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REVIEW

Syndromes that predispose to epistaxis

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Abstract

Purpose Our aim was to evaluate if epistaxis is directly associated with the etiology or pathophysiological mechanism which results in the syndrome itself or arises as a secondary effect.

Methods We performed an extensive literature review of the web-based PubMed database from the National Library of Medicine to ascertain syndromes related to this condition. Etiology, pathophysiological mechanisms, occurrence, clinical features and management were noted for each of these syndromes.

Results Epistaxis is commonly seen in syndromes that are usually directly related to vascular abnormalities or coagulation defects. However, in some cases, it is not.

Discussion and conclusion Since a number of these syndromes are rare and elaborate tests are not carried out in the absence of a positive family history or until other specific clinical features appear, a risk of underdiagnosis and the dilemma of whether epistaxis is specifically related to the syndrome or a secondary effect still remains.

Keywords Epistaxis · Syndrome · Genetic disorder · Bleeding diathesis · HHT

Introduction

Epistaxis is one of the most common emergencies in the ear, nose, and throat department with a lifetime incidence as high as 60% [1]. The distribution of epistaxis is bimodal. It is most common before age 10, and then peaks again between 45 and 65 years of age [2, 3]. Epistaxis is most commonly classified into anterior or posterior bleeds, with anterior bleeds more predisposed to younger patients. This division lies at the piriform aperture anatomically. More than 90% of episodes of epistaxis occur along the anterior nasal septum, which is supplied by Keisselbach's plexus in a site known as the Little's area [4]. The remaining 10% occurs in the Woodruff¨s plexus supplied by the sphenopalatine (SPA) and posterior nasal (PNA) arteries, terminal branches of the internal maxillary artery (IMA), which provide blood supply to the lateral nasal wall below the middle turbinate, rostrum of the sphenoid sinus, and posterior nasal septum. Therefore, a majority of posterior epistaxes arise from these two vessels [5].

Primary causes account for 85% of episodes and are idiopathic, spontaneous bleeds without any notable precipitant. Bleeds are considered secondary if there is a clear and definite cause [1, 6]. If not idiopathic, then anterior bleeds are mostly associated with local, whilst posterior with systemic causes.

Local causes may be further classified into traumatic including post-digital trauma in children [7], anatomic deformities [8], inflammatory reactions and intranasal tumors [9]; systemic causes may be hypertension, aberrations in clotting ability including liver dysfunction, chronic alcoholism [8], commonly used medications such as non-steroidal anti-inflammatory drugs (NSAIDS), warfarin, clopidogrel, and the oral factor X inhibitors [1], inherited bleeding diatheses (commonly associated with epistaxis are hemophilia A, hemophilia B, and von Willebrand disease) [8] as well as vascular diseases like Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome [10] or even cardiovascular diseases such as congestive heart failure, arteriosclerosis, and collagen abnormalities [8]. Environmental causes such as dry winter months, often associated with changes in temperature and humidity as well as circadian rhythm, with peaks in the

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morning and late afternoon [1] can also attribute to epistaxis. If we set aside, the usual causes of epistaxis and focus on cases with recurrent epistaxis or those with the tendency to bleed, then again these are mostly attributed to underlying defects in the coagulation cascade and vessel disorders [11] or otherwise just remain uninvestigated, unexplained or simply deemed unknown. Rarely, the condition can be related to a syndrome, which in turn, can be inherited or acquired.

Methods

We performed an extensive literature review of the web-based PubMed database from the National Library of Medicine to ascertain syndromes related to this condition using defined keywords. Etiology, pathophysiological mechanisms, occurrence, clinical features and management were noted for each of these syndromes. Amongst commonly occurring syndromes, only Osler–Rendu–Weber syndrome was included and other inherited bleeding diathesis were excluded.

Results

In total, 15 syndromes including the well-known HHT were ascertained; as such, 11 out of 15 were related to a genetic disorder or mutation. Pattern of inheritance was mainly autosomal dominant in familial cases. Only Gray platelet and Wiscott–Aldrich showed X-linked inheritance.

Twelve syndromes were attributed to disorders of primary hemostasis. Platelet disorders (quantitative effect or qualitative effect or both) are seen in most of the syndromes. Wiskott–Aldrich syndrome shows microthrombocytopenia, Emberger and Noonan syndromes are associated with amegakaryocytic thrombocytopenia, and MYH9-related disorder shows macrothrombocytopenia, whereas Bernard–Soulier, Glanzmann's thrombasthenia, Gray Platelet, Hermansky–Pudlak, and Heyde's syndromes have a combination of macrothrombocytopenia and thrombocytopathy. Vascular malformations were identified in Blue rubber bleb nevus, Heyde's, and Osler–Weber–Rendu syndromes. Emberger and 8p11 Myeloproliferative Syndromes are mainly myelodysplastic disorders. All these lead to prolonged bleeding time and also increase the risk of bleeding. Features associated with Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome is seen due to vasodilation (an autonomic nervous system response), which may be the most probable explanation for epistaxis. On the other hand, the remaining two had completely different causes that led to epistaxis; one being attributed to pathological fracture and the other iatrogenic.

Table 1 gives a concise summary of the syndromes along with the features and inevitable risks associated with the syndromes.

Discussion and conclusion

The findings show that 87% [10–19, 22–28, 30, 31] of syndromes related to epistaxis are attributed to disorders mainly related to platelets, blood vessels, or other coagulation factors. However, the remaining two of these syndromes were independently related to osteoclastic activity (pathological fractures leading to epistaxis) [20, 21] and hyponatremia (otorrhagia and epistaxis being the first recognizing symptoms of this syndrome) [29]. In the former, that is, Gorham–Stout syndrome (Vanishing bone disease), the cause of bleed is entirely different. This syndrome is of unknown etiology and extremely rare. It is characterized by destruction of osseous matrix and proliferation of vascular structures, hence resulting in destruction and absorption of bone. Eventually, near complete resorption of the bone occurs, resulting in the appearance of the so-called "vanishing bone" disease [21]. Epistaxis reported in such cases is attributed to pathological fractures occurring in nasal bones rather than just vascular proliferation. And, finally in the latter, in hysteroscopic surgery, a condition called operative hysteroscopy intravascular absorption syndrome can be induced due to intravascular absorption of fluid distention or irrigation medium leading to fluid and electrolyte imbalance. Interestingly, some authors mentioned that epistaxis and otorrhoea were the first reported clinical signs that mark this syndrome [29].

Management of epistaxis associated with syndromes can be rather challenging due to the nature (often recurrent and life threatening) and underlying cause of the bleed. It can be broadly categorized into two approaches: (1) preventive and (2) therapeutic.

1. Preventive:

Air humidification [8], application of lubricants, elimination of diets with high salicylate levels, natural antiplatelet activity, or high omega-3 activities [32] and finally, avoidance of nasal injury are generally the recommended preventive measures in chronic and recurrent bleeds [6, 8, 33]. Transfusion of blood and blood products including infection control should also be considered in syndromes associated with coagulopathies and immunodeficiency [13, 18, 22–24]. It is of great importance when such patients are indicated for surgical procedures or where significant blood loss is anticipated. The options are the same as systemic therapeutic approaches, which have been discussed in detail in section 2b below. Out of all the syndromes,

Table 1 A summary of syndromes that predispose to epistaxis

No.	Syndrome	Inheritence pattern	Frequency	Gene mutation	Clinical features
1	Bernard-Soulier [12, 13]	Familial AR, rarely AD	1/1000 000	GP1BA, GP1BB, GP9	Bleeding diathesis (spontaneous and post-traumatic hemorrhage)
2	Blue rubber bleb nevus [14, 15]	No hereditary pattern	200 cases worldwide	TEK	Upper digestive tract bleeding, cavernous hemangioma, consumptive coagualopathy, punctated purplish-blue skin lesions
		Familial AD rarely			In addition, arthralgia and bone deformities
3	Emberger [16, 17]	Familial AD	Less than 1/1,000,000	GATA2	Primary lymphoedema with hematological abnormalities (e.g., pancytopenia) and increased risk for myelodysplasia and leukemia
					In addition severe difuse warts, hypotelorism, epicanthus, long-tappered fingers
4	Glanzmann's Thrombasthenia [18, 19]	Familial AR, acquired autoimmune	1/1,000,000	ITGA2B, ITGB3	Bleeding diathesis, petechia, spontaneous hemarthrosis (rare)
					Common in children
5	Gorham-Stout [20, 21]	Acquired	200 cases worldwide	0	Dull aches, gradual onset of progressive weakness, osteolytic bone lesions, pathological fractures leading to bleeding diathesis
6	Gray platelet [22]	Familial AD/AR/X	60 cases worldwide	GPS	Bleeding diathesis, myelofibrosis, and splenomegaly
					Markedly high serum vitamin B12 levels
7	HHT or Osler-Weber-Rendu [10]	Familial AD	1/5000	ENG ALK-1	Visceral (cerebral, spinal, pulmonary, gastrointestinal, and hepatic) arteriovenous malformations
					Mucocutaneous telangiectasis
8	Hermansky-Pudlak [23]	Familial AR	1–9/100,000	AP3B1, AP3D1, BLOC 1S3, BLOC 1S6, DTNBP1, HPS1, HPS3-6	Bleeding diathesis
					In addition, oculocutaneous albinism. Other features such as pulmonary fibrosis, granulomatous colitis, or immunodeficiency may be seen
9	Heyde [24]	Acquired	Unknown	0	Triad of anemia due to gastrointestinal bleeding from angiodysplasia, acquired coagulopathy (von Willebrand syndrome type 2A) and calcific aortic stenosis
					Increased risk in the elderly
10	MHY9-RD includes May-Hegglin anomaly, Epstein, Fechtner and Sebastian syndrome [25, 26]	Familial AD	1–9/100,000	MYHD	Moderate risk of spontaneous mucocutaneous bleeding, including epistaxis, gum bleeding, or menorrhagia sensorineural hearing loss glomerular nephropathy cataracts (least common)
11	8p11 myeloproliferative [27]	Acquired	100 cases worldwide	FGFR1	Lymphadenopathy, hepatosplenomegaly, constitutivesymptoms related to B or T lymphoma or leukemia

Table 1 (continued)

No.	Syndrome	Inheritence pattern	Frequency	Gene mutation	Clinical features
12	Noonan [28]	Familial AD	1/1000 to 2500	PTPN11, SOS1, RIT1, RAF1 KRAS, NRAS, BRAF, and MAP2K1	Factor VIII, XI, XII deficiency Developmental delay, short stature, webbed neck, characteristic facies, congenital heart defects
13	OHIA [29]	Acquired	Rare	0	Hyponatremia, sudden increase in blood pressure, bilateral otorrhagia
14	SUNCT [30]	Acquired	1–9/100,000	0	Primary headache disorder characterized by unilateral trigeminal neuralgia and ipsilateral cranial autonomic symptoms (conjunctival injection and tearing)
15	Wiskott-Aldrich [31]	X-linked	1/100,000	WAS	Bleeding diathesis that can be life threatening Skin diseases Increased risk of developing autoimmune disorders and infections

HHT hereditary hemorrhagic telangiectasia, *MHY9-RD* Myosin heavy chain-9 related disorders, *OHIA* operative hysteroscopy intravascular absorption, *SUNCT* short-lasting unilateral neuralgiform headache with conjunctival injection and tearing

interestingly, OHIA is unique, since it is mostly iatrogenic. It has been advised that simple but essential measures such as reducing operating times, using the correct fluid irrigation medium, monitoring fluid balance, and correcting volume of deficit during hysteroscopic surgery can altogether prevent OHIA from occurring [29, 34]. Finally, genetic testing identifying underlying mutation(s) and counseling are extremely important and valuable to effectively avoid and treat any life-threatening situations in patients and their family members [10, 12–19, 22, 23, 25, 26, 28, 31]. Unfortunately, due to the common occurrence of epistaxis in the general population, rarity of these syndromes as well as unavailability, expense and lack of expertise in the field of medical genetics in many countries, genetic analysis is hardly employed.

2. Therapeutic: classified into (a) local and (b) systemic

(2a) Local: includes medical and surgical approaches.

Medical approaches:

Angiogenesis inhibitors, hormonal (combined estrogen—progesterone oral contraceptives), antifibrinolytics (tranexamic acid), and antioxidants (*N*-acetyl cysteine) [33] may be used; however, most of these carry significant side effects and still need further studies to prove complete safety and efficacy.

Surgical approaches:

These can be further divided according to severity of bleed:

Mild-to-moderate epistaxis—nasal packing, cautery (electrical or chemical), or laser coagulation [1, 3].

Severe epistaxis—endonasal ligation, where depending on the site of the bleed, the external carotid, internal maxillary, or sphenopalatine artery should be considered. 98% of posterior bleeds are controlled using ligation of sphenopalatine artery. This is one of the most widely used technique and has high specificity [1, 5]. Septal dermoplasty [35] and the Young's nasal closure procedure (nostrils sewn closed so breathing through the nose ceases) are mainly reserved for cases of HHT [36].

Two other surgical procedures to be mentioned are submucosal radiofrequency and nasal arterial embolization; nevertheless, long-term efficacy are yet to be evaluated [33].

(2b) Systemic:

Systemic management is very much based on the underlying disease. In most of these syndromes, treatment is aimed to control, correct, or prevent a coagulopathy. Blood and blood

product transfusions as well as iron supplementations are used to treat anemia in most of the coagulopathies. Platelet transfusion is of primary importance when there is a risk of life-threatening hemorrhage or excessive bleeding as seen in Bernard–Soulier, Glanzmann's thrombasthenia, Gray platelet, Hermansky–Pudlak, as well as Wiskott–Aldrich syndromes [13, 18, 22, 23, 31]. Desmopressin may be administered in cases with Factor VIII or von Willebrand factor deficiency [24, 28]. In syndromes with arteriovenous malformations such as Blue rubber bleb nevus, HHT, or Heyde, interventional procedures aiding large artery embolization reduces the risk of cerebrovascular accidents, portal hypertension, heart failure, and so on [37]. Primary lymphoedema seen in Emberger syndrome requires complete decongestive therapy (CDT) as the mainstay of treatment [16, 17]. Other options such as intravenous Ig therapy or allogenic transplantation may be considered in patients with Wiskott–Aldrich syndrome [31]. Chemotherapy is the standard approach where leukemia or lymphoma may pose a risk [16, 27]. Furthermore, sometimes, more drastic measures such as splenectomy or partial resection of the bleeding gastrointestinal tract may be necessary. The above-discussed mainly involve prevention of bleed, correction of coagulopathy, control of infection, and supportive therapy. In contrast, Gorham–Stout syndrome is managed completely differently due to the etiology. This is done by resection of osteolytic bone, radiation therapy, and, in some cases, bisphosphonates and interferon alfa-2b [20, 21].

In conclusion, 73% are related to a genetic disorder or mutation with possible incomplete or reduced penetrance making these syndromes very difficult to diagnose. Approximately 7–14% of the adult population will have experienced epistaxis at some point in their life [1], and therefore, history taking, frequency, and intensity of bleeds as well as recognition of associated symptoms become imperative. Laboratory investigations such as platelet count and function tests can be done as adjunct to genetic testing if clinical manifestations are suggestive of a particular syndrome. However it should be noted that in certain cases like HHT, there is no confirmatory laboratory test and, therefore, it is only identifiable by genetic testing. In acquired cases, other suitable diagnostic means such as radiography or bone marrow aspiration should be used. Since a number of these syndromes are rare and elaborate tests are not carried out in the absence of a positive family history or until other specific clinical features appear, a risk of underdiagnosis and the dilemma of whether epistaxis is a primary or secondary effect still remains.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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