



## Decision Making for Patients With Concomitant Pituitary Macroadenoma and Ophthalmologic Comorbidity: A Clinical Controversy

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■ **BACKGROUND:** Coexisting complex visual field defects and serious ophthalmologic comorbidities make the management of the pituitary macroadenomas more challenging. Diffusion tensor imaging (DTI) magnetic resonance imaging that tracks neural fibers in the white matter has been used recently to visualize the impact of different pathologies on cranial nerves. This study explains application of anterior optic pathway tractography for patients with ophthalmologic comorbidities and pituitary adenoma.

■ **METHODS:** Two patients with atypical visual field defects caused by nonfunctional pituitary macroadenoma and simultaneous ophthalmologic morbidities (one glaucoma and the other giant cell arteritis) were selected for surgical decompression of the anterior optic apparatus. Standard perimetry and optic pathway DTI were done preoperatively, intraoperatively, and 3 months after surgery.

■ **RESULTS:** The nontypical pattern of visual field defect could not differentiate between the ophthalmologic disease and the chiasmatic compression attributable to pituitary macroadenoma as the main cause. Preoperative visual pathway DTI tractography showed lack of decussating chiasmatic fibers in both of the patients. DTI tractography revealed the reappearance of these fibers intraoperatively in one and postoperatively in the other one. Three months after surgery, the visual field and acuity improved and DTI tractography confirmed presence of crossing chiasmatic fibers.

■ **CONCLUSION:** Visual pathway DTI tractography is a promising adjunct to the standard perimetry in preoperative assessment of pituitary macroadenoma with serious ophthalmologic comorbidities. It also may be useful in the intraoperative determination of the optic pathway decompression and for following the visual outcome of these patients after surgery.

### INTRODUCTION

Pituitary macroadenoma is a common cause of intracranial visual pathway disturbance. In general, the adenoma has to grow 10–15 mm into the suprasellar region to cause a chiasma defect (9). The various patterns of visual field defect related to these tumors include monocular defects, bitemporal hemianopia (the typical type of chiasmatic compression), and homonymous hemianopia (unilateral optic tract compression). Different factors can influence the pattern of visual field defect: position of chiasma (prefixed, normal and postfixed), symmetrical or asymmetrical extension of tumor, and tumor consistency, with a greater rate of visual loss by firm tumors. The possible mechanisms for visual field defects are ischemia, as well as compression or tension (9). Furthermore, compression of anterior visual pathway may cause optic nerve disc cupping (ODC) or optic atrophy. Nevertheless, determining a clear cause and effect relationship between the adenoma and visual field defect of the patient may not be always possible.

### Key words

- Diffusion tensor imaging
- Giant cell arteritis
- Glaucoma
- Optic pathway
- Pituitary adenoma
- Tractography

### Abbreviations and Acronyms

- DT:** Diffusion tensor
- DTI:** Diffusion tensor imaging
- FA:** Fractional anisotropy
- GCA:** Giant cell arteritis
- IOP:** Intraocular pressure
- MFL:** Minimum fiber length

**MRI:** Magnetic resonance imaging

**ODC:** Optic nerve disc cupping

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There are certain ophthalmologic conditions that cause visual field defects as the result of damage of the optic nerve fibers. Glaucoma is the most common cause of ODC. A cause-and-effect relationship between the intraocular pressure (IOP), ODC, and the visual loss due to glaucoma has been questioned in the recent years. The term normal tension glaucoma has been proposed to show that an elevated IOP and visual deterioration attributable to glaucoma could independently exist. Although the visual field defects associated with glaucoma appear to be generally nonspecific, relatively specific glaucomatous visual field defects include the nasal step defect, the temporal wedge defect, the classic arcuate defect, the paracentral defect 10–20° from the blind spot, generalized constriction (tunnel vision), temporal-sparing severe visual field loss, and total loss of field.

Giant cell arteritis (GCA) is one of the most common primary vasculitis, often affecting the medium- and large-size vessels. Eye involvement is seen in around 70% of patients with GCA. Arteritic anterior ischemic optic neuropathy is the most common ophthalmologic manifestation in GCA, but posterior ischemic optic neuropathy and retinal central artery or arterial branch occlusion are seen as well. In the arteritic anterior ischemic optic neuropathy form, it is rare to find the typical altitudinal (horizontally limited) loss of visual field; more often only a small island of visual field is spared.

Regarding variable patterns of visual field defect in suprasellar masses and these ophthalmologic diseases, it is sometimes difficult to evaluate the etiology of visual deterioration in patients who have the both conditions via the use of standard clinical and paraclinical examinations. In this study we present 2 cases of pituitary macroadenoma who had progressive visual deterioration despite optimal control of their ophthalmologic comorbidities. We explain the role of anterior optic pathway diffusion tensor imaging (DTI) in the preoperative, intraoperative, and postoperative brain magnetic resonance imaging (MRI) during the management of these patients.

### CASE PRESENTATION 1

A 70-year-old man presented with progressive visual loss since 1 year ago. He has been treated for glaucoma (high IOP and cupping of optic disks), but the visual field defect progressed despite the treatment. A brain MRI showed an intra- and suprasellar mass with compression to the optic chiasma. Pituitary hormones were in the normal range. Visual perimetry showed bilateral visual field restriction especially in the left side which was not typical for either of these 2 conditions (Figure 1F). A neurosurgical consult in another center had considered surgical removal of the mass futile because of the already-existing optic nerve damage by glaucoma.

Magnetic prepared rapid gradient echo sequence and visual pathway DTI were performed preoperatively, intraoperatively, and 3 months postoperatively. All MRI scans were performed on a Siemens 1.5-T Magnetom Espree (Siemens Healthcare, Munich, Germany) with the same technical parameters (128 × 128 × 60 voxels, voxel size: 1.875 mm × 1.875 mm × 1.9 mm, in 20 directions). The data were then processed in the commercial Brain Lab work station. The images were fused and then visual tractography with specific fractional anisotropy (FA), minimum fiber length (MFL), and region of interest was done (FA = 0.15,

MFL = 21 mm, with 3 standard region of interests: chiasma, lateral to trigone, and occipital lobe). Preoperative visual pathway tractography failed to show any crossing fiber of optic chiasma above the tumor (Figure 1A–E).

Intraoperative visual pathway tractography after a transphenoidal microsurgical tumor removal, revealed re-appearance of the crossing fibers of the chiasma (Figure 2). Pathologic examination showed a silent adrenocorticotrophic hormone pituitary adenoma. The postoperative course was uneventful. Three months after surgery the visual field and acuity improved significantly and the tractography showed improvement of chiasmatic and posterior visual pathway visualization (Figure 3).

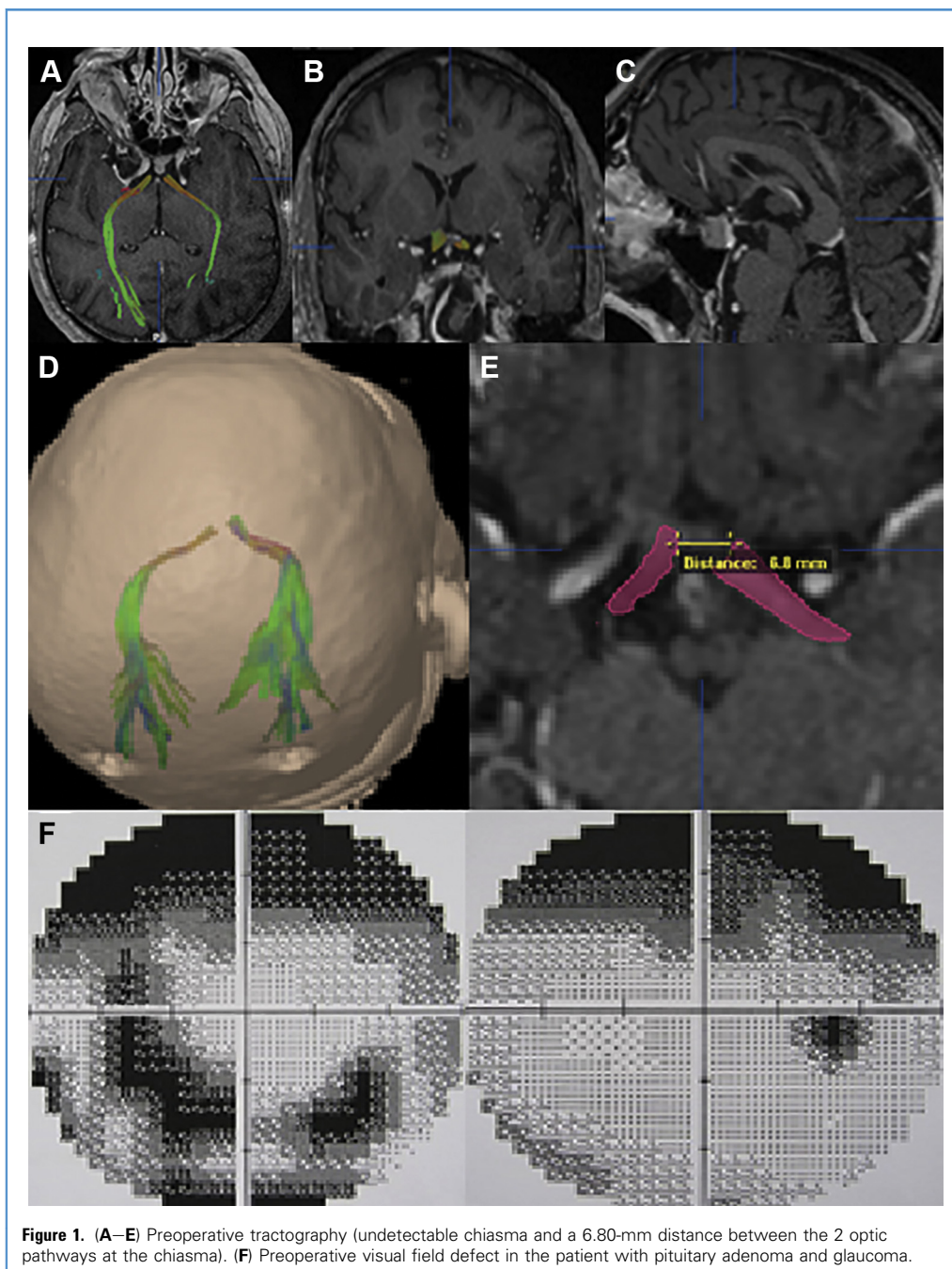
### CASE PRESENTATION 2

An 86-year-old man who was a known case of GCA presented with right eye blindness because of central retinal artery occlusion and progressive visual loss in the left side for 1 year. He had been treated with corticosteroids, and his erythrocyte sedimentation rate returned to the normal range after the beginning of the treatment. Findings of the ophthalmologic examination showed a decreased left visual acuity (5/8) and restricted left visual field (Figure 4C) and a normal IOP. MRI of the brain revealed an intra- and suprasellar mass with compression of the optic chiasma. A neurosurgical consult in another center did not recommend neurosurgical intervention and believed that it may even endanger the remaining vision of the left side.

In preoperative visual pathway tractography, the visual pathway was not detectable with the lowest FA and ML (Figure 4A–B). A hormonal study revealed secondary hypothyroidism and hypogonadism. The tumor was removed entirely via an endoscope-assisted microsurgical transphenoidal approach. The intraoperative visual pathway tractography after tumor removal indicated visual fibers posterior to the chiasma without decussating fibers in chiasma (Figure 4D–F). The pathologic examination showed a gonadotroph pituitary adenoma. The patient had an eventless postoperative course. Three months after surgery, the visual pathway tractography could detect chiasmatic crossing fibers and the posterior visual pathway even with a high FA (FA = 0.15) (Figure 5A–D). The visual acuity and field have also improved clinically during this period (Figure 5E). We fused the different-time tracking in one post op image to compare the results (Figure 6).

### DISCUSSION

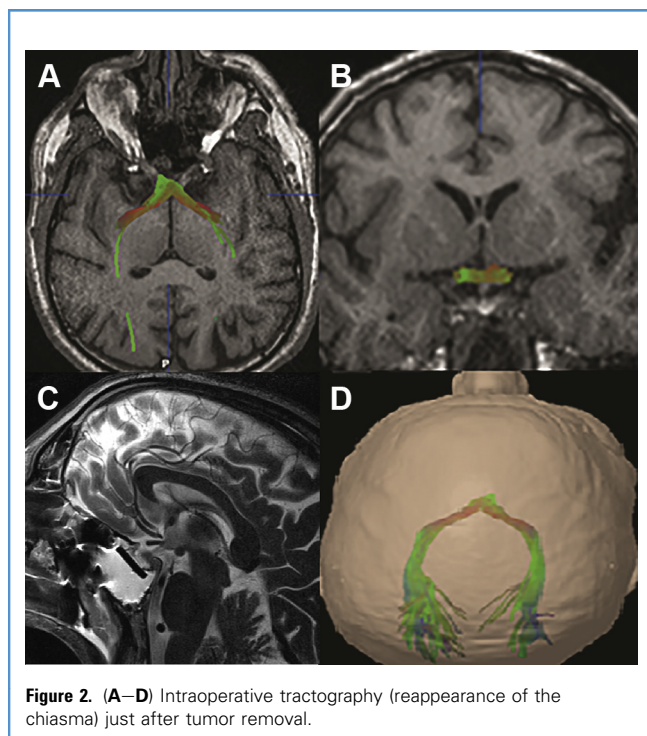
Suprasellar extension of pituitary macroadenoma compromises the arterial supply of the optic nerve and/or chiasma or directly compresses the anterior visual pathway. This nerve compression may cause decreased axoplasmic conduction with or without axonal demyelination. Axonal demyelination after nerve compression could be observed even after 2 days (6, 7). Clinically, this compression may lead to visual field defects, decreased visual acuity, and disturbance of color discrimination. Visual acuity decreased in correlation with extent of visual field defect. The prevalence of visual field defects in pituitary adenomas varies from 37% to 96% in different studies (20). Depending on the site of compression in anterior visual pathway by pituitary macroadenoma, the resultant visual field defect may include



monocular defects, bitemporal hemianopia, and homonymous hemianopia. After tumor decompression through transsphenoidal surgery this visual field defect improves in 75%–100% of the patients. Visual recovery usually happens very rapid (within the first hours and days after surgery), showing that nerve compression and direct conduction block is an important mechanism in axonal injury. Recovery phase can be categorized into early fast phase (up to 1 week after surgery), early slow phase (up to 4 months after the surgery), which is the period of most notable improvement, and the late recovery

phase (up to 3 years after the surgery) does not appear to be significant overall but mild improvements may happen in some individuals, probably as the result of remyelination and better axonal transportation (17). In fact more than 50% of eventual recovery takes place within 3 months after surgery (1).

Diffusion MRI consists of diffusion-weighted MRI and diffusion tensor (DT) MRI. Diffusion-weighted MRI applies when the observed tissue is dominated by isotropic water movement, and DT MRI applies when the tissue is dominated by anisotropic water movement. One of the applications of diffusion tensor MRI (DT



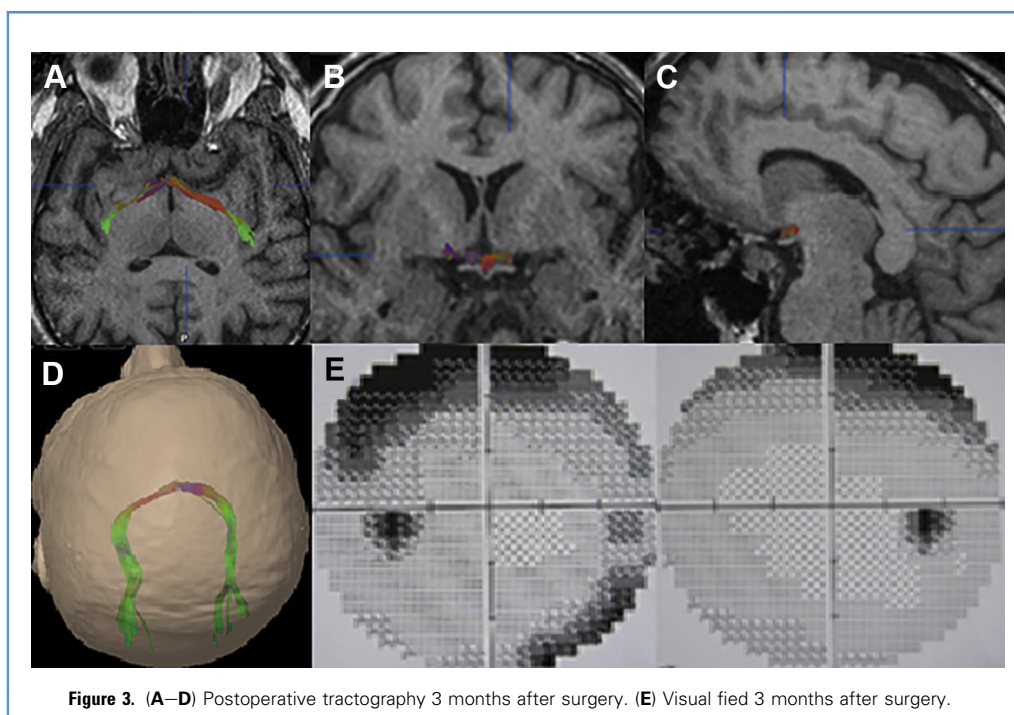
**Figure 2.** (A–D) Intraoperative tractography (reappearance of the chiasma) just after tumor removal.

MRI) is tracking the nerve fibers (so-called tractography) (10). Alterations of the 3-dimensional properties of water diffusion may reflect changes in the tissue microstructure. For each selected region of interest, DTI yields some measurements such as FA as

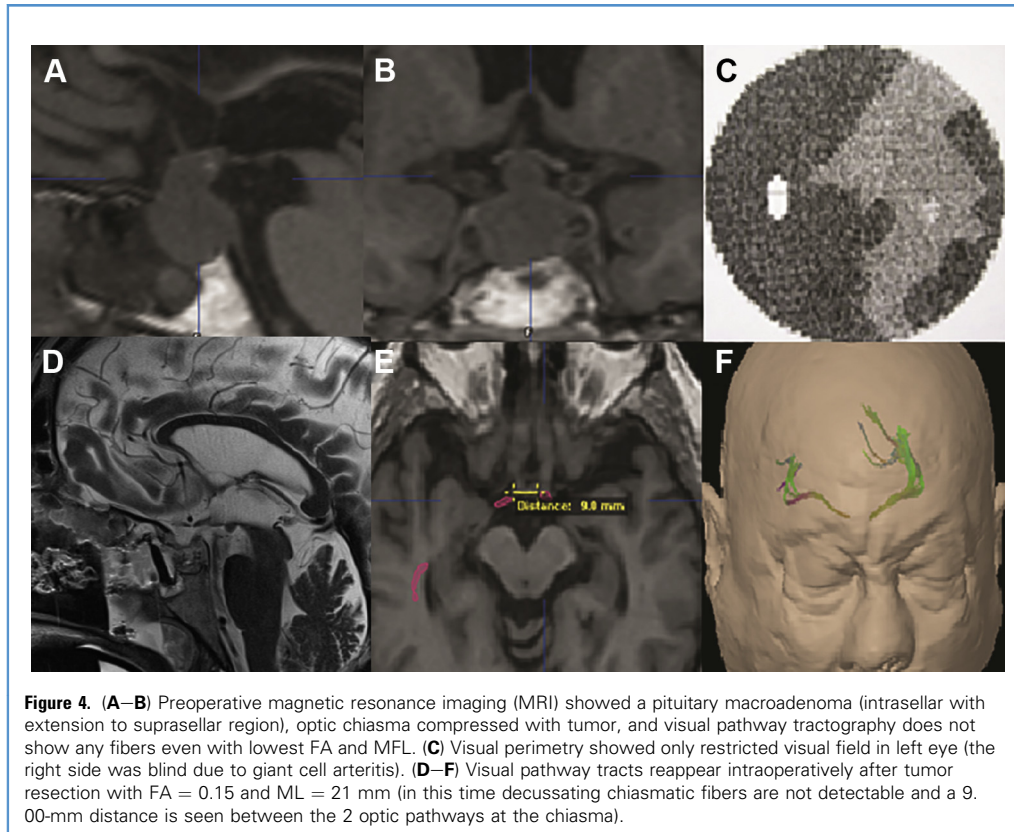
marker of axonal degeneration and mean diffusivity as an indicator of glial cell impairment and fiber demyelination (19, 27). Tractography images are derived from processing of these DTI data and can visualize fiber pathways that are otherwise not easily detectable. Despite of its fundamental limitations, DTI-based tractography is still the most widely applied tractography method in neurosurgical setting to delineate major white matter tracts (21).

In a study by Salmela et al. (24), the visual pathway tractography was performed to locate the optic nerve fibers in 2 cases with optic-hypothalamic glioma. Tractography was able to show termination of the optic fiber tracts within the tumor. They concluded that optic nerve tractography may be a useful adjunct for optimal treatment planning of suprasellar masses. In this study visual pathway tractography was performed with a low number of directional images (6 directions), and furthermore, application of DTI for the developing optic pathway of the children still seems to be challenging. In this study, we have performed visual pathway tractography to evaluate the alterations of anterior optic apparatus in our cases using at least 20 directions.

Glaucomatous optic neuropathy is characterized by a typical appearance of the optic nerve head, including a loss of neuroretinal rim, deepening of the optic cup, disc hemorrhages, parapapillary chorioretinal atrophy, decrease in the diameter of the retinal arterioles, and a diffuse and or local retinal nerve fiber layer loss (4). Formerly the definition of human glaucoma included elevation of IOP over the upper limit of the normal range (most frequently  $>21$  mm Hg) (3). However, many individuals with elevated IOP will never develop glaucoma (this apparently benign condition is termed “intraocular hypertension”), and quite a few people suffer from glaucoma although measurements of their IOP never exceed 21 mm Hg (this condition is called “normal-tension

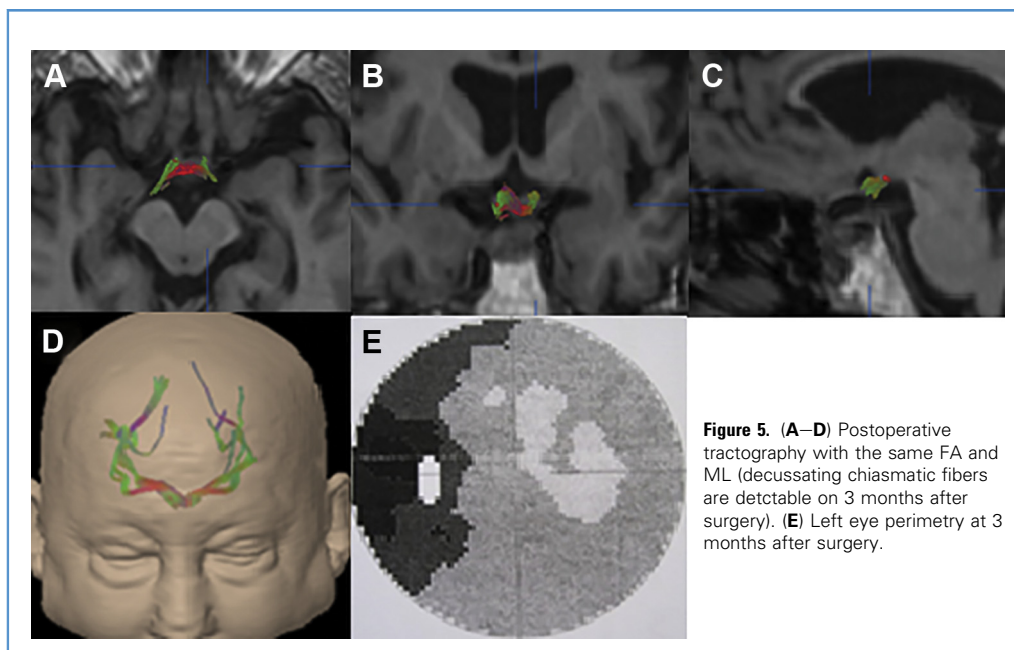


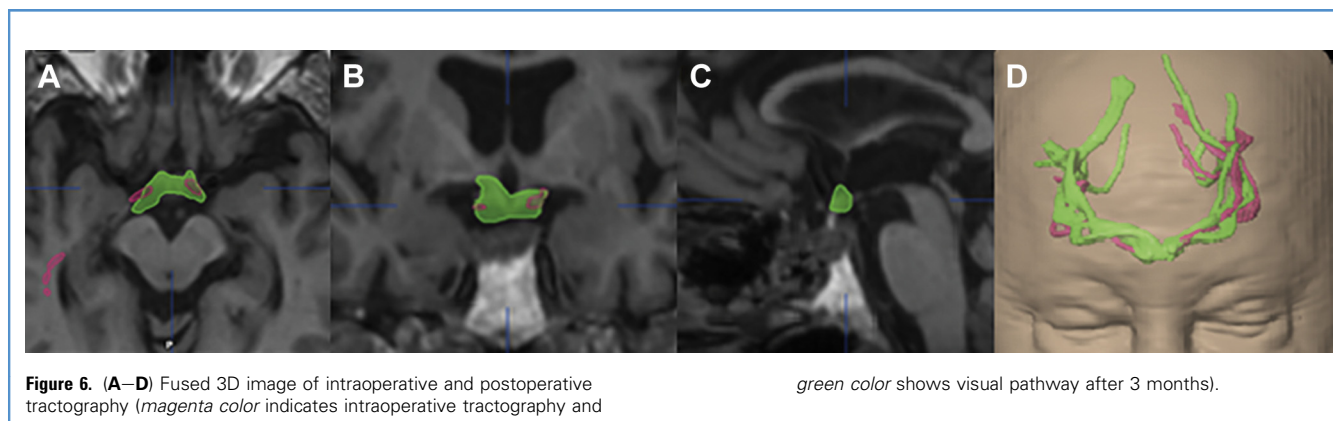
**Figure 3.** (A–D) Postoperative tractography 3 months after surgery. (E) Visual field 3 months after surgery.



glaucoma”) (10, 14). Other nonglaucomatous conditions also may produce disc cupping, including hereditary optic neuropathies, antecedent optic nerve infarction, trauma, methanol poisoning,

infection, demyelinating optic neuritis, fusiform enlargement of the intracranial carotid artery, and intraorbital and intracranial mass lesions (12, 22, 25, 28). The clinical differentiation of





glaucomatous and nonglaucomatous disc cupping is often difficult (13). In cupped optic disk retinal ganglion cell, death and atrophy of surviving retinal ganglion cells lead to visual loss. In one study, thinning of the optic nerve visible on MRI was most pronounced 15 mm behind the bulb and showed correlation with retinal nerve fiber layer thickness measured by optic coherence tomography (18). Another MRI study showed that the optic nerve diameter was significantly smaller in glaucoma patients (2.25 mm) in comparison with the control group (2.47 mm) (15).

A recent controlled study by Ramli et al. (23) proved a correlation between severity of loss in the retinal nerve fiber layer thickness and decrease of the optic nerve volume beyond the optic cup. Detectable abnormalities of the optic nerve may correlate with disease severity in glaucoma (5, 8, 29). Regarding to optic nerve degeneration and chiasmatic atrophy in glaucoma, the height of optic chiasma may be decreased in MRI, especially when significant visual field defects are present (24). Recently, structural alterations of the intraorbital optic nerve have been documented in glaucoma patients by the use of DT-MRI (2, 4, 5, 8, 11). There is a significant increase in mean diffusivity as well as a significant decrease in FA in patients with glaucoma (5, 8, 29). In a study on 60 glaucoma patients compared with 30 normal control subjects, Sidek et al. (26) concluded that DTI-derived FA values of the optic nerve has a strong correlation with disease severity in glaucoma. Kaushik et al. (16) further extended the relation between severity of glaucoma and visual pathways. They reported a remarkable correlation between degree of visual field restriction and degenerative changes of optic radiation in DTI and suggested that glaucoma should be regarded as a diffuse neurodegenerative disease that even affects posterior visual pathways.

In patients with pituitary macroadenoma and glaucoma (high pressure or normal tension) it is difficult to define the source of visual deterioration and the decision for decompression of the optic pathway by surgical removal of the adenoma may be very challenging. In our case, anterior optic pathway tractography could be used as an indicator of the compressive versus glaucomatous optic neuropathy. The disturbance of axoplasmic flow due to chiasmatic compression probably causes nonvisualization of decussating chiasmatic fibers in DTI-tractography.

GCA is another ophthalmological disease affecting the integrity of anterior visual pathway with ischemic optic neuropathy. In our case of GCA the patient had some residual vision in the left eye but tractography was not able to detect any nerve fiber. It was probably the result of a very low axoplasmic flow as a result of nerve compression. After tumor resection intraoperative tracking showed only reappearance of posterior visual pathway but still no chiasmatic fibers. It took 3 months for the chiasmatic fibers to become detectable, which was parallel to the clinical course of the visual improvement (Figure 5). This delay may be related to the microstructural changes of the optic chiasma due to tumor compression that require more time to recover.

The present study is to share our initial experience about application of DTI-based tractography of visual pathways for 2 patients with coexisting pituitary adenoma and serious ophthalmologic conditions. Our literature review did not reveal any available evidence to guide decision making for management of such complex cases. Considering the relative rarity of such complex comorbidities, studies like ours despite being limited to a small number of patients, can help achieving a guideline for management of patients with a similar problem.

## CONCLUSION

Preoperative visual pathway DTI tractography seems to be a promising adjunct to the standard clinical and paraclinical visual examinations in preoperative assessment of patients with pituitary macroadenoma and serious ophthalmologic comorbidities. This modality can help determine the source of visual compromise and predict usefulness of surgical decompression for visual outcome of these patients. Furthermore, intra and postoperative application of this technique may be useful in detecting anterior optic pathway recovery in patients with comorbid eye diseases that cause some difficulties in the clinical ophthalmologic assessments after pituitary adenoma surgery.

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