Retrobulbar Spot Sign Predicts Thrombolytic Treatment Effects and Etiology in Central Retinal Artery Occlusion

Max Nedelmann, MD; Michael Graef, MD; Frank Weinand, MD; Klaus-Heiko Wassill, MD; Manfred Kaps, MD; Birgit Lorenz, MD; Christian Tanislav, MD

Background and Purpose—Transorbital sonography may help establish diagnosis of central retinal artery occlusion (CRAO). Next to Doppler sonographic proof of CRAO, an intra-arterial spot sign can be detected in some cases. We hypothesized that it reflects calcified components. It may be associated with embolization from atherosclerotic plaques and may negatively influence thrombolysis.

Methods—Prospective monocenter study of 46 patients with ophthalmologically confirmed CRAO. Systemic tissue-type plasminogen activator thrombolysis was performed when appropriate. All patients received etiologic workup.

Results—CRAO was confirmed by Doppler in all patients. Fifty-nine percent of patients with arterio-arterial embolization were spot sign–positive compared with 20% from cardiac source (P<0.05) and none with vasculitis. Eleven patients underwent thrombolysis. Clinically relevant visual improvement was only found in absence of a spot sign (P<0.05).

Conclusions—Transorbital ultrasound is valuable for initial diagnosis and diagnostic workup of CRAO. In the light of inconsistent results of previous thrombolysis trials, ultrasound may identify patients more likely to benefit from thrombolytic treatment. (Stroke. 2015;46:2322-2324. DOI: 10.1161/STROKEAHA.115.009839.)

Key Words: central retinal artery occlusion ■ spot sign ■ thrombolysis ■ ultrasound
The etiology of CRAO was classified as embolism from LAA in 27 patients and CE in 10 (Table 1). Fifty-nine percent of LAA patients displayed a spot sign (4/5 patients with ipsilateral carotid stenosis ≥70% [NASCET] or occlusion; 10/19 stenosis <70%; 2/3 aortic arch disease) compared with only 20% in CE (1/8 in atrial fibrillation; 0/1 fibroelastoma; 1/1 endocarditis). This difference was statistically significant (P<0.05). A spot sign was found in 0/5 vasculitis cases and in 3/4 patients with undetermined cause.

Eleven patients underwent thrombolysis (Table 2; median symptom onset to treatment time 4.25 h; range 1.75–10.5). All 4 patients with spot sign negative CRAO had significant visual improvement (visual acuity ≥0.6) and restored blood flow. The 7 patients with spot sign positive CRAO had persisting visual impairment ≤0.02 (significant with P<0.05), and all arteries remained occluded. Symptom to treatment time was slightly longer in patients without a spot sign (5.75 versus 4.51 h). Intracranial hemorrhage was not detected in any of the patients.

The spot sign persisted in all 21 initially spot sign–positive cases (follow-up ultrasound between 14 h and 90 days; median 69 h).

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**Table 1. Etiologic Classification of CRAO**

<table>
<thead>
<tr>
<th></th>
<th>Total, % (n=46)</th>
<th>CRAO With Spot Sign (n=21)</th>
<th>CRAO Without Spot Sign (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>27 (59)</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>CE</td>
<td>10 (22)</td>
<td>2</td>
<td>8*</td>
</tr>
<tr>
<td>UND</td>
<td>4 (9)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>5 (11)</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

CE indicates cardioembolism; CRAO, central retinal artery occlusion; LAA, large artery atherosclerosis; and UND, undetermined cause.

*P<0.05

**Discussion**

Our study shows that transbulbar sonography is reliable for detection of CRAO. The retrobulbar spot sign, overall found in 51% of cases with embolic CRAO, is more likely found in LAA than in CE, whereas none of our patients with vasculitis displayed a spot sign. These findings support the hypothesis of the spot sign reflecting a calcified portion of the embolus. Altmann et al previously discussed its calcified nature on basis of their findings of persistence of the retrobulbar spot sign in a series of patients’ median follow-up of 17 months.5

Thrombolytic treatment repeatedly showed promise in previous studies, but effectiveness has not been confirmed in a larger trial. In a summary of reported cases, Biousse et al found visual improvement in 48.5% of IV-treated and 34.9% of IA-treated patients,2 which may be an improvement compared with the natural course.2,8 A prospective randomized multicenter trial on intra-arterial tissue-type plasminogen activator was stopped because of lack of efficacy and a higher rate of adverse events.4 A small randomized trial (n=16) on intravenous tissue-type plasminogen activator found improved visual acuity in 25% of patients, versus none after placebo.3

For the first time, we correlated treatment effects with the occurrence of a spot sign. We found relevant treatment effects only in spot sign–negative CRAO. Although the number of patients was small, the observed effect was statistically significant. These results are plausible in the light of the presumed calcified nature of the spot sign, resulting in a much smaller likelihood to respond. Our results indicate that sonographic identification of the presence or absence of a spot sign may help identify patients more likely to benefit from thrombolytic treatment. A calcified embolus being present in ≈50% of embolic CRAO may be one major reason for limited treatment effects in previous studies. We suggest to include OCCS in future studies to improve awareness of a potential subgroup being less susceptible to tissue-type plasminogen activator.

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**Figure.** A, Normal findings of the optic nerve and its sheath (A1), color-mode (A2), and pw-Doppler (A3) showing blood flow in the distal central retinal artery within the optic nerve. B, Patient No. 8 from Table 2 with spot sign–negative CRAO. Initial Doppler proves occlusion (B2). Reestablished flow after thrombolysis (B3). C, Patient No. 4 from Table 2 with spot sign–positive CRAO (arrow in C1). The artery remains occluded after thrombolysis (C3).
The main reason for exclusion from thrombolysis was time window limitation, with the majority of patients presenting later than 12 h from symptom onset. This emphasizes that emergency awareness and referral to specialized centers need to be improved.9

In conclusion, this study shows that OCCS is valuable for initial diagnosis, etiologic workup, and prognostic assessment. Ultrasound may help identify patients more likely to benefit from thrombolytic treatment.

Disclosures
None.

References
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