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RESEARCH ARTICLE

Veit Mylius
Hans Joachim Braune
Karsten Schepelmann

Dysfunction of the pupillary light reflex following migraine headache

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V. Mylius, M. D. · H. Joachim Braune, M. D. · K. Schepelmann, M. D. (✉)
Medizinisches Zentrum
für Nervenheilkunde
Neurologische Klinik mit Poliklinik
Rudolf-Bultmann-Str. 8
35039 Marburg, Germany
Tel.: +49-64 21/28-6 52 31
Fax: +49-64 21/28-6 52 74
E-Mail: Schepelm@mailer.uni-marburg.de

Abstract Using pupillometry and sympathetic skin responses we compared the changes in local and systemic autonomic function within one week of a migraine attack. We investigated whether the measurement of the pupillary light reflex provides further information on the pathophysiology of migraine.

Forty-two migraine patients and forty-two healthy age-matched controls were included. The parameters that were measured were the amplitude of the pupillary light reflex, the pupil size at the beginning of the measurement, the latency, the velocity of constriction and the velocity at the end of the dilatation.

The average pupil size was 6.43 mm in the migraine group and 6.7 mm in the control group ($p < 0.01$). Reduced velocity of constriction and smaller amplitude of constriction in migraine patients within two days of an attack were signs of a parasympathetic dysfunction ($p < 0.05$). The sympathetic skin response did not differ significantly between migraine sufferers and controls.

These findings indicate that both parasympathetic and sympathetic nerves supplying the eye are involved in migraine headache presumably due to effects on the pericarotid sympathetic fibers and involvement of trigeminal-parasympathetic reflexes.

Key words migraine · sympathetic skin response · pupillometry

Introduction

In patients suffering from migraine headache, a sympathetic hypofunction, which can be detected by pupillometry, has been described to occur following an attack. Between successive attacks of migraine and during an attack, a smaller pupil diameter and a higher degree of anisocoria with smaller pupil size on the symptomatic side has been observed [4, 8]. After local bilateral direct sympathetic activation by application of drugs such as cocaine and phenylephrine, pupillary dilatation was more pronounced in migraine sufferers than in controls [4, 12, 17], suggesting central sympathetic dysfunction [12].

Furthermore, following indirect activation of the sympathetic innervation, the pupillary dilatation was less marked compared with controls, suggesting a dysfunction of the tertiary sympathetic neuron [7]. In at least one report these pharmacological effects were observed only up to one week following the migraine attack [7].

A sympathetic dysfunction and a mild parasympathetic dysfunction have also been suggested to occur between attacks following examination of cardiovascular reflexes by some authors [15, 23]. Others have reported a sympathetic hyperfunction [5], sympathetic and parasympathetic hyperfunction [32] or sympathetic instability [3, 33].

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Aim of the study

We aimed to test the hypothesis that there is a sympathetic hypofunction in migraine patients that is reflected by a significantly reduced pupil diameter. We compared changes in local and general autonomic function using pupillometry and measurement of the sympathetic skin response. Additionally we investigated whether the pupillary light reflex is altered rather than solely the pupil diameter. We performed a controlled study employing pupillometry and sympathetic skin response in forty-two migraine patients and forty-two control subjects.

Patients and methods

Patients and diagnosis of migraine

Migraine was diagnosed according to the IHS criteria (International Headache Society) [16]. The diagnostic reference was the Kieler headache questionnaire of Göbel, which was created according to the IHS criteria [14]. Forty-two migraine patients (thirty-two female, ten male, mean age 27 ± 5.28) and forty-two healthy controls (thirty female, twelve male, mean age 26.7 ± 3.57) were included. Thirty-three out of the migraine patients suffered from migraine without aura, nine of them suffered from migraine with aura. The most recent migraine headache was considered to be unilateral in thirty patients. The groups were matched for age, since the pupil size is age-dependent (Table 1). Gender differences were not calculated, since previously differences were found only in the reaction of the pupil towards painful stimuli [11] and not concerning the measurement of the pupil diameter [18]. The patients were not currently under preventive medication nor any medication that affects autonomic function. Migraine attacks were treated either with NSAIDs or with Triptans. Exclusion criteria for pupillometry were diseases influencing the pupil reaction such as polyneuropathy, eye diseases, drugs, severe pain, severe sleeping disorders or severe stress.

Informed consent was obtained from all subjects before participation in the study. The study was performed according to the Declaration of Helsinki and with the approval of the local Ethic Committee of the University of Marburg.

Table 1 Relevant characteristics of migraine patients and controls

Patients	
n	42
Age	27 ± 5.3
Range	20–40
Migraine without aura	33
Migraine with aura	9
Disease duration (years)	11 ± 7.3
Frequency of attacks (months)	3.8 ± 2.6
Days after an attack	4.1 ± 2.4
Bilateral headache	12
Unilateral headache	30
Controls	
n	42
Age	26.4 ± 3.6
Range	21–36

Data are given as mean ± SD

Methods

Pupillometry was performed on the migraine patients within one week following an attack and on ten patients from these within 48 hours of an attack. For pupillometry, we used the Compact Integrated Pupillograph (CIP, AMTech) [2]. It uses a continuous infrared-video measurement of the pupil diameter with a frequency of 250 Hz and a duration of two seconds. The light stimulus was a yellow LED with an intensity of 10000 cd/m^2 and a duration of 200 ms. The measurements were following at least ten minutes light adaptation (55 Lux) and subsequent four minutes dark adaptation (< 1 Lux). The left and the right eye of each subject were measured alternately four times. The following parameters were measured during the pupillary light reflex:

- Latency: time interval from the beginning of the stimulus to the beginning of the constriction (s);
- Amplitude of constriction: difference between initial diameter and the smallest pupil diameter (mm);
- Pupil diameter: initial pupil size (mm);
- Velocity: velocity of constriction after the light stimulus (mm/s);
- Second velocity of dilatation: velocity at the end of the dilatation (mm/s).

The diameter and the second dilatation velocity were considered to be parameters of sympathetic activity [22, 26]. Latency, velocity and amplitude of constriction were considered to be parasympathetic [22].

Sympathetic skin response (SSR) was recorded at the palm of the hand after electrical stimulation of the median nerve using a standard electrodiagnostic device (NIHON KOHDEN Neuropack 4). Stimuli were delivered at an intensity of 30 mA and a duration of 0.2 ms. The greatest amplitude and the shortest latency of six consecutive SSR measurements were used.

Statistical analysis

For statistical analysis we used the statistical package STATISTICA. Group differences were evaluated using two-tailed t-tests for independent variables. Values were expressed as mean ± standard deviation and statistical significance was indicated at $p < 0.05$.

Results

Sympathetic parameters of the pupillary light reflex

The mean of the pupil diameter was 6.43 ± 0.7 mm in the migraine patients and 6.7 ± 0.6 mm in the control group. The difference of 0.27 mm was significant (t-test for independent variables; $p < 0.01$; $n = 42$ each; CI [0.07; 0.47], Table 2). The difference in the age of the groups was negligible (27 vs. 26.4 years), since the clinical data of Loewenfeldt present an average diameter of 6.56 mm at the age of 27 years and of 6.52 mm at the age of 26.4 years (1263 persons from 10 to 80 years) [21].

Comparing the symptomatic side with the non-symptomatic side in 30 migraine patients with unilateral headache no differences were found.

The calculation of the second velocity of dilatation (at the end of dilatation) presented no significant changes. Only a trend was found in patients who were

Table 2 Results of the pupillary light reflex measurements in patients with migraine and healthy controls. Measurements were within seven days following an attack (both eyes were included)

	Controls	Migraine	p
Diameter in mm, n = 42	6.7 ± 0.6	6.43 ± 0.7	< 0.01 CI [0.07–0.47]
Up to two days after an attack, n = 10		6.37 ± 0.4	< 0.01
Dilatation velocity in mm/s, n = 42	0.69 ± 0.2	0.67 ± 0.2	ns
Up to two days after an attack, n = 10		0.62 ± 0.1	ns
Velocity of constriction in mm/s, n = 42	4.97 ± 0.9	4.87 ± 0.7	ns
Up to two days after an attack, n = 10		4.5 ± 0.8	< 0.03
Amplitude of constriction in mm, n = 42	1.89 ± 0.3	1.84 ± 0.3	ns
Up to two days after an attack, n = 10		1.74 ± 0.3	< 0.04
Latency in s, n = 42	0.232 ± 0.02	0.231 ± 0.02	ns
Up to two days after an attack, n = 10		0.235 ± 0.02	ns

Data are given as mean ± SD

measured within two days of an attack. They had a lower dilatation velocity on both eyes compared to the headache free control group (0.62 ± 0.1 vs. 0.69 ± 0.2 mm/s, t-test for independent variables; p = 0.08, n1 = 10, n2 = 42, Table 2).

Parasympathetic parameters of the pupillary light reflex

Parasympathetic parameters were diminished only within 48 hours of an attack in ten patients. Within 48 hours of an attack the migraine patients showed a significantly lower velocity of constriction of 4.5 ± 0.8 mm/s on both sides compared to controls (t-test for independent variables; p < 0.03; n1 = 10, n2 = 38, Table 2). Comparing the other results of the velocity of constriction of the whole group no significant changes were found.

Directly after an attack patients had an amplitude of constriction of 1.74 ± 0.3 mm on both sides, the difference to the controls was significant (t-test for independent variables; p < 0.04; n1 = 10, n2 = 38, Table 2). Calculating the other values of the amplitude of constriction in the whole group no differences were found. Measuring the latency of the pupillary light reflex no significant differences were found.

Sympathetic skin response

Sympathetic skin responses did not differ significantly between migraine sufferers and controls.

Discussion

Sympathetic parameters of the pupillary light reflex

The results revealed a statistically significant reduced pupil diameter in the migraine group of 0.27 mm. In 30 migraine patients with unilateral headache, there was no difference in pupillary size on the symptomatic side as compared to the non-symptomatic side. Battistella et al. also detected a smaller pupillary diameter and a higher degree of anisocoria in adult migraine patients [4]. Drummond reported a smaller pupillary diameter on the symptomatic side [8]. Previously, Marinis et al. did not find any diminution of the basal pupillary diameter. But this is presumably because the measurement was performed in ambient light [7]. We detected no significant differences in dilatation velocity.

Putative causes of the smaller pupillary size are postganglionic changes involving the tertiary sympathetic neuron [6, 8] and alternatively a central hypofunction of the sympathetic nervous system [12].

The sympathetic pathway projects from the hypothalamus to the first spinal thoracic root [6]. The second neuron projects from the spinal cord to the thoracic sympathetic trunk. From the superior cervical ganglion tertiary neurons project to the eye via the internal carotid artery which is surrounded by a sympathetic plexus. One part of the sympathetic branch reaches the dilator pupillae via the long ciliary nerves. Measuring pupillary diameter and local blood flow, Drummond could show a unilateral sympathetic hypofunction both during and between attacks of migraine. The hypofunction was suggested to be due to compression of the pericarotid sympathetic fibers, caused by a dilatation of the carotid artery during the attack [8]. From pharmacological studies with local application of substances that indirectly activate the sympathetic nerves, De Marinis et al. assumed a transient postganglionic sympathetic hypofunction involving the tertiary neuron. They ob-

served changes in response to both direct and indirect activation of sympathetic nerves but only up to seven days following an attack. Since both sides were found to be affected and in patients with vascular features the changes had been more pronounced, a transient disturbance of the pericarotid sympathetic fibers was suggested by these authors [6, 7].

Our own studies confirm the results of previous investigations, since local sympathetic hypofunction was more pronounced within two days of an attack than following one week.

This persistence of the hypofunction for one week could be due to recovery of function of the pericarotid fibers after the attack as was shown by De Marinis et al. [7]. However, the persistence of the sympathetic instability in the migraine free interval was found in previous pupillometric studies [4, 8] and in investigations of cardiovascular parameters [3, 15, 23, 33]. Therefore we propose an additionally central sympathetic instability that affects the sympathetic innervation of the eye, the arteries and the blood pressure. A sympathetic instability of the blood pressure or the arterial tone might contribute to migraine headache via an excitation of the surrounding trigeminal sensory nerve fibers. During the attack the decrease of the sympathetic tone becomes more pronounced, due to effects on the pericarotid sympathetic fibers.

The altered sensitivity of trigeminal nerve fibers could be a result of a peripheral or a central autonomous dysfunction, or it could be a result of an altered pain transmission via the trigeminal nucleus caudalis [10, 27]. Weiller et al. measured an increased blood flow during attacks of migraine headache by employing positron emission tomography in the cerebral hemispheres in cingulate, auditory and visual association cortices and in the brain stem. After the injection of sumatriptan had induced complete relief from headache and phono- and photophobia, only the increased blood flow in the brain stem persisted. He concluded that there occurs an imbalance between brain stem nuclei regulating antinociception and vascular control [30].

Fanciullacci suggested that a central sympathetic hypofunction might result from a central sympathetic activation during the attack, leading to exhaustion of the system [12]. Experimental stimulation of the sympathetic nucleus coeruleus as well as stimulation of the trigeminal ganglion in cats induced a frequency-dependent increase in blood flow in the carotid artery [1, 13, 19]. Such a central sympathetic excitation might be part of a central generator of migraine attacks. Wilhelm concluded from lesion experiments that the retrogeniculate visual pathway is also involved in the pupillary light reflex [31]. In order to test the hypothesis that a central sympathetic dysfunction including less inhibition of the Nucleus Edinger Westphal occurs, a pharmacological study employing alpha-sympatholytic drugs should be considered in further studies.

Parasympathetic parameters of the pupillary light reflex

Velocity and amplitude of constriction of the pupillary light reflex in ten migraine patients up to two days after an attack were significantly lower than in the control group ($p < 0.05$). The slower velocity of constriction and smaller amplitude of pupil constriction within two days of an attack are signs of a parasympathetic hypofunction [22]. The latency of the pupillary light reflex was not affected.

Previously, mild parasympathetic dysfunction was described by the measurement of cardiovascular reflexes [15, 28, 29]. Because of the nitric oxide hypersensitivity of the cranial vessels in migraine patients and its release by parasympathetic fibers, the involvement of the parasympathetic nervous system has been discussed [29]. Drummond supposed that the dilatation of the dermal vessels during and after a migraine attack is caused by an increase of parasympathetic tone, due to trigeminal-parasympathetic vasodilator reflexes [9]. This parasympathetic hyperfunction during the attack may lead to a parasympathetic dysfunction immediately following the attack.

Parasympathetic hypofunction following a migraine attack headache could not occur in the manner described in the model for the sympathetic dysfunction. Parasympathetic nerve fibers do not have the anatomical relationship to the vessels that possibly explain the relationship between migraine headache and the sympathetic supply via the carotid nerve plexus. The parasympathetic function is mainly regulated in the Nucleus Edinger Westphal. This tone is influenced by the afferent fibers from the retinal nerves that regulate the pupillary light reflex, and from other inhibiting structures such as the central sympathetic system (Locus coeruleus, hypothalamus) [31]. Therefore, another possible reason for the observed parasympathetic dysfunction could be a central sympathetic hyperfunction during the attack. In previous studies employing pupillometry, no evidence for sympathetic hyperfunction during an attack was found [4, 12, 17]. If we assume a central sympathetic hypofunction, the parasympathetic tone could have been more pronounced during the attack due to less central sympathetic inhibition.

Generalized or local sympathetic and parasympathetic dysfunction

In the present study no evidence for changes in autonomic function were found employing the sympathetic skin response. The habituation of the sympathetic skin response as an evaluation of the peripheral components of the orientating response have also been reported not to be altered [20, 25].

Results of cardiovascular reflex measurements in adults during the migraine-free interval have shown sympathetic dysfunction and subtle parasympathetic dysfunction [15, 23]. A sympathetic hyperfunction in adults [5] or both sympathetic and parasympathetic hyperfunction in children with migraine [32] have also been reported. It was shown by Zigelman et al. that beta-blockage using propanolol reduced the sympathetic instability (low frequency fluctuations in heart rate) [33].

The result of investigations of cardiovascular reflexes are in contradiction to unaffected sympathetic skin response and possibly reflect autonomic fluctuation. Compared to the changes in the pupillary light reflex, the results of the cardiovascular reflex measurements favor central autonomic involvement. Previously, we discussed that the occurrence of an autonomic imbalance might provoke a migraine headache by affecting the perivascular trigeminal nerve endings [15, 24, 25].

Since the changes of the cardiovascular reflexes might depend on the duration of the illness, it is possible that the sympathetic skin response is not affected in our group of young patients. Another reason for a generalised autonomic dysfunction in illness of long duration remains to be considered and namely the possible excitation of the entire autonomic nervous system during an attack (e. g. nausea, vomiting, tiredness, diarrhoea), which leads to exhaustion afterwards.

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