Ocular Surface Disease in the Asia-Pacific

Ocular surface disease is more prevalent in underdeveloped nations in Asia, partly due to a higher prevalence of nutritional deficiencies such as vitamin A deficiency that causes xerophthalmia, a major cause of childhood blindness. Another condition that is common in Asia is pterygium, in which an abnormal overgrowth of conjunctiva invades the cornea causing scarring and blindness.

The leading causes of blindness and visual impairment in the world today are:

1) Cataract (senile clouding of the human lens)
2) Glaucoma (high pressure in the eye causing nerve damage)
3) Trachoma (eye infection from bacterial chlamydial infection)
4) Xerophthalmia (Vitamin A deficiency)

Although cataract and glaucoma are the two leading causes of world blindness, the next two major causes of blindness, trachoma and xerophthalmia, together represent a large proportion of blindness today through the damage each can cause to the surface of the eye. Ocular surface diseases may damage the surface of the cornea (the clear front window of the eye) or the conjunctiva (the epithelial surface covering the rest of the eyeball). Clouding or opacification of the cornea in turn results in visual loss. Ocular surface disorders may be due to infections such as trachoma (a chlamydial bacterial infection), chemical or thermal surface injuries of eye, or to intrinsic or autoimmune diseases such as Stevens Johnson syndrome (Figure 1) or ocular cicatrical pemphigoid.

Figure 1: An eye blinded by Stevens Johnson syndrome as an unexpected adverse reaction to a medication given for the relief of pain. (Both eyes were similarly affected.)

Figure 2: An advanced pterygium that has grown over the front of the eye causing blindness.

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Ocular surface disease is more prevalent in underdeveloped nations in Asia, partly due to a higher prevalence of nutritional deficiencies such as vitamin A deficiency that causes xerophthalmia, a major cause of childhood blindness. Another condition that is common in Asia is pterygium, in which an abnormal overgrowth of conjunctiva invades the cornea causing scarring and blindness (Figure 2).

Although prevention of blindness by means of antibiotics, and improvements in nutrition and hygiene should be a major focus in the prevention of corneal blindness, the mainstay of restoring vision to those already blind from corneal disease is corneal transplantation, in which vision is restored by transplanting a healthy, clear cornea from a cadaveric donor. An inherent problem however is lack of donor availability that is severe in Asia, and also exists even in developed countries. This limits the overall effectiveness of transplant programs to reduce the significant impact of corneal blindness in this part of the world.

In addition, conventional corneal transplantation has a uniformly poor success rate for ocular surface diseases, and we are only now beginning to understand why this is so. We now know that the epithelial surfaces of the eye, which have a constant cell turnover, rely on specific adult epithelial stem cells for regeneration and survival of the ocular surface, and these are located either at the periphery of the cornea, an area known as the limbus (which is not transplanted in conventional corneal transplantation), or are located high in the upper lid crevice (fornix) in the case of stem cells of the conjunctiva.

Scientists working in this area are now investigating the source of ocular epithelial stem cells. Limbal stem cell transplantation is now a treatment option for ocular surface disorders. At the Singapore National Eye Center, corneal specialists have pioneered new surgical techniques for limbal stem cell and ocular surface transplantation for the treatment of ocular surface disorders such as chemical burns and Stevens Johnson syndrome. Other ophthalmic centers in Taiwan and Japan are also leaders in this field. In addition, researchers in these institutes have pioneered the technique of ex-vivo stem cell expansion, and a few Asian institutes today now have the ability to clonally expand limbal stem cells in the laboratory. These are cultured onto human amniotic membrane, and retransplanted into the eyes of patients with limbal stem cell deficiency. At the Singapore Eye Research Institute, a stem cell laboratory has recently developed this technology and now patients are undergoing innovative cultured stem cell transplantation procedures which may ultimately reduce the impact of visual disability from ocular surface disorders.

Of all ocular surface disorders in Asia, pterygium is the most prevalent disorder, and has been linked to chronic sun or ultraviolet exposure. The exact pathogenesis and pathophysiological processes occurring in this disorder, in which gradual invasion of altered conjunctiva onto the cornea causes corneal scarring and irregular astigmatism, are still largely unknown. Simple excision of the lesion from the cornea is frustrating, as aggressive recurrence of the lesion may occur in up to 60 percent of cases, and complex ocular surface transplantation procedures are currently the mainstay of treatment. New insights into the molecular basis of pterygium are beginning to emerge however.

This issue reports on the first series of studies exploring the molecular and genetic basis of pterygium, utilizing DNA microarray chip technology to screen for genes implicated in this disorder. Understanding the molecular basis for pterygium occurrence and recurrence is the first stage towards the development of directed treatments or preventive measures for this common condition in the Asia-Pacific.

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Ocular Surface Stem Cells — Current Concepts & Implications

Stem cells are responsible for the ultimate cellular replacement and tissue regeneration in all self-renewing tissue. Stem cells comprise a small proportion of the total tissue and are a population of undifferentiated cells that have a high capacity for proliferation and self-maintenance, have a long life span, and are slow cycling. Stem cells give rise to their progeny, the transient amplifying cells, which are able to undergo several rounds of cell division. These ultimately divide to form post-mitotic, terminally-differentiated cells, which express the final functional characteristics of the tissue.

Much of the stem cell research in ophthalmology has been focused on the ocular surface, which is the external, visible surface of the eye. The ocular surface is divided anatomically into the cornea, limbus, and conjunctiva, the limbus being a narrow band separating the clear cornea from the conjunctiva (white of the eye). The conjunctiva consists of bulbar, fornical and palpebral conjunctiva, (lining the front of the eye, the eyelids and the deep recesses behind the upper and lower lids respectively). The epithelium covering the ocular surface comprises two main epithelial cell types — the corneal and conjunctival epithelium. Among all epithelia in the human body, corneal epithelium is unique. It is stratified, non-keratinised and highly differentiated. It plays a crucial role in maintaining the transparency and clarity of the optical surface. Current evidence points towards the limbus, a narrow 1.5—2mm band of tissue straddling the cornea and the conjunctiva, as being the site of the corneal epithelial stem cells.

A centripetal movement of the basal cells of the limbus (the putative corneal stem cells) results in the repopulation of the cornea in times of injury. Because cornea and limbus are intrinsically different in theirstromal components, the gradual differentiation from the limbal epithelium to the central corneal epithelium may be modulated by the underlying mesenchymal, vascular and neuronal elements in their respective stroma.

The conjunctival epithelium, now believed to be of a distinct lineage from the corneal epithelium, consists of a stratified squamous epithelium interspersed with mucin-secreting goblet cells. It plays a vital role in maintaining the integrity of the ocular surface and stability of the tear film. Fornical epithelial cells have been found to contain more slow-cycling cells, detected as label-retaining cells, that display a greater in vitro proliferative capacity than bulbar or palpebral conjunctival epithelial cells. This points towards the fornical zone being the area enriched in conjunctival epithelial stem cells.

Previous studies have demonstrated that goblet and non-goblet epithelial cells arise from a pluripotent precursor cell. As such, the fornical conjunctiva appears to play a major role in the maintenance and regeneration of the conjunctival epithelium.

Loss or damage of the ocular surface stem cells, such as in limbal stem cell deficiency, can arise from hereditary conditions (e.g., aniridia — a genetically determined ocular abnormality that is characterized by ocular surface abnormalities as well as absence of the iris), or more commonly, acquired conditions (e.g., chemical injuries and putative auto-immune disorders such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid). Clinically this results in conjunctivalization of the cornea, as well as recurrent epithelial defects, vascularization, scarring, ulceration and melting. Limbal stem cell transplantation has proven to be effective in the treatment of these conditions, by providing a new source of epithelium for the diseased ocular surface. More recent techniques include the transplantation of autologous cultivated limbal epithelial cells as a method for reconstructing the ocular surface.

Stem cell research, especially related to ocular surface disorders is being actively pursued in the Singapore Eye Research Institute in conjunction with the Stem Cell Group of Singapore General Hospital.
Infective endophthalmitis is a virulent, severe and sight threatening ocular inflammation. There are two main types, exogenous and endogenous. (Table 1)

Exogenous infective endophthalmitis can occur after any intraocular surgery or penetrating trauma to the eye. Patients usually present with acute ocular symptoms. A history of trauma or recent surgery can be elicited. Although rare, endophthalmitis can occur after any type of intraocular surgery, e.g., cataract surgery, glaucoma surgery, corneal transplantation, etc. The main symptoms are decreasing vision, pain, redness and eye swelling. Ocular examination will reveal a red and swollen eye. Hypopyon (pus in the anterior chamber) and vitreous haze are usually present indicating on-going intraocular inflammation (Figure 1).

Exogenous endophthalmitis is an ocular emergency and requires prompt medical attention and usually hospital admission. The main aim of therapy is to identify the infecting organism and commence the use of appropriate antibiotics as soon as possible. Vitreous and aqueous specimens from the affected eye are sent for microbiological analysis. This is followed by intravitreal injection of antibiotics. Fortified topical antibiotic therapy will also be required.
Infective endophthalmitis can be classified into two categories: exogenous and endogenous. Exogenous endophthalmitis occurs following intraocular surgery or after penetrating ocular trauma, while endogenous endophthalmitis arises from blood-borne spread to the eye from a remote primary source elsewhere in the body.

Common causative organisms include Coagulase-negative Staphylococci, Corynebacterium, Staphylococcus aureus and Streptococcal species. These organisms usually arise from the patient’s periocular tissues such as the conjunctiva, eyelids and eyelashes.

Exogenous endophthalmitis after penetrating eye injuries can progress rapidly especially if the organism is Bacillus cereus. This is an extremely virulent bacterium that can cause extensive damage to the retina very quickly if treatment is delayed. Thus urgent medical attention is mandatory. Surgery may be required to manage associated ocular problems such as retained intraocular foreign bodies, traumatic retinal detachment and corneoscleral lacerations.

Endogenous infective endophthalmitis results from blood-borne spread to the eye from a remote primary source elsewhere in the body. Patients may have predisposing medical conditions such as diabetes mellitus or may be immunosuppressed. The clinical presentation is quite similar to that of exogenous endophthalmitis although it can be subtler, thus a high index of suspicion is required. Furthermore, patients may present initially with only systemic symptoms such as fever and malaise. The common sources of infection include infections arising from the gastrointestinal (especially liver abscesses), genitourinary and cardiac systems.

An imperative in the management of endogenous endophthalmitis is to find the primary source of infection and to identify the causative organism. This involves blood, urine and other appropriate cultures. Radiological investigations may be necessary in certain cases for example, liver or renal abscesses. Intravenous antibiotics are the mainstays of treatment and roles of intravitreal antibiotics and vitrectomy are evolving and are more widely accepted as therapeutic modalities. The common causative organisms are Klebsiella, Staphylococcus and Streptococcus species of bacteria. Fungi may also be isolated especially in immunocompromised patients (e.g., on immune therapy after organ transplantation or in those suffering from AIDS). The visual prognosis is usually very guarded.

In summary, infective endophthalmitis is an important ocular emergency that requires prompt diagnosis and treatment by the physician. A high index of clinical suspicion is required so that immediate treatment can be instituted in afflicted patients and vision hopefully salvaged.

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Polymerase Chain Reaction (PCR) as a rapid diagnostic test for the identification of microorganisms causing serious ocular infections

In severe eye infections such as infective endophthalmitis and keratitis (infective corneal ulcers), the conventional techniques used for the identification of pathogenic microorganisms are based on the culture of the causative agents on selective agar media, followed by biochemical analyses using characteristics pertinent to the microorganisms involved. These methods are able to provide the identity of the pathogens up to the species level.

However, it is often necessary to take at least one day (for bacteria) or longer (for fungi and some fastidious bacteria) to obtain the results, even by using available commercial identification kits. As the identity of the pathogen is crucial in planning definitive treatment for the patient, a rapid method to identify the causative organism is desired. The molecular technique PCR has been evaluated in the diagnosis of several infectious diseases in recent years.

PCR is a molecular technique that utilizes the ability of enzymes to amplify DNA from small amounts of clinical specimens. On an average, more than one million-fold amount of DNA could be obtained with just thirty cycles of PCR amplification. This method has been used widely not only in basic research but also in clinical applications.

Owing to its high specificity and sensitivity, PCR is extremely useful for the detection of fastidious microorganisms, i.e., those organisms that either require very stringent conditions to grow, or microorganisms that require long incubation times. With the advance in technology, PCR machines today are more efficient and reliable. A single PCR reaction will be able to yield results usually within 4–6 hours. This detection time is really rapid considering that the time required just to grow the microorganism is several times longer.

The latest addition to the PCR family is real-time PCR, which not only is able to do everything that a normal PCR can do, but also provides quantitative analysis of the target genes in the clinical sample.

The Department of Ophthalmology at the National University of Hospital (NUH), in conjunction with the Singapore Eye Research Institute and the Singapore National Eye Center has a research team involved in developing PCR as a rapid diagnostic test for serious eye infections.

Supported by a grant from the National Medical Research Council (NMRC), the principal investigators of this study are Dr. Chan Tat Keong, consultant in the Department of Ophthalmology, NUH and Dr. Song Keang Peng from the Department of Microbiology, National University of Singapore. Some of the microorganisms that have been targeted and studied include Propionibacterium acnes, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumonia, Candida spp and Aspergillus fumigatus.