Thyroid eye disease associated with athyria

EDITOR,—The pathogenesis of thyroid eye disease is believed to derive from fibroblast stimulation by cytokines released by activated T lymphocytes. There is evidence of abnormal cell mediated autoimmunity and humoral autoimmune resulting in infiltration of lymphocytes and adipocytes into the extraocular muscles. The success of therapeutic immunosuppressants (steroids/azathioprine/radiotherapy) strengthens this hypothesis. A single definitive cross reacting (thyroid/retro-orbital) autoantibody has not been identified. Zhang et al found that sera from 50% of patients with thyroid eye disease reacted with an eye muscle specific protein of 55 kDa relative molecular weight. Pittsburgh data showed 67% patients with active Graves’ ophthalmopathy have antibodies against a 67 kDa mitochondrial flavoprotein subunit although it has been subsequently found in 20% of controls. They also identified a 220 kDa cell membrane specific protein known as G2S specific to eye muscle and thyroid tissue, but antibodies to this have been demonstrated in both thyroid eye disease patients and normal people. No autoantibody has been demonstrated in every case and all lack specificity. Our case demonstrates that whatever the autoimmune process may be, the presence of normal thyroid tissue or autoimmunized disease afflicted thyroid is not essential at the time of onset and development of clinical disease.

CASE REPORT
At age 30, this woman underwent partial thyroidectomy for papillary thyroid cancer. At 36 years she underwent radioactive ablation (2.2 GBq iodine-131) of the residue for suspected recurrence. At this time there was no evidence of orbital disease. At 70 years, she presented with 6 months’ diplopia and “puffy, gritty” eyes. She was clinically euthyroid on thyroid hormone, with bilateral proptosis (worse on the left) with conjunctival congestion, peri-orbital oedema, a divergent strabismus (Fig 1) and limitation of upward gaze. A clinical diagnosis of thyroid eye disease was made, which was confirmed by orbital computed tomography (Fig 2).

Both her sister and paternal grandmother had goitres without thyroid eye disease. Her sister had thyroid microsomal antibodies.

INVESTIGATIONS
Normal triiodothyronine 1.44 nmol/l (range 1.2–2.2), mildly elevated thyroxine (174 nmol/l, normal range 58–140) in an attempt to suppress the thyroid stimulating hormone (0.9 mU/l, normal range 0.3–4.0). A technetium-99 uptake scan showed no thyroid remnant. An iodine-123 tracer scan showed borderline evidence of uptake in the thyroid bed but avid uptake in the lower thoracic spine suggesting residual thyroid cancer with a vertebral metastasis. Her serum thyroglobulin was elevated at 28 mg/ml (normal range <1 in athyria) but there were no antithyroglobulin antibodies. Thyroid stimulating hormone antibodies were negative, as were her thyroglobulin antibodies and thyroid microsomal antibodies. All human and porcine retrobulbar autoantigens were negative including the aforementioned 55, 67, and 220 kDa protein antibodies despite the presence of metastatic thyroid tissue. Her general autoantibody profile was negative for antinuclear antibodies, gastric parietal cell, smooth muscle, liver/ kidney microsomal, mitochondrial and reticulolin. The RA latex was weakly positive and the Rose-Waaler was <1:32.

Her thyroid eye disease was treated with radiotherapy to good effect. Her asymptomatic metastatic thyroid cancer is being treated with radioidine.

COMMENT
This woman, with a family history of thyroid disease and whose sister has thyroid autoantibodies, has developed thyroid eye disease while possessing no significant normal thyroid tissue for 36 years. She was negative for the full array of routine and experimental thyroid autoantibodies and negative, as were her thyroid autoantibodies and thyroid microsomal antibodies. All human and porcine retrobulbar autoantigens were negative including the aforementioned 55, 67, and 220 kDa protein antibodies despite the presence of metastatic thyroid tissue. Her general autoantibody profile was negative for antinuclear antibodies, gastric parietal cell, smooth muscle, liver/kidney microsomal, mitochondrial and reticulolin. The RA latex was weakly positive and the Rose-Waaler was <1:32.

Her thyroid eye disease was treated with radiotherapy to good effect. Her asymptomatic metastatic thyroid cancer is being treated with radioidine.

Figure 1 Frontal photograph of patient demonstrating the typical clinical features of thyroid eye disease. Proptosis, lid retraction, chemosis, and ophthalmoplegia are obvious.

Figure 2 Coronal computed tomogram of orbits demonstrating typical hypertrophied ocular muscles, more marked on the left, the more proptotic eye (Fig 1).
ment mutation at nucleotide position 11778. Further mutations have been identified at positions 3460, 14484, and 15257. The 11778 mutation is responsible for 31–89% of LHON pedigrees in Europe, North America, and Australia, while the 3460 and 14484 mutations each account for approximately 10–15% of cases. The discovery of the molecular basis of LHON has provided insights into the heterogeneous clinical spectrum of disease that may result. Although these causative mutations are established, the pathophysiology of the optic nerve damage is not known. The relation between metabolic dysfunction, such as diabetes mellitus, and the development of Leber's hereditary optic neuropathy has been described only rarely.

Du Bois and Feldon described a case of a 9 year old girl with juvenile onset diabetes mellitus and LHON whose vision recovered once the diabetes was well controlled. In their series of 49 Leber's pedigrees, Newman et al. described the case of another 9 year old girl with visual loss due to LHON in the setting of 6 months of unrecognised diabetes mellitus. These authors suggest that diabetes mellitus may have placed undue stress on mitochondrial function.

The following case report suggests a relation between the development of non-insulin-dependent diabetes mellitus and LHON. Diabetes mellitus is an adult patient and the expression of Leber's hereditary optic neuropathy.

CASE REPORT

In February 1998, a previously healthy 50 year old man presented with a 5 week history of progressive deterioration of vision in both eyes. Visual field tests revealed normal retinal function and the VEP results did not reveal any abnormalities and lumbar punctation with surface capillary dilatation. The slight superior disc swelling in both eyes associated with telangiectasia, haemorrhages, and exudates was normal and fundal examination revealed subacute Leber optic neuropathy. The patient's vision continued to deteriorate and by May 1998, the visual acuities were counting fingers (CF) right and near normal within 6–12 months of retinal function and the VEP results did not reveal any abnormalities and lumbar punctation with surface capillary dilatation. The slight superior disc swelling in both eyes associated with telangiectasia, haemorrhages, and exudates was normal and fundal examination revealed subacute Leber optic neuropathy. The patient's vision continued to deteriorate and by May 1998, the visual acuities were counting fingers (CF) right and near normal within 6–12 months of retinal function and the VEP results did not reveal any abnormalities and lumbar punctation with surface capillary dilatation. The slight superior disc swelling in both eyes associated with telangiectasia, haemorrhages, and exudates was normal and fundal examination revealed subacute Leber optic neuropathy.

Leber's hereditary optic neuropathy is a recognised, though rare, condition, which must be distinguished from Leber's hereditary optic neuropathy. The disease has been described as a distinct circumscribed syndrome. Patients typically experience mild to moderate visual loss. The nature of the disc swelling ranges from minimal oedema without haemorrhages to florid swelling with capillary telangiectasia, haemorrhages, and exudates. The neuropathy may be unilateral or bilateral. Fluorescein angiography shows capillary dilatation and extravasation of dye in the region of the disc. Visual field defects may be normal, show enlarged blind spots, or central scotomas. The disc oedema clears with time and vision typically returns to normal or near normal within 6–12 months leaving residual nerve fibre bundle defects and/or optic atrophy. In cases of suspected diabetic optic neuropathy, with progressive visual loss and circumpapillary capillary dilatation which does not leak on fluorescein angiography, a diagnosis of LHON warrants consideration. This case highlights the possibility that patients labelled in the past as having diabetic optic neuropathy may have had an additional unrecognised Leber's hereditary neuropathy.

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Free conjunctival autograft harvested from the fornix for repair of leaking blebs

Editor,—In a previously reported technique of free conjunctival autograft for the repair of leaking blebs, the distance from the limbus to the harvesting site was not specified. In these reports, the paralimbal conjunctiva could have been excised, which makes future filtration surgery difficult at that site. We believe that even in the contralateral eye or the inferior quadrant of the same eye, paralimbal conjunctiva are sites for potential future filtration surgery in most cases. Butson et al stated that grafts should not be taken from the fornix because this can induce foreshortening and lid malposition if both palpebral and bulbar conjunctiva are excised. We found that grafts can be harvested from the fornix with no complications, thus preserving the potential filtration sites.

CASE REPORTS

In six eyes of four patients, we repaired persistent leaking blebs after trabeculectomy by transplanting free conjunctival autografts harvested from the fornix. Grafts were harvested from the fornix side of the leaking blebs when possible. When the intact conjunctiva of the fornix side of a leaking bleb was very narrow, the graft was harvested from the other quadrant, 5–6 mm away from the limbus. The procedure followed the previously reported technique, except for the site from which the graft was harvested. The aqueous leaks were repaired successfully, and filtering function was maintained in all cases. Two eyes of two patients required β blocker treatment to maintain satisfactory intraocular pressure after the repair surgery. Over an average follow up of 9 months (range 6–12 months), none of the eyes had significant complications, including either adhesion between palpebral and bulbar conjunctiva or lid malposition. The case series are described in Table 1.

Table 1 Clinical characteristics of the case series

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Eye</th>
<th>Indication for LEC</th>
<th>LEC to repairing</th>
<th>Site for LEC</th>
<th>Harvested site</th>
<th>Graft size (DPM/ mm)</th>
<th>Follow up (months)</th>
<th>Last IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>55</td>
<td>R</td>
<td>POAG</td>
<td>10 days</td>
<td>upper</td>
<td>upper</td>
<td>6×5</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>L</td>
<td>POAG</td>
<td>4 years</td>
<td>upper</td>
<td>upper</td>
<td>6×5</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>65</td>
<td>R</td>
<td>POAG</td>
<td>4 years</td>
<td>upper</td>
<td>upper</td>
<td>9×5</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>63</td>
<td>L</td>
<td>secondary</td>
<td>4 years</td>
<td>upper</td>
<td>upper</td>
<td>9×7</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>upper temporal</td>
<td>upper</td>
<td>upper</td>
<td>10×10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>63</td>
<td>L</td>
<td>secondary</td>
<td>4 years</td>
<td>upper</td>
<td>upper</td>
<td>6×5</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

LEC = trabeculectomy, POAG = primary open angle glaucoma, DP = diameter parallel to the limbus, DV = diameter vertical to the limbus, IOP = intraocular pressure.

*β blocker treatment.
COMMENT

We believe that the optimal site for harvesting conjunctival autografts is the fornix side of the leaking bleb, because it has almost no potential as a future filtration site. The paralimbal conjunctiva of the contralateral eye is often a potential future filtration site, since glaucoma is often bilateral. Even with a diagnosis of “unilateral glaucoma” at the time of bleb reconstruction, the potential for development of glaucoma in the contralateral eye cannot be completely excluded. A persistent bleb leak that requires total reconstruction is frequently encountered in eyes that have undergone multiple procedures and treatment with adjunctive antimetabolites.1,2 These situations are mostly encountered in eyes with refractory glaucoma, which often have little intact paralimbal conjunctiva remaining but have a high potential for multiple filtration surgeries. We believe that intact conjunctiva within 3 mm from the limbus is needed to perform a successful filtration surgery. The reported distances of the conjunctival fornix from the limbus are as follows: upper, 8-10 mm; temporal, 14 mm; lower, 8-10 mm; nasal, 7 mm. These data indicate that conjunctiva may be taken from the upper or lower quadrant, and is most easily taken from the temporal quadrant when harvesting a graft 5 mm away from the limbus. No special attention was required to avoid excising the palpebral conjunctiva during this procedure. Excising the palpebral conjunctiva may be technically difficult during this procedure. We conclude that harvesting a graft from the fornix should be considered when reconstruction surgery is performed with free conjunctival autografts for leaking blebs.

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The authors have no proprietary interest in any aspect of this report.


Five cases of thelaziasis

**EDITOR**—We report five cases of thelaziasis, including a rare case of infection of a hospital inpatient. Thelaziasis is a nematode infection of ocular tissue that is caused by Thelazia californiensis, which is found in China, India, Thailand, Korea, and Japan. This parasite has been identified in the conjunctival sac, and lacrimal gland and canal of dogs, cats, cows, badgers, rabbits, foxes, and monkeys in Asia.

Thelaziasis results when flies ingest embryonated eggs in the ocular tissue of an infected host; the eggs develop into larvae and are deposited onto the conjunctiva of a new host. Drosophilae—namely, *Amoto okadae*, *A magna*, and *A nagatai*, are the intermediate hosts.4

To our knowledge, with the exception of Japan 157 cases have been reported worldwide (China, 124; Korea, 24; Thailand, 5; India, 2; Russia and Indonesia, 1 each). In Japan, approximately 100 cases have been reported, mostly in the western regions, especially in Kyushu (66 cases).5 To date, there have been no reported cases of inpatient infections.

**Table 1 Details of five cases of thelaziasis**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Year examined</th>
<th>Infected eye</th>
<th>No of worms</th>
<th>Symptoms and ocular pain</th>
<th>Clinical findings and follicles</th>
<th>Visual disorder</th>
<th>Foreign body sensation</th>
<th>Conjunctival congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>50</td>
<td>1996</td>
<td>Left</td>
<td>3</td>
<td>Foreign body sensation</td>
<td>Conjunctival congestion</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>65</td>
<td>1989</td>
<td>Right</td>
<td>3</td>
<td>Conjunctival congestion</td>
<td>Conjunctival congestion</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>83</td>
<td>1995</td>
<td>Right</td>
<td>3</td>
<td>Conjunctival congestion</td>
<td>Conjunctival congestion</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>57</td>
<td>1995</td>
<td>Left</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>80</td>
<td>1999</td>
<td>Right</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**CASE REPORTS**

The clinical features of the five patients are summarised in Table 1. Patients (three men, two women; ages, 50-89 years) were examined at Muikaiti Hospital and Tuwanokyouzou Hospital from 1989 to 1999. Patients 1, 2, 3, 4 were outpatients, but patient 5 was an inpatient who had been hospitalised for more than a year. There were no other cases in the same hospital ward or infection of medical personnel. All patients were infected unilaterally (three right eyes, two left eyes). The patients' subjective symptoms were foreign body sensation, visual disorder, and ocular pain. Patient 5 had senile dementia and her symptoms are unknown. Clinical findings were conjunctival congestion, follicles, and whitish worms in the conjunctiva. Patients did not report having had flies in their eyes, but do keep animals such as dogs, cats, and cows. They had never visited the Kyushu region of Japan. The worms were removed (two to five worms per patient) with forceps using topical anaesthesia and antibiotic eye drops (Fig 1). The patients' symptoms resolved and there were no recurrences. The presence of the Thelazia callipaeda worms was confirmed by parasitologists.

**COMMENT**

Kirschner et al reported a case of conjunctivitis caused by Thelazia californiensis and a fly was believed to have been the possible mode of transmission in the Sierra Mountain foothills of California.6 Mimori et al reported Thelazia callipaeda infection in a man in Kumamoto Prefecture, Japan, who resided in the mountains.1 The hospitals in which our patients were examined are located in remote mountainous region of Shimane Prefecture in western Honshu. Patients lived in the suburbs in which the hospitals were located; the infections might have occurred in their places of residence.

In the case of the infection of the inpatient, the infection route is unclear. Some farms that raise beef cattle are located near the hospital, and it is possible that flies from these farms transported the parasite to the hospital.

The authors have no proprietary interest in any aspect of this report.


**Fish hook injury of the eyelid: an unusual case**

**EDITOR**—Reports of ocular fish hook injuries are uncommon in the literature. In the context of a recent case report by Krort and co-authors,1 I would like to add my experience with a rather unusual case of fish hook injury to the eyelid.

A 44 year old man presented to the casualty department with a fish hook embedded in his...
Figure 1  Fish hook loaded with nine live maggots embedded in the left upper eyelid.

left upper eyelid. He had cut off the line but made no attempt to remove the hook. The fish hook had pierced the eyelid from its conjunctival aspect near the outer canthus. It was wrapped with nine live maggots that were used as bait (Fig 1). The left eye showed a small superficial linear abrasion of the cornea but was otherwise unremarkable and the visual acuity was 6/6. Under local anaesthesia after removal of the maggots, the hook was rotated so that the barb emerged through the eyelid skin. The barb was snipped off using a wire cutter and the hook was rotated back and removed. The patient was treated with saline irrigation of the conjunctival sac and a topical antibiotic and he made an uneventful recovery.

Even in the absence of serious ocular injury, this case is interesting for the presence on the fish hook of live maggots that were kissing the conjunctiva and eyelid skin!

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Methaemoglobinemia after peribulbar blockade: an unusual complication in ophthalmic surgery

EDITOR—Peribulbar blockade is frequently used for anaesthesia in ophthalmic surgery. Owing to its short onset time and low incidence of cardiac and central nervous system toxicity, the local anaesthetic prilocaine is a popular choice for peribulbar blockade. Prilocaine is, however, the most potent methaemoglobin forming local anaesthetic. We report a case of prilocaine induced methaemoglobinemia after peribulbar blockade for ophthalmic surgery.

CASE REPORT
A 27 year old Romanian woman presented with a detached retina requiring surgical repair. Her medical history was significant for insulin dependent diabetes mellitus complicated by chronic renal failure, anaemia, and diabetic retinopathy. Her daily medication included captopril 25 mg, verapamil 240 mg, isosorbide dinitrate 40 mg, and frusemide 40 mg. A mixture of prilocaine 80 mg, bupivacaine 30 mg, hyaluronidase, and naphazoline was used to perform a peribulbar anaesthesia. Vital signs at the beginning of the operation were normal, oxygen saturation (SPO2) was 96% on room air. Sixty minutes after the peribulbar block was performed, the patient became tachypnoeic, somnolent, and the SPO2 decreased to 87% despite receiving 10 l/min of oxygen via facemask. There were no indications of myocardial ischaemia on the ECG and the breath sounds were clear. Arterial blood gas analysis demonstrated a PaO2 236 mm Hg, Paco2 32 mm Hg, pH 7.31, base excess of −5.1, SaO2 98.4%, haemoglobin 5.3 g/dl, and methaemoglobin level of 11.2%. Surgery was interrupted, methylene blue (1.5 mg/kg) was administered, and the patient improved rapidly. She was discharged home without further incident a week later.

COMMENT
Oxygen normally binds reversibly to the sixth coordination position of haem iron in haemoglobin. Partial transfer of an electron from ferrous iron to oxygen leads to the formation of superoxo-ferrihaem (Fe"O"). Failure of the electron to transfer back to oxygen results in methaemoglobin (HbFe³⁺) formation. Methaemoglobin formation in vivo is normally limited by NADH dependent methaemoglobin reductase, which serves as an electron donor for methaemoglobin. NADPH dependent methaemoglobin reductase plays a minor part (approx 5% of methaemoglobin reductase) but transfers the electron taken from methylene blue to the methaemoglobin. When methaemoglobin formation exceeds >1% of total haemoglobin, tissue oxygen transport is compromised. Furthermore, the severity of tissue hypoxaemia may be underestimated by pulse oximetry which may constantly read 85% despite increasing methaemoglobin levels. Thus, arterial blood-gas determinations are necessary in order to confirm the diagnosis of methaemoglobinemia and to fully appreciate the degree of hypoxaemia. Methaemoglobinemia may be the result of primary or secondary (acquired) causes. Genetic conditions resulting in methaemoglobinemia include mutagenic defects of haemoglobin and congenital reductase enzyme deficiency. Acquired methaemoglobinemia may be caused by oxidant drugs that overwhelm the body’s ability to limit methaemoglobin formation via enzymatic reduction. Local anaesthetics are the most common cause of perioperative methaemoglobinemia. Prilocaine is the most potent methaemoglobin forming local anaesthetic. Methaemoglobin formation is dose dependent and correlates with the rate of systemic absorption. In general, doses less than 600 mg in adults are thought not to increase the patient’s risk of methaemoglobinemia. Despite this, the administration of only 80 mg in the present case resulted in methaemoglobinemia. However, several predisposing factors may have contributed to the enhanced formation of methaemoglobin. Firstly, the risk of prilocaine induced methaemoglobinemia in patients with renal failure may be increased as metabolic acidosis increases ionised prilocaine serum levels. Further, the unbound fraction of prilocaine may be elevated in renal failure as a result of decreased serum proteins. Additionally, regular intake of isosorbide dinitrate which is also associated with methaemoglobin formation may have already predisposed this patient to the development of methaemoglobin formation. Finally, it is possible that our patient may also have suffered from an undiagnosed genetic predisposition to methaemoglobin formation. Although an abnormal haemoglobin pattern was ruled out by electrophoresis, we did not rule out a deficiency in methaemoglobin reducing enzymes such as NADH dependent methaemoglobin reductase. Thus, this patient had several underlying factors that may have predisposed her to prilocaine induced methaemoglobinemia.

In conclusion, small concentrations of prilocaine can cause methaemoglobinemia when used for peribulbar blockade in patients with reduced tolerance to oxidant drugs.

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Leber's hereditary optic neuropathy and maturity onset diabetes mellitus: is there a metabolic association?
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