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Indications for vitrectomy in uveitis

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The ability to safely sample and remove the vitreous[21] has constituted a major advance in the diagnosis and treatment of uveitis. The indications, methods, and techniques for the analysis and treatment of the vitreous humor in uveitic disease will be discussed, as well as the indications for therapeutic vitrectomy in non-bacterial panuveitis.

Indications for Diagnostic Vitrectomy

Unlike inflammatory disorders in other parts of the body, which are commonly diagnosed by biopsy, uveitic syndromes are generally diagnosed by history, demographics, and clinical appearance. Definitive diagnosis is limited by our incomplete knowledge of the pathogenesis of many uveitic conditions: about one-third of anterior uveitis is idiopathic in origin, as is about 15% of posterior uveitis[24, 16, 25]. The etiology of most cases of intermediate uveitis likewise remains obscure.

A number of the identified causes of uveitis are infectious. Toxoplamosis and cytomegalovirus retinitis are the most frequent causes of posterior uveitis in the immunocompetent and immunocompromised individual, respectively[16]. The diagnosis of either in most cases is straightforward based on clinical appearance. Other known infectious causes of uveitis include bacteria (i.e. *P. acnes* endophthalmitis), viruses (particularly the herpesvirus family, which are responsible for acute retinal necrosis, progressive outer retinal necrosis, and possibly Possner-Schlossman syndrome[35], fungi, and parasites (such as *Toxocara spp*). The microbial nature of these pathogens frequently allows detection by diagnostic vitrectomy. Among the non-infectious causes of uveitis, the masquerade syndromes of intraocular lymphoma, metastatic disease, and ocular melanoma can be diagnosed from cytopathology obtained by diagnostic vitrectomy.

Diagnostic dilemmas in uveitis can occur as a result of media opacity, precluding observation of characteristic clinical signs. Alternatiavely, unusual clinical presentations of uveitis can sometimes require a more extensive differential diagnosis that may be resolved by a more comprehensive history and clinical examination. Diagnostic uncertainty may also arise when a patient fails to respond to empiric treatment. Any of these situations may be an indication for a diagnostic vitreous tap or vitrectomy. Additionally, two disorders can only be definitively diagnosed by vitreous biopsy: isolated intraocular lymphoma[18] and intraocular Whipple's disease[27]. If either of these entities are on the differential diagnosis for a patient's uveitis, a vitreous biopsy is strongly indicated. Biopsy is, of course, also required for the diagnosis and management of bacterial endophthalmitis[11].

Key words : Vitrectomy, uveitis, diagnosis

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Methods and complications of Diagnostic Vitrecotmy

Informed consent for diagnostic vitrectomy should include a discussion of the necessity for performing the surgery, as well as possible complications. Although the procedure is generally uncomplicated, potential vision-threatening complications include retinal detachment, cataract formation, proliferative vitreoretinopathy, and iatrogenic endophthalmitis.

Preoperative management of non-bacterial endophthalmitis should include aggressive treatment of the intraocular inflammation with topical, peribulbar, or systemic steroids. Numerous studies have suggested that eyes with minimal intraocular inflammation tolerate vitrectomy well[7,8]. Cycloplegics are used preoperatively for patient comfort, to minimize synechiae formation and to maximize preoperative pupillary dilation.

Anesthesia may be peribulbar, retrobulbar, or general. The periocular region is prepped with a providone-iodine solution and the conjunctival fornices are irrigated with dilute providone-iodine. Small volume diagnostic vitreous taps may be performed as an office procedure. For a limited vitreous biopsy, the eye may be entered via the pars plana, 4 mm posterior to the limbus, with a 25 gauge needle attacched to a tuberculin syringe (1 cc). Vitreous is aspirated directly from the mid-vitreous cavity. The amount of sample removed varies with the laboratory examination anticipated, although the vitreous tap is usually limited to about 0.5 ml. Polymerase chain reaction analysis requires only 50–100 ul of fluid. Exclusion of other diagnoses may require more sample than can be acquired by a simple tap: flow cytometry for diagnosis of intraocular lymphoma, for example, usually requires a full vitrectomy in the operating room. For more extensive office diagnostic vitrectomy, a hand-held portable vitrector (i.e. Visitrec, Visitec, Sarasota FL) may be used; however, little literature exists on the relative efficacy of its use compared with a full three-port vitrectomy. For most cases, the authors prefer to perform a traditional three-port pars plana automated vitrectomy, as this technique allows both access to the cortical vitreous and much improved intraoperative control. In cases where an automated vitrector is used, it is helpful to obtain an undiluted core biopsy as the vitrectomy cassette is often too diluted to be useful for diagnostic tests. This can be performed by using the vitrectomy instrument on low suction without infusion until ~0.5–1.0 ml of vitreous is obtained. Air may be infused through the infusion line if unacceptable hypotony is induced. A larger vitreous biopsy specimen may be collected with manual aspiration with a balanced salt solution infusion.

If cultures are to be obtained, the sample should be immediately inoculated into culture media and plates. For cases where intraocular lymphoma is being considered, inoculation of the vitreous into RPMI-1640 medium with cytospin cytology performed on a Millipore filter is a useful technique. Antibody testing of vitreous should include removal of cells by centrifugation or Millipore filter. Samples for polymerase chain reaction should be frozen as rapidly as possible, preferably on dry ice or in liquid nitrogen.

Vitrectomy in chronic uveitis patients is frequently complicated by the presence of a miotic pupil with extensive posterior synechiae and cataract. Posterior synechiae can be lysed using viscoelastic and a Barraquer sweep introduced through the limbus. In more severe cases, introduction of disposable iris hooks or performance of one or more sphincterotomies may be required. Cataract surgery may be performed by a traditional anterior approach (i.e. extracapsular or phacoemulsification technique) or via the pars plana (see therapeutic vitrectomy, below).

Occasionally, endoretinal biopsy is required for definitive diagnosis[12,28]. The biopsy is generally performed at the same time as a core vitrectomy. The biopsy site should include the junction of normal and diseased retina in order to enhance the likelihood of identifying the pathologic area. Retinal vessels entering the biopsy ares are treated with endodiathermy. Scissors and forceps may be used to excise the biopsy specimen, which can then be removed through the sclerotomy. Endolaser or diathermy is applied around the biopsy site, and the retina is tamponaded with a pneumatic gas or air bubble and appropriate posi-

tioning. The retinal biopsy specimen may then be studied with light or electron microscopy, including immunohistology for the detection of specific antigens.

Postoperative management includes continued aggressive topical and, often, systemic corticosteroids to suppress intraocular inflammation. Proper positioning is essential to maintain retinal tamponade following endoretinal biopsy. Although there is a theoretical advantage to be gained by postoperative treatment with non-steroidal anti-inflammatory medications, no studies to date have shown their efficacy in decreasing inflammation following vitrectomy for uveitis.

Complications of diagnostic vitrectomy for uveitis are similar to those for therapeutic vitrectomy. Incarceration of vitreous in the 25 g needle or the sclerotomy site during a primary biopsy may cause a retinal tear. Although posterior vitreous detachment is frequently encountered during vitrectomy in chronic uveitis (reducing the risk of postoperative rhegmatogenous retinal detachment), indirect ophthalmoscopy must be performed at the conclusion of a diagnostic vitrectomy to rule out a retinal tear. Observed holes or tears should be treated with cryotherapy, endolaser or diathermy immediately. Other complications include postoperative pupillary membranes, transient hypotony, choroidal effusions, or, rarely, transiently increased intraocular pressure. Aggressive treatment of the underlying inflammatory disorder is the mainstay of treatment for most of these complications.

Diagnostic techniques using vitrectomy specimens

There are three classes of diagnostic techniques which can be used for vitreous samples: direct detection or recovery of the pathogen; detection of the host response; indirect detection of the pathogen.

Direct detection of the pathogen relies on either culture of the vitreous fluid or identification of the organism on Gram stain. Except for bacterial endophthalmitis, most intraocular pathogens are difficult to identify or recover by these techniques. Viruses are difficult to culture from the vitreous (due to the presence of low titers and coexisting intraocular neutralizing antibodies) and can only be directly detected by electron microscopy, which has a low yield on vitreous specimens.

Prior to the advent of the polymerase chain reaction monitoring of the host response had been the most widely used application of diagnostic vitrectomy. Analysis of intraocular antibodies relies on the Witmer coefficient method[34] (also known as the Goldmann-Witmer or Witmer-Desmonts coefficient). The technique assumes that an intraocular pathogen will lead to local production of antibody. The Witmer coefficient is calculated using the quotient between the intraocular IgG titer and the serum IgG for both antibodies to the pathogen and a control, non-pathogenic antibody with ELISA or radioimmunoassay. Its sensitivity is relatively high. Published reports suggest a sensitivity ranging between 50 and 80% for the diagnosis of Toxoplasmosis, with a high specificity[1, 6, 4]. Witmer coefficients have also been found useful in the diagnosis of acute retinal necrosis (ARN)[5] and toxocariasis[2]. For other disorders, such as cytomegalovirus in immunosuppressed hosts, however, the sensitivity of the technique is essentially zero[6].

The polymerase chain reaction[29] is an *in vitro* technique for the enzymatic amplification of minute quantities of nucleic acid into analytic amounts. The technique requires knowledge of the sequences to be amplified (typically, pathogen DNA in uveitis). Short DNA oligonucleotides are used as primers to direct the synthesis of DNA copies of the pathogenic DNA using a DNA polymerase enzyme and nucleotide triphosphates as building blocks. The resulting new DNA is separated from the original strand with heat, and the process is repeated. Amplification is exponential (with 2^N copies made in N rounds of amplification). Detection of the amplified DNA is either through separation of the product DNA from starting materials via agarose gel electrophoresis and staining with ethidium bromide, or through blotting of the product and hybridization with a radioactive or enzymatically labeled DNA probe. Ethidium staining has a sensitivity of about 10 ng of DNA, while the hybridization methods are capable of sub-picogram detection. Detection of

single pathogenic molecules has been documented. 30 Typical sensitivity is on the order of 10–50 viral or bacterial genome copies. This is approximately 10 times the sensitivity of culture techniques.

The polymerase chain reaction (PCR) has been used to date in the diagnosis of a number of intraocular pathogens. Most studies have demonstrated sensitivities of ~90% with nearly perfect specificity[9, 3, 17, 35, 6, 30]. However, overly sensitive PCR assays can lead to false positive results, which are of unclear significance. In one study, a single-molecule sensitivity varicella zoster (VZV) assay demonstrated positive results in seven patients with non-varicella disease[30]. Whether this represented detection of latent virus or contamination of the assay with exogenous VZV DNA is unclear. False negative results are also possible with PCR. Several groups have reported the presence of inhibitors to PCR in the vitreous[22]. These can be removed either by purifying the DNA from the vitreous using commercially available micro-DNA extraction kits or diluting the vitreous prior to performing PCR. Correct interpretation of PCR results requires the performance and analysis of multiple positive and negative controls. The results of a PCR assay should never be analyzed in the absence of such data.

Several presumed infectious uveitis cannot be diagnosed with PCR alone. Sensitivity for toxoplasmosis by PCR is only 33–50%[1, 31]. Interestingly, in at least one study, there appears to be a complementary relationship between PCR testing and Witmer coefficient testing[1]. Witmer coefficient testing alone was found to have a sensitivity of about 70%, but when combined with PCR testing, achieved a sensitivity of 85%. PCR has not been successfully used to detect histoplasmosis in the presumed ocular histoplasmosis syndrome (POHS).

Conversely, at least one cause of uveitis can be definitively diagnosed only through use of PCR. An unculture able bacillus, *Tropheryma whippelii*, causes Whipple's disease[26]. A molecular marker (the 16S ribosomal RNA gene) was recently identified for this bacterium, and has been used to establish the ocular diagnosis[27], alternatively, a jejunal biopsy can be performed.

The primary uses of PCR in the diagnosis of uveitis are presently two. PCR can be used to screen samples from patients with media opacities for common pathogens in the immunocompromised (cytomegalovirus, herpes simplex, and varicella zoster virus); when combined with Witmer testing for toxoplasmosis, this approach will yield a diagnosis in a large proportion of cases[31]. Second, PCR can be used to screen vitrectomy samples for a variety of pathogens in unresponsive or atypical uveitis, such as P. acnes endophthalmitis[17], Lyme disease[19], tuberculosis[20], and Whipple's disease[27].

Diagnosis of the masquerade syndromes requires special processing of the vitrectomy sample. In analyzing vitreous for the presence of intraocular lymphoma, the sample should be collected in tissue-culture medium (e.g. RPMI 1640), as well as in a large (5–10 ml) primary vitrectomy sample; cytospin and rapid staining should then be performed by a pathologist. Recently, a PCR-based diagnostic assay for intraocular lymphoma (amplifying a common chromosomal breakpoint in B-cell lymphomas) has been presented (Chan, CC, personal communication). Although preliminary results look promising, the long-term sensitivity and specificity of this test for intraocular lymphoma has not been established.

The overall usefulness of vitrectomy in determining a diagnosis in complicated uveitis has not been broadly examined. One study[32] included 28 eyes of 25 patients who were not responding to empiric treatment. The additional information yielded by vitrectomy led to a correct diagnosis in nine of these eyes. Three had an unexpected infectious pathology, while five had neoplastic disease (four with lymphoma, and one with a metastatic malignant melanoma). The advent of PCR may improve that yield substantially, although a consensus has not yet been reached as to the negative predictive value of PCR results.

Indications for Therapeutic Vitrectomy

The general indications for therapeutic vitrectomy in uveitis are three: media opacity (vitreous and/or lenticular) causing significant visual loss; necessity of removal of the vitreous, lens, or lens capsule (i.e. P. acnes postoperative endoph-

thalmitis); cystoid macular edema (CME) unresponsive to medical treatment. Medically unresponsive CME and marked secondary uveitic cataract with extensive posterior synechiae and vitritis are probably the two most common indications for therapeutic vitrectomy at present. Vitrectomy is also used to treat retinal complications of uveitic disease such as tractional retinal detachment or macular pucker.

As noted above, a detailed discussion of the risks and benefits of therapeutic vitrectomy for uveitic disease needs to be carried out with the patient prior to surgery. Visual outcomes for pars plana lensectomy seem to be more related to the degree of ocular damage from the uveitic process than to the specific technique used for cataract extraction. For example, in a recent metanalysis, 37/39 uveitic patients were observed to have improved vision following lensectomy, but only 10 of these patients had final best corrected acuity greater than or equal to 20/40[23]. Patients' expectations need to be adjusted accordingly. The risks of surgery are identical to those discussed above for diagnostic vitrectomy.

Methods of Therapeutic Vitrectomy

A three-port pars plana approach is generally used. An entry site 4 mm posterior to the limbus is used in phakic eyes, and 3.5 mm in pseudophakic eyes. Special attention needs to be given to the periphery of the vitreous base in uveitic vitrectomies, as this is often where fibrovascular membranes are found. Complications are similar to those for vitrectomy for other causes, and include retinal detachment, proliferative vitreoretinopathy and cataract.

Cataract extraction can be performed by extracapular or phacoemulsification methods, or through the pars plana. No consensus exists in the literature indicating the best outcome with either approach. Pars plana lensectomy is performed through combined use of a fragmentation probe and the vitrector, the lens can be emulsified and aspirated in situ[7,8]. Several authors advocate selective retention of the anterior capsule for placement of a ciliary sulcus posterior chamber secondary lens implant, but the outcomes and complications of this technique in uveitic eyes have not been studied. Although there is no published data suggesting inferior outcome in uveitic cataracts with the use of foldable silicone or acrylic intraocular lenses, standard practice has advocated use of large one-piece polymethylmethacrylate (PMMA) lenses. There is some debate as to whether intraocular lenses should routinely be placed in the capsular bag or in the ciliary sulcus, in the latter position, there is a theoretically decreased incidence of postoperative synechiae as PMMA is minimally adhesive to the iris.

Outcome of Therapeutic Vitrectomy

Relatively few studies have addressed the long-term results of therapeutic vitrectomy for uveitis. In one retrospective study[15], the results of 28 vitrectomies (with and without lensectomy) in several different causes of uveitis were examined. Visual acuity was found to improve in 83%, with 57% of eyes achieving vision of 20/80 or better. Seven of the 18 eyes undergoing vitrectomy alone developed visually significant cataracts; other complications included postoperative CME in one eye and traction retinal detachment in three. Intraocular inflammation was markedly decreased postoperatively, allowing tapering or withdrawal of corticosteroid medication in 22 of the 28 eyes. A second retrospective study of 25 eyes undergoing therapeutic vitrectomy for patients with severe vitreous clouding, macular pucker, or failure to respond to medical treatment demonstrated similar results[33]. In this study, vision was improved in 56% of eyes, and macular edema resolved in 40%. Macular pucker, however, was completely eliminated in only one of the six patients in whom it was treated. 44% of the eyes were weaned off all anti-inflammatory medications. Anecdotal reports of the use of vitrectomy in the treatment of refractory uveitis are promising; however, a prospective clinical trial needs to be performed before widespread use of vitrectomy for refractory uveitis can be placed on a sound scientific footing.

The use of vitrectomy for the treatment of CME has been explored. Fung[13] prospectively studied the role of therapeutic vitrectomy in 136 surgically aphakic eyes with CME. Eyes randomized to surgery had a significantly better visual outcome

than control eyes. However, eyes with preoperative vision of 20/80 or better improved spontaneously in a substantial number of cases. In a recent retrospective study, Harbour et al[14]. studied 24 consecutive eyes undergoing pars plana vitrectomy for medically unresponsive pseudophakic cystoid macular edema. Vision improved from a mean of 20/190 preoperatively to 20/52 postoperatively, with improvement noted in all eyes and a mean improvement of 4.7 lines. Dugel et al.[10] Retrospectively studied 11 eyes nine patients with medically unresponsive non-pseudophakic and non-aphakic CME (i.e., CME secondary to ocular inflammation) who were treated with core vitrectomy. Seven of the 11 eyes were noted to improve by four or more lines of vision in the first four weeks; however, in this study, 18% of eyes actually worsened following vitrectomy. CME was noted to improve by both clinical examination and fluorescein angiography in 9 of the 11 eyes. Although the latter two studies were retrospective, there is strong indication that therapeutic vitrectomy may have a specfic role in patients with medically intractable CME, eitheraphakic/pseudophakic or inflammatory.

Summary

Vitrectomy has an important role in the diagnosis and management of uveitis. Diagnostic vitrectomy combined with PCR can significantly improve diagnostic yield in otherwise idiopathic uveitis, and can frequently make a diagnosis in cases complicated by media opacity or other features that make traditional exam-based diagnosis difficult or impossible. Therapeutic pars plana vitrectomy provides a means for simultaneously treating uveitis-induced cataract, as well as vitreous media opacities, and perhaps, CME. Future clinical studies should explore both the use of vitreous diagnostic procedures to influence clinical outcome, as well as prospectively the effect of therapeutic vitrectomy in chronic uveitis.

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