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Abnormal visual cortex activity using functional magnetic resonance imaging in treatment resistant photophobia in Friedreich Ataxia

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ABSTRACT

Purpose: Friedreich ataxia (FDRA) is a debilitating neurodegenerative disease that can have ophthalmological manifestations including visual dysfunction, nystagmus, and optic atrophy. However, severe photophobia has not been reported nor evaluated with functional magnetic resonance imaging (fMRI).
Methods: A 64-year-old white female with a 37-year history of FDRA presented to the eye clinic with worsening photophobia of 3 years. To measure her visual cortex activation and subjective responses during episodes of photophobia, she underwent event-related fMRI with light stimuli. In comparison, the same protocol was conducted in an individual with photophobia but without FDRA. After the fMRI, both patients were treated with 35 units of BoNT-A applied to the forehead.
Results: Analysis of visual cortex activity in response to light stimulus in the FDRA patient showed no correlation between blood oxygen level dependent (BOLD) activation and light stimuli in the first ($r = -0.100$, $p = 0.235$), and a weak negative correlation in the second half of the fMRI scan ($r = -0.236$ $p = 0.004$). In notable contrast, significant positive correlations were noted between visual cortex activity and the light stimulus (1st half: $r = 0.742$, $p < 0.001$, vs. 2nd half: $r = 0.614$, $p < 0.001$) in the comparator. Six weeks later, no improvement in photophobia was noted in either patient.
Conclusion and importance: Our study highlights photophobia as one potential ocular manifestation of FDRA and suggests that one underlying contributor may be a decoupled cortical neurovascular response to light. Our study provides novel information that may guide physiologic understanding and future treatments in this disease.

1. Introduction

Friedreich ataxia (FDRA) is an autosomal recessive neurodegenerative disease that primarily affects the cerebellum and spinal cord.[1] Most cases are caused by a homozygous triple repeat expansion in the GAA sequence in the frataxin (*FXN*) gene.[2,3] It is the most common inherited ataxia in patients of European descent with roughly 1 in 50,000 being affected.[4] Pathogenesis involves the degeneration of the posterior spinal columns progressing to muscle weakness. Common clinical features include limb and gait ataxia, impaired reflexes and speech, and weakness.[5] Impaired vibration sense and proprioception as well as hearing and visual dysfunction have also been documented.[6]

Ocular manifestations have also been seen in FDRA. Nystagmus, including gaze-evoked horizontal and spontaneous vertical nystagmus, has been noted in the majority of individuals with FDRA.[7,8] In one study of 20 subjects with FDRA and oculomotor abnormalities, 12 displayed gaze-evoked horizontal nystagmus, and 9 showed spontaneous vertical nystagmus, with one subject having both types of nystagmus.[8] In this study, the presence of vertical nystagmus positively correlated with disease duration.[8] However, most subjects maintained normal vision, with only 1 of 20 subjects experiencing visual loss in one study (acuity <6/60), likely due to optic atrophy.[8] In fact, optic atrophy has been

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noted in 30.4 % (35 of 115)[9] of FDRA patients in one study and 12 % (3 of 26) in another.[7]

Subclinical central nervous system manifestations of FDRA have also been detected in the retina. Retinal nerve fiber layer (rNFL) thinning, measured by optical coherence tomography (OCT), has been noted in FDRA with lower mean average thickness noted in cases compared to controls in two studies (76 ± 12.0 μm, n = 21 vs. 100 ± 8.9 μm, n = 48, $p < 0.0001$[10]; 72.7 ± 14.7 μm, n = 10 vs. 111.1 ± 12.0 μm, n = 22 $p < 0.0001$[11]). In yet another study, 83 % (19 of 23) of individuals with FDRA were noted to have rNFL thinning, defined by a mean peripapillary thickness <5 percentile compared to the built in normative database.[12] RNFL thinning has been linked to age of FDRA onset ($r = 0.57$, $p = 0.007$)[10] and disease duration ($r = -0.52$, $p < 0.001$).[13]

In this report, we describe a case of an individual with extreme light sensitivity with concomitant FDRA. As this manifestation has not been studied with respect to FDRA, we describe clinical features of the case and functional neuroimaging responses to visual processing. As a comparator, we also examined neuroimaging responses in an individual with photosensitivity but without FDRA (control). Finally, given its utility in migraine,[14,15] we investigated the clinical impact of botulinum toxin A (BoNT-A) on light sensitivity in FDRA.

2. Methods

This study was approved by the Miami Veterans Administration (3011.08) and University of Miami (20,190,340) Institutional Review Boards and was conducted in accordance with the tenets of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act. Both patients provided written informed consent prior to study participation.

2.1. Questionnaires

The patients were administered several questionnaires during the baseline clinical visit, providing information on ocular symptoms that included the 5 Item Dry Eye Questionnaire (DEQ-5, range 0–22)[16] and the Ocular Surface Disease Index (OSDI, range 0–100).[17] Average ocular pain was reported using the Numerical Rating Scale (NRS, range 0–10).[17,18]

2.2. Ocular surface evaluation

Subjects underwent an ocular surface evaluation that included measurements of tear stability (tear break up time, TBUT, lower values indicate more tear instability), fluorescein epithelial corneal staining (rated in accordance with the National Eye Institute (NEI) scale,[19] higher values indicate more epithelial disruption), and tear production (Schirmer test, measured in millimeters of wetting in 5 min, lower values indicate decreased tear production).

2.3. Botulinum toxin protocol

Botulinum toxin A (Botox, Allergan) was administered to each patient using a modified migraine protocol.[20] A total of 35 units at 7 sites on the forehead were administered: 20 units in the frontalis, 10 units in the corrugators, and 5 units in the procerus. Six weeks after administration, subjects again filled out questionnaires regarding eye symptoms and underwent an ocular surface examination.

2.4. fMRI

2.4.1. MRI acquisition

Imaging was conducted using a 3T Siemens MAGNETOM Vida scanner (Erlangen, Germany) with a Siemens BioMatrix Head/Neck 20 channel coil. For anatomical scans, a sagittal three-dimensional T1-weighted scan (MPRAGE) was performed (TE/TR = 2.38/2100 ms; 192 1.00 mm-thick sagittal slices; in-plane resolution = 1.00 × 1.00 mm [256 x 256]). For the functional scan, a gradient echo (GE) echo planar imaging (EPI) sequence was performed (TE/TR = 30/2000 ms; 100 1.50 mm-thick oblique slices aligned to the long axis of the caudal brainstem; in-plane resolution = 1.94 × 1.94 mm [136 x 136]), with 290 vol (9 min and 40 s) captured. The oblique orientation of acquisition has proven useful for functional imaging of brainstem structures.[21]

2.4.2. fMRI protocol

For the functional scan, an event-related design based on our previous photophobia study[21] was employed using the following stimulation protocol. Briefly, our scanning protocol included two visual conditions: a black screen as the resting condition (featuring a black background with an overlaying white cross, ~0.5 lux) and a white screen as the stimulus condition (featuring a white background with an overlaying black fixation cross, ~65 lux). Subjects were shown 16 episodes of the white screen for 6 s each with resting conditions (black screen) in between stimuli that varied between 26 and 34s in 2-s increments, to avoid anticipatory responses.[21]

2.4.3. Comparison subject for fMRI analysis

The comparison subject chosen post-hoc was a 41-year-old White female who had severe migraine-associated light sensitivity that worsened 1 year after laser-assisted in situ keratomileusis (LASIK). Criteria for selection included same gender and similar response to BoNT-A as the FDRA subject.

2.4.4. fMRI data analysis

Functional imaging datasets were processed and analyzed using FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FSL 6.0.7.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl).[22] Pre-processing included elimination of the first three acquired volumes to allow for signal equilibration; motion correction using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool)[23]; removal of non-brain structures using BET [Brain Extraction Tool][24]; spatial smoothing using a Gaussian kernel of 5-mm full-width half-maximum; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian--weighted least-squares straight line fitting with sigma = 50.0 s). Voxelwise normalization was completed by dividing the signal intensity at each time point by the voxel's mean intensity. A region of interest (ROI) analysis focused on light-related activity in the intracalcarine cortex. The Harvard-Oxford Subcortical and Cortical atlases were used to create a structural anatomical mask of bilateral intracalcarine cortex (min = 50, max = 100). MRI data acquired from the subject with FDRA were compared to similarly collected data in a subject without FDRA.[25]

For the voxel clusters identified within the ROI, single-trial averages were calculated for all 16 light stimulus on-off cycles for each individual. The BOLD signal time course averaged all voxels within the mask-defined anatomic boundaries of the ROI voxels, generating a mean ROI signal time course.

A total of 288 signal intensities per functional scan were extracted from FSL. Our sampling window for analysis for each stimulus cycle included the signal intensities at 3 time points before the stimulus, the 3 time points that made up the stimulus, and 10 time points immediately following the stimulus (16 signal intensities total). There were 32 total residual time points excluded per scan – time points remaining after the 10 post-stimulus that were not part of the 3 time points preceding the following stimulus. Each trial average was calculated by averaging the first signal intensity of each sampling window, the second, third, and so on, creating 16 trial averages. The normalized change in signal intensity was compared to the light stimulus signal intensity over the full duration of the scan as well as for each half of the scan for each subject to look at stability of the signal intensity change.

2.5. Statistical analyses

Statistical analyses were performed using GraphPad Prism 10.1.1 software (GraphPad Software, LLC, San Diego, California, USA). In the pre-BoNT-A condition, relationships between ROI activation and the light stimulus were analyzed using Pearson's correlation coefficients. The statistical significance was determined by an alpha level of 0.05. Means are reported with standard deviation (M±SD).

3. Results

3.1. Case

A 64-year-old White female presented to the eye clinic for worsening photophobia, which started spontaneously approximately three years prior to presentation. She also complained of blurred vision, intermittent diplopia, and constricted peripheral vision. Her medical history was significant for a 36-year history of genetically confirmed FDRA by presence of GAA trinucleotide repeat expansions within the *FXN* gene on both *FRDA1* alleles.[26] One allele had 1005 repeats and the other had 139 repeats; the normal range is 5–33 repeats.[26] The multi-gene panel was performed by Athena Diagnostics (Marlborough, Massachusetts), a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory, and this pathologic variant was validated by repeat expansion analysis and Southern blot.

Her past ocular history was significant for cataract extraction and intraocular lens (IOL) implantation in both eyes 9 years prior to presentation. Her post operative course was complicated by recurrent cystoid macular edema (CME) in the right eye, treated with topical nonsteroid anti-inflammatory agents (NSAIDs) and epiretinal membrane (ERM) in both eyes. A few years later, due to an unknown cause, partial intraocular lens (IOL) dislocations were noted in both eyes with compression of iris tissue nasally, leading to enlarged pupils (Fig. 1A–B). In the left eye, the nasal IOL haptic was anterior to the iris (Fig. 1B). The patient underwent IOL repositioning and pupilloplasty in the left eye, without improvement in light sensitivity (Fig. 1C–D).

Given her continued symptoms, tinted contact lenses (HEMA Hydrogel lens 38 % Water content – complete black out with 6.0 mm clear pupil opening) (Fig. 1E–F) and pilocarpine drops were trialed, with no improvement in light sensitivity. Given a history of episodic migraine, external trigeminal nerve stimulation (e-TNS, CEFALY Technology, Belgium) was also trialed for three months with no relief of symptoms. FL-41 tinted glasses (Axon Optics, Bountiful, Utah, USA) were recommended which provided slight relief for the light sensitivity. Beyond migraine and FDRA, the patient's other medical conditions included atrial fibrillation and major depressive disorder. Her current medications included paroxetine, metoprolol, rivaroxaban, and vitamins D3 and B complex. She was not taking any eye drops at the time of presentation.

On presentation, visual acuity was 20/150 in the right eye and count

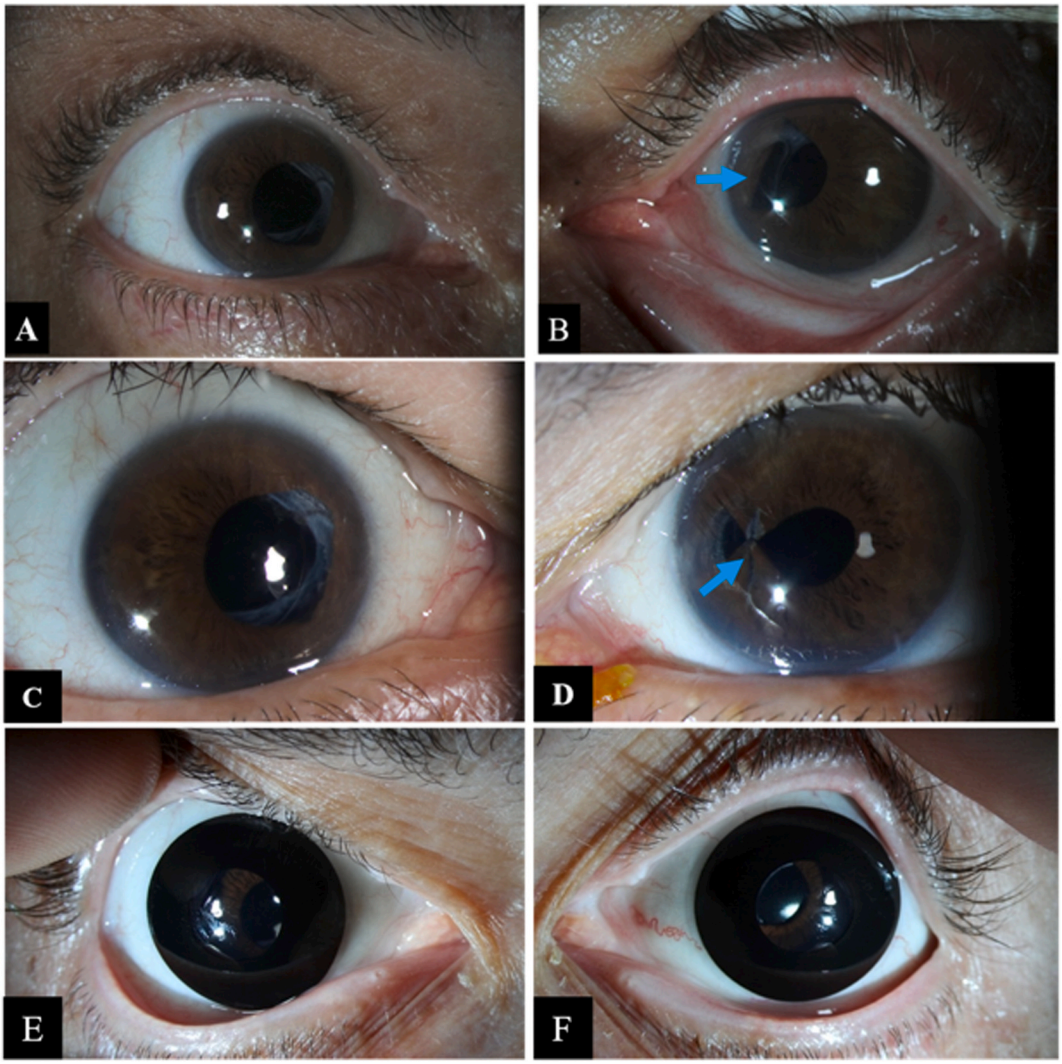

Fig. 1. Slit lamp photos demonstrating intraocular lens (IOL) and iris abnormalities in an individual with Friedreich ataxia.

fingers (CF) at 2' in the left eye. Though nystagmus was previously documented, nystagmus was not noted on baseline examination. Slit lamp examination was consistent with a nasally displaced iris in the right eye and pupilloplasty in the left eye with IOLs well positioned in both eyes. No intraocular inflammation was noted in either eye. On dilated examination, optic atrophy was noted, supported by rNFL thinning on a prior OCT (Fig. 2).

The patient endorsed severe symptoms on dry eye specific (Ocular Surface Disease Index, OSDI)[17] and light sensitivity questionnaires. Ocular surface examination demonstrated normal tear production and mild corneal staining (Table 1).

Confocal microscopy imaging demonstrated activated dendritic cells (aDC) and a paucity of corneal nerves (Fig. 3A), and infrared imaging of the Meibomian gland demonstrated dropout in both eyes (Fig. 3B). Multifocal electroretinogram (mERG) done four years prior to presentation was normal.

Table 1
Symptoms and examination findings at baseline and after botulinum toxin (BoNT-A) injection.

	Baseline	6 weeks Post-BoNT-A
Dry eye questionnaires		
DEQ5 (range 0–22)	6	3
OSDI (range 0–100)	77	58
Pain and light sensitivity questionnaires		
Light sensitivity (OSDI-Q1) (range 0–4)	4	4
Average pain rating 1 week recall (range 0–10)	0	0
Tear parameters (Right/Left)		
TBUT (seconds)	10/8	7.3/7.3
Corneal staining (range 0–15)	2/2	13/3
Schirmer score (range 0–35 mm)	14/14	2/6

DEQ5: 5 Item Dry Eye Questionnaire, OSDI: Ocular Surface Disease Index, Q1: Question 1, TBUT: tear break-up time.

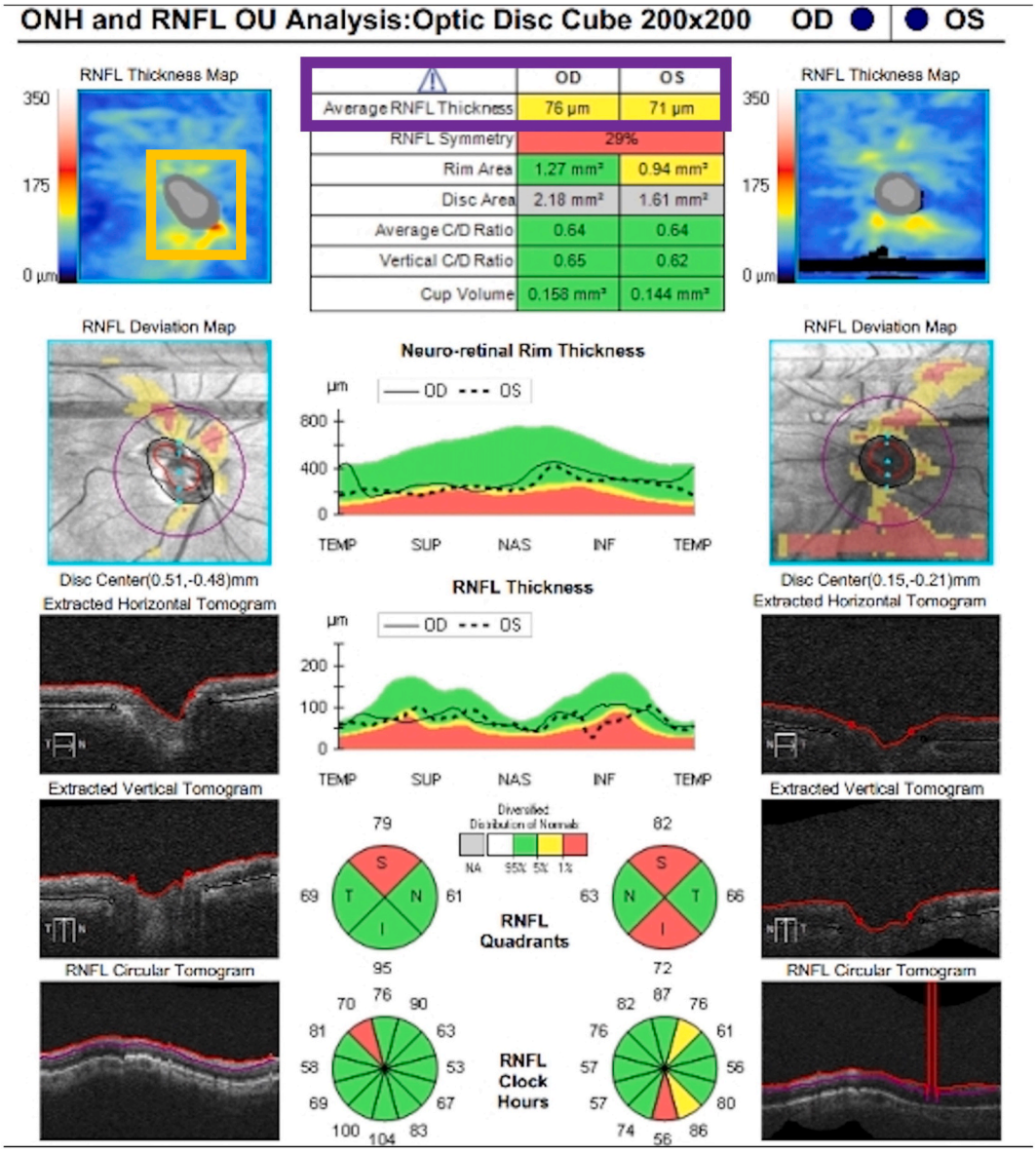

Fig. 2. Optical coherence tomography of the retinal nerve fiber layer in the Friedreich ataxia patient.

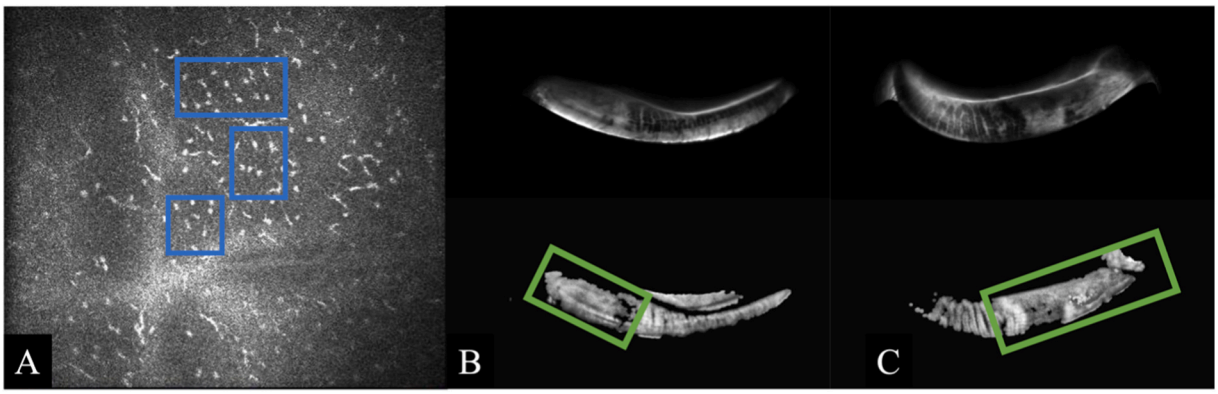

Fig. 3. Confocal imaging of the central cornea and infrared imaging of the Meibomian glands in an individual with Friedreich ataxia.

3.2. *fMRI analysis*

The patient underwent fMRI imaging to determine brain activity in response to a light stimulus.[27] Post-hoc, we selected a 41-year old White female with ocular pain and photophobia who was resistant to BoNT-A treatment from an existing cohort to act as a comparator. Blood oxygen level dependent (BOLD) responses to light in the FDRA (case) and control patients were analyzed spatially via statistical parametric maps and in a temporal dimensional way via time course plots then compared to the comparator subject (Figs. 4 and 5).

In the FDRA patient, the BOLD response during the 6-s light stimulus appears to have a delayed onset and prolonged duration in the first half, and the response in the second half appears even more delayed, becoming negatively correlated with the stimulus (Fig. 5A–B). In the comparison patient, a clear BOLD response is seen in both the first and second half of the scan (Fig. 5C–D).

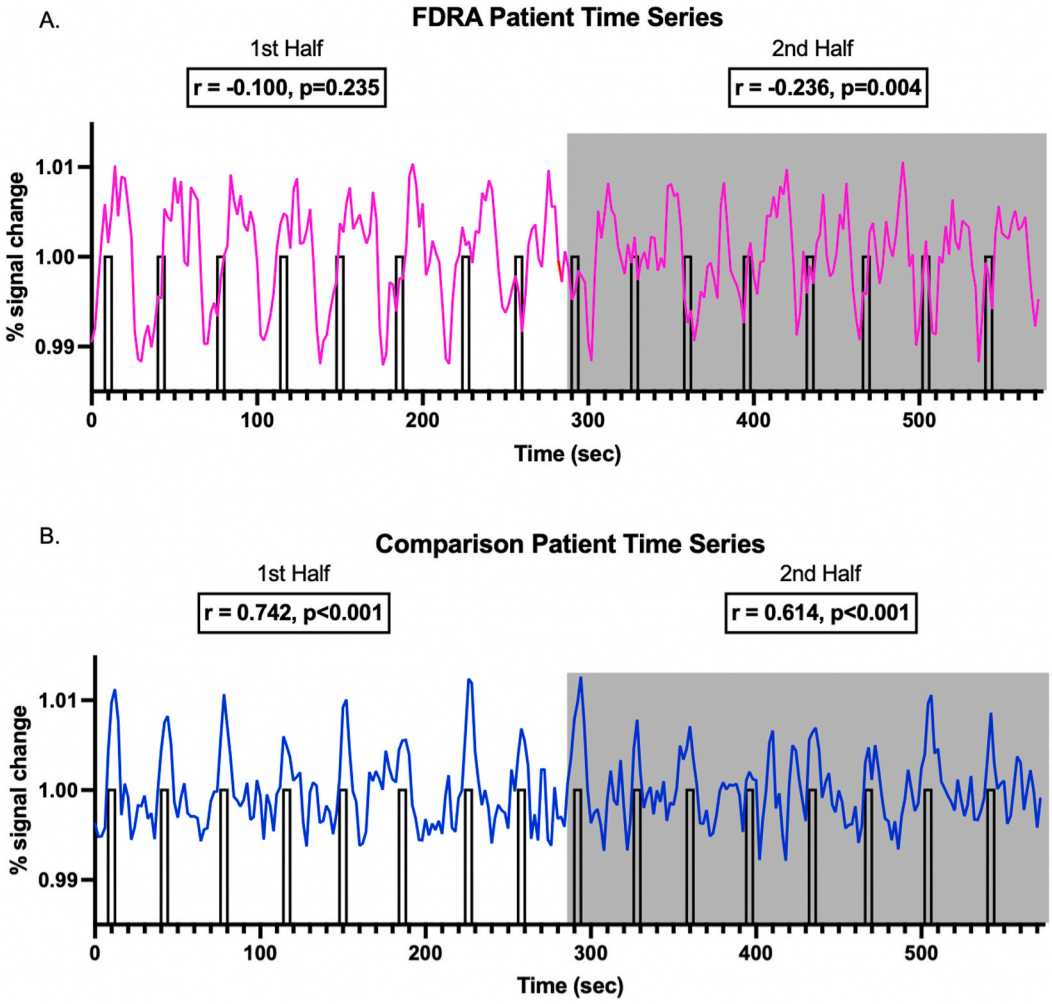

Fig. 4. Time series of blood oxygen level dependent (BOLD) responses in the visual cortex over the full duration of the scan.

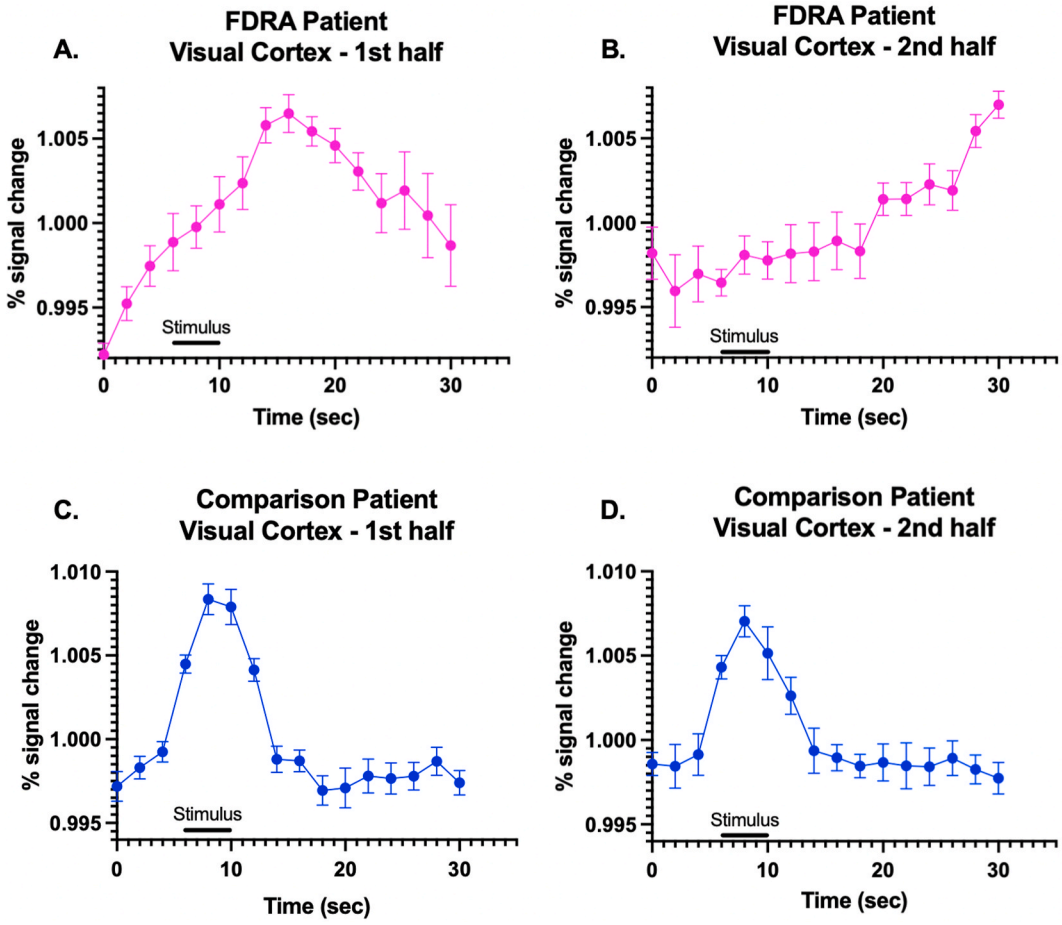

Fig. 5. Single-trial averages of region of interest (ROI, visual cortex) activation.

3.3. Photophobia treatment

Based on data in migraine,[15] the patient received 35 units of BoNT-A to the frontalis, corrugators, and procerus sites. Six weeks later, she subjectively reported unchanged light sensitivity (Table 1).

4. Discussion

Friedreich ataxia is a debilitating disease that can affect the entire body, including the eye.[2,28,29] A systematic review of 81 articles summarized neuro-ophthalmological findings in FDRA.[30] Oculomotor abnormalities, rNFL thinning, and optic atrophy were described, although unlike our patient, most individuals maintained good visual acuity. In our patient, while nystagmus was not noted during our assessment, its presence was documented on prior exams, supported by an artifact on a prior rNFL that is often seen in individuals with nystagmus. Our patient is unique as no prior reports have documented severe photophobia in patients with FDRA.

Mechanisms behind photophobia have been previously studied by examining visual cortex activity measured by fMRI in response to a light stimulus. In a prior study by our group, 8 individuals with a history of chronic ocular surface pain and photophobia and 8 controls underwent the same fMRI protocol as the present case.[27] Cases had greater activity in the visual cortex (lingual gyrus, though not intracalcarine cortex) compared to controls at baseline. In addition, cases demonstrated light-evoked activation in pain-related areas within the trigeminal brainstem, primary somatosensory cortex (S1), anterior mid-cingulate cortex (aMCC), and insula compared to controls.[27] Visual cortex activity has also been studied in individuals with photophobia in the setting of migraine. In a study of 19 individuals with migraine and 19 controls, greater occipital cortex activation was seen in cases when presented with low and medium light stimuli intensities compared to controls.[31] In our present case, we examined visual cortex function in a different way, specifically focusing on neurovascular coupling to light, which became increasingly dissociated in the FDRA but not in the control patient as the scan progressed over time. While our current methodology cannot be directly compared to that of previous studies, a common theme across studies is the presence of various visual cortex abnormalities in individuals with photophobia.

While not using light-stimulus protocols, previous studies have examined brain activation during motor and cognitive tasks in individuals with FDRA. A systematic review of 12 mixed-methods fMRI studies in FDRA subjects (n = 198) summarized overall brain activation compared to healthy controls (n = 205) while performing a variety of taks.[32] They found overall conflicting results, with a combination of hypo- and hyperactivation in a variable pattern within widespread regions of the frontal, parietal, and temporal cortices compared to controls during various tasks. This mixed pattern may be due to the variable clinical presentation of FDRA in their cohort, particularly regarding disease duration and severity. There were, however, some consistencies among studies. The left middle occipital, medial precuneus, and right fusiform gyrus were consistently hyperactivated during motor tasks, and the left central opercular and left insular cortex areas were consistently hypoactive. Though motor tasks were not included in our examination, we conducted a novel methodology to study visual cortex response to visual stimuli. This approach broadens the use of fMRI in FDRA patients with the hope of deepening understanding of the underlying mechanisms of this disease.

Though prior studies have not focused on neurovascular coupling in FDRA, this concept has been applied to the study of ischemia. One study

examined BOLD responses to a bimanual handball squeeze task in 7 individuals with anterior circulation stenosis and in 7 controls. Delayed BOLD responses in the bilateral primary motor cortices were found in the stenotic individuals in response to the task compared to the controls.[33] Another study examined BOLD responses to a lexical decision task in 5 individuals with stroke-induced aphasia and in 4 controls. They found delayed activation in the left Posterior Perisylvian Network (Wernicke's area, the angular and supramarginal gyri) in 3 aphasic individuals compared to the control patients.[34] While multiple explanations can underlie these findings, the authors postulated that abnormalities in the vascular bed may contribute to the decoupled neurovascular response. In our case, we speculate that in FDRA, abnormal cerebral autoregulation from progressive nervous system damage may contribute to the noted visual cortex abnormalities.

We chose to treat our patient with BoNT-A as this *Clostridium* derived neurotoxin is used to treat many pain related conditions including chronic migraine,[35–37] blepharospasm,[38] and neuropathic ocular pain.[38–40] Its mechanisms of action is believed to stem from the reduced muscle fiber activity due to inhibition of acetylcholine release at presynaptic nerve terminals leading to a reduction in neurogenic inflammation.[41,42] Prior studies have noted reduced levels of glutamate, calcitonin gene-related peptide (cGRP), and substance P after BoNT-A injection. This mechanism has been demonstrated in craniofacial muscles in a mouse model of migraine,[43] in temporomandibular joints in a mouse model of arthritis,[44] and in bladders in a rat model of acute and chronic cystitis,[45] as well as in numerous human models.[46–49] We have previously applied this treatment to individuals with neuropathic ocular pain (NOP), both with and without co-morbid migraine.[20,50] In a case series of four individuals with clinically diagnosed NOP, the frequency and severity of photophobia and eye discomfort were improved one month following BoNT-A.[20] In a follow up study, the impact of BoNT-A on NOP was examined using fMRI technology. In 12 individuals with NOP, 6 subjects reported reduced unpleasantness in response to light stimulation after BoNT-A while 6 reported stable or increased unpleasantness.[15] Group level fMRI analysis demonstrated that BoNT-A injections significantly reduced light-evoked brain activity in pain processing-related regions including bilateral S1, S2, hemispheric lobule VI, and crus I in addition to left crus II, and cerebellar vermis.[15] Interestingly, individuals who had a positive response to BoNT-A (responders) had greater spinal trigeminal nucleus (SpV) activation to light prior to BoNT-A compared to non-responders. This suggests diverse photophobia pathways that may have differential responses to treatment. Unfortunately, our subject did not note clinical benefit from BoNT-A and continued to report severe photophobia six weeks post-injection. This suggests that our patient may process light sensitivity through a non-trigeminal neural network.[15,51]

Though trigeminal projections have been well described as a key pathway in photophobia,[37,52] other potential pathways beyond this circuit have also been described, and may have relevance in our two patients as neither reported symptom improvement after BoNT-A.[53–55] Conventional visual processing involves rods and cones that relay photo-signals to retinal ganglion cells which travel via the optic nerve to brainstem nuclei and the brain, which can trigger autonomic responses to light that may trigger photophobia.[56] Separately, intrinsic photosensitive retinal ganglion cells (ipRGCs) contain photo-pigment melanopsin and have been found in the retina.[52] These ipRGCs transmit signals to the olivary pretectal and suprachiasmatic nuclei[52] as well as directly to posterior thalamic nuclei and subsequently to pain-processing cortical regions and have also been implicated in exacerbation of headache by light.[57] There are also melanopsin photoreceptors in the iris that bypass the retina and optic nerve which then activate nociceptors outside or inside the globe.[58] fMRI studies may help determine which pathways and brain structures are most relevant in different photophobia sub-groups.

Several limitations should be taken into consideration when reviewing this case. First, as our patient's presentation is unusual, we cannot extrapolate our fMRI findings to FDRA in general and subsequent studies are needed to examine visual cortex activity in individuals with FDRA with other ocular phenotypes to see if the observed decoupling is a salient feature of disease. It is also important to consider the multiple etiologies of photophobia, including intraocular abnormalities (e.g., CME, IOL issues), pain co-morbidities, and mood disorders and as such, the degree to which FDRA contributed to photophobia cannot be fully determined. Despite these limitations, this case highlights photophobia as a possible ocular presentation of FDRA and introduces the idea of visual cortex dysfunction as a potential consequence of disease. Future studies are needed to more robustly examine our findings.

Claims of priority

After conducting an extensive literature review utilizing PubMed and Google Scholar, we did not find any reports of severe photophobia as an ocular manifestation of Friedreich Ataxia, treated with botulinum toxin A and assessed with functional magnetic resonance imaging.

CRediT authorship contribution statement

Araliya N. Gunawardene: Writing – original draft, Formal analysis. **Nicholas Reyes:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **David Valdes-Arias:** Writing – original draft, Investigation, Data curation, Conceptualization. **Alpen Ortug:** Writing – original draft, Investigation, Data curation, Conceptualization. **Jaime Martinez:** Writing – review & editing, Investigation, Conceptualization. **Anat Galor:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Eric A. Moulton:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Formal analysis, Conceptualization.

Patient consent

This study involving human participants was reviewed and approved by The Miami Veterans Affairs (VA) and the University of Miami Institution Review Boards (IRB approval #3011.08 and 20,190,340, respectively). The patients/participants provided their written informed consent to participate in this study.

Disclosures and conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship and agree to the order of authorship presented on title page.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors have no conflict of interest.

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