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## Editorials

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### Ups and downs of optokinetic nystagmus

Optokinetic nystagmus (OKN) is an oculomotor reflex closely linked to the vestibular system which contributes to the stabilisation of retinal images. During combined vestibular and optokinetic stimulation, which occurs during natural situations of self rotation, the optokinetic input takes over as the vestibular drive declines.<sup>1</sup> When a continuously moving stimulus is viewed, a characteristic eye movement pattern consisting of a slow phase in the direction of the stimulus and a fast phase in the opposite direction is elicited. In primates, OKN represents the responses of both the smooth pursuit and optokinetic system. The response to a full field moving visual stimulus has two phases. The first response, reflecting mainly smooth pursuit, promptly generates the nystagmus within 1-2 seconds of stimulus onset. The slow phase velocity approximates stimulus velocity. The second response corresponds to a slower buildup of stored neuronal activity. The neural pathway controlling OKN involves the cortex, brainstem, and cerebellum.<sup>2-5</sup> Anatomical pathways of the OKN are known from animal studies, lesions in humans and, recently, by functional imaging. A recent study<sup>6</sup> using functional magnetic resonance imaging (fMRI) showed the cortical structures involved in small field OKN. These were the occipitotemporal cortex, posterior parietal cortex, precentral, and posterior median frontal gyrus, the anterior and the posterior insula, the prefrontal cortex, and the medial part of the superior frontal gyrus. Subcortical structures shown to be activated during OKN were the caudate nucleus, the putamen, the globus pallidus, and the paramedian thalamus. Horizontal and vertical small field OKN activated the same cortical and subcortical areas in each hemisphere. Regardless of stimulus direction, a significant right hemispheric predominance was found. Many studies suggest that the final neuronal substrate for the slow and quick phase of the OKN corresponds to that of voluntary saccades and pursuit, respectively, and arise in the same brain stem neurons.

Clinical assessment of eye movement disorders often includes examination of horizontal OKN but not vertical OKN and little is known about development of vertical OKN or about vertical OKN in patients with visual system pathology. This may be because of more difficulties in recording and stimulating vertical OKN than horizontal OKN.

For example, there is an abundant literature about horizontal OKN asymmetries in newborn babies and in patients with abnormal binocular vision.<sup>7,8</sup> In the first months of life, while the pathways to the cerebral visual

areas remain immature, monocular OKN is more readily elicited by temporal to nasal than by nasal to temporal stimulus motion. This temporal-nasal asymmetry disappears between the second and the sixth month of life. This implies that pathways from the retina to the nucleus of the optic tract and the accessory optic system are functional at birth but, with maturation of the cortical visual pathway, projections of the extrastriate cortex to the brainstem supersede. When strabismus or amblyopia prevent normal development of binocular vision, asymmetries of the horizontal OKN persist. However, little is known about anomalies of the vertical OKN in patients with disturbed binocular vision. Schor and Levi<sup>9</sup> found upward-downward asymmetries in patients with amblyopia, the upward beating OKN being smaller.

In this issue of the *BjO* (p 451), Garbutt and Harris report, by observation of eye movements, abnormal vertical OKN in infants and children with neurometabolic diseases or with brain abnormalities on MRI. This study is the first to investigate vertical OKN in addition to horizontal OKN in a large group of infants and children with pathology in the visual pathways. It is of special interest because differences between horizontal and vertical OKN in patients with abnormalities of the brainstem and/or cerebellum were found. Vertical OKN is important in the diagnosis of Niemann-Pick disease type C, a neurometabolic disease which begins with loss of vertical saccades. Indeed, in one child, vertical OKN anomaly was the presenting sign of Niemann-Pick disease type C. In Gaucher's disease, investigation of OKN is important because its anomalies indicate the neuropathic form (type II or III). However, horizontal OKN is affected first and vertical OKN anomalies are an indication of progression of the disease. Children with lesions in the cortex were most likely to have horizontal and vertical OKN changes. Nine children in this study had disturbances of vertical OKN but normal horizontal OKN. The majority of these patients had lesions in the rostral midbrain. Interestingly, saccades in only one vertical direction can be abnormal. This suggests a separation between pathways for upward and downward OKN. An important aspect of this study, underlining the importance of the examination of vertical OKN, is that vertical OKN disturbance was always associated with pathology, whereas horizontal OKN abnormalities are frequently found to be idiopathic.

This study clearly indicates the importance of examining OKN, including vertical OKN, in patients with visual

pathway disorders. In the future, quantitative recordings may show vertical OKN anomalies in a larger number of patients. It is certainly necessary to study systematically the development of the vertical OKN in normal children. In addition, the influence of the afferent visual system on vertical OKN needs to be investigated. The influence of factors such as visual acuity, amblyopia, or binocular vision needs to be examined. A quantitative comparison of smooth pursuit and saccades on one hand and OKN on the other hand would be interesting, in order to identify potential lesions which specifically affect the OKN. Certainly the study by Garbutt and Harris should stimulate investigators to use OKN examinations more frequently in visual pathway pathology.

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- 1 Leigh RJ, Zee DS. The vestibular-optokinetic system. In: Leigh RJ, Zee DS, eds. *The neurology of eye movements*. 3rd ed. New York, Oxford: Oxford University Press, 1999:19–89.
- 2 Boyle R, Büttner U, Markert G. Vestibular nuclei activity and eye movements in the alert monkey during sinusoidal optokinetic stimulation. *Exp Brain Res* 1985;57:362–9.
- 3 Heinen SJ, Keller EL. The function of the cerebellar uvula in monkey during optokinetic and pursuit eye movements: single unit response and lesion effects. *Exp Brain Res* 1996;110:1–14.
- 4 Illg UJ, Hoffmann K-P. Response of neurons of the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic tract in the awake monkey. *Eur J Neurosci* 1996;8:92–105.
- 5 Mustari MJ, Fuchs AF. Discharge pattern of neurons in the pretectal nucleus of the optic tract (NOT) in the behaving primate. *J Neurophysiol* 1989;64:77–90.
- 6 Dietrich M, Bucher SF, Seelos KC, et al. Horizontal and vertical optokinetic stimulation activates visual motion-sensitive, ocular motor and vestibular cortex areas with right hemispheric dominance. An fMRI study. *Brain* 1998;121:1479–95.
- 7 Atkinson J, Braddick O. Development of optokinetic nystagmus in infants: an indicator of cortical binocularity? In: Fisher D, Monty R, Senders J, eds. *Eye movements: cognition and visual perception*. Hillsdale, NJ: Erlbaum, 1981:53–64.
- 8 Naegel J, Held R. The post-natal development of monocular optokinetic nystagmus in infants. *Vis Res* 1982;22:341–6.
- 9 Schor CM, Levi DM. Disturbance of small field horizontal and vertical optokinetic nystagmus in amblyopia. *Invest Ophthalmol Vis Sci* 1980;19:668–83.

## Immunology and thyroid ophthalmopathy: where will the footprints lead us?

The real question: why do some people at some time develop an autoimmune disease, is still unanswered. But we can see the footprints in the snow, and learn a lot from these. Immunohistochemical analyses show us the footprints: they illustrate the situation at a certain time. By looking at different moments in time, we may get a better overall picture, although this technique will still leave us with questions regarding the cause of the footprints.

A frequently occurring autoimmune disease is thyroid autoimmune disease, which often leads to thyroid dysfunction. This disease is considered an autoimmune disease owing to the presence of antibodies and T cell responses directed against thyroid antigens. It is as yet unclear why such immune responses develop, but some predisposing factors have been identified. In the first place, family and twin studies indicate that genetic factors play a part. An association with specific HLA antigens, such as HLA-DR3, has also been found. Since HLA class II antigens have a role in the selection process of the T cell repertoire in the thymus and in the presentation of antigens to T cells, this HLA association suggests that T cells are essential in the development of thyroid autoimmunity. Antibodies have been implicated in the functional disturbances: in particular, the long acting thyroid stimulation antibodies (LATS) may stimulate thyroid cells to produce thyroid hormone and cause hyperthyroidism. Environmental factors have also been identified: a viral infection may trigger acute thyroiditis, perhaps through the induction of local HLA class II expression. Botazzo *et al*<sup>1</sup> showed aberrant HLA-DR expression on thyroid follicle cells in Graves' disease and in Hashimoto's thyroiditis. Stress may be another external factor that plays a part in the initiation of acute hyperthyroidism. The production of steroid hormones as a result of stress may influence the balance between different sets of T cells.

Thyroid ophthalmopathy is often associated with thyroid autoimmune disease. Genetic factors are similar to those described for thyroid autoimmune disease. Smoking as an

environmental factor increases the severity of thyroid ophthalmopathy. It is clear that the immune system has an important role in the initiation of this disease, but the exact pathogenesis has not yet been defined. The clinical picture is relatively well defined: patients may complain of pain, blurring of vision, pressure behind the eyes, double vision, and irritated eyes. Clinical signs include eyelid oedema, conjunctival injection and chemosis, lid lag, eyelid retraction, proptosis, extraocular muscle dysfunction, corneal exposure, etc. All of these are due to swelling of the various tissues in the orbit and dysfunction of muscles. Deposition of glycosaminoglycans and inflammatory oedema are considered the causes of this swelling. Is there a specific stimulus that causes deposition of glycosaminoglycans in these specific locations? There are suggestions that thyroid stimulating immunoglobulins also play a part in orbital disease: thyroid stimulating hormone (TSH) receptors have also been detected on the surface of cultured orbital fibroblasts. Anti-TSH antibodies might then be the stimulus that induces fibroblasts into making glycosaminoglycans. Autoantibodies against a specific 64 kDa extraocular muscle protein and a 23 kDa fibroblast protein have been described, but such antibodies are also often found in patients without ophthalmopathy. However, antibodies may be a secondary phenomenon caused by the release of tissue antigens following cellular destruction.

A cellular immune response can also be the basis of the autoimmune ophthalmopathy. The presence of increased numbers of T cells in the orbital tissue especially in patients with early thyroid ophthalmopathy (as described by Pappa *et al* in this issue of the *BJO*, p 517) suggests that T cells have a role in the early development of this disease. Pappa and colleagues' article differentiates between early and late thyroid ophthalmopathy. A comparison was made between the cellular infiltrate in the extraocular muscles of five patients with early and nine patients with late thyroid ophthalmopathy, and of 14 healthy individuals. CD4 and CD8 positive T cells were present in the biopsies of early

cases, but not in late cases and healthy controls. Expression of HLA-DR was seen on interstitial cells but not on muscle tissue, both in early and late cases. As mentioned earlier, HLA-DR is considered a major inducer of T cell responses. However, HLA-DR was also expressed on biopsies of normal controls, but at a lower level. In addition, stimulation of a T cell immune response can occur through macrophages or dendritic cells, and Pappa and colleagues observed increased numbers of macrophages in the biopsies of early cases compared with the two other groups. The fact that macrophages were also present in the biopsies of normal muscles gives a clue to the initiation of responses: resident tissue macrophages may capture antigen and present it to the immune system, thereby attracting tissue specific autoimmune T cells.<sup>2</sup>

Several investigators have shown with various techniques that among peripheral blood lymphocytes from patients with thyroid ophthalmopathy, a subset responds to muscle antigens, but such responses are often not measurable. The best proof would be the isolation from extraocular muscle or the orbit of T cells carrying a specific receptor for muscle or orbital fibroblast specific proteins. One may speculate that this situation is comparable with herpes disease in the cornea, where infiltrating cells show very specific reactions to herpes virus antigens. Such cells can

be isolated from the cornea, but their numbers in the peripheral blood are too low to be identified with the present techniques.<sup>3</sup> No proof of a viral infection occurs in thyroid ophthalmopathy, but viral disease may have an indirect role in thyroid disease; for example, in patients with mononucleosis infectiosa antithyroid antibodies are frequently observed.

In conclusion, thyroid autoimmune disease and thyroid ophthalmopathy may both be due to autoimmune T cell responses. Future work will be necessary to determine whether the T cell responses against the already known antigens can be regarded as an epiphenomenon or as a causal response. Following the footprints in the snow may help us to find the real culprit, the cause of this disease.

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- 1 Bottazzo GF, Pujol-Borrell R, Hanafusa T, *et al.* Role of aberrant HLA DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* 1983;2:1115-19.
- 2 Van der Gaag R, Schmidt ED, Zonneveld FW, *et al.* Orbital pathology in thyroid-associated ophthalmopathy. *Orbit* 1996;15:109-17.
- 3 Verjans GMGM, Remeijer L, Van Binnendijk RS, *et al.* Identification and characterization of herpes simplex virus-specific CD4+ T cells in corneas of herpetic stromal keratitis patients. *J Infect Dis* 1998;177:484-8.



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