The Low-Prothrombine-Phosphene Phenomenon of Atrial Fibrillation: First Description of a Warning Sign

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Abstract

Background: Atrial fibrillation (AF) is a precursor of stroke. Vitamin K antagonist has revealed risk reduction in ischemic stroke in many studies.

Methods: Description of an unusual, hitherto unknown phenomenon in a patient

Result: Rare attacks of blue-margined zigzag phosphenes in an elderly patient with atrial fibrillation that occurred binocularly in homonymous fields. The attacks only occurred during periods of low prothrombine, and disappeared within five to fifteen minutes after taking a vitamin K antagonist. The attacks were not influenced by valsalva provoking activity (coughing or bending). The patient had consistently normal visual acuity, and had never had a visual field defect or neurological deficits.

Conclusions: The appearance of zigzag phosphenes in this patient with a low prothrombine time is an important warning sign. This phenomenon may be considered as a biological marker for stroke prevention. The occurrence of coloured zigzag phosphenes may refer to areas of hyperexcitable cortical neurons. This phenomenon may be explained by an event involving cerebral microemboli that occurred during periods of low INR values reversible via medications.

INTRODUCTION

Devastating events in patients with atrial fibrillation

Several trials have shown that atrial fibrillation (AF) is a precursor of stroke. Wolf & coworkers [1] assessed in a follow-up study carried out over 24 years that individuals with AF, aged 30 to 62, and exhibited a fivefold increase in stroke incidence. Embolism in patients with chronic AF may lead to cerebral infarction. A review of clinical studies by Petersen [2] revealed that patients with chronic AF had an annual 3-6% risk of thromboembolic complications. This risk was 5-7 times greater than in control examinations of individuals with sinus rhythm.

In a retrospective study of 140 patients with strokes who had suffered from AF, 53 patients (38%) died after the initial infarct. That review study of records applied to the years 1970 through 1980. Eighty-nine of the 140 patients (63.6%) revealed systemic emboli [3]. Patients with non-cardioembolic strokes were likely to present left ventricular wall motion abnormalities as demonstrated echocardiographically [4].

A greatly increased stroke risk may be reduced by treatment. Anticoagulants are highly effective at preventing cardioembolic stroke in patients with AF. Thromboembolic events in non-rheumatic AF were markedly reduced in patients treated with anticoagulants. Examinations involving anti-thrombotic therapy with an oral vitamin K antagonist (Warfarin*) showed a risk reduction in ischemic stroke by about two-thirds in 568 patients with AF [5].

Five randomized clinical trials of patients with AF revealed a nearly 70% ischemic stroke reduction via anticoagulant treatment [6]. In most of 150 patients, AF had been undetected prior to cerebral infarction [7]. Most of the infarcts were large and not preceded by a transient ischemic attack [7]. Increased use of oral anticoagulants led to a marked reduction in ischemic strokes without exacerbating the bleeding rate. These studies were carried out between 2012 and 2017 [8].

The key role of anticoagulation in a patient with non-valvular AF is emphasized. In the following report. To my best of my knowledge, the occurrence of phosphenes as warning signs in periods of low prothrombine time INR has not been described in the literature.

ZIGZAG PHOSPHENES AS WARNING SIGNS DURING LOW PROTHROMBINE TIME

A 79-year-old ophthalmologist, who suffers from non-valvular AF, noticed episodic attacks of hemianopic scintillations. During these attacks, the teichopsias appeared continuously as luminous, zigzag forms with blue margins. He saw bilateral, slowly moving flaring phosphenes, in the outer hemianopic periphery of his visual field - without scotomas. The patient noticed the phosphenes when looking toward a bright background. The
zigzag phosphenes moved in conjunction with his eye movements in any direction. The episodes had occurred six times in the preceding two to three years on different occasions (but not in previous years). They appeared suddenly at different situations not entailing physical strain. The phosphenes occurred in a sitting position or during walking. There was no diurnal influence on the appearance of the photopsias. The attacks sometimes occurred during the morning or occasionally several hours after dinner or in the evening, usually a few hours after dinner. The phosphenes in this patient occurred binocularly in homonymous fields, sometimes on the right, sometimes on the left side.

The patient had normal visual acuity (20/20) that did not change during the attacks. His visual field was always normal, a factor he noticed particularly during the attacks. He never suffered from headaches, diplopia, or ocular pain. He suffered no nausea or vertigo, nor faintness during the attacks. He measured his blood pressure during an attack; it was normal. He had never suffered a transient ischemic attack (TIA). The patient usually measures his International Normalized Ratio (INR) to assess the prothrombine time about once a week or every two weeks because he takes Marcumar® (Phenprocoumon). He was alert to test his INR value when he experienced the beginning of a scintillation attack. During his attacks, he observed that his prothrombine time was low, namely 2.0 or under 2.0. After immediately swallowing one tablet of Phenprocoumon (3.0 mg), the hemianopic scintillations disappeared within five to fifteen minutes and his INR value rose shortly afterwards. Phenprocoumon, a cumarin derivate, acts as a vitamin K antagonist in a similar way as Warfarin®. The patient noted that phosphenes had occurred a few hours after consuming food especially rich in vitamin K (foods with a vitamin K concentration exceeding 100µg per 100g), i.e. onions, parsley, lettuce, brocolli, cauliflower, or cabbage.

The patient had normal blood pressure while under treatment with antihypertensive agents. Arterial hypertension had been successfully treated for about 25 years; in the last three years treatment with 1 tablet/day Exforge® (10 mg Amlodipine; 160 mg Valsartan). In addition, he was treated with Phenprocoumon (Marcumar®). His AF had been treated continuously for 20 years with Phenprocoumon. For osteoporosis propylaxis, he was treated with 1 tablet/day Calcium (100 mg) and 1 tablet vitamin D (1 tablet every two weeks). Brain CT, MRI or transcranial doppler sonography was not carried out, because the patient had no neurological problems. He never had seizures (no EEG study was performed). Echocardiography revealed an enlarged left atrium and a mitral insufficiency stage 2.

The patient had no health disorders otherwise and was used to engaging in physical exercises such as biking or jogging. His vascular risk factors were normal and had been monitored several times in previous years, with the last time in November 2018. He presented no increased platelet aggregation or hyperlipidemia. The patient only drank non-alcoholic beverages and did not smoke. He had no diabetes mellitus or hypoglycemia, and no personal history of migraine, nor any history of migraine in his family. He had no retinal disease.

Duplex ultrasonography of the carotid and vertebral arteries revealed no vascular stenoses or ulcerative atheromatous anomalies in the vessel walls.

**DISCUSSION**

In this report, I describe a patient who observed suddenly occurring zigzag phosphenes. The patient never noticed episodes of recurrent transient cerebral ischemia that might have been caused by cardiac emboli. He had no limb weakness. Risk factors as pointed out by Arboix & Alio [9], such as patent foramen ovale, complex atheromatosis of the aorta, were not present in this patient. As predictive clinical factors for cardioembolic cerebral infarction, emphasized by Arboix and coworcers [10], are male gender and age, but not congestive heart failure. In all the years of his life, the patient was engaged in physical exercises, including his previous two years.

I presume that the zigzag phosphenes might have been occurred by a cerebral embolism - presumably microemboli - that occurred during periods of low INR values (2.0 or lower), as he realized by measuring his own INR values. But the patient never developed a neurologic deficit and he had no headaches, nausea or vertigo during the attacks. His having immediately taken vitamin K antagonist tablet presumably prevented a stroke. Therefore, the appearance of zigzag phosphenes may be considered as a warning sign for such patients. I venture to conclude that this phenomenon may be a biological marker for stroke prevention. The fact that the zigzag phosphenes occurred without a scotoma in his visual field may be attributable to an incipient process involving superficial cortical neurons' hyperexcitability without damaging cells located deeper within the brain. As the phosphenes in this patient occurred binocularly in homonymous fields, sometimes on the right, other times on the left, these tachypsias may be explained by microembolic attacks not associated with any particular cerebral vessel. The occurrence in homonymous fields may be related to attacks in the posterior visual pathway. The occurrence of coloured zigzag phosphenes may have to do with areas of hyperexcitable cortical neurons, i.e., local hyperactivation of neurons belonging to specific cortical orientation columns.

In the literature, hemianopic scintillations with scotomas have been observed in patients who suffered either from migraine or, more seldom, from cerebral vascular insufficiency, particularly involving vertebral-basilar disease. Investigators assumed that scintillating scotomas might be caused by platelet microthrombi or microemboli in pial vessels in the visual cortex [11].

Fortification scintillations most often occur in individuals who suffer from migraine. These phosphenes may be caused by the hyperexcitability of cortical neurons. Fortification patterns and their scintillations are attributed to a local hyperactivation of neurons belonging to certain cortical areas in the brain. These phenomena may be triggered by local cerebral ischaemia and by functional impairment of the sodium-potassium exchange pump in glial cell membranes [12].

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1 A new zigzag phosphenes attack recently occurred when the patient bent forward with a strenuous head position lasting several minutes. However, his INR value at that time revealed a normal prothrombine time (2.4). After swallowing one tablet of Phenprocoumon, the zigzag phosphenes disappeared after 10 minutes. This observation signifies that phosphenes due to a microembolism may rarely occur in special situations without a low prothrombine time. To dissolve presumed emboli and arrest the phosphenes, it is essential that a patient taking Phenprocoumon be treated even when their prothrombine time is normal.
My patient’s zigzag phosphenes differ essentially from migrainous phosphenes as fortification phosphenes always occur in the peripheral visual field. In migraine patients, however, scintillations usually begin at or near the fovea centralis, and extend slowly into the visual field periphery of one hemifield. Migrainous phosphenes can move into the upper or lower quadrant only, or into the entire hemifield. Defective vision at the beginning of the aura, is considered to be typical in migrainous patients [12], but it differs essentially from the observation reported herein, as this patient suffered no visual defect during a zigzag phosphenes attack.

INFLUENCE OF MEDICATIONS ON SCINTILLATIONS IN THE LITERATURE

Siekert & coworkers [13] emphasized that the use of anticoagulants may prevent severe vascular disability.

Scintillating scotomas were reported in a 51-year-old woman by Raymond & coworkers [9]. The phosphenes were explained by platelet microthrombi or microemboli of cortical pial vessels. The patient was successfully treated with dipyridamole and aspirin to prevent additional platelet aggregation. Mundall & coworkers [14] reported on transient monocular blindness due to increased platelet aggregability in a 63-year-old patient. The transient ischemic episodes were abolished by aspirin.

Most of twelve patients with vertobrobasilar insufficiency (VBI) who suffered from transient visual phenomena were successfully treated with aspirin [15].

EXAMINATIONS ON PHOSPHENES

Scintillations should not be confused with phosphenes, which are luminous sensations elicited by various stimuli acting on the eye. Hitchcock & Taira [16] reported on the occurrence of phosphenes due to intracerebral stimulation during stereotactic surgery in 23 subjects. Thirteen subjects reported white phosphenes and nine patients’ coloured phosphenes. The most common phosphenes were white or described as "flashing light". The colour combination of phosphenes was red and blue.

In vascular or in demyelinating optic nerve diseases, bright flashes of light described as phosphenes were reported by Page & coworkers [17]. A 56-year-old patient suffered from right-sided hemianopic scintillating scotomas that occurred 12 times in a year, followed by migrainelike headaches after the attacks. But once, the scintillating scotomas failed to recede because a left homonymous hemianopia had developed [18].

PHOSPHENES CAUSED BY EXPERIMENTS

Transcranial magnetic stimulation (TMS) is a non-invasive tool, used to investigate aspects of human brain physiology such as motor function, visual function, and brain disorders. With this method, a pulsed magnetic field creates current flow in the brain. Specific areas may be temporarily excited or inhibited. TMS of the occipital cortex can produce visual phosphenes or even scotomas [19]. To modulate cortical excitability, Najib & coworkers [20] employed TMS, to measure cortical excitability by applying localized magnetic field pulses. Phosphenes were elicited by stimulating the V1/V2 and the V5/MT+ complex cortical regions. Elkin-Frankston & coworkers [21] emphasized having observed phosphenes in the visual hemifield contralateral to stimulation.

Phosphenes were induced when the subject’s eyes were open or closed. The spatial location of phosphenes changed with the gaze direction.

VISUAL FLEETING PHENOMENA IN PATIENTS WITH DIFFERENT DISEASES

Causes for amaurosis fugax may be cardiogenic diseases, such as AF or valvular heart disease leading to embolism. Other causes of amaurosis fugax are hypercoagulable disorders, vasculitis, such as giant cell arteritis, or migraine. Bruno & coworkers [22] who examined 100 subjects with transient monocular visual loss, reported on 42 patients suffering altitudinal (38) or lateralized (4) transient monocular visual loss.

REFERENCES


