Atrophy of optic nerve detected by transorbital sonography in patients with demyelinating diseases of the central nervous system

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Background and purpose: Transorbital sonography (TOS) has emerged as a promising imaging method for the diagnosis and follow-up of acute optic neuritis (ON). Available studies report an increase in the optic nerve diameter (OND) and the optic nerve sheath diameter (ONSD) in the case of a first episode of ON in the affected eye compared to either the contralateral unaffected eye or controls. However, the utility of TOS in the case of recurrent episodes of ON has never been assessed.

Methods: In our prospective cohort study, the diagnostic utility of TOS in patients with demyelinating diseases of the central nervous system was assessed, and the association between TOS, optical coherence tomography (OCT) and visual evoked potentials was examined further.

Results: Seventy-eight patients with a history of demyelinating disorders of the central nervous system (mean age 38.2 ± 14.2 years; 24% with acute ON) were included. No differences in the OND (3.2 ± 0.5 mm vs. 3.2 ± 0.4 mm) and ONSD (5.1 ± 0.8 mm vs. 5.1 ± 0.7 mm) measurements were found between patients with and without acute ON. Papillary swelling was more frequent in patients with acute ON (14.2% vs. 1.5%, P = 0.002). Patients with a history of previous ON were found to have lower OND (P < 0.001) and ONSD (P = 0.007) compared to patients without a history of previous ON. TOS measurements were inversely associated with disease duration and positively correlated with OCT findings. No association with visual evoked potential measurements was found.

Conclusion: No evidence was found for TOS-sensitive differences in the OND and ONSD of patients with demyelinating diseases, according to the presence of acute ON. The association between TOS and OCT measurements deserves further investigation.

Introduction

B-mode transorbital sonography (TOS) emerges as a novel, reliable and promising imaging method for the diagnosis and follow-up of various medical conditions [1–7]. Some case-control studies have also supported the potential utility of TOS in the identification of patients with acute optic neuritis (ON) but have reported inconsistent measurements on the presumed thickening of the retrobulbar portion of the optic nerve in patients with acute ON compared to their counterparts [8].

In the aforementioned studies patients with acute ON were compared to either normal controls [9], patients with contralateral eye unaffected by ON [10–12] or both [13]. Moreover, since most of the
studies have included patients with a first episode of ON, the effect of patient characteristics on the diagnostic utility of TOS in the chronic state of demyelinating diseases of the central nervous system (CNS) was not formally assessed in any of these protocols. Taking into account the aforementioned considerations a prospective cohort study was performed to assess the utility of TOS in the diagnosis of acute ON in patients with a history of CNS demyelinating disorders. Given that the effect of patient characteristics on the diagnostic utility of TOS was not mentioned in the previous studies, the relationship of TOS between patients with acute ON and patients without evidence of acute ON but with a positive history for CNS demyelinating disease was explored. Further, the association of TOS measurements with relevant clinical parameters, optical coherence tomography (OCT), visual evoked potentials (VEPs) and laboratory tests was explored.

Methods

Patient population

Consecutive patients with a history of demyelinating disorders in the CNS hospitalized in the Department of Neurology at the St Josef Hospital, Ruhr University of Bochum, Germany, during a 3-month period (February 2019–April 2019) were prospectively enrolled. Acute ON was diagnosed in the presence of pain on eye movement within 1 month from hospital admission, subacute onset of worsening of vision, a relative afferent pupillary defect and normal-appearing fundus [14]. All patients received complete neurological and ophthalmological examinations, OCT and VEPs as standard of care. All examinations were performed within 24 h from the patient’s admission to the hospital and prior to any diagnostic (e.g. lumbar puncture) or therapeutic management (corticosteroid administration, plasmapheresis) that could have an impact on study findings. Diagnosis, patient characteristics, functional impairment, current and previous medications, disease course and laboratory findings were prospectively recorded in an anonymous database. A detailed description of TOS, VEP and OCT examinations and further information on power calculation, statistical analysis, study protocol, institutional approval and data availability are provided in the Supporting information.

Comparisons and associations

The primary comparison in our study protocol was the absolute difference in optic nerve diameter (OND) between fellow eyes in patients with acute ON compared to patients without acute ON. Secondary comparisons included the differences in optic nerve sheath diameter (ONSD) measurements between the fellow eyes in patients with acute ON compared to patients without acute ON, the pooled differences in OND and ONSD measurements between patients with acute ON and patients without acute ON (Fig. S1), and the rates of papillary swelling between patients with acute ON and patients without acute ON. Parameters that were found to differ significantly between the two groups were further assessed with receiver operating characteristic (ROC) analysis. Sensitivity analyses were also performed on the aforementioned TOS measurements after excluding patients with a history of previous ON.

Besides the temporal course of ON, OND and ONSD measurements were also stratified according to gender (males versus females), diagnosis of multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) and history of previous ON. The association of OND and ONSD measurements of the total patient population with patient age, Expanded Disability Status Scale (EDSS) score, disease duration, OCT and VEP measurements was also examined, and the inter-rater agreement was assessed (Fig. S2).

Results

A total of 78 patients were included with a history of CNS demyelinating disease, 58% with a history of MS and 26% with a history of NMOSD (14% myelin oligodendrocyte glycoprotein positive and 12% aquaporin positive), consisting of 19 patients with acute ON and 59 patients without evidence of acute ON (mean age 38.2 ± 14.2 years, 64.1% females, mean EDSS score 3.7 ± 2.1) resulting in a data pool of 156 optic nerves. The median time from symptom onset to TOS examination was 10 days, interquartile range (IQR) 6–25 days. Patients with acute ON were younger (32.4 ± 13.3 years vs. 40.1 ± 14.1 years, \( P = 0.039 \)), less frequently under treatment with a disease modifying drug (26.3% vs. 61.0%, \( P = 0.008 \)) and had significantly higher rates of previous ON (36.8% vs. 11.9%, \( P = 0.014 \)) than patients without acute ON (Table 1). No correlation between timing from symptom onset to TOS examination and OND/ONSD measurements was found (OND, \( r = -0.135 \), \( P = 0.607 \); ONSD, \( r = -0.185 \), \( P = 0.478 \); Fig. S3).

No difference in the absolute differences of OND (0.3 ± 0.3 vs. 0.3 ± 0.3, \( P = 0.914 \)) and ONSD (0.5 ± 0.4 vs. 0.5 ± 0.5, \( P = 0.942 \)) measurements of fellow eyes was detected between patients with acute ON and patients without acute ON (Table 1).
Likewise, OND (3.2 ± 0.5 mm vs. 3.2 ± 0.4 mm, \( P = 0.844 \)) and ONSD (5.1 ± 0.8 mm vs. 5.1 ± 0.7 mm, \( P = 0.780 \)) measurements in TOS examination of both eyes were similar between groups (Fig. 1), whilst patients with acute ON had higher rates of papillary swelling compared to patients without acute ON (14.2% vs. 1.5%, \( P = 0.002 \)). In the ROC analysis the presence of papillary swelling was found to yield a sensitivity of 14.29% and a specificity of 98.52% for the diagnosis of acute ON. Subgroup analysis of patients with unilateral acute ON (\( n = 17 \)) revealed that patients with recurrent ON exhibited a significantly smaller OND compared to patients with first episode of ON (median 3.0 mm, IQR 2.6–3.1 mm vs. 3.5 mm, IQR 3.0–3.8 mm; \( P = 0.044 \); Fig. S4A). However, ONSD was not found to differ between the two groups (median 5.1 mm, IQR 4.3–6.1 mm vs. 5.4 mm, IQR 4.8–5.7 mm; \( P = 0.883 \); Fig. S4B).

In the sensitivity analyses after excluding patients with a history of previous ON (\( n = 14 \)), OND (3.2 ± 0.5 mm vs. 3.2 ± 0.5 mm, \( P = 0.752 \)) and ONSD (5.2 ± 0.7 mm vs. 5.1 ± 0.7 mm, \( P = 0.638 \)) measurements in TOS examination of both eyes were similar between groups, with no disparities in the absolute differences of OND (0.3 ± 0.4 vs. 0.3 ± 0.3, \( P = 0.836 \)) and ONSD (0.5 ± 0.4 vs. 0.4 ± 0.5, \( P = 0.952 \)) measurements between patients with and without acute ON.

In subgroup analyses patients with a history of previous ON had significantly lower OND (\( P < 0.001 \)) and ONSD (\( P = 0.007 \)) measurements compared to patients with no history of previous ON episodes, whilst females were found to have lower ONSD (\( P = 0.011 \)) measurements compared to males.

In correlation analysis of eye measurements without evidence of acute ON, OND was found to be inversely related to disease duration (\( \rho = -0.276 \), \( P = 0.005 \); Fig. 2), whilst no association of any TOS measurement with patients’ age or EDSS score was uncovered (Table 2). Significant correlations were also found between TOS and retinal nerve fiber layer (RNFL) thickness measurements, especially in the central and temporal poles (Fig. 3). Finally, no association of OND and ONSD with any of the VEP parameters was found (Table 3).

**Discussion**

It was found that patients with demyelinating diseases of the CNS and acute ON have similar OND and ONSD in TOS to patients with demyelinating diseases of the CNS and no evidence of acute ON. The presence of papillary swelling was more frequent in the TOS examinations of patients with acute ON compared to their counterparts, but was found to have a low sensitivity in establishing the diagnosis of acute ON.
ON. TOS measurements were found to be inversely associated with disease duration and RNFL thickness in OCT.

As history of previous ON was found to be associated with reduced OND and ONSD (Table 2) and patients with acute ON were found to have higher rates of previous ON (Table 1), it could be hypothesized that any potential thickening of the retrobulbar portion of the optic nerve in the setting of acute ON was counterbalanced by the previously induced optic nerve atrophy as a result of past ON episodes [15,16]. Indeed, in a further analysis comparing patients with first episode to the group of patients with recurrent episodes of ON, a significant difference regarding the OND was identified. However, it remains unclear whether the larger OND in the group with a first episode is due to an acute swelling of the nerve or whether the lower OND in the group with recurrent episodes is related to a preexisting atrophy [9].

Finally, the presence of papillary swelling was found in 14% of patients with acute ON, a prevalence rate that is within the range reported by a systematic review of a total of seven studies reporting papillary swelling presence by TOS in 6%–43% of patients with acute ON [8], with this wide variability reflecting the potential differences in latency between onset of symptoms and TOS examination between studies. The low sensitivity of papillary swelling in the diagnosis of acute ON that was detected in our TOS protocol is in accordance with literature data, suggesting that optic nerve swelling is present in approximately one-third of patients with acute ON [17,18].

The lack of association of TOS measurements with age has been reported in previous studies, recruiting healthy individuals [19,20]. A lower ONSD in female patients compared to male patients was also detected, an observation that is in accordance with previous studies on healthy volunteers [21,22]. The inverse relation of disease duration and RNFL thickness as well as OND has been reported in a previous study including 17 patients with first-ever unilateral acute ON [12]. Numerous studies report a significant reduction in RNFL thickness in eyes affected by ON compared to fellow eyes and eyes of healthy controls [23], whilst further suggesting that retinal atrophy in OCT not only predicts long-term visual impairment after acute ON [24] but also reflects brain atrophy and is associated with both physical and cognitive disability [25,26]. Similarly to our findings, TOS measurements were not associated with VEP findings in the aforementioned study and in another case–control study of 21 patients with acute ON [8]. The lack of association between TOS and OCT measurements and VEP findings could be attributed to the limited utility of RNFL thickness measurements at a single time-point, and thus potentially a single OND measurement by TOS, in detecting prior clinically silent ON [27].

**Figure 1** Graphical representation of the differences in (a) optic nerve diameter (OND) and (b) optic nerve sheath diameter (ONSD) between patients with and without acute optic neuritis (ON).

**Figure 2** Graphical representation of the association between optic nerve diameter (OND) measured by transorbital sonography and disease duration.
The results from the first adequately powered prospective cohort study evaluating the utility of TOS in diagnosing acute ON episodes in patients with a history of CNS demyelinating diseases are presented. Compared to previous studies, including only patients with a first episode of ON, the utility of TOS in the course of an underlying demyelinating disease was evaluated and thus whether the utility of TOS is potentially limited in patients with a first episode of ON was assessed. Despite the strengths of the current report several limitations should be taken into consideration. Although a predefined protocol was used and several subgroup and correlation analyses were performed, the presence of unmeasured confounders cannot be excluded. No evidence for any potential association between disease modifying treatment and OND or ONSD measurements was found. However, our sample size was considered to be limited for this analysis, whilst no adjustment was made for potential confounders regarding patient characteristics (e.g. age, gender, disease duration, previous ON) and treatment characteristics (type of disease modifying treatment, duration of current treatment, previous disease modifying treatments and their duration). Likewise, our sample size should also be considered as limited for the subgroup analysis between patients with MS and NMOSD, and thus the lack of existing differences in

### Table 2 Subgroup and correlation analyses between patient clinical characteristics and transorbital sonography measurements

| Subgroup analyses | OND (mm) | ONSD (mm) |
|-------------------|----------|-----------|
| Females versus males | 3.1 ± 0.3 vs. 3.1 ± 0.4, *P* = 0.279 | 4.9 ± 0.7 vs. 5.2 ± 0.7, *P* = 0.011 |
| MSa versus NMOSDb | 3.0 ± 0.4 vs. 3.0 ± 0.4, *P* = 0.911 | 5.0 ± 0.8 vs. 5.0 ± 0.5, *P* = 0.986 |
| History of previous ON | 2.8 ± 0.4 vs. 3.1 ± 0.4, *P* < 0.001 | 4.7 ± 0.8 vs. 5.1 ± 0.7, *P* = 0.007 |
| Current DMD treatment | 3.1 ± 0.4 vs. 3.1 ± 0.4, *P* = 0.599 | 5.1 ± 0.8 vs. 5.0 ± 0.7, *P* = 0.607 |
| Correlation analyses | | |
| Age | ρ = −0.004, *P* = 0.957 | ρ = −0.058, *P* = 0.468 |
| EDSS | ρ = −0.015, *P* = 0.857 | ρ = 0.036, *P* = 0.673 |
| Disease duration | ρ = −0.276, *P* = 0.005 | ρ = −0.189, *P* = 0.060 |

DMD, disease modifying drug; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; OND, optic nerve diameter; ONSD, optic nerve sheath diameter; aIncluding patients with clinically isolated syndrome, relapsing–remitting multiple sclerosis, secondary progressive multiple sclerosis and primary progressive multiple sclerosis; bIncluding aquaporin-4 positive, aquaporin-4 negative and myelin oligodendrocyte glycoprotein patients.

### Table 3 Correlation analyses between transorbital sonography and visual evoked potential measurements

| | OND | ONSD |
|-----------------|-----|-----|
| P100 latency    | ρ = 0.053, *P* = 0.543 | ρ = 0.048, *P* = 0.581 |
| N75 amplitude   | ρ = −0.014, *P* = 0.875 | ρ = 0.018, *P* = 0.838 |
| P100 amplitude  | ρ = −0.086, P = 0.332 | ρ = −0.036, *P* = 0.683 |
| N125 amplitude  | ρ = −0.086, P = 0.336 | ρ = 0.036, *P* = 0.686 |

OND, optic nerve diameter; ONSD, optic nerve sheath diameter.
TOS measurements between these two groups cannot be excluded with certainty. Finally, an inverse relationship of OND with disease duration was found, but not with EDSS score. This finding contradicts a previous TOS study protocol suggesting significant associations of OND measurements with both EDSS score and disease duration, but not with previous history of ON [28].

Despite being a highly accessible, safe and user-friendly imaging method TOS does not appear to assist in the diagnosis of acute ON in patients with a history of demyelinating diseases of the CNS. Our finding should be confirmed by other large scale observational studies, which should further assess the impact of other potential parameters including disease modifying treatment history. Taking into account that optic nerve atrophy and RNFL thinning following acute ON have been associated with brain atrophy [29], future study protocols should also assess the potential association of OND measured by TOS with brain atrophy also in neurodegenerative diseases.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Transorbital sonography examination of the eye using B-mode ultrasound imaging: the optic nerve (ON) is depicted posterior to the ocular bulb and optic nerve fibers themselves appear hypoechoicogenic.

Figure S2. Correlation between measurements of both investigators for (A) OND and (B) ONSD.

Figure S3. Linear regression analyses on the association of OND and ONSD measurements with time from symptom onset to transorbital sonography examination.

Figure S4. Comparison of (A) OND and (B) ONSD measurements between patients with first and recurrent episodes of unilateral acute optic neuritis.

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