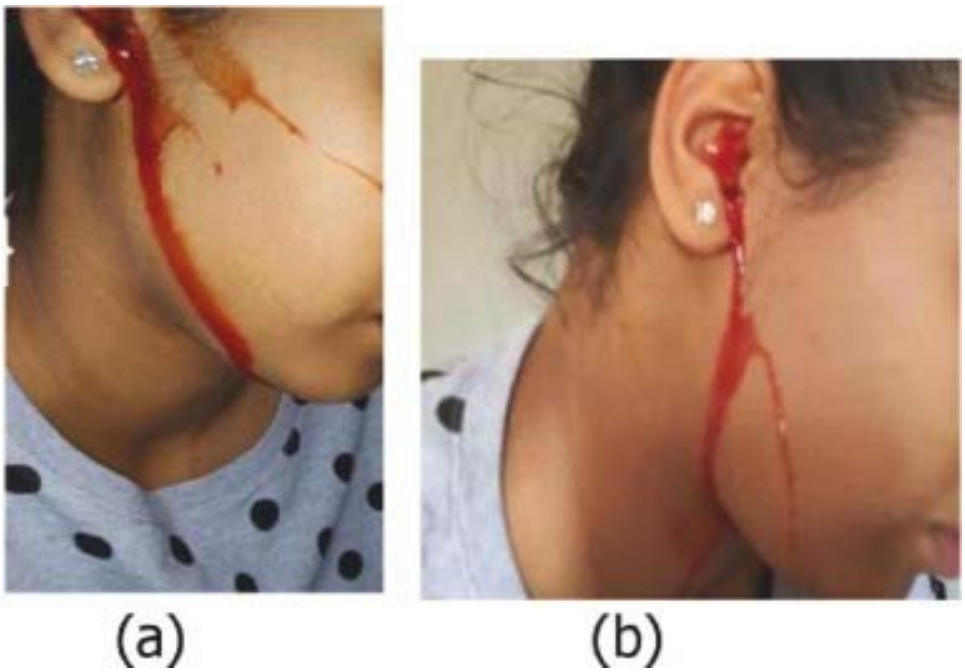

Fig. 1. Bilateral bloody otorhia pictures in a patient with miigrain headach-hematidrosis

The bleeding could only be explained as hematohidrosis associated with primary headache of epilepsy/migraine type, infection and stress. The patient experienced three to four attacks a year. In the last five years, most of the attacks were associated with epileptic fits and fainting attacks. The attacks started when she was 6 years old, and she is now 23 years old.

Six months ago (January 2021), a neurologist started her on migraine prophylaxis and antiepileptic drugs together with propranolol. Since being on this regimen, her attacks are controlled with no more frequent attacks and bleeding. The bleeding resolved spontaneously with anti-epileptic agents (Epilim 600 mg, Propranolol 10 mg, Tramacet) and supportive psychotherapy.

We reviewed 15 articles reporting case reports of hematohidrosis of bleeding from sites, including the ENT area – ears and nose. The articles were published between 2008 and 2020 and reported hematohidrosis cases were mainly children (Table I)-cases of hematohidrosis;. In these articles, symptoms can be explained to a certain extent by SEHP and PHD, of migraine variant, which would explain the presentation of hematohidrosis.

Table I. Literatures review of hematohidrosis cases reports.

Article	Race/cases	Gender	Age	Onset	Site	Duration frequency	Stress personality	Treatment	Ass. symptoms	Psychotherapy	B. Blocke	Anxiolytic	Topical	Prognosis
1. Deshpande et al. Indian J. Psychiatry	Indian Middle socioenomic	M	10 yrs	No cause found spontaneous	Navel Eyes Ear lobe Nose-epistaxis Mouth	Monthly oozing blood (Repeated) 10 months	Temperamentally Adamant defiant boy (special child) EXTREME level STRESS: mental anxietyvasoconstriction -blood A pressure			Behavioral Intervesion Psychoeducation Recurrent (Stigmatic)	Propranolol BD 10 mg	Lorazepam 1 mg daily	None	Settled Healed 2–3/12
2. Raksha 2010 Indian Journal		M	13 yrs	11	Face Sweating Blood	2007–2010	Stress chronic (psychiatric) extreme xylogenic stigmatic			Breath exercises Recurrent		Alprazolam 0.2 mg daily 10 days 20% aluminum lotion (OH) - Hexahydrate		
3. 2012 Indian Journal Psychology Varalakshmi	Indian	F	10 yrs.		Eyes	3/12	Psychological stressor Temperamentally difficulties Conflicts Depression			Psycho-edmition	Propranolol	Clonazepam	Sertraline Antidepressant	
4. Tshifularo 2014 Head Neck Journal 2018	Indian Idian African African	F F F F	10 yrs. 30 Yrs 18 Yrs 24 Yrs			2 years 2 episodes 3 episodes per year 3–4 a year	Intense stress Headaches Stress headaches Stress Anxiety Headaches Stress, Job/work/menstrual emotion, headaches	Headaches Recurrent Recurrent Single attack Headaches tiredness Recurrent		Bed rest Ear drops Analgenic Ear drop Bed rest Brufen				

	Indian Black	F F	13 Yrs 30 Yrs			Few days, +−30 times (6 years) 2–3 months (stress)	Stress/schooling, sports, anxiety, headaches, extreme cold weather Stress, headaches	Headaches Dizziness Flu Stigma		Tramulor Augmentin drops Quidridor				
2017 Medical news (online publication)	Indian	F	18 yrs.		Forehead, eyes, hands navel, fingers	Daily weeks	Psychology stress Anxiety disorder (mental health condition)	Recurrent		Aleviate cause Physical – emotional strem	Propranolol	Yes, depression anxiety		
2017 Indian Journal Psychology Kannam Jayaramanel (Psychiatry)	Indian	F	10 yrs			Daily ×2 (weekly)	Psychosocial stress mixed anxiety depressive disorder (Fight co-student) Punishment stress	Bedwetting enuresic Stigma		Psychoeducation (stress etiology) Family/Parents Relaxation technique	–	Clonazepam		
2016 Jafar Ahmed Dermatological medicine	Indian	F	12 yrs			Daily	Faint attacks	Mild periorbital tenderness single attack		Gum bleeds	–	Anxiolytic		
2013 Biswas et al. Indian dermatology Journal	Indian	F	12 yrs			Daily	Poor insight (stress)	Recurrent		–	–	–		
2012 Vincent et al. Indian Pediatric Journal	Indian	F	10 yrs		Nose Forehead Ears Neck Umbilicus Wrists Legs	2–3/week 4–5/day	Stress psychosocial-event soreness (bleeding sites) 30 min before headache Post traumatic stressor	Recurrent type		Stress management Relaxation	Propranolol	Lorazepam		
2010 Wang et al. Clinical Dermatology	Chinese	F	13 yrs		Tongue Palms Feet	2 months	Emotional excitement	Recurrent		–	Propranolol 10 mg BD-1/12			

					Thighs Trunk		Running (physical exercise)				5 mg BD-1/12			

In my opinion, most hematohidrosis cases in children are presentations of SEHP in PHD. All patients who present with hematohidrosis should be assessed for migraine with PEADMIDAS and Pead QL. Patients should be treated prophylactically and abortive acute therapy may control most symptoms. In my opinion, this approach will contribute to managing pediatric patients who suffer from the devastating emotionally taxing condition of hematohidrosis.

Hematohidrosis is an excretion of blood or blood pigments in the sweat glands according to Stedman's Medical dictionary. Aristole even commented “some sweat with a bloody sweat” (Hist.Animal 111,91). The reported cases of hematidrosis appear to be associated with a severe anxiety reaction with fear implicated as the inciting factor. Cases of hematohidrosis have been reported in the French literature by Broeg in 1907 and by Darier in 1930, in the British literature in 1918 by Scott, in the German literature by Riecke in 1923 and by Gadzhiev and Listengarten in 1962. Hematohidrosis is a rare condition, of unknown etiology but has been associated with extremely high blood pressure causing blood to seep into sweat glands and escape through the pores-creating the illusion of sweating blood. Hematohidrosis, may also be caused by vasculitis, a condition where spontaneous bleeding occurs through unbroken skin in any part of the body. Hematohidrosis is diagnosed when red blood corpuscles (erythrocytes) and other blood components are present, with no other blood or physical abnormalities found to account for the phenomenon. The bleeding usually starts around a period of intense headaches and anxiety or stress (nervous excitement), worry, activity or fear. Hematohidrosis is usually diagnosed by the attending doctor or physician.

2.2. Childhood migraine

Clinically, childhood migraine resembles adult migraine. As with adults, childhood migraine is diagnosed according to the certain characteristics, namely uni/bilateral pain location, pulsatile quality of pain, nausea and vomiting, photophobia and phonophobia, prodromal symptoms and aura, aggravation by routine daily activities and relief after rest or sleep, except for the duration of pain [1], [2], [3], [4], [5], [6]. Compared to adults, migraine attacks in children are usually shorter in duration and have a bilateral location. Adult migraines can last for 4–72 h, whereas childhood migraine usually ends in 1–4 h [8], [10], [11], [12], [13]. This is important because migraines are classified based on their duration. To be classified as a migraine, headaches need to last for longer than an hour, which is problematic for diagnosing childhood migraine. Currently, many authors propose reducing the lower limit to 1 h and others have proposed a further reduction to 30 min [10], [11], [12].

The age-specific prevalence of migraine headache from childhood to adulthood represents a steadily increasing trend [14]. In epidemiological studies designed according to HIS-1998 criteria, migraine prevalence was between 2.4% and 28% [16]. It is important to find a solution to the problem of migraine headache because of its impact on children's school, home and social life.

2.3. Migraine variant

Migraine variant or episodic syndromes (MV) may be associated with recurrent migraine which occur periodically, otherwise known as episodic paroxysmal disorders in children and adolescents [17], [18]. Migraine variant is the official term used by the ICHD-3 [4]. These disorders are also referred to as childhood periodic syndromes, migraine precursors, migraine subtypes, migraine equivalents, complex migraine and migraine accompanied [19], [20].

These syndromes are common and frequently encountered in children and adolescents, especially those with a family history, but are uncommon in adults [17].

Migraine variant is only diagnosed once all other possible disorders have been excluded. Many different and overlapping symptoms of episodic syndromes may be associated with migraine [17]. These symptoms may be frightening and dramatic, especially when associated with other severe symptoms.(Table II, Table III).

Table II. Autonomic symptoms of migraine variant in children.

Mood change	**Autonomic**	**Neurological**
Euphoria	Anorexia	Hemiparesis (focal)
Depression	Abdominal pain	Nystagmas
Irritability	Phono/photophobia	Ophthalmoparesis
Lethargy	Periorbital discoloration	Loss of consciousness syncope
Cognitive impairment	Syncope	Ataxia
	Pallor	Vertigo
	BP changes	Diplopia
	Fever	Visual field cuts
		Aphasia
		Tinnitus
		Hearing loss
		Confusion
		Dysarthria - aphasia
		Sensory abnormalities
		Loss of vision
		Chorea/dystonia
		Facial weakness

Table III. Migraine variant classification in children migraine.

ICHD	
Hemiplegic migraine	BPV
Familial/sporadic	Cold migraine
Migraine with brainstem aura	Abdominal migraine
(Basilar migraine)	Cyclic vomiting
Aura without headache	
(Migraine sine hemicranias)	
Retinal migraine	
Doubtful/questionable	
Alternating hemiplegia	Exertional migraine
Colic	Oculomotor palsy
Epilepsy/migraine syndrome	Transient global amnesia
Trauma-triggered migraine	
Other	
Ophthalmoplegic	Paroxysmal torticollis
Confusional migraine	Periodic syndrome

Episodic syndromes often start suddenly, resolve spontaneously and have no lasting effects, and may or may not be associated with headaches [17], [18]. Symptoms of episodic syndromes are variable and may include mood changes, autonomic symptoms and neurologic features [17]. Headaches may last minutes, hours, days or weeks. Their ages of onset vary by syndrome, with a wide range of differentials. They may appear to be secondary to structural brain disease, vascular disease, congenital abnormalities, infections, trauma, toxins, endocrine disorders, behavioral disorders, neoplasms, mitochondrial disorders,

channelopathies, inborn errors of metabolism (IEM) or their true etiology may never be discovered. Most patients have normal general (ENT and Neurological) physical examinations between attacks [17], [18].

Epidemiologically, 9.8% of migraine headaches had MV with 10–70% having coexisting migraine. There is much variation in the distribution and types of MV, with the most common headache types being benign paroxysmal vertigo (BPV) (38%), acephalgic headache (29%), abdominal migraine/cyclic vomiting syndrome (CVS) 19%, benign paroxysmal torticollis (BPT) 10% and confusional migraine (5%) [17].

2.4. Migraine prophylaxis and treatment

Childhood migraines can have a severe impact on quality of life, school performance, and family functioning. Use of objective, age-appropriate measures of disability and quality of life can effectively guide clinicians in how they prescribe prophylactic agents such as antidepressants, antihypertensives, anticonvulsants, antihistamines, as well as botulinum toxin (Table IV).

Table IV. Prophylaxis treatment for childhood migraine.

Medication	Initial dose	Dose range
Amitriptyline	0.25–0.5 mg/kg (max 10 mg)	10–75 mg/day
Nortriptyline	10 mg	10–75 mg/day
Topiramate	0.5–1 mg/kg/day	2–3 mg/kg/day
Valproic acid	250 mg/day	250–1000 mg/day
Zonisamide	1–2 mg/kg/day	4–6 mg/kg/day
Levetiracetam	250 mg/day	250–1500 mg/day
Cyproheptadine	0.2 mg/kg/day	0.2–0.4 mg/kg/day
Proranolol	10 mg	1–4 mg/kg/day divided tid
Verpamil	60 mg	60–360 mg/day
Botulinum toxin	155 units	155–200 units

Knowledge of these options including dosing, efficacy and potential adverse effects can lead to much improved care of children and adolescents with this chronic condition. For medications for which there is no evidence, dosing ranges have been provided based on manufacturer's recommendations and the author's clinical experience.

2.5. Epilepsy/migraine

Headache, especially migraine, has long been associated with epilepsy, based on the common clinical features of these disorders. Both migraine and epilepsy have a genetic predisposition and share common pathophysiological mechanisms including an imbalance between excitatory and inhibitory factors that result in spells of altered brain function and automatic symptoms. There are well-documented reports on headache as a sole manifestation of

epileptic seizure and headache is commonly associated with as preictal, ictal and postictal symptoms in epilepsy patients. In addition, migraine and epilepsy are frequently described as highly comorbid conditions and several antiepileptic drugs are used for the patients with migraine as well as epilepsy.

2.6. Haemorrhagic characteristics

From the reviewed literature, the median time from first headache to initial haemorrhaging was 1.5 years (range 0–3 years). The median number of hours between start of pain of and the SEHP was 1 h in patients with epistaxis, 21 h in ecchymosis patients and 0.5 h in patients with hematohidrosis (Table I). Thirty-two percent of all patients with epistaxis and PHD reported the relief of their headache following epistaxis. Eighty percent of ecchymosis and 100% of hematohidrosis patients described severe pain during the episodic attack.

2.7. Site of SEHP

From the reviewed literature, sites for spontaneous ecchymosis included bilateral periorbital (11%), temporal (11%), conjunctival (8%), buccal (8%), preauricular (5.5%), palpebral (2.8%), glabellar (2.8%), glabellar (2.8%), and suborbital (2.8%) (Fig. 1(b)). The distribution of bleeding in the hematohidrosis chort included bilateral nasal mucocutanoeus (5.6%), bilaterial hemolacria (lacrimal ducts) (11%), forehead (22%), bilateral hands (5.6%), umbilicus (17%), ear canal (17%), nasal bridge (5.6%), neck (5.6%), and wrists and leg (5.6%). Bleeding in the epistaxis cohort was either from one or both nares.

2.8. Literality of SEHP

Among patients with migraine, the distribution of ecchymosis was ipsilateral to the side of head pain 67% and bilateral in 33% of cases. Among patients with TACs, the ecchymosis was always ipsilateral. Among the epistaxis-migraine cohort, 53% had nose bleeding ipsilateral to the site of head pain, whereas this was bilateral in the remaining 47%. In the two reported cases of TACs with epistaxis, bleeding was ipsilateral to the site of head pain. Any laterality of hemorrhagic phenomena was not specified in the hematohidrosis cohort.

2.9. Associated features

Vomiting in association with SEPH was reported in 13% of the reviewed case reports of ecchymosis, in 2.5% of case reports of epistaxis, and none in case reports of hematohidrosis. Of the patients who had CAS occurring in association with SEHP, the presentations included lacrimation (43%), ptosis (14%), eye redness (14%), facial flushing (14%) and nasal congestion (14%).

Biopsy of the skin in ecchymosis lesions was consistent with extensive red blood cell in the absence of vascular damage. No underlying vasculitis or amyloid change was noted [14], [15]. A skin biopsy was obtained from patient with hematohidrosis and was normal [19].

3. Conclusion

The mechanism by which SEHP occurs in PHD is unknown. Spontaneous haemorrhagic phenomena are common in the general population, with up to 60% of patients developing epistaxis in their lifetime. Currently there are no estimates of the prevalence of spontaneous ecchymosis and hematohidrosis. In terms of PHDs, 11% of the population suffer from migraines. It is also possible that SEHP is a rare feature of PHDs with shared pathophysiology. The relative infrequency of SEHP associated with PHDs compared with other features of PHD such as photophobia and CAS suggests that patients with SEHP may also have specific anatomical, biochemical haemorrhagic phenomena.

This case of a South African 23-year-old Asian girl, which I followed for 8 years with recurrent bloody otorrhea associated with epileptic/migraine variant headache, demonstrates that SEHP may also occur in the ear as recurrent bloody otorrhea. This case demonstrated that long-term follow up might uncover new information and possible diagnosis. There is no treatment for hematohidrosis/bleeding except managing primary headache in our case being epilepsy/migraine variant which has been successfully controlled. Currently our patient is very stable and the family are happy, now that the condition has been diagnosed. Family confirmed that there is strong history of migraine and epilepsy in the family. Hematohidrosis or any unusual SEHP may be an early indication of migraine with its variant, which will require awareness and multidisplinary approach to control and manage this debilitating primary headaches with SEHP·I hope this hypothesis, and conclusion may answer many questions on hematohedrosis and SEHP in PHD.

Acknowledgements

Patient and family for allowing me to publish this article, my secretaries for typing and Dr. Cheryl Tosh for scientific editing.

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