Transient monocular blindness and antiphospholipid antibodies in systemic lupus erythematosus

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Article abstract—Background and Objective: Among patients with systemic lupus erythematosus (SLE), the presence of antiphospholipid antibodies (APA), notably the lupus anticoagulant, and anticardiolipin antibodies (aCL) characterizes a subset of patients with a thrombotic tendency. During the regular follow-up care of patients with SLE, we noticed that many described transient visual disturbances. Because a hypercoagulable state may cause transient monocular blindness (TMB), we determined the frequency of TMB and studied its relation to the presence of APA in patients with SLE. Methods: We asked 175 unselected patients with SLE whether they had transient visual disturbances and reviewed their medical charts. All patients were examined with specific attention to the presence of livedo reticularis. Blood was examined for APA. Results: Visual disturbances were recorded for 136 (78%) patients. According to predefined criteria, the symptoms were diagnosed as TMB for 10 (6%) patients and as visual disturbances associated with migraine for 18 (10%) patients. Five of the 10 patients with TMB had attacks in either eye. The 175 patients with SLE accrued a maximum total of 6,349 patient years in their lifetime. From this, the incidence of TMB can be calculated to be at least 158 per 100,000 per year. Lupus anticoagulant was detected in 3 of 10 patients with TMB and 41 of 165 patients without TMB (odds ratio, 1.3; 95% CI, 0.2 to 6.0). aCLs were found in 5 of 10 patients with TMB and 91 of 165 patients without TMB (odds ratio, 0.8; 95% CI, 0.2 to 3.7). Conclusions: The frequency of TMB among patients with SLE is at least 158 per 100,000 compared with the normal population (14 per 100,000 per year). However, among patients with SLE, no significant relation could be shown between TMB and the presence of APA or livedo reticularis.

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Transient monocular blindness (TMB) is usually attributed to temporary ischemia of (a part of) the retina of one eye. Such episodes are therefore considered a transient ischemic attack (TIA) in the supply territory of the internal carotid artery (ICA) similar to TIs that affect the brain. Because these patients have a risk for serious vascular complications (vascular death, stroke, or myocardial infarction) of about 3% per year, TMB is an alarming symptom.1 TMB classically is diagnosed if the complete or partial visual field of one eye is obscured for only a few minutes (blackening, graying, or blurring). Apart from emboli that originate from atheromatous changes in the ipsilateral ICA, other pathogenetic factors, such as vasospasm and a hypercoagulable state, may cause this phenomenon.5-8

Among patients with systemic lupus erythematosus (SLE), persistently positive tests for antiphospholipid antibodies (APA), especially the lupus anticoagulant (LA), and anticardiolipin antibodies (aCL) characterize a subset of patients with a thrombotic tendency.16 APA consequently are associated with (transient) cerebral ischemia and venous thrombotic events.10-18 In particular, the presence of aCL has been found to be an independent risk factor for ischemic stroke, especially among young patients.17,18 Furthermore, patients with LA, moderate to high levels of aCL, or both, and those who had TMB or cerebral TIs are prone to SLE later in life.19 The combination of APA, thrombosis, recurrent fetal loss, or thrombocytopenia has been recognized as the antiphospholipid syndrome.19 Livedo reticularis (LR) is a cutaneous manifestation of antiphospholipid syndrome. It is defined as cyanotic discoloration of the skin with a characteristic network pattern.20,21 The association between stroke and LR is known as Sneddon’s syndrome.22,23 TMB can occur among patients with SLE or Sneddon’s syndrome.24,25 An association between TMB and elevated levels of APA, especially aCL, has been suggested.11,13,14

Physicians involved in the care of patients with SLE often encounter patients who report transient disturbances of the visual field of one eye. It may be difficult to interpret these visual symptoms. In this cross-sectional study among patients treated for SLE in our hospital, we determined the incidence of TMB and tested the hypothesis that TMB among patients with SLE is associated with the presence of APA or LR.

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Patients and methods. A total of 175 unselected patients with SLE who were treated at the University Hospital Utrecht, the Netherlands, gave their consent to participate in the study. All patients fulfilled at least four criteria of the American College of Rheumatology for the classification of SLE.26 In addition to extensive analysis of the clinical charts, each patient was interviewed for the presence of transient visual disturbances. A physical examination focused on blood pressure and the presence of carotid murmurs and cardiac arrhythmia. Funduscopia was performed, and the presence of LR was assessed. LR was classified as mild, moderate, or severe according to the criteria of Weinstein et al.,27 which are based on the color and location of the lesions. Mild LR consists of nonconfluent areas that are light purple and are present only on the lower limbs. In moderate LR the lesions may be confluent, are darker purple, and involve only the limbs. LR is classified as severe if the lesions are deep purple, have confluent patterns that form a complete network, and involve the limbs and other areas.

Blood samples were taken for detection of APA.28 We recorded the following baseline characteristics: sex, age, disease duration, cardiovascular risk factors, presence of Raynaud's phenomenon (defined as at least biphasic episodes of acral discoloration induced by cold or emotions), and previous episodes of objectively verified arterial thrombosis (cerebral TIA or infarction, retinal occlusion, myocardial infarction). Current disease activity was rated with the SLE Disease Activity Index, which has a theoretic maximum score of 105.29

All patients were interviewed by one of us (R.C.J.M.D.). They were asked initially whether they had “ever suffered from any problems with vision.” If this question was answered in the affirmative, details about any such symptoms were recorded by means of a standardized questionnaire. Based on this information, visual disturbances were classified as TMB, retinal migraine, primary ocular disease, or nonspecific symptoms by two of the investigators (L.J.K., R.C.J.M.D.) independently. In the absence of established criteria for the diagnosis of TMB, we used predefined criteria, which were chosen in consultation with several stroke experts in the Netherlands. For the diagnosis of TMB, at least four of the following criteria had to be present: transient loss of vision in one eye that involved the complete visual field or part of it; loss of vision consisting of so-called negative symptoms (blackening, graying, or blurring of the visual field); alternate covering of the eyes during the attack to prove involvement of one eye only; sudden onset of symptoms or a “curtain” that suddenly moved into the visual field; and duration of symptoms from a few minutes to a maximum of a few hours.

Ocular symptoms were attributed to migraine when four of the following criteria were present: attacks of transient monocular scotoma or blindness, the presence of “positive” symptoms (enlarging star-shaped figures with scintillations or flashing lights), unilateral headache, gradual development of symptoms, and duration of symptoms less than 1 hour.30 Symptoms were classified as primary ocular disease when a definite cause had been proved by means of previous ophthalmologic assessment. Symptoms were classified as nonspecific when they could not be classified into one of the aforementioned categories. Disagreement in classification of symptoms was resolved by means of discussion. In all clinical evaluations (interview concerning visual disturbances, SLE Disease Activity Index, review of medical charts, and physical examination) and in classification of the visual symptoms, the assessors were blinded to test results for APA detection.

For the definition of LA we used a cascade of coagulation tests, including the dilute prothrombin time with recombinant human tissue factor (Innovin; Baxter Diagnostics, Deerfield, IL) and the dilute Russell’s viper venom time (IL Test LAC screen and IL Test LAC confirm; Instrumentation Laboratory, Milan, Italy), as described previously.30,31 Results were reported as positive or negative. In the aCL ELISA, nine immunoglobulin (IgG/IGM calibrators (Louisville APA Diagnostics; Louisville, KY) were used in duplicate to report IgG and IgM levels as IgG phospholipid (GPL) and IgM phospholipid (MPL) units. Levels 10 GPL or 10 MPL units or less were considered negative; levels between 11 and 20 units were low positive; levels between 21 and 80 units were moderately positive; and levels more than 80 units were highly positive.28

Data analysis. For statistical analysis, LR was categorized as absent or mild versus moderate or severe.27 For aCL analysis, levels 10 GPL or 10 MPL units or less were considered negative, and levels higher than 10 units were considered positive. In the primary analysis, the different categories of ocular symptoms and the presence of vascular risk factors were related to the presence of aCL (IgG or IgM) or LA, or both. The results are reported by means of odds ratio (OR) with the corresponding 95% CI.

Results. Of 175 patients with SLE, 136 (78%) answered yes to the question about occurrence of transient visual disturbances at any time in the past. On the basis of predefined criteria, we diagnosed TMB for 10 (6%) patients. One of these patients had had two different types of attacks, one of which was classified TMB and the other migraine. For statistical analysis this patient was categorized as having TMB only. One patient with TMB also had infarction in the supply territory of the posterior cerebral artery. Another patient with TMB also had nonspecific symptoms. Migraine was diagnosed for 18 (10%) patients; 6 of these had had attacks that included hemianopia, and four also had nonspecific symptoms.

Two patients were found to have persisting hemianopia only, from an infarction in the supply territory of the posterior cerebral artery. One patient had both infarction in the middle cerebral artery territory and retinal detachment. Fourteen (8%) patients were categorized as having primary ocular disease only as follows: vitreous floaters (6), sicca syndrome (3), retinal detachment (1), glaucoma (1), coloboma (1), both vitreous bleeding and retinal infarction (1), and retinopathy caused by use of hydroxychloroquine (1). Nonspecific ocular symptoms occurred among only 91 (52%) patients. The 175 patients with SLE accrued a maximum of 6,349 patient years in their lifetime. From this, the incidence of TMB can be calculated to be at least 158 per 100,000 per year.

Tables 1 and 2 summarize the relation between the main categories of visual symptoms (see table 1) and important vascular risk factors (see table 2) and the presence of APA. LA were not present more frequently among patients with TMB than among patients with migraine or patients without these symptoms (OR TMB versus no TMB, 1.3; 95% CI, 0.2 to 6.0; see table 1). The frequency of
presence of aCL did not differ among the three groups of patients (OR TMB versus no TMB, 0.8; 95% CI, 0.2 to 3.7; see table 1). Even when the threshold for positivity for presence of aCL was chosen to be moderate or high, there was no correlation with TMB. However, patients with previous cerebral infarction or TIA had a higher frequency of presence of aCL than patients without previous cerebrovascular disease (OR, 4.3; 95% CI, 1.3 to 18.3; see table 2).

Table 3 describes the characteristics of patients with TMB, migrainous visual phenomena, or neither. The median SLE Disease Activity Index score for these groups of patients was 3, indicating that the vast majority of patients were seen at an inactive stage of the disease.29 Only one of the 10 patients with TMB had a history of cerebral infarction. TMB was not significantly associated with the presence of Raynaud’s phenomenon (OR, 1.5; 95% CI, 0.3 to 9.7).
to 7.2). The distribution of vascular risk factors was essentially similar between patients with TMB and patients with migraine. Of 18 patients with migraine, two (11%) had a history of cerebral infarction and one (6%) of myocardial infarction. LR was present in 2 of the 10 patients with TMB, both in severe form, and in five patients with migraine (see Table 1). LR was present in 8 of 15 patients (53%) with a cerebral infarct and in four of seven patients (57%) with cerebral TIAs. The combination of moderate and severe LR was significantly correlated with the presence of aCL (OR, 2.2; 95% CI, 1.0 to 5.1 and LA (OR, 4.2; 95% CI, 1.8 to 9.7). The relation was stronger with higher cutoff values for aCL and with the combination of aCL and LA (data not shown). However, the association between LR and TMB was statistically nonsignificant (OR, 0.9; 95% CI, 0.1 to 4.8). Ultrasonography of the carotid arteries was performed on 7 of 10 patients with TMB. None of these patients had stenosis or occlusion of the ipsilateral ICA. Funduscopy was performed on all patients and showed hypertensive retinopathy in 9 (5%) patients, only one of whom had TMB.

Table 4 specifies the characteristics of the attacks among 10 patients classified as having TMB. Five patients had attacks of TMB in one eye only, and 5 had attacks in either eye. Six patients had had more than 10 attacks. Nine patients had performed a cover test. Eight patients had a sudden onset of symptoms. Two patients described a curtain that moved into the visual field of one eye. Nine patients had attacks that lasted minutes. Loss of vision almost always consisted of blackening or blurring of the monocular visual field.

**Discussion.** This study showed that TMB, diagnosed by means of predefined strict criteria, is frequent among patients with SLE. On the basis of a maximum total of 6,349 patient years accrued by the 175 patients with SLE, the incidence was calculated to be at least 158 cases per 100,000 per year. In a normal population, the mean incidence of TMB is estimated to be 14 cases per 100,000 per year for all ages and in the age group 25 to 44 years to be 3 per 100,000 per year. The observed frequency of visual migraine phenomena (11%) is comparable to that for the normal population, in which it is estimated to be at 6% among men and between 15% and 17% among women. The frequency of the presence of APA among patients with SLE in our study was comparable with that in other studies, which showed APA in 30% to 60% of patients with SLE.

Our cohort can be considered representative of patients with SLE. Nevertheless, there was no statistically significant relation between TMB and the presence of moderate or high levels of aCL. We also confirmed the relation between presence of LR and that of aCL or LA.10,13,16,37 Our study had limited power to detect such relations, and positive relations therefore cannot be ruled out. For example, for APA and TMB the current size allowed detection of an odds ratio of only 4.5 or higher with sufficient precision ($\alpha = 0.05; \beta = 0.20$).

Although we used predefined, generally accepted criteria for the diagnosis of TMB, one might question whether diagnostic bias might have led to overestimation of TMB. The finding of a normal frequency of migraine counteracts this argument. Conversely, some patients may not have been recognized as having had TMB, for example, because the symptoms were transient and patients may have forgotten theirs.

In another study, we found that patterns of TMB vary extensively and that compared with typical symptoms
of TMB, atypical TMB is associated with a relatively high risk for future vascular complications.34

Although the clinical features of TMB among these patients were almost identical to those among patients with known atheromatous disease of the ICA (see table 3),6,7 ultrasonographic findings on the ICA, which were available for 7 of 10 patients with TMB, showed no atherosclerotic changes in the carotid arteries. The frequency of previous thrombotic events among patients with TMB was low, and atherosclerotic changes at funduscopy were rare. Moreover, demographic characteristics and the frequency of vascular risk factors were very similar for patients with SLE and those without TMB. Therefore, a hypercoagulable state or atherosclerosis seems to be unlikely as the explanation for TMB among patients with SLE. The finding that 5 of 10 patients with TMB had attacks in both eyes also is an argument against atherosclerosis. Review of the medical charts and additional information given by the patients showed no temporal relation between episodes of TMB and major exacerbations of disease activity. The absence of positive retinal findings makes vasculitis an improbable cause of TMB.

An embolic source in the heart is improbable, because we found no cardiac arrhythmia or other cardiac abnormalities among patients with TMB. Vasospasm in the retina may be a possibility, although we found no significant relation between TMB and Raynaud’s phenomenon. Burger et al.5 suggested the release of a vasospastic substance in the retinal vasculature as a cause of TMB. Four of the 11 patients described in their report had a local or systemic inflammatory illness (temporal arteritis, periarteritis nodosa, and eosinophilic vasculitis) as an associated condition. The frequency of attacks of TMB was rather high, as in our series.

The prognostic implications of TMB with respect to risk for cerebral ischemia among patients with SLE remain uncertain. In general, risk for major vascular complications following TMB is estimated to be 3% per year.14 On the basis of our results, one might speculate that given the absence of atheromatous disease, the prognosis concerning future cardiovascular complications after TMB among patients with SLE is favorable. It is questionable whether these patients should undergo evaluations for TIA (e.g., ultrasonography of the carotid arteries) or be treated with antithrombotic drugs. To address the question whether prognosis for TMB among patients with SLE is different from TMB due to atherosclerosis, we have embarked on a prospective follow-up study.

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Phenotypic variation in leukoencephalopathy with vanishing white matter

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Article abstract—Objective: The objective of this study is to describe milder and later onset variants of a recently described leukoencephalopathy with vanishing white matter. Background: The diagnostic criteria used currently for this disease include an early-childhood onset of neurologic deterioration. Methods: Clinical, MRI, and spectroscopic findings of five patients were reviewed who fulfilled all inclusion criteria for the disease of vanishing white matter, apart from the age at onset. In one patient histopathologic findings were documented. Results: Onset of the disease was in late childhood or adolescence in four patients, and one patient was still presymptomatic in his early twenties. The course of the disease tended to be milder than in the patients with early-childhood onset. MRI revealed a diffuse cerebral hemispheric leukoencephalopathy with evidence of white matter rarefaction. MRS of the abnormal white matter showed a serious decrease but not complete disappearance of all “normal” signals and, in some patients, the presence of extra signals from lactate and glucose. Changes in relative spectral peak heights were compatible with axonal damage or loss, but not with active demyelination or substantial gliosis. Autopsy in one patient confirmed the extensive rarefaction of the cerebral white matter. There was a commensurate loss of axons and myelin sheaths. Within the brainstem, pontine lesions were present, also involving the central tegmental tracts—a phenomenon previously described in early-onset patients. Conclusion: Later onset does occur in the disease of vanishing white matter, and both MRS and histopathology are compatible with a primary axonopathy rather than primary demyelination.

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In 1993, a “new” disease entity was defined among the leukoencephalopathies of unknown origin on the basis of characteristic MRI and MRS.1 Since its first description, other groups have confirmed the existence of the disease2-4 and provided criteria for the diagnosis.4 The condition is referred to as “vanishing white matter,” and it is characterized by neurologic deterioration with progressive cerebellar ataxia and spasticity but relatively preserved mental abilities. The disease course is chronic progressive with, in most patients, additional episodes of rapid deterioration following infection and minor head trauma. MRI shows a diffuse abnormality of the cerebral hemispheric white matter. Both MRI and MRS provide evidence that in the course of time increasing parts of the abnormal white matter vanish and are replaced by CSF.4 Autopsy has confirmed the presence of white matter rarefaction and cystic degeneration.4 It is highly probable that the disease has an autosomal recessive mode of inheritance.

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