Glaucoma

How much is the brain involved in glaucoma?

A Alm

Information from clinical material is essential

Should glaucoma specialists turn some of their attention towards the brain instead of the eye? The question is a reasonable one, as emphasised by a case report in this issue of *BJO* (p 674). Gupta *et al* present the autopsy findings from a case with bilateral open angle glaucoma with severe visual field loss in both eyes. Their main finding was a neural degeneration engaging all parts of the central visual pathways, from the intracranial optic nerves to the visual cortex. Neurons in the lateral geniculate nucleus (LGN) were smaller and had smaller nuclei compared to controls. The changes affected both the magnocellular and parvocellular layers of the LGN but were slightly more pronounced in the magnocellular layers.

These findings resemble those previously reported from studies on experimental glaucoma in monkeys.^{1,2} This is perhaps not surprising since trans-synaptic degeneration or atrophy seems to be a non-specific consequence of retinal ganglion cell loss. It has been reported before in human glaucoma³ but also after enucleation in the macaque monkey.^{4,5} It is, however, of some interest to note that the pattern of loss in this case report, although not very pronounced, resembles that described in experiments on monkeys.^{1,2} Chronic open angle glaucoma is a slowly progressing disease and a good animal model would be a powerful tool for studies on the development and treatment of the disease. The primate experimental glaucoma model has been accepted as such a model and it has been widely used. It produces damage which closely resembles that seen with clinical glaucoma both in terms of damage to the optic nerve⁶ and pattern of visual field loss.⁷ Still, it is not obvious that it should be a good model for chronic open angle glaucoma. In the monkey eye pressure has been increased to very high levels, almost 50 mm Hg,² and the animals are mostly young and healthy. That is very different from a 79 year old individual with an eye pressure well within the normal limits. As clinicians we know that it is difficult, if not impossible, to draw a clearly

dividing line between normal tension glaucoma and high pressure glaucoma and it is quite possible that the primate experimental glaucoma model can also teach us many things about the clinical disease. Still, information from clinical material is essential and the case report from Gupta *et al* is a welcome contribution for a better understanding of glaucoma.

Clinical trials will have to clarify if treatment aimed at the central visual pathways is of benefit to patients

In the present case the investigators looked closer at the "posterior-lateral LGN representing the superior visual field." It is a reasonable choice considering the marked loss of the superior visual field in this case. But it would have been interesting to know if the cytoarchitecture in other parts of the LGN was also affected. It is often pointed out that there may be a considerable loss of retinal ganglion cells before there is a clear visual field loss. Would the same be true for neurons in the LGN? In the monkey model damage to LGN neurons is an early event, and changes can be seen in the magnocellular layers even at very modest axon loss.² The visual fields in figure 1 of the case report show mild damage also in the lower fields and some effect on LGN neurons could be expected. In fact, in the report by Yücel *et al*² there was a tendency towards a more marked difference between magnocellular and parvocellular layers in monkeys where axon loss was less pronounced. Examining parts of the LGN representing different levels of field loss may confirm if there is also a similar pattern for the loss of neurons in the LGN in humans.

What is the significance of the shrinkage of LGN neurons observed both in the monkey model and in the human eye. In the monkey model shrinkage was proportional to the loss of retinal ganglion cells⁸ and it is reasonable to assume that it reflects a decreased activity of the LGN neurons. It is not clear if the degree of shrinkage simply reflects the number of

axons still in contact with that particular LGN neuron or if neighbouring cells in the LGN may also influence each other by, for example, release of growth factors. In young monkeys, visually deprived by monocular closure at the age of 2 months or later, there is a marked shrinkage of both undeprived and deprived cells in the LGN.⁹ This raises the interesting possibility that cells within the LGN influence each other and that part of the damage seen in glaucoma may in fact originate in the LGN. A similar observation was, interestingly enough, also made in the monkey model. Neurons that received input from the normal eye in monocular experimental glaucoma also showed some reduction in cell size.¹ Against that background and with the observations made in the present case report it is easy to understand why Gupta *et al* conclude that "treatment strategies to prevent disease progression in glaucoma should also consider central neural degeneration beyond the retina and optic nerve head." They will find further support for their statement in the recently reported study demonstrating that the NMDA open channel blocker memantine protects LGN neurons from shrinkage in the monkey model.¹⁰ This case report by Gupta *et al* demonstrates that the LGN is involved in glaucoma but the functional significance of this is unclear and clinical trials will have to clarify if treatment aimed at the central visual pathways is of benefit to our patients. While we await the result of such trials it would be interesting to learn more about the LGN neurons in glaucoma. How well does shrinkage of LGN neurons reflect the level of ganglion cell loss? Are LGN neurons affected at an early stage of glaucoma? What is the effect of unilateral glaucoma on layers innervated by the fellow eye? These questions are in fact raised by observations made in the monkey model.

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Strabismus

Anatomical diagnosis

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Important even in strabismus surgery

In the 21st century, it is uncommon for modern general and specialty surgeons to operate without preoperative imaging studies to clarify the anatomy of the surgical site.¹ A frequent exception to this rule has been ophthalmology, since direct visual inspection of the beautifully transparent eye permits ophthalmologists to see anatomical detail at exquisite resolution with no more than the array of optical instruments routinely maintained in our offices. Nevertheless, the paper by Ela-Dalman and colleagues, in this issue of *BJO* (p 682), illustrates the importance of application of modern magnetic resonance imaging (MRI) to the preoperative evaluation of complex strabismus.

Ela-Dalman and colleagues describe two patients in whom complicated endoscopic sinus surgery invaded the orbit and resulted in severe iatrogenic trauma to the medial rectus muscle. Clinical recognition that these patients developed a large exotropia with severe limitation of adduction did not uniquely narrow the differential diagnosis of the strabismus; possibilities included multiple entities requiring differing management. Endoscopic injury to the orbit can avulse or deeply transect extraocular muscles so severely that no recovery would be possible.² In this event, there is nothing to be gained by delaying definitive treatment, and resorting promptly to nasal transposition of the vertical rectus muscles to mitigate the adduction defect would more expeditiously confer functional benefit. Invasion of the orbit by endoscopic sinus surgical instruments may contuse the nerve to innervating an extraocular muscle. Contusion to a motor nerve or to its intramuscular branches is likely to result in a transient weakness, with a good possibility of

spontaneous recovery without surgery. On the other hand, nerve avulsion (iatrogenic motor neurectomy) is unlikely to be associated with realistic hope of functional recovery, and should be treated in the same manner as deep myotomy or substantial myectomy. Finally, invasion of the orbit by an endoscopic cutter can entrap connective tissues or other structures to restrict duction, a situation in which prompt surgical release may be optimal management. None of the foregoing pathogenetic mechanisms can be ascertained by external examination, particularly of an ecchymotic, oedematous orbit in an uncomfortable patient.

Advances in the technology of MRI of the orbit have taught us much in recent years.³ The use of surface coils to improve signal to noise ratio and permit smaller fields of view has improved resolution.⁴ Recognition of the importance of control of movement artefacts during scanning that minimise ocular motion and permit multipositional imaging for demonstration of residual contractility of extraocular muscles based on changes in their cross sectional area related to gaze effort.⁴ Rapid sequence contrast techniques can distinguish contusion within the motor nerve arborisation of extraocular muscles. Using excellent technique, the individual motor nerves can nearly always be demonstrated to medial rectus, inferior rectus, and lateral rectus muscles,⁵ the most common targets of iatrogenic trauma during endoscopic sinus surgery.

We owe it to our patients to appreciate the progress in clinical anatomy, and to apply relevant and appropriate imaging techniques in our presurgical evaluations

The paper by Ela-Dalman and colleagues emphasises the importance of “sagittal” orbital imaging. In this regard, it is crucial to be precise about anatomical terminology. Sagittal images, defined relative to the head as a whole, will typically parallel the plane of normal medial rectus and superior oblique muscle bellies.⁶ Such true craniotopic sagittal images would have been optimal for the study by Ela-Dalman and colleagues. It appears in their study, however, that direct sagittal images were not acquired, but were obtained by reformatting of sets of coronal images. The major disadvantage to this reformatting technique is that the resolution of the reformatted images is reduced approaching the plane thickness of the original image set. Thus, with 2 mm thick coronal images, reformatting will provide resolution closer to 2000 µm than to the original in-plane images of 312 µm in this series. Although the reformatted images were adequate to make the clinical distinctions required by Ela-Dalman and colleagues, the reduced resolution might be insufficient in other clinical situations. Modern MRI scanners are capable of acquiring oblique image planes of arbitrary orientation without reformatting. Thus, it is worthwhile to instruct the radiologists and MRI technicians directly to acquire images in the planes that are clinically relevant. This optimises resolution, and maximises the odds that relevant anatomical features will be demonstrated.

“Quasi-sagittal” image planes are defined as parallel to the long axis of each orbit.⁶ These can be obtained only by scanning each orbit separately, and are optimal for the vertical rectus muscles whose paths parallel the quasi-sagittal planes. In the case of the two patients described by Ela-Dalman and colleagues, quasi-sagittal image planes would not have been as well suited to demonstrate trauma to the medial rectus muscle as would true cranial sagittal image planes.

The foregoing anatomical complexity argues that ophthalmologists direct the strategy for orbital imaging in complex strabismus. Before ordering an MRI scan of the orbit in such a situation, it would be prudent for the referring