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

Central retinal artery occlusion (CRAO) should be regarded similar to stroke because of comparable etiology, potentially concurrent cerebral ischemia, and disabling consequences. Mostly its cause is cardiac or arterio-arterial embolization, and vasculitis accounts for 4% of cases. There is no generally agreed treatment regimen. Studies investigating intra-arterial or intravenous thrombolysis have yielded inconsistent results.

Ocular color-coded duplex sonography (OCCS) allows direct examination of the central retinal artery. Only few studies report on its value. Next to Doppler evaluation, B-mode may reveal a hyperechoic structure within the occluded artery, the so-called retrobulbar spot sign (Figure). It may help discriminate vasculitic from embolic occlusion, as it does not seem to occur in vasculitis. On the other hand, a spot sign is only found in a proportion of embolic CRAO. It has been suggested that it may represent a calcified portion of the embolus.

Following this suggestion, we hypothesised that the spot sign is associated with arterio-arterial embolization and designed this prospective study. In a subset of patients receiving intravenous thrombolysis, we evaluated its influence on treatment results.

Methods
We prospectively included consecutive patients with ophthalmologically confirmed CRAO (May 2012 to December 2014; study approval by the ethics committee of the Justus-Liebig-University Giessen). Patients were examined at the Department of Ophthalmology and then referred to the Department of Neurology for workup and treatment.

All patients had OCCS examination. CRAO was defined as absence of color-mode and pw-Doppler flow in the distal course of the central retinal artery (Figure). Presence or absence of a spot sign was assessed by B-mode. Follow-up examination was before discharge and post-treatment in case of thrombolysis. Vascular workup followed stroke guidelines. Etiology of CRAO was classified as embolism from large artery atherosclerosis (LAA; severe atherosclerosis >4 mm of carotid arteries or aortic arch), cardioembolism (CE), vasculitis, or undetermined cause.

Systemic tissue-type plasminogen activator thrombolysis was applied within a 12 h time window, when appropriate (0.9 mg/kg; 10% bolus; written informed consent for off-label use; Actilyse, Boehringer Ingelheim, Germany; cranial CT before and 24 h after treatment). The Chi square test was used to compare the incidence of the spot sign in CE and LAA and Fisher exact probability test for evaluation of thrombolytic treatment (SPSS for Windows; version 21).

Results
OCCS confirmed occlusion in all 46 patients with CRAO (mean age 69.8±10.9 years; range 45–88; 60% male).
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 $\geq 70\%$ [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 $\geq 0.6$) and restored blood flow. The 7 patients with spot sign positive CRAO had persisting visual impairment $\leq 0.02$ (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).

### 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>
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</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.5

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 $\approx 50\%$ 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.
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


Table 2. Characteristics of Patients Who Received tPA Treatment of CRAO

<table>
<thead>
<tr>
<th>Source of Embolus</th>
<th>Spot Sign</th>
<th>Symptom to Needle Time, h</th>
<th>Flow Before tPA, cm/s syst./diast.</th>
<th>Flow Post Treatment, cm/s syst./diast.</th>
<th>Flow Contralateral, cm/s syst./diast.</th>
<th>Visual Acuity* After tPA</th>
<th>Visual Acuity* After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UND Yes</td>
<td>4</td>
<td>0/0</td>
<td>0/0</td>
<td>12.0/3.0</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td></td>
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<tr>
<td>UND Yes</td>
<td>1.75</td>
<td>0/0</td>
<td>0/0</td>
<td>16.1/3.3</td>
<td>0</td>
<td>0.1</td>
<td></td>
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<tr>
<td>LAA Yes</td>
<td>3.3</td>
<td>0/0</td>
<td>0/0</td>
<td>25/10</td>
<td>0</td>
<td>HM</td>
<td>0.01</td>
</tr>
<tr>
<td>LAA Yes</td>
<td>4</td>
<td>0/0</td>
<td>0/0</td>
<td>10.0/2.9</td>
<td>0</td>
<td>HM</td>
<td>0.01</td>
</tr>
<tr>
<td>LAA Yes</td>
<td>10.5</td>
<td>0/0</td>
<td>0/0</td>
<td>11.4/3.1</td>
<td>HM</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>LAA Yes</td>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
<td>19/6</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>LAA Yes</td>
<td>5</td>
<td>0/0</td>
<td>0/0</td>
<td>16/5</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>LAA No</td>
<td>5.5</td>
<td>0/0</td>
<td>15.6/6.3</td>
<td>20.0/5.8</td>
<td>0.1</td>
<td>0.9</td>
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<tr>
<td>LAA No</td>
<td>4.25</td>
<td>0/0</td>
<td>6.9/0.9</td>
<td>14.1/0.3</td>
<td>0</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>CE No</td>
<td>4.25</td>
<td>0/0</td>
<td>8.9/2.7</td>
<td>11.3/3.7</td>
<td>HM</td>
<td>0.8</td>
<td></td>
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<tr>
<td>CE No</td>
<td>9</td>
<td>0/0</td>
<td>17.5/4.7</td>
<td>16.1/3.3</td>
<td>HM</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

CE indicates cardioembolism; CRAO, central retinal artery occlusion; HM, hand movement (no object recognition, but better than mere light perception); LAA, large artery atherosclerosis; tPA, tissue-type plasminogen activator; and UND, undetermined cause.

*Right columns show the decimal visual acuity (VA). VA 0.8 corresponds to 0.1 logMAR, VA 0.01 to 2.0 logMAR. VA 0 was scored in case of no light perception.
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