Syncope : an integrative physiological approach

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Part IV

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Clinical Studies

Syncope in migraine. The population-based CAMERA study

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Chapter 9

Abstract

Objective: To examine the association between migraine and syncope-related autonomic nervous system (ANS) symptoms.

Methods: We conducted a population-based study among migraineurs with and without aura (n = 323) and control subjects (n = 153). A systematic questionnaire and cardiovascular measurements during rest, while standing and after venipuncture addressed the prevalence of syncope, orthostatic intolerance, orthostatic hypotension (OH) and the postural tachycardia syndrome (POTS) in migraineurs and controls.

Results: The lifetime prevalence of syncope in all participants was 41%, more often in women (45% vs. 32%, p = 0.02). Compared to controls, migraineurs had a higher lifetime prevalence of syncope (46% vs. 31%, p = 0.001), frequent syncope (≥5 attacks) (13% vs. 5%, p = 0.02) and orthostatic intolerance (32% vs. 12%, p < 0.001). There was no association between ANS symptoms and the severity of migraine or migraine subtype. Cardiovascular measurements and the prevalence of POTS and OH did not differ significantly between migraineurs and controls.

Conclusion: This population-based study demonstrated an elevated prevalence of syncope and orthostatic intolerance in migraineurs without clear interictal signs of autonomic nervous system dysfunction.

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Introduction

Migraine is an episodic multifactorial neurovascular disorder characterized by recurrent attacks of disabling headache, autonomic dysfunction (migraine without aura; MO) and focal neurological aura symptoms (migraine with aura; MA).[87,105] Syncope is a paroxysmal symptom consisting of a brief, self-limiting transient loss of consciousness due to global cerebral hypoperfusion.[28] The prevalence of both syncope and migraine is high in the general population.[28,146] Several reports suggest that both conditions co-occur together more frequently than chance would predict. Fainting spells occurred more often among women with "migrainous headache" (11%) compared to controls (2%; $p < 0.001$) in a population based study.[165] Syncope has also been reported to frequently occur during migraine attacks.[211] However, neither study used standardized and validated methods for the diagnosis of migraine[105] and syncope.[28]

The autonomic nervous system (ANS) has been studied extensively in migraineurs, mostly in clinic-based samples and for cardiovascular reflex responses mostly in-between attacks.[21,89,102-104,174,197,221,274] Results were conflicting in that both sympathetic hypo-function[21,89,102-104,174,197] and hyperfunction[274], and both parasympathetic hypofunction[102,103] and hyperfunction[274] have been reported. In the only population-based study to date, migraineurs with disabling attacks were more prone to ANS dysfunction than those with non-disabling attacks.[221] This underscores the importance of a population-based approach to avoid bias in assessing the relationship between migraine and ANS dysfunction.

Previous studies did not address clinical symptoms of ANS failure, including syncope, orthostatic intolerance and the postural orthostatic tachycardia syndrome (POTS). Here, we assessed the prevalence of syncope and related symptoms in migraine using a population-based design.

Methods

A complete description of the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study population and methods has been detailed elsewhere.[143] In brief, cases and controls were randomly selected from the Genetic Epidemiology of Migraine (GEM) study, a population-based survey of 6491 Dutch adults aged 20-60 years living in two representative Dutch municipalities (Maastricht and Doetinchem).[146] 863 Cases of migraine were identified according to International Headache Society (IHS) criteria;[105] 54 % of the cases had not been previously diagnosed by a physician. We randomly selected both MA and

MO patients as well as a control group that frequency matched the cases by sex, municipality and 5-year age strata. Controls were selected from those who had indicated that they had no severe headaches interfering with daily activities, and who had rated any headaches they had as 0 on the pain scale. This effectively excluded people with chronic daily headache and cluster headache. We invited 631 individuals; 476 participated in the present study (80% of migraineurs, 67% of controls). Of the remainder, 114 actively declined participation, 36 could not participate for various logistic reasons and five individuals (four migraineurs, one control) were excluded, as they had not completed the syncope questionnaire. There were no significant differences between responders and non-responders or between non-responding cases and non-responding controls concerning the following items: age, sex, cardiovascular risk factors (i.e., body mass index [BMI], smoking, cholesterol, blood pressure [BP], diabetes and oral contraceptive [OC] use). There was a trend for responders having had more years of schooling than non-responders (p=0.07). The study protocol was approved by the ethics committees of the cooperating institutions. All participants gave written informed consent and participated without any financial reimbursement.

The study protocol included a structured telephone interview, a clinic visit for a standard physical and neurological examination, blood draw, and a brain MRI study. The telephone interview was carried out by one of three trained interviewers, who used a computerized, structured interview, with relevant questions presented on the computer screen that had to be read aloud literally. The hospital visit took place within 10 days of the telephone interview.

Sociodemographic and medical characteristics were assessed by interview and physical examination. Education was categorized into low (primary school or lower vocational education) and high. The average alcohol intake in the past year was based on responses to questions on frequency and quantity of drinks per occasion and categorized into none, moderate (1-3 drinks/day) and high (≥3 drinks/day). Self-reported weight and height were used to calculate BMI (weight [kg]/height^2[m]). A structured telephone questionnaire investigated the prevalence of syncope and the occurrence of symptoms (syncope, near syncope or avoidance) during prolonged standing (queues, during receptions), long hot shower, after a heavy meal, after exercise or at the sight of blood or during a venipuncture. These circumstances are known syncope triggers for patients with autonomic failure, vasovagal syncope or orthostatic intolerance, with as exceptions that venipuncture only acts as a syncope trigger for patients with vasovagal syncope and a heavy meal only for patients with autonomic failure.[28,128]

In the interview, syncope ("fainting") was explained, to all participants with the same standard text, as a brief loss of consciousness that may be provoked by the sight of blood or while standing for a long time in the heat but that can occur without a clear provocation. Loss of consciousness due to head injury or an epileptic seizure was excluded as syncope. 'Near syncope' was defined as the symptoms which usually precede a faint but can also occur separately, and consist of dizziness, light-headedness, loss of concentration, ringing in the ears or darkening of sight. The occurrence of syncope was defined twice, first as at least one attack ("syncope ever") and secondly as "frequent syncope", i.e. five syncopal attacks or more.

Diabetes mellitus, history of myocardial infarction, BMI, high alcohol intake, and use of antihypertensives, were examined as potential risk factors for syncope.[47] At the clinic visit blood pressure (BP) and heart rate (HR) were measured with an electronic oscillometric BP monitor [OMRON 711, OMRON Matsusaka Co, Japan].

Two autonomic reactivity tests were performed: the orthostatic change of BP and HR and the difference after venipuncture. BP and HR measurements were made with the subject sitting, after 5 minutes supine rest, during 1, 2, 3 and 4 minutes standing, and directly after venipuncture. The average of the measurements while standing was defined as 'standing BP' or 'standing HR'. The maximal decrease while standing was calculated by subtracting the lowest BP value while standing from the resting BP. Similarly, the resting HR value was subtracted from the highest HR while standing to calculate the maximal increase while standing. The difference after venipuncture was calculated by subtracting the value after venipuncture from the resting value. Orthostatic changes of BP and HR were measured in all but 34 participants (23 migraineurs, 11 controls). Migraine cases underwent all examinations in a headache free period (≥ 3 days after a migraine attack).

Combined end points

Orthostatic hypotension was defined as a fall in BP of at least 20 mm Hg systolic or 10 mm Hg diastolic within three minutes after standing up.[242]

Orthostatic intolerance was defined as the provocation of syncope or near syncope (dizziness, light-headedness, loss of concentration, ringing in the ears or darkening of sight) upon standing or the avoidance of prolonged standing.

POTS was defined as orthostatic intolerance accompanied by a HR increase of > 30 beats per minute (bpm) or by a HR > 120 bpm within 5 minutes of standing.[156]

Hypertension was defined as a systolic BP of 160 mm Hg and higher or a diastolic BP of 95 mm Hg and higher or current use of anti-hypertensive drugs. For this definition, BP was the mean of three supine BP measurements obtained at 1-minute intervals.

Data of controls and migraineurs were compared with the χ^2 test for the comparison of proportions, the two-sided Student's *t*-test for normally distributed continuous variables and the nonparametric Mann-Whitney *U* test for continuous variables without a normal distribution. Linear regression analysis was used to explore the relation of two continuous variables. Significance was set at the 5% level.

Results

Population

Migraineurs (n=323) and controls (n=153) participated in the study. Compared to controls, fewer migraineurs had a high alcohol intake (Table 1). No other significant differences were found in baseline population characteristics between both groups.

Table 1 Characteristics of study participants

	Migraineurs (n = 323)	Controls (n = 153)
Male / Female ratio	32%	38%
Age (yrs)	48 (8)	48 (8)
Body Mass index (BMI)	25 (4)	24 (4)
Medical history (% present)		
- diabetes mellitus	4 (1%)	6 (4%)
- myocardial infarction	1(0.3%)	-
Currently uses antihypertensive medication	40 (12%)	12 (8%)
High alcohol use (≥3 drinks/day)	23 (7%)*	23 (15%)*
Low education†	171 (53%)	81 (53%)
Migraine with Aura (MA)	174 (54%)	-
≥ 1 migraine attack per month	156 (48%)	-

Values are expressed as number (%) or as mean (SD)

* $p < 0.01$ χ^2 test for the comparison of proportions.

† Low education indicates primary school or lower vocational education.

Syncope questionnaire

The lifetime prevalence of one or more syncopal events in all participants was 41%. A female preponderance was found for syncope (45% vs. 32%, p = 0.02).

None of the potential risk factors for syncope (diabetes mellitus, history of myocardial infarction, BMI, high alcohol intake, and use of antihypertensives) had a significant association with the prevalence of syncope.

Compared to controls, migraineurs had a significantly higher lifetime prevalence of both syncope and frequent syncope (Table 2). Migraineurs reported symptoms (syncope/near syncope/avoidance) during prolonged standing, a long hot shower, or after exercise significantly more often than controls.

Table 2 Syncope questionnaire

	Migraineurs (n = 323)	Controls (n = 153)	*p* value
Syncope ever	46%*	31%*	0.001
- women	50%	32%	
- men	35%	26%	
Frequent (≥5x) syncope	13%*	5%*	0.02
- women	17%	6%	
- men	1%	5%	
fainters			
Age at first faint (years)	21 ± 13	23 ± 13	0.3
Age at last faint (years)	30 ± 14	29 ± 13	0.6
Fainted previous year	12%	9%	0.5
Total number of faints	6 ± 16*	6 ± 14*	0.005
Symptoms			
- prolonged standing	32%*	12%*	<0.001
- long hot shower	11%*	2%*	0.001
- after a heavy meal	4%	3%	0.4
- after exercise	23%*	5%*	<0.001
- at the sight of blood	9%	7%	0.6
OH	16%	14%	0.7
POTS	3%	2%	0.5

Values are expressed as proportion or as mean ± standard deviation * Significance $p < 0.05$

χ^2 test (proportions) or Mann-Whitney U test (continuous variables)

Table 3 Orthostatic test

	Migraineurs (n = 300)	Controls (n = 142)
SBP (mmHg)		
Supine	133.3 (20.2)	133.0 (20.0)
Standing	133.8 (17.4)	134.8 (17.7)
Max. decrease while standing	6.6 (10.9)	5.3 (11.2)
Difference after venipuncture	-0.7 (10.7)	-1.6 (11.2)
DBP (mmHg)		
Supine	85.5 (10.8)	83.8 (11.2)
Standing	92.7 (10.4)	92.3 (9.5)
Max.decrease while standing	-2.8 (7.3)	-3.7 (7.3)
Difference after venipuncture	-4.0 (7.4)	-5.4 (8.9)
HR (bpm)		
Supine	68.1 (10.6)	67.6 (11.2)
Standing	78.6 (11.7)	78.8 (11.6)
Max. increase while standing	14.5 (7.7)	14.8 (7.2)
Difference after venipuncture	-4.2 (6.9)	-4.2 (6.8)

Values are expressed as mean (SD); SBP=systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate.

Table 4 Syncope questionnaire by migraine subtype

	N	Syncope ever	Frequent Syncope	Orthostatic Intolerance	POTS	OH
Migraine overall	323	46%	13%	32%	3%	16%
Migraine w/ Aura	174	43%	11%	32%	3%	14%
Migraine w/out Aura	149	50%	15%	32%	4%	17%
≥ 1 Migraine attack per month	156	44%	14%	37%	3%	6%
< 1 Migraine attack per month	167	49%	12%	28%	4%	15%

Cardiovascular measurements

The BP and HR measurements supine, while standing and after venipuncture did not differ significantly within both groups (Table 3). There was no significant difference in the prevalence of POTS and OH between the groups.

Neither migraine type nor attack frequency (≥ 1 vs. < 1 attack per month) was associated with the presence of syncope, orthostatic intolerance, OH or POTS (Table 4). No correlation was found between the total number of migraine attacks and syncopal spells within the migraineurs.

Discussion

In this population-based study, we examined clinical presentations of ANS dysfunction as well as BP and HR reflex tests in migraine.

The lifetime prevalence of syncope we found in controls is in accordance with previous studies in air force personnel and medical students.[52,80] The population-based Framingham study of adults aged 30 to 62 years reported a lower lifetime prevalence of syncope (3.0% for men, 3.5% for women).[210] However, it seems plausible that these data referred to the incidence of syncope during the 26 year period of surveillance.[21] Moreover, syncope was not strictly defined in the Framingham study, resulting in inclusion of epilepsy, and even stroke or TIA as forms of syncope.[246] This may explain why risk factors for syncope identified in the Framingham Study lacked significance in our study. Given the high prevalence of vasovagal syncope, triggers for this type of syncope are more likely to affect estimates of the prevalence of syncope.[28,52]

We found a higher lifetime prevalence of syncope and frequent syncope among migraineurs. The reported symptoms of migraineurs during prolonged standing, a warm shower, exercise, in the absence of complaints at venipuncture or after a heavy meal are best interpreted as orthostatic intolerance.[28,128]

It is unclear why migraineurs have an increased tendency towards syncope and orthostatic intolerance. Our cardiovascular measurements underline that there is no gross abnormality of the ANS in migraine. However, we cannot exclude a slight sympathetic dysfunction as our study lacked a continuous blood pressure monitoring upon standing and therefore did not address the initial orthostatic response. Arguments favoring a slight sympathetic dysfunction in migraineurs, are the reduced plasma noradrenaline levels and alpha-adrenergic hypersensitivity.[194] Alternatively, syncope and orthostatic intolerance may occur as paroxysmal abnormalities without clear interictal signs of ANS dysfunction; if so, this parallels migraine itself, also characterized by largely normal interictal functions.

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