The retrobulbar spot sign in sudden blindness — Sufficient to rule out vasculitis?

Michael Ertl a,*, 1, Mathias Altmann b, 1, Elisabeth Torka a, Horst Helbig b, Ulrich Bogdahn a, Anreea Gamulescu b, Felix Schlachetzki a

a Department of Neurology, University of Regensburg, Bezirksklinikum Regensburg, Universitätsstraße 84, 93042 Regensburg, Germany
b Department of Opthalmology, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

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Summary
Introduction: Sudden retinal blindness is a common complication of temporal arteritis (TA). Another common cause is embolic occlusion of the central retinal artery (CRA). The aim of this prospective study was to examine the diagnostic value of hyperechoic material in the CRA for exclusion of vasculitis as a cause. The authors used orbital color-coded sonography (OCCS) for the detection of hyperechoic material.

Materials and methods: Twenty-four patients with sudden visual loss were included in the study after ophthalmoscopic exclusion of other causes (e.g. vitreous bleeding, retinal detachment). Parallel to routine diagnostic workup OCCS was performed in all patients.

Results: 7 patients with the diagnosis of TA presented with different degrees of hypoperfusion in the CRA without hyperechoic material (referred to as a "spot sign") detected by OCCS. Diagnostic workup in the remaining 17 patients did not reveal any signs of TA. The hyperechoic spot sign was visible in 10 of 12 patients (83%) with embolic CRA occlusion. Altogether the frequency of the spot sign in this group was 59%.

Detection of embolic CRAO using the spot sign had a sensitivity of 83% and a specificity of 100%. The missing spot sign in patients with TA was a highly specific finding (p-value 0.01).

Conclusions: The "spot sign" is a highly specific finding, and its detection excludes the diagnosis of temporal arteritis in patients with sudden blindness. The finding of a spot sign helps prevent patients from receiving long-term steroid treatment, or an invasive temporal artery biopsy, with its imminent risks.

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Introduction

Sudden retinal blindness is a common complication of temporal arteritis (TA) due to ischemic optic neuropathy (ION) caused by vasculitic occlusion of the central retinal artery (CRA), the posterior ciliary artery (PCA) and other orbital arteries [1]. Depending on the affected arteries central retinal artery occlusion (CRAO), anterior optic neuropathy (AION) or posterior optic neuropathy (PION) are the results. In the elderly other common causes for hypoperfusion of the retina are thromboembolic events [2,3]. As a tool for the detection of TA, high-resolution ultrasonography of the superficial temporal artery has had a significant impact, with a high positive predictive value for the diagnosis of TA (specificity of 91%). However, a missing “halo” sign, suggestive for vessel wall inflammation seen on ultrasonography, does not sufficiently rule out presence of the disease (sensitivity 68%) and, therefore, superficial temporal artery biopsy remains the gold standard in the diagnosis of TA [4]. The differentiation of embolic versus arteritic occlusion remains a diagnostic challenge in elderly patients with ischemic optic neuropathy, because symptoms of TA, such as headache and elevation of inflammatory parameters, often coexist with significant cerebrovascular risk profiles. Additionally, depending on the cause of occlusion, different acute management strategies need to be applied quickly to improve long-term outcomes in these patients.

It is evident that we still need additional criteria with high negative predictive values to exclude the presence of vasculitis.

In a previously published series of patients with criteria for TA and sudden blindness, we found a hyperechoic embolic occlusion of the CRA in the area of the optic nerve head, which could be used to exclude TA; we called this a retrobulbar "spot sign" [5]. Foroozan et al. published a series of 29 patients with acute vision loss irrespective of the criteria for TA and observed this phenomenon in 9 patients with central retinal artery occlusion (CRAO) detected by retinal fluorescein angiography [6].

High-resolution color-coded ultrasonography can also be applied to the orbit since vitreous gel does not lead to any significant absorption of the incident ultrasound beam. Orbital color-coded sonography (OCCS) allows detection of retrobulbar arteries and veins in addition to an assessment of orbital structures [7]. An analysis of Doppler flow spectra further aids the assessment and, to some degree the quantification, of retinal hypoperfusion due to CRA stenosis or occlusion. Normal flow velocity values within the CRA have been established previously [8].

This is the first prospective study in which patients suffering from acute vision loss due to either thromboembolic events or vasculitic changes in vessel walls were examined to identify the frequency of the "spot sign" in these specific disease patterns. We demonstrate that OCCS can be used to significantly discriminate embolic CRAO from arteritic causes of sudden ocular blindness in the elderly.

Materials and methods

Population and study protocol

The study protocol was approved by the local ethics committee at the University of Regensburg in accordance with the Declaration of Helsinki. Patients were first seen and screened at the Department of Ophthalmology of the University Hospital Regensburg. After exclusion of other reasons for visual loss, such as vitreous bleeding or retinal detachment, patients were referred to the Department of Neurology for OCCS and a routine neurovascular workup that included assessment of the superficial temporal artery. The funduscopic results were not disclosed before OCCS was performed. Before enrollment in the study, patients were made aware of the noninvasive and safe nature of OCCS and provided their written informed consent. In accordance with the study protocol, patients underwent routine diagnostic workups in the Departments of Ophthalmology and Neurology at our hospital, including registration of cerebrovascular risk factors, laboratory tests to detect criteria associated with TA (including the erythrocyte sedimentation rate [ESR]) according to American College of Rheumatology (ACR) criteria, a visual acuity test, retinal fundoscopy and color-coded sonography of brain-supplying arteries. All tests were performed within 24 h after admission.

Ultrasound equipment and data acquisition

For the visualization of retrobulbar structures, a high-resolution linear-array transducer with frequencies ranging from 8 to 15 MHz was used in combination with a Siemens Acuson system (Siemens AG, Erlangen, Germany) and a Toshiba XarioXG device (Toshiba, Tokyo, Japan). The acoustic output of the ultrasound systems was adjusted to the requirements of orbital sonography according to the ALARA principle ("as low as reasonably achievable") to avoid damage to the lens and retina [9]. The settings for orbital sonography were the following: for B-mode, transmit frequency 14 MHz, mechanical index (MI) = 0.1, single focal zone at 2.5 cm, and bandwidth 74 dB; for C-mode, transmit frequency 10 MHz, MI = 0.2, color scale optimized for low velocities, and no wall filter; and for PW-mode, transmit frequency 2 MHz and MI < 0.44.

For OCCS the patients were placed supine with their eyes closed and asked to gaze forward. From above and slightly lateral, the transducer was placed with minimal pressure on the patient’s orbit using plenty of contact gel. By definition the nasal side is depicted on the left image side.

Patient groups and statistical analysis

Depending on the final diagnosis and specific findings, patients were sorted into two different groups: (1) patients with a final diagnosis of TA; and (2) patients with visual loss on the basis of other pathologies. Patients were then further sorted depending on their funduscopic findings.

The frequency of the retrobulbar "spot sign" in patients with TA (group 1) was compared with that in patients...
without TA (group 2) by using a 2 × 2 table. A subgroup analysis was performed for patients with CRAO in funduscopy in both groups. Data analysis was performed using statistical software (IBM SPSS Statistics, Version 18, 2009, Armonk, USA). The independence of both variables (vasculitis and "spot sign") was tested using the exact Fisher test. Sensitivity and specificity were calculated including their respective confidence intervals.

Results

Between June 2010 and June 2011 we enrolled 24 patients with monocular blindness in this prospective study.

Group 1: 7 patients (3 male and 4 female) had retinal hypoperfusion due to TA. All 7 patients had 3 or more positive ACR criteria. In all but one patient, fundoscopic examination demonstrated AION with a blurred rim of the optic disc with optic disc edema and hyperemia with or without small splinter hemorrhages (Fig. 1d).

One patient had findings equivalent to CRAO, the diagnosis of TA was validated years before on the basis of ACR criteria by the Department of Rheumatology.

In 3 of the 7 patients we found a halo sign in the ipsilateral and/or contralateral superficial temporal artery during the ultrasound examination. The diagnosis was confirmed in 4 of 7 patients by means of temporal artery biopsy. In 1 patient, who was unable to undergo biopsy because of ongoing anticoagulation therapy with warfarin, a positive "halo" sign was identified in the left temporal artery. One patient had 4 out of 5 positive ACR-criteria but a negative finding in temporal artery biopsy. None of the patients in this group had a retrobulbar spot sign, but there was absent or pseudovenous flow in the CRA (Fig. 1a–c). Arterial hypertension was present in 4 patients, diabetes mellitus in 2 patients, hypercholesterolemia in 1 patient, and atrial fibrillation (AFIB) in a single patient who was treated with warfarin accordingly. One patient was a former smoker. The average number of risk factors per patient in this group was 2.

Group 2: 17 patients (8 male and 9 female) had sudden monocular blindness based on other pathologies than TA.

12 patients had CRAO in funduscopy. In 2 female patients we found typical fundoscopic findings of anterior ischemic optic neuropathy (AION). One male patient had small splinter hemorrhages in funduscopy but normal flow in both CRAs, probably as a result of recanalized CRAO. One male patient had an occlusion of a big retinal artery (CRA branch) with absent flow in the CRA, based on an ipsilateral ICA occlusion with collateralization from the contralateral ICA. One male patient with risk factors of hypertension, former tobacco use, and hyperuricemia, had a 90% stenosis (graded according to ECST criteria [10]) in the left ICA and visual loss in the left eye due to hypoperfusion of the left CRA; he was referred to vascular surgeons for carotid endarterectomy.

All of these patients had a maximum of 2 positive ACR criteria. On OCCS 10 (59%) of 17 patients had a visible hyper-echoic plaque, known as "spot sign," at the tip of the CRA; taken in account only the patients with CRAO in funduscopy in this group, 10 of 12 patients (83%) had a visible "spot sign" and absent arterial flow (Fig. 2a and b). Moderate ipsilateral ICA stenosis (50–60% according to ECST criteria) was present in three patients (27%) and an additional 3 patients had contralateral ICA stenosis.

The average number of risk factors per patient in this group was 2.2. Arterial hypertension was present in 14 patients, AFIB in 2 and hypercholesterolemia in 7. Six patients had a history of smoking, 1 patient had hyperuricemia and 1 patient had comorbid migraine. Both of the patients with AFIB also had ICA stenosis on the ipsilateral side (both measuring 60% according to ECST criteria).

Summarizing, no patient with TA had a visible spot sign.

The spot sign was detectable in 10 out of 13 patients (73%) with CRAO. With the exception of one patient, CRAOs were not associated with TA. Taken in account only the patients with embolic CRAO (12 out of 13) the spot sign was present in 83% of the cases. No spot sign could be seen in patients with other forms of ischemic optic neuropathy (e.g. AION, retinal artery branch occlusion).

Statistical analysis

Using the exact Fisher test comparing the frequency of the spot sign in TA and non-TA patients we found a p-value of 0.01, the sensitivity of detecting embolic CRAO using the "spot sign" was 83% (95% CI: 65–99%). The specificity for embolic occlusions was 100% (95% CI: 65–100%).

Discussion

In this prospective study we demonstrate the diagnostic significance of retrobulbar ultrasonography for the differentiation of embolic and vasculitic causes of ischemic optic neuropathy.

The causes for ION can be subdivided into different groups, depending on the affected retinal arteries: CRAO, AION and PION [11]. TA, embolism or hypoperfusion are responsible for retinal ischemia in all subgroups. Reliable techniques to discriminate between the different forms are funduscopy and fluorescence angiography. Moreover FA can be helpful to show delayed filling or vascular leakage in choroidal vessels in AION for example. However, both methods cannot elucidate the underlying etiology because they lack sensitivity or depth penetration beyond the retina and thus cannot elucidate the underlying cause of ION.

Temporal arteritis (Horton disease or giant cell arteritis) and embolism from cerebrovascular disease require different acute and long-term therapeutic managements: for an embolic event, anticoagulation or platelet inhibition plus control of vascular risk factors should be initiated; whereas in TA, rapid initiation and long-lasting steroid therapy is essential. Due to the significant side effects of long-term steroid treatment, it is clear that a correct diagnosis is mandatory. So far, the only valid list of diagnostic criteria for TA has been established by the American College of Rheumatology. According to the ACR, 3 or more of the following criteria must be present for a diagnosis of TA: (1) age of 50 years or older; (2) new onset of localized headache; (3) temporal artery tenderness on palpation or decreased pulsation; (4) ESR of 50 mm/h or higher; (5) abnormal findings of a temporal artery biopsy. The sensitivity for this diagnosis was reported to be 93.5%, with a specificity of 91.2% for the discrimination of giant cell arteritis from other forms
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Figure 1  Ultrasound and funduscopic findings in patients with CRAO due to temporal arteritis. (a) Patient 1: a 84-year-old woman with visual loss for 2 days. Duplex- and color-mode OCCS images showing reduced flow in the affected CRA. (b) Patient 1: Duplex- and color-mode OCCS images showing normal flow in the unaffected contralateral CRA. (c) Patient 2: a 71-year-old man with visual loss for 2 weeks. Duplex- and color-mode OCCS images demonstrating zero flow in the affected CRA. (d) Patient 2: Funduscopic image showing a blurred rim of the optic disc, optic disc edema, and hyperemia, as well as a small splinter hemorrhage.

of vasculitis [12]. The main disadvantage of these criteria is that they were not developed and validated for diagnosis in the general population [13]. Secondly, a temporal artery biopsy with its immanent risks can provide false-negative results because of the possible "skip lesion" type of distribution of vasculitis-induced changes in the vessel wall. High-resolution ultrasonography of the superficial temporal artery has been proposed as an adjunct diagnostic tool in the workup of TA, and, indeed, an unequivocal finding of the halo sign has a high positive predictive value of > 90% [4]. Unfortunately, however, no halo finding does not sufficiently rule out presence of the disease.

Embolic artery occlusions are mainly due to atherosclerotic changes in the vessel wall, cardioembolism, or pathologies of the aortic arch [6]. Well-characterized risk factors for cerebral arterial occlusive diseases are hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, hypercholesterolemia, and tobacco use [14]. Within our patient groups an approximate mean of 2 of the aforementioned risk factors were present independent of the eventual cause of the occlusion. This underlines the inability to discriminate vasculitic from embolic causes of CRAO according to a specific risk profile.

The presence of the spot sign is highly suggestive for embolism, whereas vasculitic hypoperfusion is represented by absent or low-flow only. We found OCCS to be a highly specific tool in the further discrimination of these disease patterns in patients with sudden visual loss. The sensitivity of detecting embolic CRAO using the spot sign was 83% (95% CI: 65—99%), with a specificity of 100% (95% CI: 65—100%) to rule out vasculitic causes of ION. The missing spot sign in patients with TA was a highly significant finding (p = 0.01) despite the relatively small patient sample size. Thus, retrobulbar ultrasonography, an easy, safe, and rapid technique, should be considered in the workup in cases of sudden retinal blindness.

The only two retrospective studies of patients with sudden monocular blindness seem to have underestimated the frequency of the retrobulbar hyperechoic plaque, here referred to as the "spot sign". In the previously mentioned study by Foroozan et al. [6], the authors found the spot sign in 31% of patients using OCCS. In the second study, Ahuja et al. did not see any visible emboli in 18 patients with CRAO [14]. However, Ahuja et al. did not use OCCS in their study; they used only fundoscopy, a technique that visualizes typical signs of CRAO but no underlying pathological characteristics beyond the retinal level.
Figure 2  Ultrasound findings in a 77-year-old patient with embolic CRAO and visual loss for 3 days. (a) B-mode: hyperechogenic ’spot sign’ in the optic nerve head, representing an embolus in the distal CRA. (b) Duplex- and color-mode OCCS image depicting absent flow in the CRA. (c) Duplex- and color-mode OCCS image demonstrating normal flow in the unaffected contralateral CRA. (d) Funduscopic image showing a blurred rim of optic disc, the typical finding of a pale retina with a cherry-red macula (cherry-red spot) seen in patients with CRAO.

The presence of a spot sign on OCCS should lead to a detailed workup looking for sources of cardiac emboli (electrocardiography, echocardiography, long-term electrocardiography, and holter monitoring) and atherosclerosis (intima-media thickness measurements using carotid ultrasonography, presence of hemodynamically relevant carotid stenoses, and so forth). This may also prevent patients with a borderline diagnosis of giant cell arteritis (age >50 years, headache, elevated ESR due to other causes, or patients with ongoing steroid treatment obscuring the diagnosis) from receiving long-term steroid treatment with all its negative side effects or an invasive temporal artery biopsy with its immanent risks such as scalp necrosis [15] and facial nerve injury [16,17].

Conclusion

In summary, OCCS is a widely accessible method that can be used to discriminate different causes of sudden monocular blindness. Safety is ensured by the aforementioned technical modifications. Presence or absence of the “spot sign” helps to further discriminate embolic from vasculitic occlusion of the CRA. The expenditure of time for the examination is short and the technique is easily applied, even in the hands of less-experienced ultrasonographers.

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