Optical coherence tomography in Susac's syndrome

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Abstract
Susac's syndrome is an autoimmune endotheliopathy with predilection for brain, retina and cochlea (Susac, 1994). Optical coherence tomography (OCT) is a non-invasive method, which is increasingly used in the diagnosis of retinal as well as primary central nervous system diseases. OCT is suggested as a useful diagnostic tool in differentiating Susac's syndrome from multiple sclerosis (MS) (Brandt et al., 2012). This report demonstrates the OCT findings in 3 patients with Susac's syndrome in different stages of the disease. The OCT demonstrated decreased retinal nerve fiber layer (RNFL) thickness, which was patchy in nature and more prominent in the nasal quadrants. We also observed loss of the normal foveal contour, which is uncharacteristic for MS. The extent and degree of the OCT abnormalities in our patients correlated with the stage and severity of the disease and correlated with the findings on the visual field studies. We confirm that OCT is a useful diagnostic tool in Susac's syndrome and helps to differentiate it from MS. Furthermore, OCT may be a non-invasive alternative to fluorescein angiography in longitudinal follow up of these patients.

1. Introduction
Susac's syndrome was first described by John Susac in 1979 (Susac, 1994). It is more common in women with an average age of onset of 30 years (Bitra and Eggenberger, 2011). Susac's syndrome can be differentiated from MS by clinical features such as branch retinal artery occlusion (BRAO), mental status changes, and hearing loss as well as characteristic MRI features, and lack of oligodendral bands in the CSF. However, as the characteristic symptomatology often does not occur at the same time, Susac's syndrome is often misdiagnosed as MS (Brandt et al., 2012; O'Halloran et al., 1998). As Susac's syndrome has a distinctive pathogenesis and is treated differently from MS, early diagnosis and treatment is essential to avoid poor outcomes (Bitra and Eggenberger, 2011).

OCT is a non-invasive infrared technique that uses light interference patterns to generate a cross-sectional image of the retina (Frohman et al., 2006, 2008). OCT has been used to evaluate patients with MS and Neuromyelitis Optica (NMO) (Naismith et al., 2009), and a recent study has
suggested its usefulness in Susac’s syndrome (Brandt et al., 2012). We report the OCT findings in 3 patients with Susac’s syndrome at different stages: a patient in the sub acute stage, a patient with treated chronic disease with minimal residual neurological deficits, and a patient with untreated chronic disease with permanent neurological deficits.

Case 1. 22 year-old woman presented with confusion, headaches, abnormal gait and memory loss over a period of two months. She received intravenous (IV) methylprednisolone followed by a month-long prednisone taper, and was treated with interferon β-1a three times weekly for presumed diagnosis of MS. The patient was referred to our center after she had increasing confusion, visual blurring, and abnormal hearing. Examination 2 months after the onset of symptoms showed visual acuity of 20/50 on the right and 20/800 on the left with a left afferent pupillary defect. Fundoscopy showed cotton wool spots in the inferior meridian of the right eye, left optic atrophy and left BRAO. Hearing was impaired on the left side. She had normal motor strength, right-sided hyperreflexia, normal sensory exam and coordination, and abnormal tandem gait. She was diagnosed with Susac’s syndrome and treated with IVIG and prednisone. One year after initial diagnosis and therapy with pulse IVIG and low-dose prednisone at 20 mg/day, she is asymptomatic, with visual acuity of 20/20 and 20/40 in right and left eyes respectively.

Case 2. 21 year-old female presented with new onset headaches and visual blurring. Two months later, she developed right-sided weakness, lethargy, confusion, and abnormal balance. She was treated with IV methylprednisolone followed by prednisone taper. Over the following month, during the prednisone taper, she developed severe confusion, lethargy and blurry vision, and was referred to our center. On admission her Mini Mental Status Exam was 17/30. Visual acuity was 20/25 bilaterally. There was also mild right hemiparesis, diffuse hyperreflexia, and bilateral ankle clonus and Babinski signs. She was diagnosed with Susac’s syndrome after the confirmatory fundoscopic findings described below. She was then treated with steroids and monthly IVIG infusions. Over the next year, she developed hearing loss and required bilateral hearing aids. Mycophenolate was initiated as the IVIG and prednisone were tapered. 4 years after the onset of her symptoms, she continues to have hearing impairment but is otherwise without any other neurological symptoms.

Case 3. 21 year-old female presented with abnormal vision in the right eye and headache. Ophthalmologic evaluation revealed a BRAO in the right eye. She later developed right-sided hearing loss and a left BRAO. The disease had a progressive course for the next 5 years. She stopped working secondary to gait imbalance, memory loss, difficulty concentrating, inability to alphabetize, disorientation, and poor concentration. The diagnosis of Susac’s syndrome was established nearly 15 years after the onset of symptoms based on findings of ophthalmological assessments (including FA), MRI, and exclusion of conditions such as hypercoagulability state, vasculitis, spinocerebellar ataxia, and Sjogren’s syndrome. Her examination nearly 20 years after the onset of symptoms, revealed impaired memory, dysarthric speech, ataxic gait and generalized hyperreflexia and bilateral Babinski reflexes. As the course of the disease was not active (“burned-out” stage) when initially seen at our center, she never received immunomodulatory treatment.

1.1. Paraclinical tests

1.1.1. OCT
Sequential RNFL and macular scans were obtained during clinic visits using Heidelberg Spectralis® OCT. The resolution of Spectralis® OCT is ~7 μm with a data-acquisition speed of 40,000 Å scans/s, using a single horizontal B-scan image centered on the fovea (1536 Å-scans; scan angle, 30°; scan length 8.8 mm). Heidelberg Spectralis provided normative database©.

1.1.2. Magnetic resonance imaging (MRI)
MRI studies were performed on all of our cases. Brain and cervical spinal MRI (1.5 T) were done using standard T1 and T2 weighted images, diffusion weighted imaging, and post gadolinium T1 weighted sequences.

1.1.3. Fluorescein angiography
Fluorescein angiography was performed using a Fluorescein Lite 10% solution (5 mg/mL used; concentration 100 mg/mL), which is injected into the brachial vein, and reaches the retinal circulation in approximately 10-15 s. Once it has reached the eye, its course is tracked throughout the retinal vasculature and images are taken using the Zeiss FF 450 plus IR fundus camera. The dye is followed for at least 10 min and images are taken periodically throughout this time period to assess retinal vessel occlusion, and other abnormalities such as leaky vessels.

1.1.4. Audiology
Pure-tone audiometry was performed using traditional audiology format.

1.1.5. Others
Formal visual fields were performed with Humphrey automated visual fields (HVF). Pattern Visual Evoked Potentials (VEP) and Low Contrast visual acuity were obtained in these patients.

2. Results

Case 1. A brain MRI showed innumerable white matter lesions throughout the cerebrum, cerebellum, brainstem and corpus callosum, several with enhancement (Fig. 1). The Cerebrospinal Fluid (CSF) showed elevated protein of 151 mg/dl and 4 white cells/μL (76% lymphocytic), elevated myelin basic protein of 6.75 ng/mL (nl 1-4.1 ng/mL) but no oligoclonal bands. Further lab workup included negative titers for ANA, SSA, SSB, VDRL, and HSV I/II. Fundus photography and fluorescein angiography (FA), done about 2 months after the symptoms started, showed inferotemporal branch retinal artery occlusion (Fig. 2A) and arteriolar wall hyperfluorescence in the left eye (Fig. 2B). HVF testing shortly after the initial symptoms showed a dense scotoma on the left and patchy visual defects, predominantly affecting the
left superior nasal quadrant on the right eye. Follow up HVF exam 3 months later showed dense binasal defects, which was more severe in the left eye. Audiogram showed moderate mid-frequency hearing loss, so called “cookie bite pattern” bilaterally. An OCT was done about 6 months after the onset of symptoms and demonstrated loss of normal foveal contour in the left eye (G=66 μm, normal=76-117 μm) (Table 1, Fig. 4A and B).

There was also reduction of the central foveal sector (CFS) at 254 μm (normal 270-300 μm) (Table 2, Fig. 5).

Case 2. MRI showed numerous areas of abnormal T2WI and FLAIR signal in subcortical and periventricular white matter, pons and corpus callosum without pathological enhancement. CSF examination showed a protein of 104 mg/dl and 5 white cells/μL with lymphocytic predominance, and no oligoclonal bands.

Macular volume was normal bilaterally. Workup for vasculitis and hypercoagulability state was negative. Indirect fundoscopy showed normally appearing optic discs and small areas of dot-blot hemorrhages in the superior nasal periphery of the left eye. HVF study showed no obvious visual defects. FA demonstrated areas of capillary non-perfusion with pinpoint areas of intraluminal hyper-fluorescence compatible with microaneurysms.

OCT obtained 4 years after diagnosis demonstrated bilateral RNFL thinning in the nasal quadrants (36 μm OS and 44 μm OD) (normal 48-95 μm) as well as global RNFL thinning of 69 μm OS and 80 μm OD (normal 82-111 μm) (Table 1, Fig. 4C and D).

Case 3. Upon presentation to our institution 15 years after onset of symptoms, MRI showed subcortical white matter changes, cerebral and cerebellar atrophy, severe atrophy of...
Fig. 4  OCT in Cases 1 (A, B), 2 (C, D) and 3 (E, F). The values in parentheses are the respective normal means. Green: normal, yellow: borderline abnormal (between the 1st and 5th percentiles), red: abnormal (<1st percentile), blue: abnormally thick >5th percentile.

Fig. 5  Macular scan in Case 1, shows reduced thickness and volume of central foveal sector.
corpus callosum, and subcortical white matter disease. HVF study showed a dense temporal loss which did not respect the vertical meridian, as well as superior and inferior arcuate defects on the right side; and superior arcuate loss on the left side.

Baseline OCT scans, obtained about 20 years after diagnosis, showed right RNFL loss globally but most severe in the nasal quadrant 29 μm (normal 82–111 μm). Left RNFL loss was also most severe in the nasal quadrant, 30 μm (normal 48–95 μm) (Table 1). Right macula volume was reduced to 6.34 mm³ and left volume 8.31 mm³ was normal. Macular central subfield (CSF) in the right was 251 μm (normal 315 μm) and left was 282 μm (Fig. 6, Table 1, Fig. 4E and F).

3. Comments

Due to its ease of use, non-invasive nature and relatively low cost, OCT is increasingly used in neurological diseases that also involve the optic nerve or retina, and in particular, MS and demyelinating disorders (Frohman et al., 2006; Subei and Eggenberger, 2009). Parameters such as RNFL thickness, macular volume (MV), and abnormalities in ganglion cell and inner plexiform retinal layer have been investigated as biomarkers for disease activity and for evaluating effectiveness of new treatments for MS (Frohman et al., 2006; Ratchford et al., 2013). The RNFL abnormalities in MS correlate with a history of optic neuritis as well as visual function, but can be present even in the absence of optic neuritis (Frohman et al., 2006, Costello et al., 2006). Furthermore, RNFL thinning is more severe in secondary progressive MS compared to the relapsing remitting and clinically isolated syndrome (Henderson et al., 2008; Costello et al., 2009). OCT findings can therefore be incorporated into the paraclinical data to assist with demonstration of dissemination in time and space to confirm the diagnosis of MS and to exclude other disorders.

Here we demonstrate the OCT changes in 3 patients in different stages of Susac’s syndrome. RNFL abnormalities were found in all of our patients, consistent with the findings of a previous report (Brandt et al., 2012). RNFL thinning was most severe in Case 3 (burnt-out stage) and mildest in Case 1 (recent onset, appropriately treated) (Table 1, Fig. 4). RNFL thinning was overall patchy in distribution and was more severe in the nasal quadrants in 2 of our 3 patients, which is not typical for the pattern commonly encountered in MS in which the RNFL thinning is more pronounced in the temporal quadrants (Pueyo et al., 2008, Table 1, Fig. 4). RNFL thinning in OCT correlated with presence of abnormalities on the Humphrey Visual Field (HVF), but OCT was also abnormal even when HVF remained normal, suggesting that OCT is a more sensitive tool for monitoring retinal injury in Susac’s syndrome. Another interesting observation was the loss of foveal contour on OCT in two of our cases (Figs. 3 and 6); see Fig. 7 for a normal control. Loss of foveal contour secondary to sectoral retinal thinning has been described in the chronic stage of retinal ischemia (Takahashi and Iijima, 2009), and is not seen in MS and demyelinating diseases. Macular volumes and central foveal thickness were reduced in the affected eyes of two of our patients (Table 2). The OCT changes in
our patients correlated with the findings of the fundoscopic examination and FA.

OCT has been suggested to be a useful diagnostic tool in differentiating MS form Susac’s syndrome in a previous study (Brandt et al., 2012). This study further confirms that notion. Furthermore, we showed that the OCT findings of Susac’s syndrome are different from MS, as in the former, the thinness of RNFL is patchy in nature and there could be loss of macular contour. We therefore suggest OCT be considered as an additional tool in the physician’s toolbox, to be used in patients with atypical clinical presentations to distinguish Susac’s syndrome from MS. Longitudinal studies on larger cohorts of patients are needed to further assess the usefulness of OCT in the diagnosis and follow up of patients with Susac’s syndrome.

Conflict of Interest statement

None of the authors have any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence this work. This is an unfunded research project.

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