Fundus examination showed stable retina findings in both eyes with marked atrophy of RPE in the mid- and peripheral retina. Fluorescein angiography showed delayed arteriolar filling in both eyes, with no hypo- or hyperfluorescent areas (Figure 1E) in all phases. Repeat review of histopathology showed neuroepithelium elements, retinal pigment epithelium, mature choroidal plexus and immature brain tissue (Figure 1 E). Repeat pattern VEP revealed improvement in latency in both eyes and increased amplitude in the left eye.

Discussion

To our knowledge, our patient is the only child in literature diagnosed with CAR after oophorectomy for an immature ovarian teratoma. CAR, an autoimmune process mediated by the Abs directed against the retinal proteins, is characterized by visual disturbances such as sudden decrease in vision, night blindness, photopsias, constricted visual fields, uveitis, optic atrophy, retinal vascular attenuation, chorioretinal atrophy, and negative ERG responses.[1-4] The Abs associated with CAR are anti-recoverin (23 kDa), α-enolase (46 kDa), arrestin (48 kDa), transducing-α (40 kDa) and β (35 kDa), heat shock cognate protein (65 kDa), anti-carbonic anhydrase II (30 kDa), photoreceptor cell-specific nuclear receptor (46.5 kDa), interphotoreceptor retinoid-binding protein (145 kDa), and tubby-like protein-1 (78 kDa).[1-3]

Kim and colleagues[6] reported a patient of >50 years of age with an ovarian tumor who presented with visual disturbances, abnormal ERG response, and positive Abs; she died despite systemic chemotherapy. Our patient was successfully treated with immunosuppressive therapy initially and is currently on continuing long-term immunosuppressive medication. Cybulska and colleagues[5] reviewed 28 cases with gynecologic malignancies (7/28 from ovary), with an average age of 64 years for patients with paraneoplastic retinopathy. These patients developed ocular manifestations over a period of 3-12 months after treatment,[5] whereas our 14-year-old patient developed ocular manifestations immediately after treatment of primary ovarian tumor.

The goal of therapy in CAR was to decrease circulating Abs in order to prevent the progression of retinal damage and stabilize current disease condition. Various treatment modalities in treatment of CAR include systemic steroids, plasmapheresis, intravenous methylprednisolone, immunosuppressive agents, intravenous immunoglobulins, monoclonal pan-lymphocytic or B-cell Abs, and periocular/intravitreal steroids.[2,3,5] All of the above agents have been reported by different authors over many years with varying success rates. Our patient received a combination of these treatments, which stabilized her vision and may have prevented further damage to retinal photoreceptors.

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Abnormal white matter tractography of visual pathways detected by high-angular-resolution diffusion imaging (HARDI) corresponds to visual dysfunction in cortical/cerebral visual impairment

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Cortical (cerebral) visual impairment (CVI) is characterized by visual dysfunction associated with damage to the optic radiations and/or visual cortex. Typically it results from pre- or perinatal

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hypoxic damage to postchiasmal visual structures and pathways. The neuroanatomical basis of this condition remains poorly understood, particularly with regard to how the resulting maldevelopment of visual processing pathways relates to observations in the clinical setting. We report our investigation of 2 young adults diagnosed with CVI and visual dysfunction characterized by difficulties related to visually guided attention and visuospatial processing. Using high-angular-resolution diffusion imaging (HARDI), we characterized and compared their individual white matter projections of the extrageniculo-striate visual system with a normal-sighted control. Compared to a sighted control, both CVI cases revealed a striking reduction in association fibers, including the inferior frontal-occipital fasciculus as well as superior and inferior longitudinal fasciculi. This reduction in fibers associated with the major pathways implicated in visual processing may provide a neuroanatomical basis for the visual dysfunctions observed in these patients.

Methods

High-angular-resolution diffusion imaging (HARDI) was used to compare the white matter projections of the extrageniculo-striate visual system in 2 cases with cortical (cerebral) visual impairment (CVI) and 1 unimpaired control subject. All 3 subjects provided written informed consent in accordance with procedures approved by the Massachusetts Eye and Ear Infirmary Institutional Review Board and conformed to the requirements of the United States Health Insurance Portability and Accountability Act of 1996.

Using the occipital pole and primary visual cortex as a seed point, the inferior frontal-occipital fasciculus (IFOF), projecting to frontal and prefrontal cortical areas, the superior longitudinal fasciculus (SLF), projecting to parietal cortical regions and frontal eye fields, and the inferior longitudinal fasciculus (ILF), projecting to the inferior temporal gyrus, were reconstructed. HARDI images were acquired using a single-shot EPI sequence (TE 73 ms, TR 17844 ms, 64 directions, Bmax 3000, Bmin 0, 2 mm isotropic voxel size). White matter fiber tracking and reconstruction were performed using DSI Studio software (http://dsi-studio.labsolver.org/) with diffusion decomposition, a sparse solution of fiber orientation distribution function. The entire pericalcarine and precuneus regions of the posterior pole were used as seeding points. Termination criteria were based on a threshold of quantitative anisotropy of 0.055 and a conservative angle change of >45°. Both T1-weighted and HARDI images were acquired in the same scanning session. HARDI images were acquired with an 18-minute scan time.

Case 1

A 16-year-old girl (CVI 1) with a history of spastic diplegia was followed at Boston Children's Hospital for visual dysfunction secondary to premature birth. Born at 32 weeks' gestation, she developed a grade 3 intraventricular hemorrhage and subsequent posthemorrhagic hydrocephalus. Visual acuity was 20/50 in the right eye and 20/40 in the left eye, with impaired contrast sensitivity. She underwent surgery at 11 months of age to correct her esotropia and latent nystagmus. A bilateral inferior visual field defect was documented using Goldmann perimetry; mild optic atrophy was noted in each eye. A combination of self-reporting and informal assessment using targeted questioning identified a number of visual-cognitive difficulties associated primarily with visually guided attention and visuospatial processing, visual crowding, and mathematical computations.

Structural T1-weighted magnetic resonance imaging (MRI) revealed markedly enlarged ventricles and irregular lateral ventricular borders in the posterior regions typical of periventricular leukomalacia (PVL; Figure 1B). However, no further details regarding underlying brain connectivity could be discerned by standard radiological examination. Images acquired by HARDI allowed for a more complete three-dimensional visualization of white matter tracts. Visual inspection revealed marked reduction of white matter fibers within posterior occipital cortical regions as well as along all three fasciculi (Figure 2C). Most notably, fibers normally associated with the IFOF were not evident on reconstruction, and projections along the SLF and ILF appeared markedly reduced compared to the sighted control (Figure 2B).

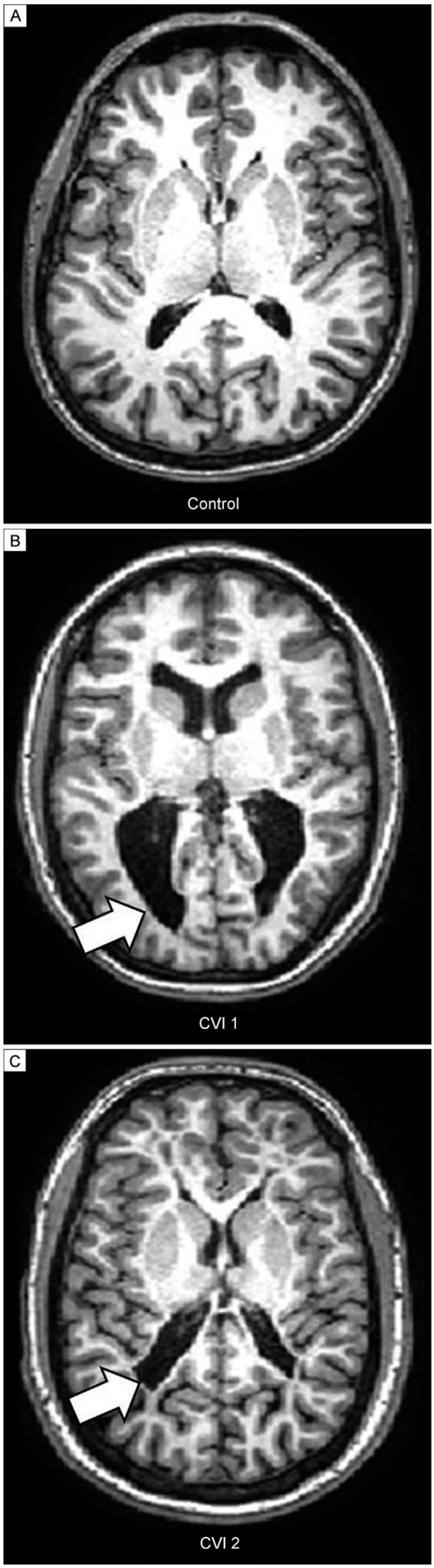
Case 2

A 22-year-old man (CVI 2) with cerebral palsy was also followed at Boston Children's Hospital for a history of visual dysfunction associated with prematurity. Born at 28 weeks' gestation, he suffered from hypoxic brain injury secondary to perinatal brain hemorrhage. Visual acuity was 20/100 in each eye, with impaired overall contrast sensitivity. He underwent strabismus surgery at 3 years of age to correct esotropia and subsequently developed a consecutive exotropia and latent nystagmus. Visual field testing using Goldmann visual perimetry revealed dense inferior visual field loss bilaterally. Ophthalmoscopic examination confirmed diffuse bilateral optic atrophy. Self-reporting and informal assessment identified difficulties with visual attention, visually guided movements, identifying objects in a crowded scene, and visual fatigue.

Axial T1-weighted MRI images revealed markedly enlarged ventricles and irregular lateral ventricular borders (Figure 1C) consistent with PVL. As with CVI 1, visual inspection of visual association pathways reconstructed with HARDI revealed a reduced density of white matter fibers within posterior occipital cortical regions as well as within all three fasciculi (Figure 2D). Fibers normally associated with the IFOF were not evident on reconstruction. White matter tracts traversing the SLF and ILF were evident, although they were markedly reduced compared to the control (Figure 2B).

Discussion

Compared to standard radiological procedures (ie, T1— and T2—weighted imaging), diffusion-based imaging



allows for the noninvasive assessment and full characterization of the microstructural organization of white matter axonal trajectories.[1] HARDI represents an ideal approach for this purpose. Unlike the inherent limitations associated with diffusion tensor imaging (DTI), HARDI can reveal intravoxel white matter fiber heterogeneity and delimit multiple fiber orientations within an individual voxel (eg, crossing fibers within the optic chiasm) and with image acquisition times that are aligned with more typical clinical applications.[2] Diffusion spectrum imaging (DSI) can also reveal intravoxel white matter fiber heterogeneity, but it is burdened with comparatively much longer image acquisition times (see Hagmann and colleauges[3] for a comparison of different diffusion based imaging modalities).

This investigation focused on delineating pathways of the extrageniculo-striate visual system in order "virtually dissect" association fibers known to connect key regions of the brain implicated in visual information processing—the SLF, ILF, and the IFOF, which is known to play a key role in mediating visual guided attention and eye movement control (see Figure 2A).[4]

To our knowledge, this is the first report examining white matter organization of extrageniculo-striate visual pathways in CVI and using the HARDI technique. However, diffusion-based imaging has been used previously to correlate structural brain changes with impairments in visual perception. Recently, Ortibus and colleagues[5] used DTI to report correlations in compromised ILF integrity (quantified by decreased fractional anisotropy) with impaired object recognition performance. Thus diffusion-based studies may serve as a key approach in helping to broaden our understanding of brain anatomical-functional relationships as they relate to developmental and cognitive disorders.

It is important to note that the descriptions of white matter projections described here are largely qualitative in nature. Furthermore, the paucity of tracts revealed by diffusion-based reconstruction techniques does not necessarily correspond to an outright absence of these connections; it may also reflect uncharacterized reorganization of white matter connections related to underlying pathology and/or possible false negatives inherent to the reconstruction algorithms employed. Future work will concentrate on quantification of observed morphological changes (eg, voxel-based analytics and tract-based spatial statistics) in a larger study sample to correlate microstructural organization and integrity with various outcomes of

FIG 1. Axial T1-weighted MRI images in a normally sighted 28-year-old male control subject (A) and in CVI 1 (B) and CVI 2 (C). Enlarged lateral ventricles with irregular posterior borders are immediately apparent in the visually impaired patients (arrows). T1-weighted images were acquired using an eight-channel head coil on a 3.0T TX magnetic resonance imaging (MRI) system (Achieva; Philips Healthcare, Andover, MA) using a MP-RAGE pulse sequence (TE 3.1 ms, TR 6.8 ms, flip angle 9 deg, 1 mm isotropic voxel size).

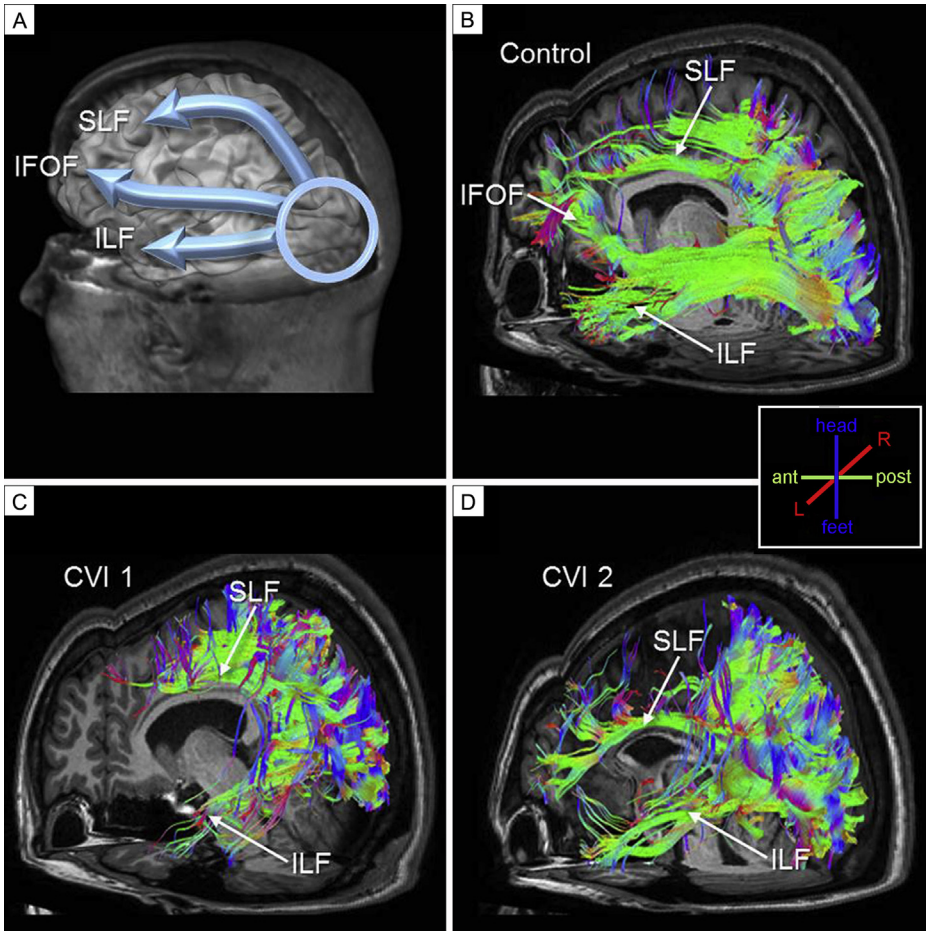


FIG 2. Corresponding white matter tractography revealed with high-angular-resolution diffusion imaging (HARDI). A, Schematic of a posterior projection of the left hemisphere illustrating the pathways of the inferior (ILF) and superior longitudinal (SLF), as well as inferior frontal-occipital (IFOF) fasciculi along with the corresponding seed region within the occipital pole (transparent circle). B, Normally sighted control subject. C-D, CVI patients. In both patients white matter tractography reconstruction reveals a striking reduction of fibers within all three major fasciculi; inferior frontal-occipital fasciculus projections were largely absent. Similar patterns of white matter tractography emerged from both hemispheres for each patient, thus for simplicity, only the left hemisphere is shown. The color scheme corresponds to fiber orientation plane (green: anterior to posterior; red: left to right; blue: head to feet).

visual dysfunction. Revealing associations between underlying structural changes with clinical observations may help not only in delineating neuroanatomical damage in CVI (eg, comparing subcortical vs geniculo-striate vs extrastriate visual areas) but also in understanding, from a rehabilitative perspective, how children adapt and develop in response to early damage to the visual system.

Literature Search

A PubMed and Ovid MEDLINE search was performed without date restrictions (English language only) using the following search terms: *cortical visual impairment*, *cerebral visual impairment*, *high-angular-resolution diffusion imaging*, *diffusion tensor imaging*, *diffusion spectrum imaging*, *dorsal stream*, *ventral stream*, *visual guided attention*, *visuospatial processing*, *extrageniculo-striate visual system*.

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