Pinealitis accompanying equine recurrent uveitis

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Abstract

There is no direct verification of pineal gland involvement in human uveitis. Specimens of pineal tissue are not available during active uveitis in human patients. Naturally occurring uveitis in horses gives us an opportunity to examine tissues during active ocular inflammation. We examined the pineal gland of a horse that was killed because it had become blind during an episode of uveitis. The clinical history and histopathology of the eyes were consistent with post-leptospirosis equine recurrent uveitis. The pineal gland of this horse had significant inflammatory infiltration consisting mainly of lymphocytes with some eosinophils. This observation of pinealitis accompanying equine uveitis supports the animal models of experimental autoimmune uveoretinitis with associated pinealitis and suggests that the pineal gland may be involved in some human uveitides.

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Although laboratory studies predict pineal gland pathology accompanying immunological uveitis,¹ there is yet no direct evidence of pineal gland pathology coincident with naturally occurring uveitis. Specimens of human pineal gland are generally not available during an active uveitis. Equine recurrent uveitis² (ERU) is a naturally occurring uveitis in which tissues can be obtained from horses killed for humane reasons. We report the ocular and pineal gland histopathology of a mare killed during an episode of uveitis.

Case report

In 1986 a 2-year-old, half thoroughbred mare was brought to a stable that housed seven horses, two of which were blind as a result of recurrent uveitis. Three years later in June 1989 this mare had a 3 day episode of anorexia and lethargy. A complete blood count revealed mild anaemia (haematocrit 28.2%, normal range 32.0-53.0%). Serum chemistry was unremarkable. The signs resolved within 1 week and the haematocrit returned to 37.8%.

In October 1989, this horse was examined for acute, bilateral ocular pain. Direct ophthalmoscopic examination revealed inflammatory signs in the anterior chamber, iris, and vitreous of both eyes. There was no history of ocular trauma. A diagnosis of ERU was made and the horse was treated with topical 0.1% dexamethasone and 1% atropine sulphate eye ointment (initially six times a day, tapering schedule for 6 weeks) and systemic phenylbutazone (2 g twice daily for 1 week).

In November 1989, sera of five of the horses at the stable were tested for microscopic agglutina-

tion reactivity to *Leptospira interrogans* serovars (Diagnostic Laboratory, New York State College of Veterinary Medicine, Ithaca, NY). This mare had a titre of 1:3200 to *L. interrogans* serovar pomona. Titres of 1:1600 or above suggest previous infection and generally remain elevated following infection.³ One of the blind horses was available for testing and had a titre of 1:6400 to *L. interrogans* serovar pomona. Three of the unaffected horses had no leptospiral titre, and normal ophthalmoscopic examinations.

In April 1990, there was a bilateral recurrence of uveitis which was most severe in the left eye. Treatment was similar to the above with the addition of oral prednisone every other day (500 mg initial dose tapered to 100 mg over 6 weeks). Subsequent episodes of uveitis occurred in June 1990 (right eye more severe), August 1990 (right eye more severe), February 1991 (left eye more severe), and June 1991 (left eye more severe). Each episode was treated with the same medication as the initial one. Signs of pain resolved in 2 to 4 weeks, but each episode resulted in inflammatory sequelae (vitritis, focal cataract, posterior synechiae, and detached retina) and gradual loss of visual acuity. During the June 1991 episode, the lenses of both eyes developed dense cataracts and vision was lost. Medication was stopped and 5 days later the horse was killed with a lethal injection of succinylcholine and sodium pentobarbitone. The eyes, pineal gland, and a portion of the brain stem were removed, fixed in cold 95% ethanol and embedded in paraffin.

Histopathology

Light microscopy of haematoxylin and eosin stained sections of the eyes revealed pathology consistent with the description for ERU.² Both eyes were similar, with slightly more involvement of the left eye, which showed greater inflammation in the last episode of uveitis. In the ciliary body there were prominent nodules of lymphocytes (Fig 1). These focal lymphoid collections were well circumscribed and were observed throughout the ciliary body. The infiltrate of the ciliary processes and that in the adjacent aqueous contained monocytic cells in addition to lymphocytes. There was also lymphocytic infiltration of the rest of the uvea. In the choroid and iris there were clusters of lymphocytes, though less numerous and less well defined than in the ciliary body.

Various stages of retinal pathology were observed including detachment, degeneration, and infiltration. In the right eye there was loss of outer segments and some loss and disorganisation of the rest of the photoreceptor cells (Fig 2a). There was prominent mononuclear infiltrate in the inner retina. In the left eye there was extensive subretinal exudate containing lymphocytes, mononuclear cells, and epithelioid cells

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Figure 1 Lymphocytic nodule in the ciliary body of a horse with equine recurrent uveitis (haematoxylin and eosin, magnification, $\times 6$).

Figure 2 Detached degenerating retina of a horse with equine recurrent uveitis. (a) In the right eye there is loss of outer segments, disorganisations of the photoreceptor cell layer, and mononuclear infiltrate in the inner retina. (b) In the left eye there is subretinal exudate containing lymphocytes, mononuclear cells, and epithelioid cells. The outer segments of the photoreceptor cells are absent (haematoxylin and eosin, magnification, $\times 178$).

Figure 3 (a) Pineal gland of a normal horse. (b) Infiltration of the pineal gland of a horse with equine recurrent uveitis. The infiltrate (arrows, b) is primarily in the connective tissue area of the normal horse pineal gland (arrows, a) (haematoxylin and eosin, magnification $\times 6$).

(Fig 2b). The outer segments of the photoreceptor cells were absent, but the organisation of the remaining retina was more preserved than that of the right eye.

The pineal gland of a normal horse is parenchymal with prominent connective tissue areas (Fig 3a). In the pineal gland of this horse there was significant infiltration of these connective tissue areas (Fig 3b). The infiltration was predominantly lymphocytic with some eosinophils (Fig 4). The morphology of the pinealocytes was not overtly affected. There was no such infiltration observed in a portion of brain stem of this horse.

Discussion

We have demonstrated significant lymphocytic infiltration of the pineal gland of a horse that had clinical signs and histopathology consistent with a diagnosis of ERU as a sequela of leptospirosis.³

Laboratory animals sensitised with photoreceptor cell specific autoantigens develop not only experimental autoimmune uveoretinitis but also lymphocytic infiltration of the pineal gland.¹ This has been reported in guinea pigs, rats, rabbits, and non-human primates.⁴⁻⁷ An autoimmune response in both eye and pineal gland is not unexpected since both retinal photoreceptor cells and pinealocytes contain the photoreceptor cell specific proteins, used for sensitisation – that is, S-antigen,⁸ interphotoreceptor cell retinoid binding protein (IRBP),⁹ or rhodopsin.¹⁰ Although these models were developed to explore the immunological aspects of various human uveitides, histopathological confirmation of pineal gland pathology during active uveitis or as a sequela of uveitis has yet to be reported.

There is physiological evidence of pineal gland involvement in human uveitis, such as a decrease in nocturnal peaks of the pineal neurohormone melatonin in patients with uveitis.¹¹ There is also preliminary radiological evidence of pineal gland pathology accompanying uveitis (Mitchel E Opremcak, personal communication, Cleveland Clinic).

Since it is difficult to obtain appropriate human specimens for study – that is, pineal gland tissue during active uveitis, we studied a naturally occurring uveitis in horses.^{2,3} ERU affects horses worldwide. It is mainly an iridocyclitis with some later involvement of the posterior portions of the eye. ERU is probably an immune-mediated sequela to trauma or systemic infection.¹²⁻¹³ Systemic infection with *L. interrogans* serovar *pomona* has been implicated as an initiating event in both naturally occurring¹⁴ and in experimentally induced ERU.¹⁵ Horses that become blind may be killed and thus provide a source of tissue for study.

Lymphocytic infiltration of the pineal gland is probably not normal but is related to the uveitis. Reports of lymphocytes in mammalian pineal glands are limited to select murine strains¹⁶⁻¹⁷ and lymphocytic infiltration of some tumours of human pineal gland.^{18-19,20} Small groups of lymphocytes have been observed adjacent to the pineal gland of rats²¹ and in some human pineal glands.²² Lymphocytes have not been described in the pineal gland of normal horse.²³ We have not

Figure 4 Higher magnification of infiltration of the pineal gland of a horse with equine recurrent uveitis. The infiltrate is predominantly lymphocytes with some eosinophils (arrows) (haematoxylin and eosin, magnification $\times 194$).

observed infiltration of the pineal glands of several normal horses (unpublished observation).

The immune-mediated nature of ERU is supported by immunohistochemical studies of this horse in which we have demonstrated immunoglobulin and MHC Class II antigen on infiltrating and resident cells of both eye and pineal gland.²⁴

In conclusion, our observation of pinealitis in naturally occurring uveitis suggests that the pineal gland may participate in some human uveitides. This finding also gives relevance to the observation of pinealitis in experimental models. Further studies of ERU will allow us to obtain more specimens during active uveitis and to follow more closely the pedigrees and environmental and infectious parameters of a given uveitis.

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