A Thromboembolic Predisposition and the Effect of Anticoagulants on Migraine

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Objective.—To investigate the presence of thromboembolic risk factors and the effect of low-dose acenocoumarol therapy on migraine in patients who spontaneously reported a reduction of their migraine attacks during previous therapeutic use of anticoagulants.

Background.—The positive effect of anticoagulants on migraine has been described in case reports and observational studies. It remains unclear whether this concerns only a select group of migraineurs with certain common characteristics.

Methods.—In 4 migraineurs with a self-reported reduction of attack frequency during previous use of anticoagulants (international normalization ratio [INR], 2.5:4.0), the presence of thromboembolic risk factors and the effect of low-dose acenocoumarol therapy (INR, 1.5:2.0) on migraine attacks were prospectively investigated in an open study.

Results.—All patients had one or more thromboembolic risk factors. Two patients, both with factor V Leiden heterozygosity, experienced a clear improvement of migraine during low-dose acenocoumarol therapy.

Conclusions.—Our findings support the hypothesis that migraine, as a phenotype, has different underlying mechanisms, amongst which a thromboembolic tendency. In this group of patients, oral anticoagulants may be a suitable form of migraine prophylaxis, but this needs further clinical investigation.

Key words: migraine, migraine prophylaxis, anticoagulants, acenocoumarol, thromboembolic predisposition, hemostasis

Abbreviations: INR international normalization ratio
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During the last decade, attention has been given to the increased risk for ischemic events in patients with migraine. Crassard et al reviewed the contribution of hemostasis to the ischemic risk in patients with migraine, particularly with regard to platelet hyperaggregability, antiphospholipid antibodies, and congenital thrombophilia.[1] They concluded that all 3 factors might contribute to the ischemic risk of migraine.

Much less attention, however, has been focused on the effect of anticoagulation in migraineurs. Since 1979, 5 case reports have been published describing patients with migraine in whom the frequency of migraine attacks clearly decreased during treatment with an oral anticoagulant.[2-6] In addition, a questionnaire study among 400 patients treated with the oral anticoagulant, acenocoumarol (for nonneurologic indications), reported an improvement of headache in 63% of patients with migraine and 38% of patients with nonmigrainous headaches.[7] Furthermore, a recent, observational, retrospective, follow-up study showed a clear decrease in sumatriptan and ergotamine use during acenocoumarol therapy.[8]

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Although no randomized clinical trials have been conducted so far and the mechanism has not been fully elucidated, these observational findings suggest that coumarin therapy may offer beneficial prophylactic effects for the migraineur. It may well be that only a select group of migraineurs, with certain common characteristics, will respond to treatment with anticoagulants.

This study investigated the presence of thromboembolic risk factors in 4 patients who spontaneously reported a decrease in migraine attacks during previous use of oral anticoagulants. The effect of low-dose acenocoumarol (target international normalized ratio [INR], 1.5:2.0) in these patients also was evaluated.

PATIENTS AND METHODS

An open study was performed, which involved 4 patients with migraine (diagnosed according to the criteria of the International Headache Society [IHS]) who reported a substantial decrease in the frequency of migraine attacks during previous use of oral anticoagulants.

Two patients spontaneously reported improvement of their migraine to a nurse at the Thrombosis Services during therapeutic use of oral anticoagulants (for a deep venous thrombosis after a broken ankle without thrombosis prophylaxis in one patient and atrial fibrillation in the other). The third patient noticed a remarkable decrease in attack frequency (1 attack in 6 months) during use of oral anticoagulants (for a posterior inferior cerebellar artery infarction after a vertebral dissection), which subsequently returned to the normal attack frequency of about one attack per month after discontinuation of the oral anticoagulant. He spontaneously reported this experience to his general practitioner. The fourth patient recalled a time without migraine during anticoagulation (for placement of a spondylodesis) when reading about an ongoing trial with low-dose acenocoumarol as migraine prophylaxis. All patients were referred to a neurologist.

The patients were informed about the nature of the study by a neurologist and by written information. The Ethics Committee for Medical Research of the hospital approved the study protocol. All patients gave informed consent before enrollment.

We took blood from the patients to screen for thrombotic risk factors including anticardiolipin antibodies (aCL), lupus anticoagulant (LA), protein C/S deficiency, factor V Leiden, antithrombin III deficiency, prothrombin G20210A, hyperhomocysteinemia, factor VIII, von Willebrand factor, and thrombocythemia. An independent cardiologist performed a transesophageal echocardiography to screen for patent foramen ovale (PFO) and atrial septal aneurysm, both risk factors for ischemic stroke. Magnetic resonance imaging (MRI) was performed to look for ischemic brain lesions.

Before we allowed the patient to start acenocoumarol, it was necessary for the following parameters to be within reference range: bleeding time (INR and activated partial thromboplastin time), complete blood count, liver function, renal function, and sodium and potassium levels.

After a run-in period of 8 weeks, the patients received low-dose acenocoumarol for 12 weeks (target INR, 1.5:2.0). During this period, the INR was checked at the Thrombosis Services at least once every 2 weeks. There was continuous surveillance of possible interactions with co-medication. After discontinuation of acenocoumarol, the patients were followed for another 8 weeks. Throughout the entire study, patients kept diary cards on which they registered attack characteristics. Patients were allowed to use the following symptomatic medications: metoclopramide, domperidone, acetaminophen, and triptans. Use of prophylactic treatment of migraine other than the study medication was not allowed during the study. Each month the patient visited the outpatient clinic of neurology for evaluation.

The primary end point was the difference in attack frequency between the treatment period and the run-in period. Secondary end points were number of hours with migraine, use of drugs for symptomatic relief, patient preference, and adverse events.

RESULTS

All 4 patients had one or more thromboembolic risk factors (Table). None of the MRI scans showed ischemic abnormalities other than known from former clinical diagnosis.

Patient 1, with factor V Leiden heterozygosity, showed 71% fewer migraine attacks during low-dose

Results of Screening for Thromboembolic Risk Factors*

Patient	Sex Age, y	Age at First Migraine Attack, y	Indication for Therapeutic Anticoagulation	Blood Tests	TEE	MRI
1	F, 29	23	Deep venous thrombosis	Factor V Leiden heterozygote	No abnormality	No abnormality
2	F, 69	54	Atrial fibrillation Brain stem infarction	Factor VIII 197% vWF antigen 161% vWF activity 178%	Patent foramen ovale	Pons infarct
3	M, 29	23	Vertebral dissection with PICA infarction	Factor VIII 186% vWF antigen 203% vWF activity 150% LA positive, aCL negative	No abnormality	PICA infarct
4	F, 46	40	Surgery for spondylodesis	Factor V Leiden heterozygote Homocysteine 22 μmol/L	Not performed	No abnormality

*TEE indicates transesophageal echocardiography; MRI, magnetic resonance imaging; vWF, von Willebrand factor; PICA, posterior inferior cerebellar artery; LA, lupus anticoagulant; aCL, anticardiolipin antibodies.

acenocoumarol therapy than during the run-in period (Figure). In both patients with factor V Leiden heterozygosity (patients 1 and 4), the attack duration in hours was reduced by 84% in patient 1 and by 73% in patient 4. After discontinuation of acenocoumarol, the observed improvement disappeared and both patients preferred to restart low-dose acenocoumarol. Patients 2 and 3 discontinued treatment, because, in contrast to previous use, no improvement of migraine was observed (Figure). No serious adverse events were noted.

COMMENTS

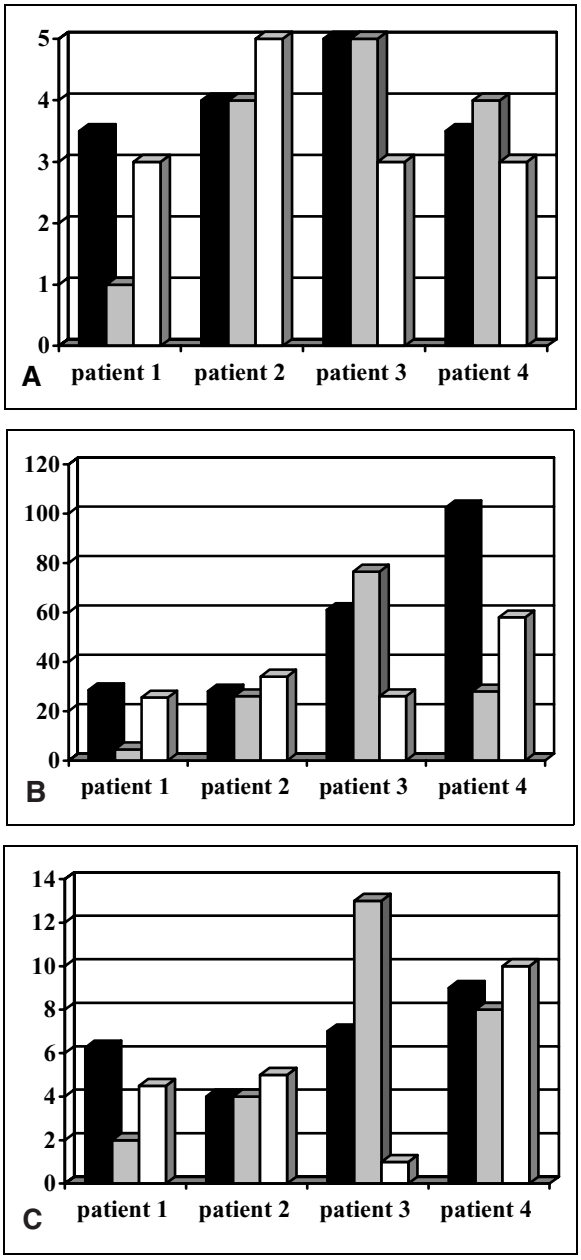
All 4 patients who experienced a decrease in attack frequency during previous use of anticoagulants had one or more thromboembolic risk factors. During repeated anticoagulation with a lower target INR, 2 patients experienced, again, a clear improvement of their migraine.

The positive effect of anticoagulants on migraine, as described in case reports and observational studies,[2-8] also has been observed in 2 specific groups of patients with thromboembolic risk factors. Cuadrado et al observed a dramatic improvement of migraine during treatment with warfarin in 8 patients with the antiphospholipid syndrome (caused by aCL, LA, or both) and subsequent stroke.[9]

In patients with a right-to-left shunt, migraine, especially migraine with aura (MWA), may improve after anticoagulant therapy. In a study that investigated the frequency of PFO and MWA in 74 patients admitted for acute stroke, 5 of 6 patients having PFO and MWA who were treated with anticoagulants in order to prevent recurrent stroke, noticed complete disappearance of their MWA attacks.[10]

The presence of thromboembolic risk factors in all 4 of our patients suggests that improvement of migraine during treatment with anticoagulants may be applicable to a select group of patients with a prothrombotic predisposition or PFO. Only 2 of the patients showed improvement of migraine during treatment with low-dose acenocoumarol, suggesting that the effect may be dependent on the degree of anticoagulation. We used the low INR target range for ethical reasons.

The small number of patients and lack of controls limited our study. Nevertheless, when randomly screening 4 patients with migraine for thrombotic risk factors, it is unlikely to find a prothrombotic state in all 4. The open study limits the interpretation of the results. The strong reduction found in 2 patients, however, is probably not only due to a placebo effect, which is normally not more than about 30%. Moreover, initially all patients spontaneously reported improvement of their migraine before entering the study. Initially, worsening of migraine after discontinuation of previous use of anticoagulants could bias the results. The period between discontinuation of previous



Efficacy parameters in 4 patients with migraine during the run-in period, treatment period (patient 1, 12 weeks; patient 2, 11 weeks; patient 3, 7 weeks; and patient 4, 12 weeks), and after discontinuation of acenocoumarol. The run-in period (8 weeks) is compared with the last 4 weeks of the treatment period and the last 4 weeks of the evaluation period (taking a washout period into account). 1A, Attacks per month. An attack which is successfully treated, but returns within 24 hours is considered as 1 attack. 1B, Hours with migraine per month. 1C, Defined daily dose for symptomatic treatment per month. Black shading indicates run-in period; gray shading, treatment period with acenocoumarol; no shading, after discontinuation of acenocoumarol.

use of anticoagulants and the start of the run-in period of the current study, however, was 8, 7, and 4 months and 6 years—long enough to assume the normal attack frequency to return.

Our findings support the hypothesis that migraine, as a phenotype, has different underlying mechanisms, amongst which a thromboembolic tendency. In this group of patients, oral anticoagulants may be a suitable form of migraine prophylaxis. Use of oral anticoagulants for migraine prophylaxis, however, needs further investigation, raising the question whether the potential benefit of a better health-related quality of life outweighs the potential risk of bleeding complications.

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