Equine recurrent uveitis - the European viewpoint

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Historical perspective
Equine recurrent uveitis (ERU) has been a scourge for the equine population for many centuries and was also an important economic factor when the horse population in Europe was significantly larger than today (Bayer 1900). ERU was in many areas enzootic and the disease so prevalent, that some studs had to be closed altogether. The largest equine populations of that time were found in the armies and the great losses of horses due to ERU spurred the interest in this disease (Braun 1995).

All through the Middle Ages the knowledge of the so-called oculus lunaticus was very limited and treatment usually consisted of various methods of bloodletting (Bayer 1900; Jakob 1920; Braun 1995). With the formation of the first veterinary schools in Europe in the 18th century a more scientific approach to diseases in general and to ocular diseases in particular was established. The development of veterinary ophthalmology was largely driven by the need to increase the knowledge about ERU. The advent of the first ophthalmoscope by Helmholtz in 1851 and the introduction of extracts of Bella Donna were important steps in the establishment of ophthalmology as a specialty in human and veterinary medicine (Braun 1995).

Prevalence
The prevalence varies with geographic location and climate and has been reported to be as high as 40% in endemic areas (Rosenfeld 1905; Möller 1910; Cross 1966). In certain river valleys in France the prevalence increased from 23% to 40% after severe flooding occurred in 1881 (Möller 1910). It was also noted, that in areas with clay soil and frequent flooding the prevalence could reach 70%, while in drier areas with chalky soil the incidence was around 5% (Jakob 1920). More recent reports documented a prevalence of 8% to 10% in western Germany (Szemes 2000; Deeg, Thurau et al. 2002).

Aetiology of ERU
The aetiology of ERU is still not absolutely clear today (Dwyer 2005). In a 1987 editorial, Barnett concluded that equine periodic ophthalmia was “a continuing aetiological riddle” (Barnett 1987). In earlier days heredity has been hotly disputed (Bayer 1900; Möller 1910; Lorbeer 1940). And there is still evidence of a possible genetic component to ERU (Angelos, Oppenheim et al. 1988; Alexander and Keller 1990; Dwyer, Crockett et al. 1995). There appears to be a breed predilection for the Appaloosa (Dwyer, Crockett et al. 1995). Although the total population of Appaloosas in Switzerland is not known, they are definitely over-represented in our ERU cases with 11/15 (73%) of Appaloosas diagnosed with ERU compared to 154/1115 (14%) of all other breeds combined.

It was also observed that horses in low-lying wetlands tended to be more commonly affected than those in higher and drier areas (Zipperlen 1877). This view was still supported half a century later (Jones 1942; Jones 1949). Viral causes have been suspected but this has never been proven (Komar 1968; Attenburrow 1983).

At one point microfilariae of Onchocerca cervicalis were thought to play a role in the aetiology of ERU, although today this seems to be rather exceptional (Gmelin 1935; Attenburrow 1983; Cook and Harling 1983; van der Velden and Schuitemaker 1985).
One of the first to propose Leptospira as the causative agent for ERU was Heusser in 1948 (Heusser 1948). Since then there is mounting evidence, that Leptospira sp. is at least the triggering factor for ERU (Roberts, York et al. 1952; Yager, Gochenour et al. 1952; Bryans 1955; Roberts 1958; Roberts 1969; Trap 1979; Hathaway, Little et al. 1981; Davidson, Nasisse et al. 1987; Matthews, Waitkins et al. 1987; Sillerud, Bey et al. 1987; Dwyer, Crockett et al. 1995; Wollanke, Gerhards et al. 1998; Wollanke, Rohrbach et al. 2001; Wollanke 2002; Wollanke 2004; Niedermaier, Wollanke et al. 2006; Gilger, Salmon et al. 2008) and it has been shown, that vaccination with a specific vaccine was successful in preventing new cases in an endemic horse population (Rohrbach, Hendrix et al. 2002; Wollanke 2004; Rohrbach, Ward et al. 2005). There are, however, geographical differences in the prevalence of Leptospira in the equine population (Verma, Biberstein et al. 1977; Slatter and Hawkins 1982; Matthews 1987; Dwyer, Crockett et al. 1995; Wollanke, Gerhards et al. 1998). In our own case records 79% of horses with ERU test positive for Leptospira sp. by microagglutination of aqueous and/or vitreous samples (Toemoerdy 2009). Nine different serovars of Leptospira were tested, the most common being L. grippothyphosa, followed by L. Canicola and L. bratislava (Toemoerdy 2009).

ERU is most likely an immune-mediated disease initiated by various causes resulting in recurrent delayed hypersensitivity reactions at variable intervals (Spiess 1997a; Spiess 1997b; Dwyer 2005) (Deeg, Hauck et al. 2008). Recent studies give compelling evidence, that ERU is an autoimmune reaction with horses expressing the MHC haplotype, ELA-A9 being more susceptible to develop the disease (Deeg, Kaspers et al. 2001; Deeg, Thurau et al. 2002; Deeg, Hauck et al. 2007; Deeg, Raith et al. 2007; Deeg 2008).

Clinical signs of ERU
The many clinical signs and different manifestations of ERU have been extensively described elsewhere (Cook and Harling 1983; Spiess 1997; Dixon and Coppack 2002; Dwyer 2005) (Fig. 1). In our case load ERU is the most common form of uveitis seen in horses. The clinical presentation of ERU is variable. The vast majority of horses presented with clinical signs of anterior uveitis, which are easily recognisable by owners and referring veterinarians. Some of them may also have Panuveitis, although examination of the posterior segment is initially precluded by the intense miosis. A small number of patients exhibit a less obvious form of ERU, usually intermediate uveitis (pars planitis) with marked inflammatory changes of the posterior segment (vitreous). Since these horses exhibit less obvious clinical signs, they are usually presented because of visual deficits at a late stage of the disease. There appears to be no correlation between the form of uveitis and the Leptospira status of an individual patient (Toemoerdy 2009). The association between peripapillary choroidal degeneration (butterfly lesions) and ERU is equally unclear (Matthews, Crispin et al. 1990). In ponies experimentally infected with Leptospira sp. peripapillary chorioretinitis developed along with anterior uveitis (Williams, Morter et al. 1971).

Diagnosis
The diagnosis of ERU is based on the clinical signs of uveitis and a documented history of recurrent episodes of inflammation. In central Europe it is prudent to consider any equine uveitis to be ERU until proven otherwise. There are of course, other forms of uveitis, especially those associated with trauma. Blunt or sharp trauma to the eye is usually accompanied by some degree of uveitis (Habin 1994; Moore, Halenda et al. 1998; Grahn and Cullen 2000). Iridocyclitis and chorioretinitis have been seen in foals with septicaemia (Latimer and Wyman 1985). We have seen bilateral anterior uveitis in a foal with an umbilical infection and bacteraemia. Uveitis may also be the result of multi-centric neoplasms (Germann, Richter et al. 2008). Most forms of equine ulcerative keratitis are accompanied by some degree of anterior uveitis (Nasisse and Nelms 1992)
Therapy past and present

As stated earlier, the most common form of therapy for centuries was bloodletting (Braun 1995). Bloodletting was still practised in human ophthalmology in the early 20th century for the management of chronic uveitis. Six to 8 leeches were applied to the temple of the affected side (Fuchs 1945). For a time extirpation of the third eyelid or the cartilage of the nictitans was advocated (Stietenroth 1906; Möller 1910). Hair rope was pulled under the skin below the affected eye and left there for long times to cause artificial suppuration (Zipperlen 1877; Bayer 1892; Bayer 1900). In 1900 Bayer still stated bluntly that therapy for ERU was “powerless”.

The situation improved somewhat when solutions of 2-5% cocaine and/or 1-2% atropine were instilled. Adrenalin was also used topically to induce vasoconstriction and to minimize anterior chamber exudation (Möller 1910). This was certainly a less invasive approach than lancing the cornea and draining the exudate (Jakob 1920). Another form of surgical therapy for ERU was the iridectomy practised in the late 19th and early 20th century (Bayer 1900; Möller 1910). A point was made to perform this surgery under general anaesthesia, because it proved too stressful and difficult under topical cocaine anaesthesia alone. The iris was described as being “rotten” in these cases (Jakob 1920). The surgical results were far from desirable and this form of therapy was later abandoned.

Ophthalmology at the time was taught by human ophthalmologists at most European veterinary schools and not surprisingly, new insights from human ophthalmology were applied to veterinary patients. Eversbusch was the first to use systemic sodium salicylicum with its anti-inflammatory properties in the treatment of ERU (Eversbusch 1882). Non-specific protein therapy was utilized in both human and veterinary ophthalmology (Fuchs 1945; Perera 1949; Smythe 1958). In most cases increasing amounts of sterilized milk were injected subcutaneously or intramuscularly. Smythe stated in 1958, “it is always difficult to decide whether recovery is due to the treatment in these cases or whether it supervenes in spite of it ….” In any case, results appear to have encouraged its continuance for years to come (Smythe 1958).

In the middle of the 20th century synthetic corticosteroids became available and were increasingly used in veterinary ophthalmology. Topical applications every 2 to 3 hours were reported, as well as subconjunctival injections of cortisone solutions (Smythe 1958; v. Salis 1963; Komar 1968).

For the next fifty years there was little progress in the management of ERU. Topical and systemic steroidal and non-steroidal anti-inflammatory drugs and topical mydriatics were the mainstay of the therapeutic armamentarium. In cases of suspected leptospiral infection systemic doxycycline has been used in an attempt to minimize or eliminate recurrent inflammatory episodes. Intracameral injections of tissue plasminogen activator (tpa) have been used in cases of severe anterior chamber exudates. A comprehensive summary of current medical therapies for ERU has been published recently (Dwyer 2005).

Despite constant improvement of medical therapies over the years, the long-term prognosis for ERU remained guarded to poor.

It was therefore a significant step forward, when Werry and Gerhards introduced a novel surgical therapy for ERU almost 20 years ago (Werry 1991; Werry and Gerhards 1992).

Pars Plana Vitrectomy (PPV)

For more than 25 years PPV (Becker, Harsch et al. 2003) has been used in the management of chronic endogenous uveitis (CEU) in people (Diamond and Kaplan 1978; Diamond and Kaplan 1979; Binder and Freyler 1983; Werry and Honegger 1987; Kloti 1988). The main goal was to improve vision by clearing the media or removing membranes. However, it turned out that PPV in eyes with CEU also altered or diminished the severity as well as the
frequency of attacks (Binder and Freyler 1983). Despite the reported complications (i.e. vitreal haemorrhage, cataract formation, retinal detachment) following PPV an overwhelming majority of the patients were able to switch from rigorous systemic preoperative medication to simple eye drops or no treatment at all (Kloti 1988).

Vitrectomy has been studied in experimental, protein-induced uveitis in rabbits (Kaplan, Diamond et al. 1979; Kaplan, Diamond et al. 1979), but it was not until 1991 that PPV has been described in the management of equine recurrent uveitis (Werry 1991). PPV has since been increasingly employed in the treatment of ERU in Europe (Werry 1991; Fruhauf, Ohnesorg et al. 1998; Gilger 2006). Similar to the human counterpart, the most common complications reported in horses are transient hypopyon, vitreal and/or retinal haemorrhage, retinal detachment, and cataract formation.

In the majority of reported cases in Europe, Leptospira sp. has been identified in serum and diluted vitreous samples. This indicates, that ERU is probably often a sequel of systemic Leptospira infection. The presence of intact Leptospira and specific antibodies in eyes affected with ERU indicates a local antibody production to Leptospira organisms and/or their antigens (Brem, Gerhards et al. 1998; Brem, Gerhards et al. 1999; Wollanke, Rohrbach et al. 2001; Wollanke 2004).

Because of the possible serious complications of PPV, patient selection is of great importance. The diagnosis of ERU is based on the typical signs of acute or chronic uveitis and a documented history of recurrent episodes of acute uveitis. Recent clinical evidence suggests that horses with aqueous humour and/or vitreous samples testing positive for Leptospira sp. should be considered suitable candidates for PPV, while those testing negative should receive alternative therapies (Toemoerdy 2009).

Horses ideally are operated in the quiescent stage of the disease. Because of the trans-pupillary visualization of the vitrectomy probe during the procedure, the optical media (i.e. cornea, anterior chamber, lens) should be as transparent as possible. The pupil should dilate maximally with no or few posterior synechiae. Pre-existing focal cataracts are likely to progress following PPV. In patients with secondary glaucoma, phthisis bulbi, or pre-existing retinal detachment, PPV should not be recommended.

Topical 0.1% dexamethasone drops in combination with Neomycin and Polymyxin B are administered QID beginning one week prior to surgery. Systemic nonsteroidal anti-inflammatory drugs (i.e. vedaprofen, flunixin meglumine) are administered beginning three days preoperatively. The pupil is diluted with 1% atropine drops on the day of surgery. Postoperatively, topical Dexamethasone/Neomycin/Polymyxin B eye drops are continued TID for 2 weeks, and then tapered over another 4 weeks. Systemic NSAIDs are continued for one week (Gilger 2006).

The surgical procedure has been described in detail elsewhere (Gilger 2006). Briefly, a standard two-port PPV is performed in lateral recumbence under general inhalation anaesthesia. After preparation for intraocular surgery the eye is draped and an eyelid speculum is inserted. A limbal stay-suture in the 12 o’clock position is placed for globe manipulation. Using a CO2-laser a first sclerotomy is performed 10 mm posterior to the limbus (Fig. 2&3). The irrigation port is inserted and its footplate sutured to the sclera (Fig. 4&5). Balanced salt solution with 40 mg of Gentamicin added per 500 ml is used as irrigation fluid. A second laser sclerotomy is performed and the vitrectomy probe is carefully inserted and advanced in the direction of the centre of the vitreous (Fig. 6&7). The central and anterior parts of the vitreous can be removed by direct visualization through the dilated pupil (Fig. 8). Indirect opthalmoscopy using a 20 D lens is used to visualize posterior and peripheral parts of the vitreous. Aspiration of vitreous can easily be observed, especially if there are inflammatory materials. The procedure is continued until all turbid vitreal material has been removed. Under continuous irrigation, the vitrectomy probe is removed and the sclerotomy closed (Fig. 9). Subsequently the irrigation port is removed and closed (Fig. 10).
At the end of surgery 20 mg of methyl-prednisolone is injected subconjunctivally in the inferior bulbar conjunctiva.

Possible intraoperative complications include vitreal/retinal haemorrhage and retinal detachment. Maintaining IOP at around 40 mm Hg and using a CO2 laser for the sclerotomies instead of surgical blades or canulas can avoid haemorrhage. Touching the retina should also be avoided as it results in immediate haemorrhage and subsequent detachment (Werry and Gerhards 1991; Werry and Gerhards 1992; Fruehau, Ohnesorg et al. 1998).

Early postoperative complications (less than 3 months) include cataract formation and retinal detachment. Late complications occurring after 3 months include cataract formation as well as recurrence of active uveitis (Fruhau, Ohnesorg et al. 1998; Scott, Haynes et al. 2003).

73% of horses, which underwent pars plana vitrectomy showed no further recurrence of uveitis (Toemoerdy 2009). 22% continued to suffer from recurrent episodes of uveitis. The remaining horses were reported to have experienced only one more episode of uveitis, which was easily controlled with topical anti-inflammatory therapy.

Vitreous samples of every horse were submitted and 78% were positive for Leptospira spp. The most common serovars were L. grippothyphosa, L. copenhageni, L. Bratislava, L. canicola, L. pyogenes and L. Pomona (Toemoerdy 2009).

Of the Leptospira-positive horses, 81% showed no further recurrences after vitrectomy, while of the Leptospira-negative patients 83% had further recurrences (Toemoerdy 2009).

It appears as PPV represents a successful surgical therapy for horses suffering from Leptospira-related ERU, while patients testing negative for Leptospira sp. are poorer candidates for this surgery (Toemoerdy 2009). They may, however, be more suitable candidates for the implantation of cyclosporin-releasing devices (Gilger, Salmon et al. 2006).

Clinical experience would suggest that aqueous humour and/or vitreous samples of horses suffering from ERU should be tested for Leptospira sp., and that the decision to perform PPV should be based on these results.

In another study of 38 cases 5 eyes showed recurrence of uveitis between 10 days and 3 years postoperatively (Fruhau, Ohnesorg et al. 1998). Thirty-three eyes showed no recurrence during a follow-up period of up to 5 years. Vision remained stable in 28 eyes and improved in one eye. The remaining eyes showed marked vision loss as a result of cataracts (3), phthisis bulbi (1), or unknown cause (1). Of the 5 eyes with recurrent uveitis 2 demonstrated marked loss of vision, while 3 maintained preoperative vision.

In an earlier study of 43 eyes post PPV, 42 remained free of recurrent uveitis during the follow-up period of 67 months. 70% of these eyes retained some vision. The most common complication was cataract formation in 19/43 eyes, followed by phthisis bulbi in 6 eyes, and retinal detachment in 4 eyes (Winterberg 1997).

Most veterinary ophthalmologists agree that long-term prognosis for ERU with medical therapy alone is poor. Even aggressive therapy is often insufficient to prevent recurrent painful inflammatory episodes. Cumulative intraocular damage often leads to phthisis bulbi, glaucoma, or loss of vision as a result of cataract formation or retinal detachment.

In selected patients with consenting owners, PPV offers a promising alternative to conventional therapy. A high percentage of eyes show no recurrence of uveitis after PPV. However, a number of postoperative complications may cause visual impairment or blindness. The most common long-term postoperative complication appears to be cataract formation. It is unclear, whether pre-existing lenticular opacities progress despite PPV or if the progression is caused by the procedure. Touching the posterior lens capsule during PPV invariably leads to focal cataracts, which very often progress.

Retinal and vitreal haemorrhage is the most common intraoperative complication. Maintaining a high normal IOP, careful manipulation of the vitrectomy probe, and avoidance of touching the retina usually prevents such complications. Choroidal haemorrhage can be avoided with the use of a CO2 laser instead of a surgical blade.
PPV appears to be a promising method for long-term control of Leptospira-associated equine recurrent uveitis and has certainly changed our approach to ERU in the last ten years.

**Summary**

Equine recurrent uveitis (ERU) has always been and still is an important disease with a significant impact on the horse industry with a prevalence in Europe today of 8% to 10%. It has spurred the development of veterinary ophthalmology in general. The aetiology of ERU remains hotly disputed to this day. It is most probably an autoimmune disease triggered, at least in Europe in the majority of cases by Leptospira sp. The therapy of ERU has evolved over the centuries from various methods of bloodletting to rational medical therapy using mydriatics and steroidal and non-steroidal anti-inflammatory drugs, to surgical therapies, such as vitrectomy or implantation of cyclosporin-releasing devices. In Europe, pars-plana vitrectomy in horses testing positive for Leptospira sp. appears to be the most successful form of therapy today.

**Figures and legends**

Fig. 1: ERU of the right eye: Enophthalmos with protrusion of the nictitans; possibly beginning phthisis bulbi; diffuse corneal oedema and mild aqueous flare; dyscoria with multiple posterior synechiae; cortical cataract.
Fig. 2: The first sclerotomy has just been created using the CO2-Laser.
Fig. 3: The sclerotomy is slightly enlarged with a lachrymal dilator.
Fig. 4: The infusion port has been introduced into the vitreous and is set on continuous irrigation mode.
Fig. 5: The infusion port is anchored to the sclera with 4-0 Vicryl.
Fig. 6: The location of the second sclerotomy is identified 10 mm posterior to the limbus
Fig. 7: The CO2-Laserbeam is creating the sclerotomy for the vitrectomy probe.
Fig. 8: The vitrectomy probe is seen behind the lens. The aspiration port is facing the surgeon for better control of the vitrectomy.
Fig. 9: The vitrectomy probe has been removed and the sclerotomy is closed with a single suture using 4-0 Vicryl.
Fig. 10: The infusion port has been removed and the sclerotomy closed. The conjunctival incisions are closed with 6-0 Vicryl in a continuous pattern.


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