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Original Articles

Migraine and Recurrent Epistaxis in Children

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Recurrent epistaxis is a common pediatric problem with uncertain etiology in most cases. We observed frequent complaints, or history of epistaxis in children with migraine. The aim of this study was to determine whether there is an association between epistaxis and migraine in children. A detailed questionnaire was used to conduct a study of 45 consecutive patients, ages 6-11 years, with migraine, diagnosed according to the 1997 proposed pediatric revisions to the International Headache Society criteria; the patients were evaluated in our Pediatric Neurology Clinic. Control subjects consisted of 64 children without recurrent headaches, matched as a group for age and sex, and drawn as a convenient sample from two general pediatric practices and an elementary school. Sixteen (36%) of 45 patients with migraine had epistaxis as compared with 7 (11%) of 64 control subjects (odds ratio = 4.5; 95% confidence interval 1.6-12.1; $P = 0.002$). Epistaxis began an average of 3 years before migraine with similar characteristics to idiopathic epistaxis in habitual nosebleeders, such as onset in early childhood, high incidence in sleep, and family history of epistaxis. This study 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. The two disorders may share a common pathogenesis, and a prospective, longitudinal study is required to define further the relationship between them.

Jarjour I, Jarjour L. Migraine and Recurrent Epistaxis in Children. Pediatr Neurol 2005;33:94-97.

Introduction

Nosebleeds are quite common in children and are rarely life-threatening. The majority of nosebleeds are mild, self-limited, spontaneous, and recurrent [1,2]. Nosebleeds often cause significant parental concerns and remain a challenging problem to patients and physicians alike. A study of 1218 schoolchildren ages 11-14 years found that 78 (6.5%) children had at least one nosebleed [3]. Another study found that an estimated 8% of children below age 20 years are habitual nose-bleeders with three or more nosebleeds per year [4]. Moreover, 70% of these habitual nose-bleeders have no apparent cause or trigger [4]. Schulman evaluated 34 children with recurrent nosebleeds with coagulation studies [5]. Half of the children with no other bleeding problem besides epistaxis had normal coagulation and bleeding studies. He emphasized that "the question of causation is the most difficult of all," "several suggested factors such as upper respiratory infections, hypertrophic adenoids and tonsils, picking the nose, allergies, dry and overheated rooms," "but I must say that by and large the pathogenesis is obscure" [5]. Similar conclusions of unknown etiology of most nosebleeds were reached in a study of 1724 pediatric and adult patients [6]. In our Pediatric Neurology Clinic, frequent complaints, or history, of nosebleeds in children being treated for migraine were observed. A computer-aided search of the medical literature identified brief case reports of the coexistence of migraine and epistaxis in adults [7-9], but we found no controlled studies. Given the high prevalence of migraine in childhood, which is 4-11% in children ages 7 to 11 years [10], one may expect migraine and nosebleeds to coexist by chance alone. Therefore, this study was conducted to reveal whether there is an association between recurrent epistaxis and migraine, and to explore whether recurrent epistaxis in children with migraine has similar or different characteristics to epistaxis in habitual nose-bleeders.

Methods

The study was undertaken of children with migraine, ages 6-11 years, who were examined consecutively for evaluation of recurrent headaches in the same Pediatric Neurology Clinic over a 3-year period from 1996

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Received November 17, 2004; accepted February 14, 2005.

doi:10.1016/j.pediatrneurol.2005.02.006 • 0887-8994/05/$—see front matter

to1999. This age group of children was selected because they are more commonly affected by recurrent nosebleeds than infants or adolescents [2,11]. Moreover, many children outgrow the problem of recurrent nosebleeds by adolescence [12]. Migraine was diagnosed using proposed pediatric migraine revisions to the International Headache Society criteria [13,14]. These revisions included duration of headache of 1-48 hours, bilateral frontal or temporal, or unilateral location, and photophobia or phonophobia or both [13,14]. Control subjects consisted of 64 children, ages 6-11 years, without recurrent headaches, matched as a group for age and sex, and drawn as a convenience sample, between September 1997 and January 1998, from an elementary school (23 children) and two general pediatric medical practices (41 children). These three settings represent a diverse geographic and socioeconomic population in the greater Pittsburgh region, from which most of our patients come. Participation in the study was voluntary, and all children ages 6-11 in the school or pediatric practices' waiting rooms were eligible to participate. An informed consent was obtained from the parents. Figure 1 illustrates the study flow.

The prevalence of recurrent epistaxis in patients and control subjects was evaluated by means of a detailed questionnaire with 50 questions concerning the presence or absence of recurrent headaches and nosebleeds, the frequency of headaches, age of onset, duration, location, quality of pain, influence of physical activity, associated symptoms, use of nonsteroidal anti-inflammatory drugs or aspirin, various characteristics of nosebleeds, and relevant family history. The word "migraine" did not appear in the questionnaire. The same questionnaire was used in patients and control subjects and was completed by parents as a self-report. Controls were excluded if the parents indicated that the child has had recurrent headaches. A child was identified as having recurrent epistaxis if the parents answered yes to the question: "Has your child ever had recurrent nosebleeds?" In the case of control subjects, the provision of the child's name was optional. All patients with migraine had complete general and neurologic examinations, and appropriate diagnostic testing when necessary. No secondary causes for recurrent headaches were determined in these patients.

Statistical differences for discrete variables between the two groups were evaluated with chi-square and logistic regression analysis. The association between migraine and recurrent epistaxis was evaluated by Spearman's rho correlation and by logistic regression, after controlling for family history of recurrent headache, age, and sex. Differences between the age of patients and control subjects were evaluated with Student's *t* test, while sex differences were evaluated with chi-square test. The data analysis was conducted using the SPSS software package, version 11.5, and power calculations were performed using the NQUERY program.

Results

There were 45 patients with migraine with a mean age of 8.84 years, and 23 were males. Control subjects consisted of 64 children with a mean age of 8.45 years; 38 were males. There was no statistical difference between patients and control subjects with respect to sex and age. The prevalence of recurrent epistaxis in patients with migraine was 16 (36%) of 45, as compared with 7 (11%)

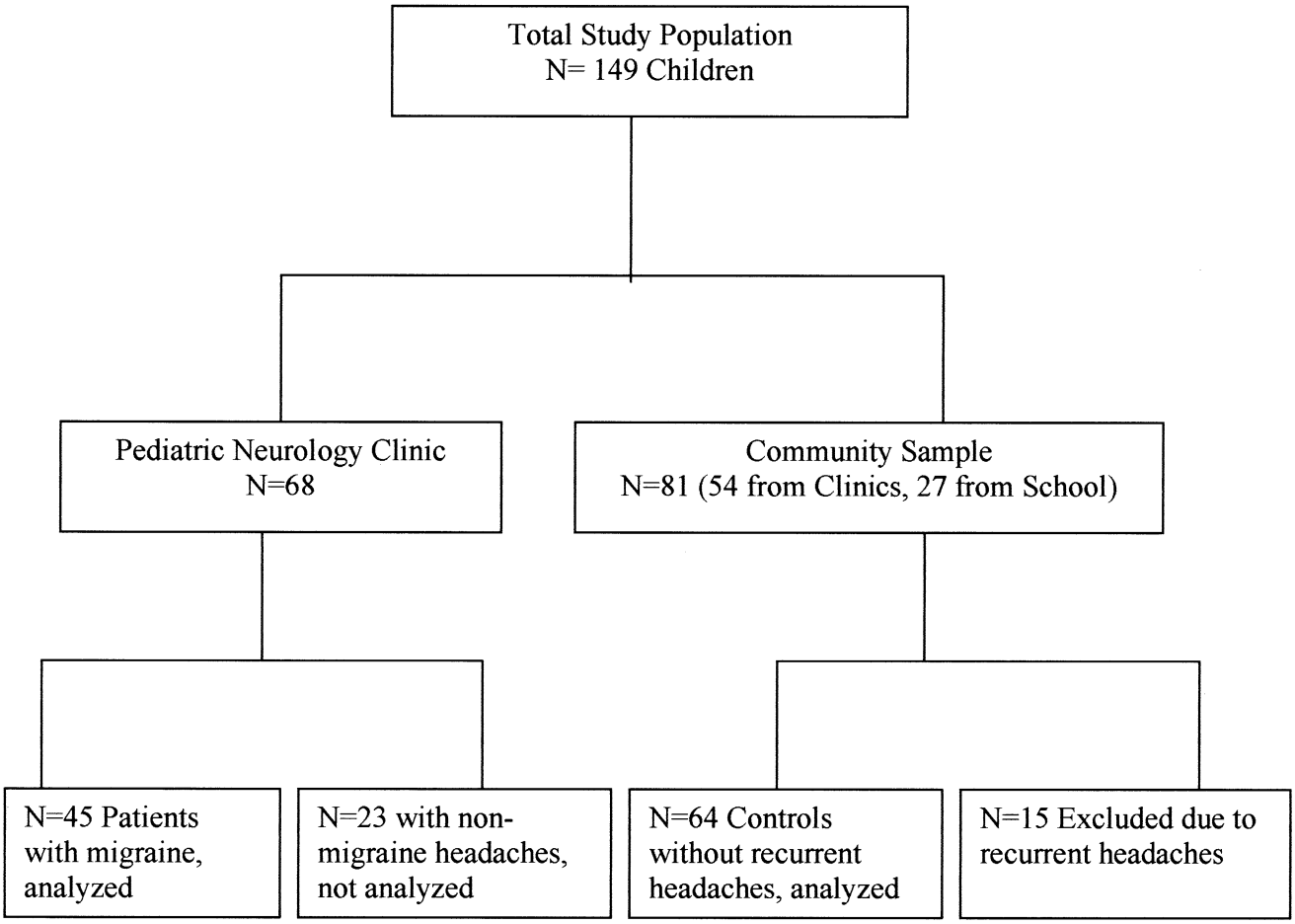

Figure 1. Study flow diagram illustrates subject recruitment.

of 64 control subjects (odds ratio [OR] = 4.5; 95% confidence interval [CI] 1.6-12.1; $P = 0.002$). Spearman's rho analysis confirmed a significant correlation between migraine and recurrent epistaxis ($r = 0.297$, $P = 0.002$). Patients with migraine were 4.5 times more likely to have a history of recurrent epistaxis than control subjects, even after controlling for age, sex, and family history of recurrent headache (OR = 4.3; $F = 5.6$; 95% CI 1.2-14.3; $P < 0.02$). With the sample size of 45 patients and 64 control subjects, the power to detect the observed odds ratio value of 4.3 is 90%. The prevalence of epistaxis in patients with migraine with aura was 4 (44%) of 9 patients, as compared with 12 (33%) of 36 patients with migraine without aura (P not significant). The prevalence of epistaxis in females with migraine (9/22, 41%) did not differ significantly from that in males (7/23, 30%). Nosebleeds were temporally related to headache attack in 5 (11%) of 45 patients. Recurrent epistaxis began 6 months to 8 years (mean interval of 3 years) before migraine in 13 patients (81%), around the same time in 2 patients (13%), and 1 year later in one child (6%). The prevalence of epistaxis in patients with migraine who did not receive nonsteroidal anti-inflammatory drugs was 8 (38%) of 21, as compared with 7 (11%) of 64 control subjects (OR = 5; 95% CI 1.5-16.3; $P = 0.005$). Table 1 describes the characteristics of epistaxis in patients and control subjects.

The prevalence of recurrent epistaxis among children who were excluded from data analysis (Fig 1) was 3 (13%) of 23 neurology clinic patients with nonmigraine headaches and 6 (40%) of 15 children with migraine (4 children) or probable migraine (11 children) in the community sample.

Table 1. Characteristics of epistaxis in patients with migraine and controls

Characteristic, n (%)	Migraine	Controls
Prevalence of epistaxis	16 (36)	7 (11)*
Age at onset, year (range)	3.9 (1–10)	4.8 (2–9)
Family history	10 (62)	6 (86)
Diurnal pattern†		
Anytime	11 (69)	6 (86)
Sleep only	4 (25)	0
Daytime only	1 (6)	0
Seasonal pattern		
Winter	2 (13)	1 (14)
Spring	0	0
Summer	2 (13)	0
Fall	2 (13)	2 (29)
Same all seasons	9 (56)	4 (57)
Medication history‡	4 (25)	3 (43)
Evaluation by physician	2 (13)	3 (43)

* $P < 0.01$, prevalence of epistaxis in patients with migraine vs control subjects, Pearson chi-square test, and Spearman's rho correlation.
† One control has missing data.
‡ Medications taken around the time of nosebleeds did not include aspirin or nonsteroidal anti-inflammatory drugs in any of the patients or control subjects.

Discussion

This study reveals that the prevalence of recurrent epistaxis is significantly higher in children with migraine than in control subjects. Recurrent epistaxis in childhood increased the odds of migraine more than fourfold. Moreover, epistaxis in children with migraine has similar characteristics to recurrent, idiopathic epistaxis as described in otolaryngology literature [1,2,4,5,12]. The similarities include onset in early childhood, high incidence in sleep, rarity of seeking medical evaluation for epistaxis, and high prevalence of epistaxis in immediate family members. Recurrent epistaxis begins an average of 3 years before migraine, suggesting that epistaxis may represent another precursor to migraine. The new International Headache Society criteria list cyclic vomiting, abdominal migraine, and benign paroxysmal vertigo as childhood periodic syndromes that are common precursors of migraine [14].

The majority of recurrent epistaxis in children originates in the anterior septum from the Kiesselbach plexus [1,2]. 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 [15]. Stimulation of the trigeminal nerve in the mucosa of the nose or paranasal sinuses, or via a brainstem reflex, has been demonstrated to increase blood flow in the extracerebral, but not intracerebral circulation [16]. Another study demonstrated increases in cerebral blood flow with noxious stimulation of nasal trigeminovascular nociceptors [17]. We speculate that epistaxis, without or with concurrent migraine, in the migraine-prone child, results from repeated partial activation of the trigeminovascular system leading to extreme nasal, arteriolar dilatation and bleeding [18]. Observations by Tunis and Wolff [19] of dilated extracranial arteries between migraine headaches with facial flushing before headaches lend support to such a hypothesis.

One potential risk factor for epistaxis in children with migraine is therapy with nonsteroidal anti-inflammatory drugs or aspirin. This mechanism is unlikely in the present study. First, epistaxis began months to years before migraine in most patients. Second, recurrent epistaxis was five times more likely in patients with migraine who did not receive nonsteroidal anti-inflammatory drugs than in control subjects ($P = 0.005$). Third, none of the children with migraine received aspirin. Finally, the four patients who received medications around the time of nosebleeds did not take nonsteroidal anti-inflammatory drugs.

One potential limitation of this study is the Berkson's bias [20]. Our patient ascertainment was from a headache clinic with more difficult-to-treat patients, which would theoretically increase the likelihood of epistaxis from causes unrelated to migraine. However, we do not find any evidence for such a bias in the present study because the prevalence of epistaxis in the patient group with migraine

of 36% was close to the 40% prevalence in children with migraine identified at random from the community. Moreover, of the 16 children with migraine and epistaxis, only one child had a history of concurrent paranasal sinus disease and blood disorder, and the remaining 15 children were in good general health.

The prevalence of epistaxis in this study was dependent on parents' recall of whether their child has ever had recurrent nosebleeds. One may assume that parents are more likely to report epistaxis to a physician because of their concern that bleeding points to some potentially alarming pathogenesis. An extended, longitudinal study would help us address this potential recall bias.

Another potential limitation of this study is the difference in the period of recruitment between patients and control subjects. Patients were enrolled between 1996 and 1999, and control subjects were enrolled between 1997 and 1998. If epistaxis has a seasonal association, then this issue might result in bias of the findings. However, our data on seasonal pattern of epistaxis in patients with migraine (Table 1) do not suggest a seasonal association.

In summary, this study demonstrates a significant association between migraine and recurrent epistaxis in children, and raises an important question of whether recurrent epistaxis is a precursor to migraine in childhood. Advancing our understanding of the comorbidity of migraine and epistaxis through future prospective and longitudinal studies has diagnostic and therapeutic implications and may provide clues to the pathophysiology of migraine and epistaxis.

We acknowledge Sati Mazumdar, PhD, for her help with data analysis and statistical expertise. We thank the physicians and staff at Bellevue Pediatric Associates and AGH Pediatrics, and the staff and families at Trinity Christian School in Pittsburgh for help with subject recruitment.

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