

# PostScript

## LETTERS

### Mitochondrial DNA abnormalities in NAION

We reported that a group of 19 patients with non-arteritic ischaemic optic neuropathy (NAION) had an increased number of mitochondrial (mt) DNA nucleotide changes<sup>1</sup> and significantly increased relative mtDNA content compared to age and sex matched controls.<sup>2</sup> We were pleased that Carelli and Sadun thought that our most recent manuscript in *BJO* warranted an editorial response.<sup>3</sup> In this letter, we clarify data about mtDNA nucleotide changes and relative mtDNA content in NAION.

Referring to our first report, they stated that "... most of the polymorphisms found in NAION patients are ancient, well known mtDNA variants defining specific haplogroups (mtDNA maternal lineages) of European populations." In fact, we made two observations in that report.<sup>1</sup> The first was that both synonymous and non-synonymous nucleotide changes from the Cambridge Reference Sequence<sup>4</sup> were more common in NAION patients than in ethnic controls. Second, the NAION group also had 11 novel mtDNA changes and one other nucleotide change that was reported previously in a single mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS) patient. These unusual changes in 10 patients of the NAION group were clearly not ancient polymorphisms.

Referring to our recent report of increased relative mtDNA content in NAION patients,<sup>2</sup> Carelli and Sadun noted that metabolic stresses known to be associated with NAION, such as diabetes and hypertension, could increase relative mtDNA content. We agreed that a control group matched for major atherosclerotic risk factors would address the question of whether these metabolic stresses are responsible for increased relative mtDNA content in NAION patients. Therefore, we have simultaneously assessed relative mtDNA content as described previously<sup>2</sup> in the same 19 NAION patients and in 85 controls selected from a previous cardiovascular study<sup>5</sup> who were matched for ethnic background, age, sex, diabetes, hypertension, smoking history and coronary artery disease.

Table 1 shows that age, sex and prevalence of diabetes, hypertension, smoking and coronary artery disease were well matched

between NAION patients and controls. Nevertheless, relative mtDNA content in NAION patients was again more than twice that in controls, indicating that these metabolic stresses were not responsible for the dramatic increase in relative mtDNA content. This data is pertinent to the points raised by Carelli and Sadun for at least two other reasons. First, new mtDNA content values in NAION patients were strongly correlated with values reported previously<sup>2</sup> (Pearson correlation 0.977,  $p < 0.001$ ), proving the reproducibility of relative mtDNA content measurement. Second, increased relative mtDNA content was again predictive of worse vision in both eyes (Pearson's correlation  $-0.383$ ,  $p = 0.018$ ).

These data answer the concern that known metabolic stresses might induce changes in relative mtDNA content in NAION patients. Compared to controls, this small group of NAION patients in Saudi Arabia has more total mtDNA sequence changes, more novel mtDNA changes and elevated relative mtDNA content. These observations taken together with the association between mtDNA content and visual acuity suggest that mitochondrial abnormalities may constitute a risk for NAION. Similar studies should be performed in NAION populations from other ethnic backgrounds.

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### References

- 1 Bosley TM, Abu-Amero KK, Ozand PT. Mitochondrial DNA nucleotide changes in non-arteritic ischaemic optic neuropathy. *Neurology* 2004;**63**(7):1305-8.
- 2 Abu-Amero KK, Bosley TM. Increased relative mitochondrial DNA content in leucocytes of patients with NAION. *BJO* 2006;**90**(7):823-5.

- 3 Sadun AA, Carelli V. The role of mitochondria in health, ageing, and diseases affecting vision. *BJO* 2006;**90**(7):809-10.
- 4 Brandon MC, Lott M, Nguyen KC, et al. MITOMAP: A human mitochondrial genome database-2004 update. *Nucleic Acids Res.* 2005;**33**: D611-13, <http://www.mitomap.org> (accessed 27 May 2006), (Database Issue).
- 5 Abu-Amero KK, Al-Boudari OM, Mohamed GH, et al. E-selectin S128R polymorphism and severe coronary artery disease in Arabs. *BMC Med Genet* 2006;**7**:52.

### Controversies in the history of glaucoma: is it all a load of old Greek?

Contemporary medical terminology frequently stems from ancient Greek origins. However, there is some controversy relating to the true derivation of the word "glaucoma". The disorder, now defined as glaucoma, was first documented by the Ancient Greeks in 400 BC.<sup>1</sup> "Glaucoma" was first mentioned in Hippocratic writings as a blinding disease occurring most commonly in the elderly.<sup>2</sup> The description stated "that once the pupil has the colour of the sea - eyesight is destroyed and you will often find that the other eye is also blind". It is thought that this condition probably included various sight-threatening conditions including cataract and keratitis in addition to glaucoma. Opacification of the cornea or the lens resulting in apparent discolouration of the eye would have made the condition recognisable without ophthalmoscopic or slit-lamp technology. It is highly likely that the only type of glaucoma recognised in ancient times was symptomatic acute glaucoma and that the associated corneal oedema resulted in the disorder being grouped together with other conditions such as cataracts or those affecting the cornea.

It has been proposed that the word glaucoma originates from the ancient Greek word γλαῦξ - γλαῦκος (glaukos) a noun and adjective originating from the verb 'γλαῦσσω' (glauosso), meaning "to glow" or "to shine". The adjective describes someone who or something that glows or shines, this perhaps relating to the "hot" eye with acute glaucoma. However, with respect to colour, the ancient word also represents "blue-white" or "blue-green" and in the case of eyes it is thought to represent eyes having the light-blue or sea-green hue attributable to corneal oedema/opacification or cataract. In the English literature the derivation of the word glaucoma is always stated as relating to this bluish or greenish colour. However, the Greek word "glaukos" also means owl, which is thought to be so-named because of the bird's fierce, big and glowing eyes. The ancient Greek goddess Athena and the city named after her (Athens) was named γλαυκώματι in Greek and this translates to "glaucomati" meaning "having the eyes of an owl", thought to reflect the fact that she was so wise (like an owl). This ornithological (from greek ornitha meaning bird or chicken) issue increases the controversy relating to the exact origin of the word 'glaukos' and thus 'glaucoma'. There is thus a chicken (or perhaps owl!) and egg problem, since it is unclear as to whether the word glaukos was first used as a verb (to glow/shine), adjective (blue-green) or

**Table 1** Age, sex and prevalence of diabetes, hypertension, smoking and coronary artery disease between NAION patients and controls

	NAION (n = 19)	Controls (n = 85)	p Value
Age in years (SD)	58.8 (8.5)	58.2 (7.0)	0.087
Male:female	14:5	62:23	0.895
Diabetes mellitus (yes:no)	13:6	54:31	0.381
Hypertension (yes:no)	10:9	37:48	0.645
Smoking (yes:no)	7:12	37:48	0.200
Coronary artery disease (yes:no)	2:17	16:69	0.063
Relative mtDNA content (SD)	2.95 (1.13)	1.33 (0.34)	<0.001

NAION, non-arteritic ischaemic optic neuropathy.

noun (owl). Another possibility in favour of the noun is that congenital glaucoma was recognised in ancient times and that large buphthalmic eyes had the appearance of large owl eyes.

In addition to its controversial glossological (from the Greek "glossa", meaning language) derivation, glaucoma management and especially the introduction of the trabeculectomy has been another centre of debate. Although the first trabeculectomy is often attributed to Cairns in Cambridge,<sup>3</sup> a year earlier, the Greek Koryllos was the first to publish details of this guarded penetrating filtration procedure that he called a trabeculectomy.<sup>4</sup> Koryllos described this filtering surgical technique with the construction of a scleral flap and subsequent drainage of fluid via the gap between the scleral and conjunctival flap, little different to the trabeculectomy that is commonly performed today. His publication, however, received little attention since it was published in a Greek journal infrequently read worldwide. Perhaps glaucoma is more Greek than we realise.

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## References

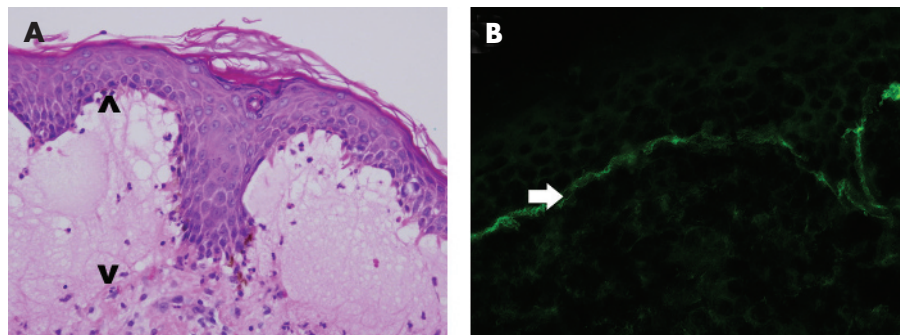
- 1 **Fronimopoulos J, Lascaratos J.** The terms glaucoma and cataract in the ancient Greek and Byzantine writings. *Doc Ophthalmol* 1991;**77**:369.
- 2 **Fronimopoulos J.** Glaucoma and cataract. *Hell Ann Ophthalmol* 1964;**3**:99–108.
- 3 **Cairns JE.** Trabeculectomy: preliminary report of a new method. *Am J Ophthalmol* 1968;**66**:673–9.
- 4 **Koryllos K.** The excision of the corneoscleral meshwork (trabeculectomy) as an antiglaucomatous operation. *Delt Ell Ophthalmol* 1967;**35**:147–55.
- 5 **Koryllos K.** Technique and results of goniotomy in glaucomas. *Hell Ann Ophthalmol* 1963;**4**:11–22.
- 6 **Grewe R.** Zur Geschichte des Glaukoms. *Klin Mbl Augenheilk* 1986;**188**:167–9.

## Cicatrising conjunctivitis due to paraneoplastic pemphigoid

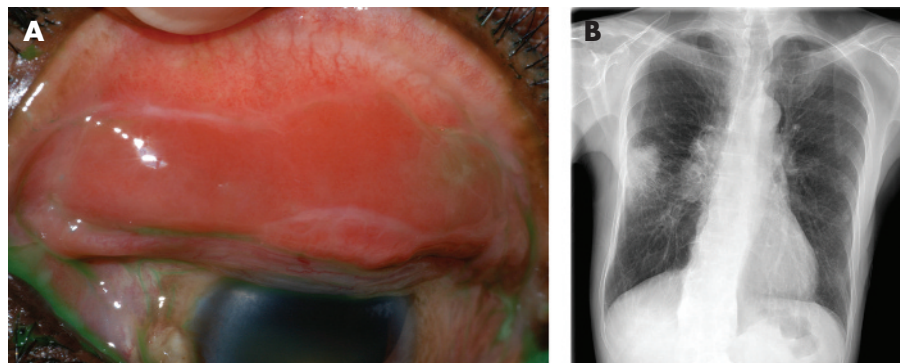
Ocular cicatricial pemphigoid (OCP) is a putative autoimmune, chronic, inflammatory, subepithelial blistering disease affecting mucous membranes.<sup>1</sup> It is characterised by linear deposition of immunoglobulins and complement along epithelial basement membranes.<sup>1</sup> In this report, we describe a cicatrising conjunctivitis that was clinically and pathologically similar to ocular cicatricial pemphigoid but occurred concurrently with systemic malignancy.

## Case report

A 69-year-old cachectic man with chronic obstructive pulmonary disease presented with painful mouth and skin blisters. He developed a painful red eye 1 week later. Visual acuity was 20/25 on the right and 20/30 on the left. Slit-lamp examination showed bulbar



**Figure 1** (A) Subepidermal serous fluid (arrowheads) and perivascular inflammation consisting of neutrophils and eosinophils in a biopsy specimen of a skin bulla. Haematoxylin and eosin, original magnification 20 $\times$ . (B) Direct immunofluorescence showing linear C3 staining of the basement membrane along the dermal-epidermal junction (arrow). IgG staining (not shown) was similar. Original magnification 40 $\times$ .



**Figure 2** (A) Slit-lamp photograph showing bullae, an intense papillary reaction and subepithelial scarring of the superior palpebral conjunctiva. (B) Chest x ray showing a 5.7 $\times$ 3.5 cm spiculated opacity in the patient's right lung and mediastinal lymph node enlargement.

conjunctival injection and an intense papillary reaction of the palpebral conjunctiva on the right. At examination 10 days later, the patient had new fornix foreshortening and symblepharon formation. A skin biopsy revealed subepidermal bullous dermatosis with eosinophils and neutrophils (fig 1A). Direct immunofluorescence showed linear IgG and C3 staining along the basement membrane (fig 1B). These results were consistent with cicatricial pemphigoid. The patient began aggressive ocular lubrication and oral prednisone 80 mg daily.

During the following week, his ocular symptoms improved dramatically, although he developed bullae of the superior palpebral conjunctiva on the right, and bilateral subepithelial scarring, fornix foreshortening and symblepharon (fig 2A). The patient was hospitalised that same week because of increasing difficulty with oral intake and weight loss. A chest x ray suggested lung cancer (fig 2B). Bronchoalveolar lavage and systemic evaluation confirmed non-small cell lung carcinoma, most likely squamous cell, stage IIIA. The patient underwent radiation and chemotherapy with cisplatin and etoposide. While on moderate-dose steroids, he developed new cutaneous bullae. Mycophenolate mofetil was added but had no effect. Alkylating agents were not tried due to profound neutropenia. At a 5-month follow-up, visual acuity remained 20/25 in each eye, with clear corneas despite cicatricial entropion and trichiasis of the right lower eyelid.

## Comment

Previously reported cases have shown a temporal association between cicatricial pemphigoid and systemic solid malignancies, including non-small cell lung cancer (adenocarcinoma, squamous cell, large cell), gastric adenocarcinoma and endometrial adenocarcinoma.<sup>2–8</sup> In some patients, the pemphigoid responded to chemotherapy or surgical resection of the tumour, suggesting a paraneoplastic process.<sup>2–6,8</sup> Antibodies to laminin-5, a basement membrane protein elaborated by lung and gastrointestinal epithelia, have been found in patients with cicatricial pemphigoid and lung and gastric cancers.<sup>2–4,6–8</sup> Aberrant synthesis of laminin-5 by tumour cells, or tumour-related inflammation and invasion, may expose the antigen to the immune system.<sup>2,9</sup> Pemphigoid, an autoimmune disease characterised by intraepithelial blisters, can also present as a paraneoplastic process, although it is primarily associated with lymphoreticular malignancies.<sup>10</sup>

In a similar reported case of paraneoplastic pemphigoid, the diagnosis of squamous cell lung cancer was made 2 months after the patient developed cicatrising conjunctivitis.<sup>7</sup> The differential diagnosis for cicatrising conjunctivitis is broad and includes OCP, Stevens Johnsons syndrome, chemical burns, radiation, toxic conjunctivitis, post-infectious conjunctivitis, graft versus host disease, atopic keratoconjunctivitis and conjunctival squamous cell carcinoma.<sup>1</sup> Paraneoplastic pemphigoid should also be considered in the differential diagnosis, and this case