RETRACTED
MOTION SICKNESS IN CHILDHOOD MIGRAINE

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ABSTRACT

Background: *Migraine is a chronic, progressive, and debilitating disorder that has an impact on the lives of millions of individuals. The origins of the disability can be traced into childhood and adolescence for most adult migraine sufferers. The group of periodic syndromes consists in symptoms related to migraine, thought to be migraine equivalent or precursors.*

Aim of this study is to assess the role of MS as risk factors for childhood migraine.

Materials and methods*: 441 subjects (211 Females) aged 6-13 years (mean 9.20; SD 2.42), consecutively referred between October 2007 to March 2009 for primary headaches to pediatric Centers for Headache in Childhood. Control group consisted of 365 subjects (175 F) aged 7-13 years (mean 9.08; SD 3.02).*

Results*: Two groups were not different for age (F=0.390; p=0.539) and sex ratio (Chi-square=0.002; p=0.966). Headache percentage distribution was the following: MoA 38.32%, MA 11.11%, FETTH 16.78%, CTTH 20.63%. Logistic regression shows a greater OR for CVS and MS associated for migraine group (MoA and MA patients), respectively 8.28 (IC95% 2.35 - 29.16) for CVS and 5.22 (IC95% 3.5 - 7.77); moreover, CVS cause a consistent increase in OR of 3.69 (IC95% 2.21 - 6.17) also for headache group (CTTH and FETTH patients).*

Discussion*: Periodic syndromes could be considered the natural precursors of migraine almost but not only in children, as reported in some studies in adulthood.*

Keywords*: childhood migraine, periodic syndromes, Abdominal Migraine, Motion Sickness, Cyclic Vomiting, Growing Pains.*

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Introduction

Migraine is a chronic, progressive, and debilitating disorder that has an impact on the lives of millions of individuals. The origins of the disability can be traced into childhood and adolescence for most adult migraine sufferers[(1)].

In the twentieth century, clinical reports have been recognized some migraine precursors occurring from infancy to adolescence that lack a prominent headache component[(2, 3)]. These specific syndrome complexes have been labeled migraine equivalents, or periodic syndromes of childhood with a decrease in frequency and duration linked to growth.

These are thought to share a pathogenetic and causal relationship to more typical childhood migraines by their periodic nature, similarity to more well-established adult migraine syndromes, backdrop of a strong family history of migraines in

the affected child, and the later evolution in the individual child to more typical migraines[4].

Synthetically, the group of periodic syndromes consists in symptoms related to migraine, thought to be migraine equivalent or precursors.

The International Headache Society (IHS) criteria[5] computed only three "periodic syndromes" as precursors of migraine: Cyclical Vomiting Syndrome (CVS) [G43.82] (Table1), Abdominal Migraine (AM) [G43.820], Benign Paroxysmal Vertigo of childhood (BPV) [G43.821]. In clinical practice, it's well known that also other recurrent syndromes such as Growing Pains (GP), Periodic Fever (PF) and sleep disorders are very frequent in children with migraine, particularly in paediatric age range.

	Migraine (n=218)		Headache (n=165)	
	OR	IC95%	OR	IC95%
MS	5,22	3,5 - 7,77	0,90	0,52 - 1,55
CVS	8,28	2,35 - 29,16	4,74	1,88 – 11,98
AM	2,82	1,71 - 4,65	3,69	2,21 – 6,17
GP	3,63	2,22 - 5,93	1,78	0,99 – 3,21

Table 1: Shows the OR of each periodic syndromes in migraine and headache subjects versus control group. *MS: Motion Sickness; CVS. Cyclic.Vomiting; AM: Abdominal Migraine; GP: Growing Pain.*

Moreover, CVS and AM are relatively unusual periodic syndromes, characterized by recurrent and severe paroxysmal episodes of vomiting and/or abdominal pain lasting hours to days separated by weeks to months of no symptoms. Anyway, it's important to pinpoint that AM includes also a subset of patients with chronic recurrent abdominal pain who have features that overlap with those of migraine without aura (MoA)[6].

Although these syndromes have been known for decades[7, 8], their suggested relationship to migraine remains a matter of debate.

For example, regarding sleep disorders, it's interesting to note that migraineous children show a variety of sleep troubles such as parasomnias, sleep breathing disorders and excessive daytime sleepiness as reported in literature and confirmed by polysomnographic findings[9, 10]. On this perspective, also sleep disorders could be considered precursor of migraine because are frequent in intercritical periods and their resolution could improve sensibly migraine symptoms such as pain intensity and temporal duration of attacks.

Another syndrome strictly associated with migraine is Motion Sickness (MS), a condition dominated by disagreement between visually perceived movement and the vestibular system's sense of movement. The most common symptoms MS are dizziness, fatigue, and nausea. MS is not coded in the actual IHS classification as migraine precursor or migraine equivalent, even if MS was reported in children with recurrent vomiting suggesting a predisposition for developing migraine[11].

Aim of this study is to assess the role of MS as risk factors for childhood migraine.

Materials and methods

Study population consists of 441 subjects (211 F) aged 6-13 years (mean 9.20; SD 2.42), consecutively referred between October 2007 to March 2009 for primary headaches to pediatric Center for Headache in Childhood.

Headache types were diagnosed according IHS-2004 criteria by an expertise clinicians. In headache group were diagnosed only Chronic tension-type headache (CTTH) and Frequent Episodic Tension-Type Headache (FETTH); in migraine group were diagnosed Migraine with Aura (MA) and Migraine without Aura (MoA).

In order to select only patients with primary headaches, each patient was evaluated by clinical interview and examination as well by neurophysiological recordings (wake and sleep EEG) and neuroimaging assessment (TC scan and MRI).

Exclusion criteria were neurological (i.e. epilepsy, cerebral tumors, movement disorders), psychiatric (i.e. anxiety, depression, eating disorders) and muscular disorders, otolaryngology problems (i.e. vestibular alterations, Meniere syndrome, otitis), gastrointestinal diseases, rheumatic arthritis. All subjects and parents of both groups were interviewed about the presence of migraine equivalents with an ad hoc questionnaire.

Results were compared with findings obtained in a control group of 365 subjects (175 F) aged 7-13 years (mean 9.08; SD 3.02), recruited in local schools of Campania region. Informed consent was obtained from all parents' subjects and from children of both groups.

Statistical analysis

Chi-square test and logistic regression were performed in both group to assess the difference in prevalence and the role of single migraine precursor

and MS as risk factor for headache and for migraine. According to a previous Italian report motion sickness prevalence (alone or associated with other symptoms) in migrainous children was 61% vs. 17% of control group[12]. Herein, to calculate the sample size was used the online software www.dssresearch.com/toolkit/sscalc/size_p2.asp.

The P level was set at <0.05 for statistical significance. All data were coded and analyzed using the commercially available STATISTICA 6.0 package for Windows (StatSoft, Inc., Tulsa, OK).

Results

Control group consists of 365 subjects (175 F) aged 7-13 years (mean 9.08; SD 3.02); matched for age (F=0.390; p=0.539) and sex ratio (Chi-square=0.002; p=0.966).

Headache percentage distribution was the following: MoA 38.32%, MA 11.11%, FETTH 16.78%, CTTH 20.63% (Figure 1). In 13.15% of headache subjects was not possible a diagnosis according to IHS criteria and coded as CNC (Criteria Not Classified) and excluded from study group.

About PF and BPV, no one in study group and in healthy controls was affected.

Moreover, sleep disorders prevalence was assessed but not computed in this study in order to avoid a potential confounding effect.

In healthy control group the percentage of symptoms of periodic syndrome was the following: MS 13.97%; CVS 1.92%; AM 8.22%; GP 7.95%.

Periodic syndromes are more prevalent in migraine group than headache group. Moreover, MS is strongly associated with migraine (Chi-square = 46.217; p<0.001), as GP prevalence (Chi-square = 6.010; p=0.014). CVS and AM shows no statistic differences in migraine group respect of headache subjects.

Logistic regression shows a greater OR for CVS and MS associated for migraine group (MoA and MA patients), respectively 8.28 (IC95% 2.35 – 29.16) for CVS and 5.22 (IC95% 3.5 - 7.77); moreover, CVS cause a consistent increase in OR of 3.69 (IC95% 2.21 - 6.17) also for headache group (CTTH and FETTH patients) as summarized in Table 1.

In Table 2 has been shown the OR of association of two migraine equivalents; in migraine group the strongest association is AM plus GP with an OR of 24.98 (IC95% 3.26 - 191.35), but the same association cause a significant increase in OR also in headache group (OR 21; IC95% 2.64 - 167.17). The association with MS causes an increase in OR in migraine group and less in headache subjects. Specifically, the association of MS plus CVS has an OR of 10.30 (IC95% 1.23 - 86.15) in migraine subjects and in headache group its OR is 4.47 (IC95% 0.40 - 49.61).

	Migraine (n=218)		Headache (n=165)	
	OR	IC95%	OR	IC95%
MS plus CVS	10.3	1.23 – 86.15	4.47	0.40 – 49.61
MS plus AM	11.16	3.82 – 32.64	4	1.15 – 13.85
MS plus GP	9.75	3.68 – 25.80	1.79	0.47 – 6.75
CVS plus AM	10.3	1.23 – 86.15	9.04	1.0 – 81.55
CVS plus GP	12.08	1.48 – 98.83	4.47	0.40 – 49.61
AM plus GP	24.98	3.26 – 191.35	21	2.64 – 167.17

Table 2: Shows the OR of association of two migraine equivalents in migraine and headache subjects versus control group.
MS: Motion Sickness; CVS: Cyclic Vomiting Syndrome; AM: Abdominal Migraine; GP: Growing Pain.

Moreover, MS associated with AM has an OR of 11.16 (IC95% 3.82 - 32.64) and MS associated with GP has OR of 9.75 (IC95% 3.68 - 25.80) both in migraine group. In headache subjects, respectively the same associations show an OR of 4.0 (IC95% 1.15 - 13.85) for MS plus AM and 1.79 (IC95% 0.47 - 6.75) for MS plus GP.

Table 3 shows the differences in OR between MoA and MA group and the MS increases strongly the OR to have MoA (OR = 6.08; IC95% 3.99 - 9.28), and CVS increases strongly the OR to have MA (OR = 5.81; IC95% 1.77 - 19.10).

	Migraine (n=49)		Headache (n=165)	
	OR	IC95%	OR	IC95%
MS	2.99	1.53 – 5.81	6.08	3.99 – 9.28
CVS	5.81	1.77 – 19.10	2.88	1.05 – 7.86
AM	3.62	1.71 – 7.67	2.61	1.53 – 4.46
GP	4.63	2.24 – 9.59	3.36	1.99 – 5.67

Table 3: shows the OR of each migraine equivalent in migraine without aura (MoA) and in migraine with aura (MA) subjects versus control group.
MS: Motion Sickness; CVS: Cyclic Vomiting Syndrome; AM: Abdominal Migraine; GP: Growing Pain.

Discussion

Periodic syndromes could be considered the natural precursors of migraine almost but not only in children, as reported in some studies in adulthood[13-15].

In school-aged children there are only few reports and the prevalence of migraine precursors in a large paediatric sample could be estimated in 68% for BPV and 65% for AM associated with CVS in positive family history of migraine children[16].

In a previous Italian paediatric samples[11], in migraine children the prevalence of CVS was 40% and AM was 30%, differing from our findings (respectively 6.42% for CVS and 20.18% for AM). A possible explanation in this difference could be found in difficulty in discriminating the symptoms of CVS and AM from signs of irritable bowel syndrome, frequent in children particularly with migraine[16, 17]. In our study, MS has been strongly associated with migraine symptoms, particularly with MoA as reported by Lanzi et al.[11].

MS results in a variety of symptoms, including dizziness, nausea, cold sweat, pallor, lethargy, headache and can be induced by motion alone or conflicts among difference balance systems, including vestibular, visual, and proprioceptive systems.

Actually, the phenomenon of MS has no a clear explanation even if could be hypothesized that is "an eliciting or reinforcing stimulus for conditioned avoidance of potentially dangerous situations"[18].

Moreover, it's well known the susceptibility of migraineurs to symptoms induced by optokinetic stimulation[19] with an unknown pathogenesis.

Anyway, because serotonergic drugs with triptans block emesis during motion sickness[20, 21], low levels of serotonin in the vestibular or emetic pathways of migraineurs might increase susceptibility to nausea. Moreover, an abnormal central serotonin turnover and an associated increase in serotonin receptor sensitivity may compromise pain modulation and increase susceptibility to migraine[22; 23].

In order to our findings, when MS is associated with another migraine equivalent, the OR increases but it seems that the weight of AM and MS in migraine group could be similar (Table 2).

Moreover, in MoA children the prevalence of parasomnias is higher than control[8], how if the alteration of serotoninergic neurotransmission typical of disorders of arousal group (i.e. sleepwalking, sleeptalking) could be reinforced or sustained by the similar imbalance due to migraine syndrome, confirming the 5-HT role in MS and the effects of triptans[21, 22].

On other hand, in MA subjects is frequent the restless leg syndrome (RLS) linked to dysfunction in dopaminergic systems (24-26) and related to sympathetic hyperactivity as CVS[27-74].

Conclusions

According to our findings, we suggest that MS could be included into IHS classification as childhood periodic syndromes that are commonly precursor of migraine, considered its strong prevalence, its similar weight to increase the risk to develop migraine headache and association with others migraine equivalents in school-aged children.

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