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Migraine and Epistaxis: Clinical and Therapeutic Evidences

V. Pizza, G. Volpe^, A. Agresta*, V. Busillo°, A. Capasso*
U.O. Neurofisiopatologia, P.O. S. Luca, Vallo della Lucania (SA), ^ U.O. Neurologia, P.O. SS. Giovanni di Dio e Ruggi d'Aragona, Salerno, ° U.O. Neurologia, P.O. Maria SS Addolorata, Eboli, *Department of Pharmacy, University of Salerno, Italy.

Abstract

Migraine is a common neurological disorder characterized by painful episodes sometimes preceded by transient neurological symptoms and reversible defined migraine aura. Rarer forms of migraine are hemiplegic migraine, familial and sporadic, the retinal migraine and migraine equivalents. For the two most common forms of migraine with and without aura, the prevalence appears to be higher in females (5% and 11% respectively). In the literature there are very rare reports of primary migraine associated with epistaxis.

Therefore, in the present study we have observed a series of patients with migraine-associated phenomena recurrent epistaxis in order to define the clinical features and therapeutic response to flunarizine.

The study sample consists of 12 patients (7F and 5 M) suffering from migraine without aura (ICHD-II04 criteria) accompanied by epistaxis, migraine with a history of at least one year and an average age of 23.2 years (range 20-38). In 10 patients, episodes of migraine most often presented themselves during the day with epistaxis small claims, in a case of such gravity as to refer for medical treatment under emergency. In the other 2 patients, the headache, the higher frequency compared to the previous cases, it appeared only during sleep and is constantly accompanied episodes of moderate epistaxis. All patients were subjected to neurological examination, ENT and cardiology, holter pressure, routine laboratory tests and PT, PTT, fibrinogen, AT-III, d-dimer, EEG, CT and / or MRI brain, CT High focused on the definition of the facial complex ostiomeatale. All examinations were normal. Patients were subjected to drug therapy at a dose of flunarizine with 5mg/die, for three months, with significant ($P < 0.05$) reduction in the frequency of attacks monitored through a paper diary to monthly follow-ups and disappearance of the episodes of epistaxis.

In literature there are rare case reports of forms of primary headache associated with epistaxis. In our series of patients there is a definite diagnosis of migraine without aura with epistaxis closely associated with headache without any risk factor for epistaxis. The pathogenesis of epistaxis in migraine may be related to the complex vascular disorder at the base of this frequent neurological disorder. Based on this consideration, we subjected the patients to prophylactic therapy with a calcium channel blocker, the flunarizine, which resulted in not only a significant reduction in episodes of headache, but also the disappearance of epistaxis. Thus we seem to be able to conclude that migraine with epistaxis is an uncommon variant of migraine, the frequency is higher in females and can present an optimal response to drugs that modulate the tone of the vessel wall, such as calcium channel blockers.

Key words: migraine, epistaxis, prophylactic therapy, flunarizine

Introduction

Migraine is a neuro-vascular syndrome characterised by recurrent headache attacks associated with photophobia, phonophobia, nausea and vomiting. Migraine occurs in about 18 % of women and 6% of men, regardless of race or geographical location [1]. Currently, migraines are divided into two categories: migraine without aura (previously termed common migraine), and migraine with aura (previously also termed classical migraine) preceeded by a 15-20 minute episode of visual or sensory aura. Auras are most commonly visual alterations, such as hemianopsic field defects and scotomas that enlarge and spread peripherally [2] Visual auras are associated with spreading cortical depression; sensory auras are usually experienced as paraesthesias of the arm and face.

While the exact etiology of migraine headaches is unknown, several theories have been proposed. The vascular theory attributes migraines to an initial intra-cranial arterial vasoconstriction, resulting in reduced blood flow to the visual cortex, followed by a period of extra-cranial vasodilation [3]. Modern imaging techniques have shown that during a common migraine attack there are in fact only minor changes in cerebral blood flow, and the proposed initial vasoconstrictive phase may actually last much longer than the aura [4]. It has also been hypothesised that migraine sufferers have an inherent vasomotor instability and are more susceptible to the vasodilatory effects of certain physical and chemical agents. This point of view has been reinforced by the observation that organic nitrates, which are capable of delivering nitric oxide, trigger migraine attacks in migraineurs, at low doses, ineffective in normal subjects [5] .

Moskowitz's theory involves the trigeminovascular complex, which links the aura and the headache of migraine [6]. In this theory the trigeminovascular neurons release substance P and other neurotransmitters in response to various triggers .

The affected trigeminal nerve release of substances such as substance P, neurokinin A, calcitonin gene-related peptide, and nitric oxide which interact with the blood vessel wall to produce dilatation, protein extravasation, and sterile inflammation, stimulating the trigeminocervical complex as shown by induction of c-fos antigen by positron emission tomography (PET) scan.[7-9] This chain of events is further mediated by mast cells that release histamine and platelets that release serotonin. [8-15].

The release of these chemicals causes inflammation, and what is called peripheral sensitization. This is most likely, what results in the throbbing pain of migraine. Information then relayed to the thalamus and cortex for registering of pain and central sensitization explaining coetaneous allodynia. Involvement of other centers may explain the associated autonomic symptoms and affective aspects of this pain [12].

Nosebleed is a common pediatric complaint usually occurs in children aged 2-10 years with uncertain etiology in most cases. Its estimated that approximately 80% to 90% of all epistaxis occurs anteriorly, especially in children and young adults, and arise from the Little area, where the Kiesselbach plexus forms on the septum. The Kiesselbach plexus is where vessels from both the internal carotid artery (anterior and posterior ethmoid arteries) and the external carotid (sphenopalatine and branches of the internal maxillary arteries) converge [16,17]. Epistaxis that occurs in individuals older than 50 years is more likely to be severe and to originate posterior [18]. Epistaxis typically occurs when the mucosa is eroded and vessels subsequently break. Various local inflammatory reactions can alter the normal mucosa, causing dryness and crusting permitting the introduction of bacteria and subsequent formation of granulation tissue which characterized by increased vascularity and greater friability of the vessels which is easily bleed [16,17]. Jarjour et al [19] demonstrates a significant association between migraine and recurrent epistaxis in children. Recurrent epistaxis increased the odds of migraine more than fourfold. Moreover, these data raise the question of whether epistaxis may represent a precursor to childhood migraine and the two disorders may share a com-

mon pathogenesis.

Given the above evidences, in the present study we have observed a series of patients with migraine-associated phenomena recurrent epistaxis in order to define the clinical features and therapeutic response to flunarizine.

Patients and methods

The study was performed and approved by Neurophysiopatology Service, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA), Italy.

The study sample (See Table I) consists of 12 patients (7F and 5 M) suffering from migraine without aura (ICHD-II04 criteria)[20] accompanied by epistaxis, migraine with a history of at least one year (4.1 years, SD 3.4) and an average age of 23.2 years (range 20-38, SD4.9). In 10 patients, episodes of migraine most often presented themselves during the day with epistaxis small claims, in a case of such gravity as to refer for medical treatment under emergency. In the other 2 patients, the headache, the higher frequency compared to the previous cases, it appeared only during sleep and is constantly accompanied episodes of moderate epistaxis. All patients were subjected to neurological examination, ENT and cardiology, holter pressure, routine laboratory tests and PT, PTT, fibrinogen, AT-III, d-dimer, EEG, CT and / or MRI brain, CT High focused on the definition of the facial complex ostiomeatale. All examinations were normal. All patients were monitored using a paper diary and underwent follow-up monthly. Patients were subjected to drug therapy at a dose of flunarizine with 5mg/die (for 20 days/months), for three months. The comparative statistical analysis of the results was carried out through the use of t-test

Results

The baseline frequency of monthly attacks (6, SD 2.5) were compared to follow-up at 1, 2 and 3 months, respectively (3, SD 1.3, 1.6, SD 0.6, 0.6 , SD 0.9) (See Fig. 1) through statistical analysis using t-test and flunarizine was able to reduce significantly ($P < 0.05$) the frequency of attacks. Two patients complained of nausea and other two patients showed sleepiness by using the drug, but these side effects have not proved to be of such magnitude as to compel discontinuation of treatment.

Discussion

In literature there are rare case reports of forms of primary headache associated with epistaxis. In our series of patients there is a definite diagnosis of migraine without aura with epistaxis closely associated with headache without any risk factor for epistaxis. The pathogenesis of epistaxis in migraine may be related to the complex vascular disorder at the base of this frequent neurological disorder. Based on this consideration, we subjected the patients to prophylactic therapy with a calcium channel blocker, the flunarizine, which resulted in not only a significant reduction in episodes of headache, but also the disappearance of epistaxis.

Although the efficacy of flunarizine in migraine patients was already reported [21-24], this is the first study indicating the efficacy of flunarizine not only in migraine but also in the disappearance of epstaxis

The majority of recurrent epistaxis in young adults originates in the anterior septum from the Kiesselbach plexus. Terminal branches from external and internal carotid arteries coalesce in this area to form an arterial border zone, which is part of the trigeminovascular system. This system is implicated in the pathogenesis of migraine [25]. Stimulation of the trigeminal nerve in the mucosa of the nose or Para nasal sinuses, or via a brainstem reflex, has been demonstrated to increase blood flow in the extra cerebral, but not intracerebral circulation [26]. Another study demonstrated increases in cerebral blood that epistaxis in the migraine patients, results from repeated partial activation of the trigeminovascular system leading to extreme nasal arteriolar dilatation and bleeding [27]. Concurrent timing of epistaxis with the throbbing headache which is the

phase of vasodilatation, 8 majority of epistaxis occurred at the same side of headache and the observations by Tunis and Wolff [28] of extra cranial vessels become distended and pulsatile during a migraine attach lend support to such a hypothesis. Epistaxis, possibly facilitated by altered nasal mucosa [16,17] as a result of recurrent vasoconstriction and sterile inflammatory reaction during migraine attach [9,10] and Altered hemostasis in migraine [29].

The migraine headache relived repeatedly fallowing epistaxis in some patients, a result, which can be explained by the response of local vasoconstriction fallowing any bleeding [30] it is the mechanism of action in some pain abortive medications for migraine [12,31].

Due to its multiple physiologic effects, including interference with vasoconstriction, protection against brain hypoxia, antihistaminic activity and serotonin antagonism, Flunarizine, a calcium channel blocker, is being considered as an agent for the prophylactic treatment of migraine [32-42] .

Flunarizine interfere with mechanisms possibly involved in migraine pathogenesis. Its direct protection on brain cells, inhibition of vasoconstriction, reduction of"spreading cortical depression" (in experimental conditions) and modulation of some neurotransmitter systems may be involved in the multifactorial genesis of migraine, thus accounting for its efficacy in the prophylaxis of this disease [32-42].

Used in the prophylaxis of migraine, occlusive peripheral vascular disease, Flunarizine inhibits the influx of extracellular calcium through myocardial and vascular membrane pores by physically plugging the channel. The decrease in intracellular calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload [32-40]. Therefore, the ability of Flunarizine to block epistaxis in migraine patients may be related to the its vasocostrictive properties.

In summary, this study demonstrates a significant association between migraine and recurrent epistaxis in adults, and raises the question of whether recurrent epistaxis is a precursor to migraine. Advancing our understanding of the comorbidity of migraine and epistaxis and may provide clues to the pathophysiology of migraine and epistaxis. Moreover, it may have diagnostic and therapeutic implications.

Thus we seem to be able to conclude that migraine with epistaxis is an uncommon variant of migraine, the frequency is higher in females and can present an optimal response to drugs that modulate the tone of the vessel wall, such as calcium channel blockers.

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N° patients	sex	age	D. Y.	F. A.	F.A. > 1month	F.A. >3months	F.A. >6months	C. D.	S. E.
1	F	24	4	8	4	2	0	N	somnolence
2	M	24	5	5	3	2	0	N	N
3	F	22	12	6	6	1	0	N	N
4	M	38	9	9	4	2	1	N	N
5	F	22	6	4	3	1	1	N	N
6	M	23	3	6	4	2	0	N	N
7	M	23	2	4	2	3	3	N	N
8	F	20	1	5	2	1	1	N	nausea
9	F	21	1	4	2	1	1	N	nausea
10	F	20	1	6	2	2	0	N	N
11	F	20	2	12	1	1	0	N	N
12	M	22	3	3	3	2	1	N	somnolence

Table 1. Patients data

Legend:
D.Y.: disease years
F.A.: frequency attacks
C.D.: concomitant disease
S.D.: side effects

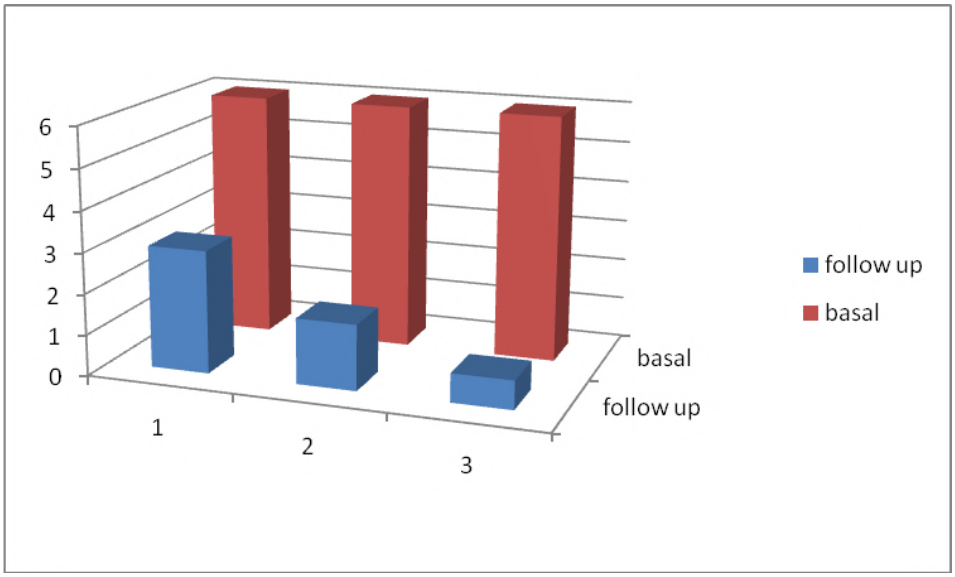

Fig. 1 Comparison values vs. baseline seizure frequency follow-up

Legend:
1= 1 month
2= 2 months
3= 3 months