PhotoQuiz

What do these pictures show? What is the likely cause?

A  B  C  D

Please send your entries to: cmeneuletter@snec.com.sg or fax to (65) 6226 3395 Attention: Ms Chia Hui Yien
All winners will be notified by post and the answers will be published in the next issue.
Choroidal Neovascularization

Work on Primates

presented by Dr Lee Shu Yen on 22 Jan 2003

Our doctors on Overseas Fellowship Training in 2003

Dr Edmund Wong was on overseas fellowship training with the Joslin Diabetes Centre from 1 August 2002 to 31 July 2003. This centre conducts laboratory and clinical research in ophthalmology, genetics, epidemiology, metabolism, islet cell transplantation and cell biology. Their pioneering work included the development of protocols in laser photoocoagulation. One of their studies, the effects of perfusion injury and disease protocols enabling women with diabetes to safely have babies. More recently they demonstrated the role of VEGF in diabetic eye disease.

At the diabetes centre, the main supervisor was Dr LP Antio. Apart from clinical work, Dr Wong was involved in research training. The fellowship also included surgical vitreoretinal opportunities. Calls as first-on-call covered the Lombardi area of Boston. During clinics, the importance of history taking was often stressed including asking about the occupation of the patient. Clinical findings were carefully documented and a treatment plan was formulated. He assisted in patient recruitment and evaluation, specimen collection and processing, and protocol writing.

Among research activities, the use of topical neoplastic and its inhibitory effect on subretinal leakage was investigated in animals. He learnt research techniques including retinal endothelial cell, RPE and pericyte cell culture and performing VEGF assays on ROP specimens. There was also a data club involving pre-publication data under Dr George King. Current research topics encompass a wide range of topics including anti-angiogenicity, anti-angiogenesis and anti-proliferation treatments. At the Joslin Diabetes Centre, current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King. Current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture, and having a core group of committed people seem much more important than the equipment. Time for getting to know your new colleagues is as important as the equipment. Goniotomy, the least invasive, was also a data club involving pre-publication data under Dr George King.
years ago. The tube of the VP shunt could still be felt behind her right ear and the scalp scar was seen on careful examination. The diagnosis was post papilloedema optic atrophy. Retrospective review of the CT scans showed the tip of the VP shunt in the lateral ventricles.

Our third and fourth cases were cases with bilateral swollen discs. These cases were discussed to illustrate how management can be complicated by the patients’ other systemic problems, and may sometimes require a multidisciplinary approach.

**Patient 4** was a 56 year old Chinese man with a past medical history complicated by the patient’s other systemic problems, and may sometimes require a multidisciplinary approach. He was cleared of recurrence on MRI and CT scans prior to being referred to us for diplopia of 1 month duration. He had no headache or vomiting. His vision was good but his pupils were sluggishly and mid-dilated. His colour vision and visual fields were normal. A mild sixth nerve palsy was noted and bilateral swollen discs were seen (Fig 4a). MRI of the brain showed left transverse venous thrombosis and a torcular dural lesion with the appearance of a meningioma (Fig 4c). There was no hydrocephalus. A diagnostic and therapeutic LP (opening pressure 33cmH2O) was performed and diazox was given to reduce the ICP with improvement of symptoms and a decrease in the disc swelling in both eyes (Fig 4b). Our diagnostic problem was whether the meningioma-like dural lesion involving the torcular was the cause of the transverse venous thrombosis, or whether this dural lesion was a metastatic lesion. Our management challenge was that despite the chronic papilloedema, he had good optic nerve function. After discussion with neuroradiologist, neurosurgeons, oncologist and the patient, we decided to watch for further deterioration before offering a more permanent solution of a VP shunt as we thought that the lesion was unlikely to be a metastatic lesion.

**Patient 5** was shown to illustrate the importance of examining for multiple cranial nerve involvement to help localize the pathology. Our patient, a middle aged Chinese man, presented with diplopia from a fourth nerve palsy. He was also found to have loss of hearing (vestibular nerve abnormality) but had no other cranial nerve involvement. A CT scan showed a large acoustic neuroma as the cause of the fourth nerve palsy (Fig 5), and he was referred to the neurosurgeons for excision. A CT scan showed a large acoustic neuroma as the cause of the fourth nerve palsy (Fig 5), and he was referred to the neurosurgeons for excision.

Currently phase 3 has been completed and subretinal injection was the only route of delivery which was found to result in uptake of a recombinant virus with subsequent expression of the associated protein (green fluorescent protein). The primate model is currently being considered for further studies on CNV as well as diabetes and myopia.

**Key Learning Points**

- **Choroidal neovascularization can be induced effectively by a diode laser in monkeys.**
- **Subretinal injection of recombinant virus results in uptake and expression of the associated genetic material.**
- **The primate model of retinal disease could be considered for further studies on other retinal diseases.**

**Novel Therapeutic Approaches in the Treatment of Diabetic Retinopathy**

Presented by Prof Lloyd Paul Aiello on 5 February 2003

Diabetic retinopathy (DR) is a spectrum of disease ranging from mild retinal changes with no visual deterioration to blinding disease. Recently, laser treatment has tremendously reduced the rate of visual loss. However, DR is still a major cause of loss of vision. Current laser treatments are not ideal and destroy the retina resulting in visual field loss and nyctalopia. Therefore novel approaches are being sought aiming for the following targets:

- **Prevention of the development of PDR**
- **Preventing the onset or progression of macular oedema**
- **Preventing the progression of NPDR**

Retinal ischaemia as well as multiple growth factors (e.g. VEGF, GH, IGF, TGF, HGF PDGF, TFG) have been identified as potential causes of the various complications seen in DR. Blocking them may prevent complications even in the face of ongoing retinal ischaemia.

**Key Learning Points**

- A careful history is important
- Management may be complicated by the patient’s other systemic problems and may require a multidisciplinary consult
- Importance of multiple cranial nerve examination to localize pathology
Vascular Endothelial Growth Factor (VEGF) is a protein which induces new vessel growth and vascular leakage. Its levels are increased by hypoxia and high levels have been found in diabetic patients with new vessel growth and macular oedema. A special molecule to inhibit VEGF was recently produced and used in a mouse model of proliferative diabetic retinopathy (PDR) with significant reduction in neovascularisation. Macugen (an intravitreal aptamer-chemically synthesized short strands of RNA) (phase 2 trials) and rhuFab V2 (monoclonal anti VEGF antibody fragment) are 2 VEGF inhibitors currently being investigated. The use of Macugen requires 6-weekly repeat intravitreal injections. RhuFab is also intravitreally injected (every 4 weeks) and may be expected to reduce proliferation.

Can we prevent the retina from secreting growth factors (GF)? Steroids can decrease mRNA stability and alter the transcriptional regulation of VEGF. Sustained release implants and slow release bidegradable implants have been tried. However, they have considerable side effects including increased risk of cataract and raised IOPs.

Even if the GF binds to the receptor; can we influence the resulting cellular transduction cascades? When VEGF binds to its receptor, intracellular pathways including protein kinase C (PKC) are activated. PKC is one of a family of serine-threonine kinases and is involved in basement matrix protein synthesis, activation of leukocytes, cytokines, endothelial cells, smooth muscle contraction, endothelial permeability and angiogenesis. Hyperglycaemia activates PKC by various ways including the diacyl glycerol (DAG) pathway. So far, it has been shown using transgenic animals in a mouse model that producing too much PKCβ in the retina causes increased neovascularisation in the retina. Knockout (KO) PKC animals appear normal and demonstrate a reduction of neovascularisation. Overexpressing non diabetic mice show changes of diabetic retinopathy including microaneurysms and pericyte loss. Some possible ways to inhibit PKC include:

- High dose Vitamin E
- Specific PKC inhibitors

Inhibiting DAG kinase by high dose Vitamin E has been demonstrated and larger clinical trials are in the planning stage. Recent concerns with adverse effects with Vitamin E though are under investigation. Ly333531 is one very specific PKC inhibitor and can be taken orally once a day. It inhibits diabetes induced retinal blood flow changes, including ischaemia, retinal neovascularisation and vascular permeability in animals. Phase IIb studies showed no change in diabetic control and good safety and tolerability. There was a dose dependent normalization of retinal blood flow. It was well tolerated over 30 months of treatment, but in the dose used did not significantly reduce retinopathy progression. However, using it appeared to reduce moderate visual loss by 30% and progression of macular oedema although the final results are not yet known.

In conclusion, advances in the mechanistic understanding of diabetic microvascular complications are leading to novel therapeutic approaches. Some of these are now in trials. However their actual efficacies still await the results of these trials.

**Optic Nerve Repair & Regeneration**

**Presented by Prof NR Miller**

We were fortunate to have Prof NR Miller with us for the neuro-ophthalmology symposium from 29th September to 4th October 2003.

It has long been thought that a mammalian retina has a very limited regenerative capacity. The retina is supposed to be lost from dying once it has been injured. Even if regeneration could be induced, the resulting axon could not be directed toward its correct target. However, recent experiments seem to indicate otherwise. In general, treatment for optic nerve injury aims to provide neuroprotection (prevention of ganglion cell death after damage) and neurorepair (restoration of nerve function after injury).

After injury, neuronal cells can undergo both necrosis as well as apoptosis. In recent experiments on mice which overexpress bid-2, 100% of retinal ganglion cells survived 1 month after optic nerve crush injury. Bcl-2 protein is thought to promote cell survival by antagonizing the activation of specific cytokine proapoptotic (caspases) that can initiate apoptosis. The role of apoptosis is further demonstrated by the fact that surrounding retinal ganglion cells in monkeys which were not directly injured by trauma also died. In order to prevent apoptosis, we need to eliminate substances that initiate apoptosis (e.g. glutamate, nitric oxide) or provide substances that inhibit apoptosis.

The action of glutamate and its N-methyl-D-aspartic acid (NMDA) receptor is to increase intracellular calcium which leads to apoptosis via caspase and other pathways. Substances which may inhibit glutamate release or block its binding to NMDA and are currently under investigation include memantine, dizolical (MK801), SB203580, NBQX and DNXQ.

Nitric oxide has also been implicated in causing apoptosis. In fact intravitreal injection of nitric oxide synthase (NOS) can cause photoreceptor and ganglion cell death.

Although older patients have a higher risk of glaucoma, the risk of being injured from glaucoma is much higher in a younger patient. Risk not only varies with age but also with gender and race. The incidence of glaucoma is 3 times higher in African Americans as compared to the Caucasian population. Prof Quigley also gave us an insight on the patients for whom he had a lower threshold for starting treatment. Besides the patient with known risk factors such as thinner corneas, positive family history and myopia, he also tended to treat patients who cannot perform reliable fields, one-eyed patients, patients of a lower socio-economic status, patients with other ocular diseases and patients who are non compliant. His threshold for treatment is also dependent on the patient’s attitudes towards the condition. He would tend to treat people who are more worried about the condition progressing as opposed to a patient who is constantly worrying about the side effects of the medications.

He reminded us that before starting treatment, it is important to determine a patient’s baseline pressure from an average of 3 pressures on different days, so that target pressures can be set. Target pressures are also determined by the patient’s risk of field damage and progression.

“Screening should start with the families of glaucoma patients” He also spoke of his experience with a community eye screening project in Baltimore. They found that people with eye diseases, especially glaucoma, access the health care system less frequently. He recommended that screening for glaucoma should start with relatives of glaucoma patients. A first degree relative developing glaucoma is 10 times higher than the normal population.

Prof Quigley believes that smaller diameter discs also have a higher risk of being damaged from glaucoma as they have less reserve. Larger optic discs have more nerve fibres but also have larger cup-disc ratios.

He further believes that glaucoma is at risk of being over-diagnosed as we become over reliant on machines. We should always correlate the patient’s clinical status with the results from a visual field or other investigations such as the HRT. He cautioned against the patient’s knowledge of their disease since often the treatment is associated with 50% more cataract formation and could result in serious side effects (Coleman et al).

He also reminded us that many of our patients are not putting their eye drops despite being given prescriptions for them. The main reason for this failure to understand the disease condition.

He ended the talk by highlighting the public health impact of glaucoma in the US, where glaucoma care costs $1.43 billion/year.

**Key Learning Points**

- Intraocular pressure of 21mmHg is no longer the magic number
- Not all glaucoma patients need to be treated
- Screening should start with the families of glaucoma patients

**Written by Dr Alicia How**

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# Neuro-Ophthalmology

**Presented by Dr Anita Chau, Dr Alvin Fong & Dr Gowan Tan on 20 Oct 2004**

In neuro-ophthalmology, we are often referred to interesting cases that prove to be both a diagnostic and management challenge. A careful history, detailed clinical examination and appropriate neuro-imaging are important in the diagnosis of these cases. During our CME session, we presented 5 cases to illustrate these points.

**Patient 1**

A 63 year old Chinese male with a past medical history of hypertension, adult polycystic kidney and liver disease with a previous left thalamic cerebral vascular accident. He presented with an acute onset of bilateral blurring of vision for one day. Clinically, he had decreased vision of OS 6/18 and VL 6/30 and loss of color vision in both eyes, no relative afferent papillary defect (RAPD), and a left homonymous hemianopia visual field defect. However, inconsistent with the rapid history of onset, he was also noted to have bilateral pale discs. A CT scan showed an acute haemorrhage in the parieto-occipital region (Fig 1a). The patient was referred to the neurosurgeons for further management. But, what was the cause of the patient’s symptoms? A more detailed history was obtained from his daughter who revealed that the patient had sustained a severe head injury at the age of 32 years. When he fell from a height and required emergency surgery performed. Our subsequent diagnosis was bilateral pale discs secondary to previous papilloedema or traumatic optic neuropathy. Retrospective review of the CT films showed a focal defect in left frontal bone possibly due to previous surgery (Fig 1b).

**Patient 2**

A 61 Chinese female with a history of hypertension and diabetes. Her medical history included papilloedema and hypertension. She presented with a first degree relative developing glaucoma 10 years later than the normal population.

Prof Quigley believes that smaller diameter discs also have a higher risk of being damaged from glaucoma as they have less reserve. Larger optic discs have more nerve fibres but also have larger cup-disc ratios.

He further believes that glaucoma is at risk of being over-diagnosed as we become over reliant on machines. We should always correlate the patient’s clinical status with the results from a visual field or other investigations such as the HRT. He cautioned against the patient’s knowledge of their disease since often the treatment is associated with 50% more cataract formation and could result in serious side effects (Coleman et al). He also reminded us that many of our patients are not putting their eye drops despite being given prescriptions for them. The main reason for this failure to understand the disease condition.

He ended the talk by highlighting the public health impact of glaucoma in the US, where glaucoma care costs $1.43 billion/year.

**Key Learning Points**

- Intraocular pressure of 21mmHg is no longer the magic number
- Not all glaucoma patients need to be treated
- Screening should start with the families of glaucoma patients

**Written by Dr Alicia How**

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# Key Learning Points

- Current laser treatment is effective in diabetic retinopathy but associated with side effects.
- Intravitreal injections of Macugen may inhibit vascular endothelial growth factor and retinal neovascularization.
- Protein kinase C inhibitors also show promise in inhibiting diabetes induced retinal vascular changes.

**Written By Dr Por Yang Ming**
inflammation of the lacrimal glands but the extraocular muscles and tendons were normal. The patient was thought to have non-specific orbital inflammation and was treated with high dose intravenous methylprednisolone that was later converted to oral prednisolone and then slowly tapered off. His vision improved to 6/12 in the right but remained 6/10 in the left due to a cataract. Colour vision also improved in both eyes, as did ocular pain and proptosis.

Three months later the patient suffered a relapse of orbital inflammation resulting in eye pain and blurring of vision. The vision in the right eye was now 6/24 and his colour vision had worsened in both eyes again. He was given oral Prednisolone with immediate improvement in vision and reduction of symptoms. Over the next few years, the patient suffered several relapses that caused pain, poor vision, proptosis and limitation of extraocular movements in both eyes. (Fig 1) These episodes responded transiently to oral corticosteroid therapy, only for the condition to flare up again a few months later.

In November 2003, the patient had yet another recurrence of inflammation that caused severe proptosis of both eyes - 27.5mm in the right and 23mm in the left. CT scan of the orbits showed an infiltrative mass around the right optic nerve that had spread to involve the peripapillary fat. (Fig 2) All the extraocular muscles were also enlarged. Biopsy of the mass revealed a polymorphous population of plasma cells, lymphocytes and histiocytes in the presence of abundant fibrous tissue. (Fig 4) The diagnosis of sclerosing orbital inflammation was made and he was promptly treated with oral prednisolone and Methotrexate. This enabled marked improvement in his clinical condition and symptoms, with no recurrences since.

Conclusion

In summary, idiopathic sclerosing orbital inflammation is an uncommon cause of orbital inflammation that is more closely related to desmoplastic processes elsewhere in the body than non-specific orbital inflammation. It is an immune-mediated disease characterized by fibrosis of the orbit with resultant visual loss. This disease is best treated with early aggressive therapy using multiple immunosuppressive agents to prevent visual disability.

Key Learning Points

Idiopathic sclerosing orbital inflammation is:

• an uncommon cause of orbital inflammation that causes blindness through orbital fibrosis
• distinct from non-specific orbital inflammation
• immune-mediated and should be treated with multiple immunosuppressive agents

Management of Glaucoma in the 21st Century

Professor Harry Quigley presented to us his approach to the management of glaucoma in the 21st century. He also highlighted the public health aspects of glaucoma and its impact in the health care sector.

“Our intraocular pressure of 21mmHg is no longer the magic number” Glaucoma is today defined as a slowly progressive disease of the optic nerve with sequential loss of visual field and a typical optic nerve appearance of the optic disc called excavation. Glaucoma is no longer considered to be just a disease that occurs only when the intraocular pressure is more than 21mmHg. Population surveys have shown that up to 25-50% of glaucoma patients have intraocular pressures of less than 21mmHg and intraocular pressures are no longer important in defining glaucoma. He believes that there are other variables which contribute to glaucoma which need to be further studied. These include blood flow of the optic nerve head, optic disc sizes, and connective tissue abnormalities of the optic disc. Professor Quigley also highlighted the importance of a careful examination of the optic nerve head to detect glaucomatous changes as opposed to relying on eye pressures. However, intraocular pressure being the only modifiable risk factor in glaucoma, should be used to determine the severity of the disease and its progression rate.

“Not all glaucoma patients need to be treated” He went on to give examples of when patients should be treated, according to their risks of developing a visual field defect. Based on the Ocular Hypertensive Treatment Study, the risk of an ocular hypertensive subject developing a first field defect is 2% per year. He then brought up the concept of “exposure time”, whereby the lifetime risk of a younger ocular hypertensive patient developing a field defect is much higher than an older one.

Death. On the other hand, systemic inhibition of NOS reduced retinal ganglion cell (RGC) loss in a rat model of retinal ischemia. This mechanism is thought to be involved in the neuroprotective effect of FK506. Brimonidine also exerts neuroprotection, although the mechanism of action is unknown.

Apart from these pharmaceutical agents, nerve growth factors may also protect CNS neurons from death. These include fibroblast growth factor (FGF) and brain derived neurotrophic factor (BDNF). In fact, focal injection of FGF protects ventral horn neurons after injury in rats and intravitreal injections of BDNF were found to increase ganglion cell survival in cats after optic nerve crush injury. Other endogenous protective agents include heat shock proteins. Vaccination with nonencephalitogenic peptides of proteolipid protein or myelin oligodendrocyte glycoprotein has also been shown to increase survival of ganglion cells.

All efforts at increasing cell survival will prove useless unless, however, the disconnected cells can be induced to extend axons towards their proper targets. This process requires an appropriate and ‘permissive’ environment. In most instances, the presence of factors that inhibits growth (eg myelin and oligodendrocyte components) and lack of factors that promote axonal growth make the environment ‘non-permissive’. Strategies to overcome this include the introduction of antibodies against inhibitory components. Growth factors such as fibroblast and nerve growth factor also enhance axonal regeneration. Intravitreal peripheral nerve implants may also induce optic nerve regeneration across a region of crush injury.

At this point, however, no in vivo studies of regeneration have been performed in primates. In vitro, studies have documented the growth of axons in permissive environments. A large number of potential axonal guidance molecules have been identified. These include extracellular matrix, semaphorins, netrins, ephrins and receptor tyrosine kinase ligands. Although their mechanisms of action are not yet elucidated, it has been demonstrated that in rats, regenerating axons preferentially innervate the nucleus of the optic tract and the olivary pretectal nucleus.

Stem cells represent another alternative to optic nerve repair. Some stem cells present in the retina and oligo body of mammalian embryos can be induced to become RGCs. Subsequently, like retinoic acid, these stem cells can cause rat optic nerve formation in vivo. In conclusion, many optic neuropathies ranging from glaucoma to toxic optic neuropathies can potentially be treated with novel approaches in the future. More studies need to be carried out in non-human primates, in particular looking at glutamate inhibitors, introduction of antiapoptotic genes and to test the vaccination hypothesis. We also need to assess the effect of various factors that inhibit or promote growth. Overall, there is little doubt that in the next century, neuroprotection and neurorepair will be used to treat patients for a wide range of conditions.

Key Learning Points

• Current strategies in the treatment of optic nerve trauma aim to provide neuroprotection and possibly in the future, neurorepair.
• Factors which facilitate cellular death and injury include glutamate and nitric oxide while others substances such as memantine, brimonidine and various growth factors exert a neuroprotective effect.
• Neurorepair remains experimental with efforts being aimed at regenerating neural cells as well as directing them in forming the correct neural connections.

A novel treatment for adult amblyopia, hitherto considered untreatable, is now available. Vision scientists have recently reported on the use of the visual neuroscience concept of “perceptual learning” to enhance visual acuity and contrast sensitivity in adult amblyopia. According to A/Prof Donald Tan, results of a randomized controlled trial indicate that perceptual learning could reverse amblyopia and improve visual acuity in adult unilateral amblyopes. This is the essence of NeuroVizion’s innovative Neural Vision Correction (NVC) technology, which is a commercialized, non-invasive, patient-specific computerized treatment, based on perceptual learning and involving visual stimulation and facilitation of neural connections responsible for vision. It has been developed through research focused solely on optimizing performance of the neural or “back-end” of the visual system.

The visual system is classically described as a hierarchy of visual processing stages, starting from light detection and transduction in the eye through several stages of spatial integration to stage for stage receptive fields of increasing complexity. An important stage in image analysis, in the primary visual cortex, includes receptive fields that are sensitive to image contrast that varies in a specific direction on a specific scale. Human contrast sensitivity is best described by the aggregate response of these units.

Recent research points to spatial interactions between oriented receptive fields as an important factor in modulating activity of the corresponding neuronal units. Local contrast sensitivity can be increased or decreased depending on the light distribution within neighboring locations. More specifically, facilitation of oriented contrast detection is obtained by presenting a target flanker stimulus at an optimal distance. Suppression is obtained by presenting the target with more proximal co-oriented flankers. Responses of individual neurons to repeated presentations of the same stimulus are highly variable (noisy). Noise may impose...
Idiopathic Sclerosing Orbital Inflammation

presented by Dr Anita Chan on 14 Apr 2004

Introduction

Idiopathic sclerosing orbital inflammation is a condition marked by insidious, progressive sclerosing inflammation that damages orbital structures through cicatricial entrapment. It is a unique clinicopathological entity that is immune-mediated, and distinct from non-specific orbital inflammation (previously called orbital pseudotumour).

It is an uncommon cause of orbital disease. Rootman et al found that sclerosing orbital inflammation caused 7.8% of all cases of orbital inflammation and 1.4% of all orbital tumours, as compared to 60.8% and 10.9% respectively in non-specific orbital inflammatory disease.

Up to the 1990s, the inflammatory and immune processes of this condition were not well understood and treatment was non-specific. As a result, incomplete response, relapse, and relentless progression with visual disability were common. This changed when the pathophysiology of the disease was elucidated.

Clinical Manifestations

Idiopathic sclerosing orbital inflammation is not a respecter of persons; it can affect children as well as the elderly, and both men and women are equally affected. Patients often present with orbital pain, proptosis, mild conjunctival lid swelling and redness, as well as restriction of extra-ocular movement and ptosis.

A significant number also have visual loss on presentation. The disease may be unilateral or bilateral, with inflammation mainly in the anterior or superolateral orbit, and involvement of the lacrimal gland is common. Only about 20% of patients suffer apical disease without involvement of the anterior orbit. Such patients may have intracranial and bone involvement due to progression of the disease along fat and connective tissue planes. Furthermore, extension into the pterygopalatine fossa and cavernous sinus has been observed.

The differential diagnosis of idiopathic sclerosing orbital inflammation includes inflammatory processes of local and systemic origin e.g. thyroid orbitopathy, tuberculosis, sinusitis, Wegener's granulomatosis and sarcoidosis. Primary and secondary tumours must also be excluded especially metastatic breast, prostatic and colonic carcinomas that are associated with desmoplasia.

Diagnostic Investigations

Characteristic CT scan findings in idiopathic sclerosing orbital inflammation are of a homogeneous enhancing anterior, supero-lateral mass with irregular margins involving the extra-ocular muscles and lacrimal gland and downward displacement of the globe.

Surgical biopsy of the orbital lesion and histopathologic examination are necessary for diagnosis, and the typical findings are a paucicellular chronic inflammatory infiltrate of lymphocytes, plasma cells, histiocytes, occasional neutrophils, eosinophils and nuclear debris within an infiltrative desmoplastic stroma. Fibrosis, being constant in all cases, distinguishes idiopathic sclerosing orbital inflammation from other non-specific inflammatory conditions of the orbit. Interestingly, this histopathologic appearance is more closely related to scleroderma cholangitis, Reidel fibrous thyroiditis, sclerosing mediastinitis and retroperitoneal fibrosis than non-specific orbital inflammation. In fact, some of the patients with idiopathic sclerosing orbital inflammation were found to have sclerosing mediastinitis and retroperitoneal fibrosis as well.

Immunopathological analysis has shown T lymphocyte involvement and cell-mediated immune processes to be responsible for the disease. T cell activation results in the release of a cascade of cell mediators, including platelet derived growth factor and transforming growth factor, so that fibroblast proliferation and collagen synthesis occurs.

Witten by Dr Chau Wei Han

Key Learning Points

- Unilateral adult amblyopia can be treated with NeuralVision Correction, a computerized treatment based on perceptual learning and involving visual stimulation and facilitation of neural connections responsible for vision.

- NeuralVision Correction appears to improve visual acuity in patients with low myopia without changing the refraction.

- Neural Vision Correction treatment is applied in 30-minute sessions, administered 2-3 times a week, with a total of about 20-30 sessions.

Treatment

Previously, a lack of understanding of the pathological process, the absence of specific treatment modalities, and delayed initiation of effective therapy resulted in generally poor visual outcome in most patients. The infiltrative nature of the disease made surgical excision difficult so systemic corticosteroids and radiotherapy was prescribed for treatment. But these modalities were not specific and the condition usually required treatment at an advanced stage of the disease process, after fibrosis has already set in. Hence a poor outcome was not surprising.

Rootman et al proposed in 1994 that earlier introduction of immunosuppressive agents directed at the cell-mediated arm of the immune system would more effectively inhibit fibroblast proliferation and collagen production, reduce fibrosis in the orbit and enable a better visual outcome. Hence, first-line therapy should comprise a combination of either Methotrexate or Azathioprine with systemic corticosteroids, failing which Cyclosporin A would be used in place of Methotrexate/Azathioprine. Cyclophosphamide would be used as a last resort if the former agents failed to adequately control inflammation. Certainly the potential risks associated with the use of these immunosuppressive agents must be made known to the patient before commencement and the patient closely monitored thereafter.

Case Report

A 58 year old Chinese male presented in March 1998 having had bilateral eye pain and blurring of vision for 3 years. He had a visual acuity of counting fingers in the right eye and 6/120 in the left. His colour vision was poor in both eyes but there was no relative afferent papillary defect. There was limitation of abduction and depression of the right eye and the right eye was proptosed by 24mm compared to 19mm in the left. Investigative work-up revealed a normal thyroid function test and MRI of the brain.

A CT scan of the orbit showed diffuse enlargement of the extraocular muscles in both eyes with involvement of the tendons as well. The lacrimal glands were enlarged and both eyes were proptosed. Biopsy revealed mild chronic periarteriitis

A/Prof Tan went on to provide an overview of the NVC treatment. In the first stage, the subject is exposed to a set of visual perception tasks, the aim of which is to analyze and identify each subject’s neural inequalities. The images are presented to the patient on a monitor screen. The patient has to perform visual tasks indicating whether he sees a target arrangement. The indications are made by means of a computer mouse. The treatment system analyzes subject’s performance following which a treatment plan is initialized and subject specificity is achieved by this patient-specific stimuli in a controlled environment.

Each session is designed to train, directly and selectively, those functions in the visual cortex that were diagnosed to be ineffective. At each session, an algorithm analyzes the patient’s responses and accordingly adjusts the level of visual difficulty to the range most effective for further improvement. Between sessions, the progress of the patient is measured and taken into account by the algorithm for the next therapeutic session. Thus, for each subject and individual training schedule is designed based on the initial state of visual performance, severity of dysfunction and progress in therapeutic training.

The treatment is applied in successive 30-minute sessions, administered 2-3 times a week, with a total of about 20-30 sessions.

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Study subjects comprised 10 male and 10 female Asian volunteers with mean age of 32 years (range 19 to 53 years). Twenty-eight out of 34 (82%) eyes showed consistent improvement during treatment. Mean baseline logMAR UCVA was 0.318, and this improved to 0.095 following treatment. Mean refractive error after treatment remained unchanged. Interestingly, eyes with a higher refraction showed greater visual improvement.

Consistent improvement in visual acuity was also observed in the 34 eyes with low myopia occurring at the respective frequencies: at 1.5 cycles per degree (cpd) contrast sensitivity improved from 45 to 75, at 3 cpd from 63 to 100, at 6 cpd from 42 to 95, at 12 cpd from 11 to 45, and at 18 cpd from 4 to 9. No side effects were encountered during treatment.

A/Prof Tan was concluded that early results of this pilot study suggest that NVC treatment is able to improve both visual acuity and contrast sensitivity in low adult myopia. Further follow-up data of this pilot study will evaluate retention rates in visual improvement and enhanced contrast sensitivity function.

Fig 1 Different types of Gabor Patches
Idiopathic Sclerosing Orbital Inflammation

Introduction

Idiopathic sclerosing orbital inflammation is a condition marked by insidious, progressive sclerosing inflammation that damages orbital structures through cicatrization and entrapment. It is a unique clinicopathological entity that is immune-mediated, and distinct from non-specific orbital inflammation (previously called orbital pseudotumour).

It is an uncommon cause of orbital disease. Rootman et al. found that sclerosing orbital inflammation caused 7.8% of all cases of orbital inflammation and 1.4% of all orbital tumours, as compared to 60.8% and 10.9% respectively in non-specific orbital inflammation.

Up to the 1990s, the inflammatory and immune processes of this condition were not well understood and treatment was non-specific. As a result, incomplete response, relapses, and relentless progression with visual disability were common. This changed when the pathophysiology of the disease was elucidated.

Clinical Manifestations

Idiopathic sclerosing orbital inflammation is not a respecter of persons; it can affect children as well as the elderly, and both men and women are equally affected. Patients often present with orbital pain, proptosis, mild conjunctival lid swelling and redness, as well as restriction of extra-ocular movement and ptosis. A significant number also have visual loss on presentation. The disease may be unilateral or bilateral, with inflammation mainly in the anterior or superolateral orbit, and involvement of the lacrimal gland is common.

Only about 20% of patients suffer apical disease without involvement of the anterior orbit. Such patients may have intracranial and bone involvement due to progression of the disease along fat and connective tissue planes. Furthermore, extension into the pterygopalatine fossa and cavernous sinus has been observed.

The differential diagnosis of idiopathic sclerosing orbital inflammation includes inflammatory processes of local and systemic origin e.g. thyroid orbitopathy, tuberculosis, sinusitis, Wegener’s granulomatosis and sarcoidosis. Primary and secondary tumours must also be excluded especially metastatic breast, prostatic and colonic carcinomas that are associated with desmoplasia.

Diagnostic Investigations

Characteristic CT scan findings in idiopathic sclerosing orbital inflammation are of a homogenously enhancing anterior supero-lateral mass with irregular margins involving the extra-ocular muscles and lacrimal gland and downward displacement of the globe.

Surgical biopsy of the orbital lesion and histopathologic examination are necessary for diagnosis, and the typical findings are a paucicellular chronic inflammatory infiltrate of lymphocytes, plasma cells, histiocytes, occasional neutrophils, eosinophils and nuclear debris within an infiltrative desmoplastic stroma. Fibrosis, being constant in all cases, distinguishes idiopathic sclerosing orbital inflammation from other non-specific inflammatory conditions of the orbit. Interestingly, this histopathologic appearance is more closely related to sclerosing cholangitis, Reidel fibrous thyroiditis, sclerosing mediastinitis and retroperitoneal fibrosis than non-specific orbital inflammation. In fact, some of the patients with idiopathic sclerosing orbital inflammation were found to have sclerosing mediastinitis and retroperitoneal fibrosis as well.

Immunopathological analysis has shown T lymphocyte involvement and cell-mediated immune processes to be responsible for the disease. T cell activation results in the release of a cascade of cell mediators, including platelet derived growth factor and transforming growth factor, so that fibroblast proliferation and collagen synthesis occurs.

Case Report

A 58-year-old Chinese male presented in March 1998 having had bilateral eye pain and blurring of vision for 3 years. He had a visual acuity of counting fingers in the right eye and 6/120 in the left. His colour vision was poor in both eyes but there was no relative afferent papillary defect. There was limitation of abduction and depression of the right eye and the right eye was provoked by 24-mm compared to 19-mm in the left. Investigative work-up revealed a normal thyroid function and MRI of sinuses were normal. CT scan of the orbit showed diffuse enlargement of the extra-ocular muscles in both eyes with involvement of the tendons as well. The lacrimal glands were enlarged.

The patient was referred to the National Cancer Centre for treatment. To the patient’s surprise, the patient had to perform visual tasks indicating whether he sees a target arrangement. The indications are made by means of a computer mouse. The treatment system analyzes subject’s performance following which a treatment plan is initialized and subject specificity is achieved by analyzing this patient-specific stimuli in a controlled environment.

Each session is designed to train, directly and selectively, those functions in the visual cortex that were diagnosed to be ineffective. At each session, an algorithm analyzes the patient’s responses and accordingly adjusts the level of visual difficulty to the range most suitable for further improvement. Between sessions, the progress of the patient is measured and taken into account by the algorithm for the next therapeutic session. Thus, for each subject and individual training schedule is designed based on the initial state of visual performance, severity of dysfunction and progress in therapeutic training.

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No side effects were encountered during treatment.

A/Prof Tan concluded that early results of this pilot study suggest that NVC treatment is able to improve both visual acuity and contrast sensitivity in low adult myopia. Further follow-up data of this pilot study will evaluate retention rates in visual improvement and enhanced contrast sensitivity function.

Key Learning Points

• Unilateral adult amblyopia can be treated with NeuralVision Correction, a computerized treatment based on perceptual learning and involving visual stimulation and facilitation of neural connections responsible for vision.

• NeuralVision Correction appears to improve unaided visual acuity in patients with low myopia without changing the refraction.

• Neural Vision Correction treatment is applied in 30-minute sessions, administered 2-3 times a week, with a total of about 20-30 sessions.

Written by Dr Chua Wei Han

Treatment

Previously, a lack of understanding of the pathological process, the absence of specific treatment modalities, and delayed initiation of effective therapy resulted in generally poor visual outcome in most patients. The infiltrative nature of the disease made surgical excision difficult so systemic corticosteroids and radiotherapy was prescribed for treatment. But these modalities were not specific and the disease was usually initiated at an advanced stage of the disease process, after fibrosis has already set in. Hence a poor outcome was not surprising.

Rootman et al proposed in 1994 that earlier introduction of immunosuppressive agents directed at the cell-mediated arm of the immune system would more effectively inhibit fibroblast proliferation and collagen production, reduce fibrosis in the orbit and enable a better visual outcome. Hence, first-line therapy should comprise a combination of either Methotrexate or Azathioprine with systemic corticosteroids, failing which Cyclosporin A would be used in place of Methotrexate/Azathioprine. Cyclophosphamide would be used as a last resort if the former agents failed to adequately control inflammation. Certainly the potential risks associated with the use of these immunosuppressive agents must be made known to the patient before commencement and the patient closely monitored thereafter.

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inflammation of the lacrimal glands but the extraocular muscles and tendons were normal. The patient was thought to have non-specific orbital inflammation and was treated with high dose intravenous methylprednisolone that was later converted to oral prednisolone and then slowly tapered off. His vision improved to 6/12 in the right but remained 6/120 in the left due to a cataract. Colour vision also improved in both eyes, as did ocular pain and proptosis.

Three months later the patient suffered a relapse of orbital inflammation resulting in eye pain and blurring of vision. The vision in the right eye was now 6/24 and his colour vision had worsened in both eyes again. He was given oral Prednisolone with immediate improvement in vision and reduction of symptoms. Over the next few years, the patient suffered several relapses that caused pain, poor vision, proptosis and limitation of extraocular movements in both eyes. (Fig 1) These episodes responded transiently to oral corticosteroids therapy, only for the condition to flare up again a few months later.

In November 2003, the patient had yet another recurrence of inflammation that caused severe proptosis of both eyes - 27.5mm in the right and 23mm in the left. CT scan of the orbits showed an incompressible mass around the right optic nerve that had spread to involve the peripapillary fat. (Fig 2) All the extraocular muscles were widened. Biopsy of the mass revealed a polymorphous population of plasma cells, lymphocytes and histiocytes in the presence of abundant fibrous tissue. (Fig 4) The diagnosis of sclerosing orbital inflammation was made and he was promptly treated with oral prednisolone and Methotrexate. This enabled marked improvement in his clinical condition and symptoms, with no recurrences since.

**Conclusion**

In summary, idiopathic sclerosing orbital inflammation is an uncommon cause of orbital inflammation that is more closely related to desmoplastic processes elsewhere in the body than non-specific orbital inflammation. It is an immune-mediated disease characterized by fibrosis of the orbit with resultant visual loss. This disease is best treated with early aggressive therapy using multiple immunosuppressive agents to prevent visual disability.

**Key Learning Points**

**Idiopathic sclerosing orbital inflammation is:**

- an uncommon cause of orbital inflammation that causes blindness through fibrotic process
- distinct from non-specific orbital inflammation
- immune-mediated and should be treated with multiple immunosuppressive agents

Management of Glaucoma in the 21st Century

Professor Harry Quigley presented to us his approach to the management of glaucoma in the 21st century. He also highlighted the public health aspects of glaucoma and its impact in the health care sector.

“`Intraocular pressure of 21mmHg is no longer the magic number” Glaucoma is today defined as a slowly progressive disease of the optic nerve with sequential loss of visual field and a typical optic nerve appearance of the optic disc called excavation. Glaucoma is no longer considered to be just a disease that occurs only when the intraocular pressure is more than 21mmHg. Population surveys have shown that up to 25-50% of glaucoma patients have intraocular pressures of less than 21mmHg and intraocular pressures are no longer important in defining glaucoma. He believes that there are other variables which contribute to glaucoma which need to be further studied. These include blood flow of the optic nerve head, optic disc sizes, and connective tissue abnormalities of the optic disc.

Professor Quigley also highlighted the importance of a careful examination of the optic nerve head to detect glaucomatous changes as opposed to relying on eye pressures. However, intraocular pressure being the only modifiable risk factor in glaucoma, should be used to determine the severity of the disease and its progression rate.

Not all glaucoma patients need to be treated” He went on to give examples of when patients should be treated, according to their risks of developing a visual field defect. Based on the Ocular Hypertensive Treatment Study, the risk of an ocular hypertensive suspect developing a first field defect is 2% per year. He then brought up the concept of “exposure time”, whereby the lifetime risk of a younger ocular hypertensive patient developing glaucoma is higher than an older one. Death. On the other hand, systemic inhibition of NOS reduced retinal ganglion cell (RGC) loss in a rat model of retinal ischemia. This mechanism is thought to be involved in the neuroprotective effect of RGS6. Brimonidine also exerts neuroprotection, although the mechanism of action is unknown.

Apart from these pharmaceutical agents, nerve growth factors may also protect CNS neurons from death. These include fibroblast growth factor (FGF) and brain derived neurotrophic factor (BDNF). In fact, focal injection of FGF protects ventral horn neurons after injury in rats and intravitreal injections of BDNF were found to increase ganglion cell survival in cats after optic nerve crush injury. Other endogenous protective agents include heat shock proteins. Vaccination with nonencapsulated peptides of proteloid protein or myelin oligodendrocyte glycoprotein has also been shown to increase survival of ganglion cells.

All efforts at increasing cell survival will prove useless unless, however, the disconnected cells can be induced to extend axons towards their proper targets. This process requires an appropriate and ‘permissive’ environment. In most instances, the presence of factors that inhibits growth (eg myelin and oligodendrocyte components) and lack of factors that promote axonal growth make the environment ‘non-permissive’. Strategies to overcome this include the introduction of antibodies against inhibitory components. Growth factors such as fibroblast and nerve growth factor also enhance axonal regeneration. Intraocular peripheral nerve implants may also induce optic nerve regeneration across a region of crush injury.

At this point, however, no in vivo studies of regeneration have been performed in primates. In vitro, studies have documented the growth of axons in permissive environments. A large number of potential axonal guidance molecules have been identified. These include extracellular matrix, semaphorins, netrins, ephrins and receptor tyrosine kinase ligands. Although their mechanisms of action are not yet elucidated, it has been demonstrated that in rats, regenerating axons preferentially innervate the nucleus of the optic tract and the olivary pretectal nucleus.

Stem cells represent another alternative to optic nerve repair. Some stem cells present in the retina and olary body of mammalian embryos can be induced to become RGCs. Substances like retinoic acid can cause downregulation of the stage forming receptive fields of increasing complexity. An important stage in image analysis, in the primary visual cortex, includes receptive fields that are sensitive to image contrast that varies in a specific direction on a specific scale. Human contrast sensitivity is best described by the aggregate response of these units.

Recent research points to spatial interactions between oriented receptive fields as an important factor in modulating activity of the corresponding neuronal units. Local contrast sensitivity can be increased or decreased depending on the light distribution within neighboring locations. More specifically, facilitation of oriented contrast detection is obtained by presenting a target flanked by light stimuli. Intensity contrast stimuli at an optimal distance. Suppression is obtained by presenting the target with more proximal co-oriented flankers.

Responses of individual neurons to repeated presentations of the same stimulus are highly variable (noisy). Noise may impose
Vascular Endothelial Growth Factor (VEGF) is a protein which induces new vessel growth and vascular leakage. Its levels are increased by hypoxia and high levels have been found in diabetic patients with new vessel growth and macular oedema. A special molecule to inhibit VEGF was recently produced and used in a mouse model of proliferative diabetic retinopathy (PDR) with significant reduction in neovascularization. Macugen (an intravitreal aptamer-chemically synthesized short strands of RNA) (phase 2 trials) and rhuFab V2 (monoclonal anti VEGF antibody fragment) are 2 VEGF inhibitors currently being investigated. The use of Macugen requires 6-weekly repeat intravitreal injections. RhuFab is also intravitreally injected (every 4 weeks) and may be expected to reduce proliferation.

Can we prevent the retina from secreting growth factors (GF)? Steroids can decrease mRNA stability and alter the transcriptional regulation of VEGF. Sustained release implants and slow release biodegradable implants have been tried. However, they have considerable side effects including increased risk of cataract and raised IOPs.

Even if the GF binds to the receptor, can we influence the resulting cellular transduction cascades? When VEGF binds to its receptor, intracellular pathways including protein kinase C (PKC) are activated. PKC is 1 family of serine-threonine kinases and is involved in basal matrix protein synthesis, activation of leukocytes, cytokines, endothelial cells, smooth muscle contraction, endothelial permeability and angiogenesis. Hyperglycaemia activates PKC by various ways including the diacyl glycerol (DAG) pathway. So far, it has been shown using transgenic animals in a mouse model that producing too much PKCβ in the retina causes increased neovascularization in the retina. Knockout (KO) PKC animals appear normal and demonstrate a reduction of neovascularization. Overexpressing non diabetic mice show changes of diabetic retinopathy including microaneurysms and pericyte loss. Some possible ways to inhibit PKC include:

- High dose Vitamin E
- Specific PKC inhibitors

Inhibiting DAG kinase by high dose Vitamin E has been demonstrated and larger clinical trials are in the planning stage. Recent concerns with adverse effects with Vitamin E though are under investigation. LY333531 is one very specific PKC inhibitor and can be taken orally once a day. It inhibits diabetes induced retinal blood flow changes, including ischaemia, retinal neovascularization and vascular permeability in animals. Phase IIb studies showed no change in diabetic control and good safety and tolerability. There was a dose dependent normalization of retinal blood flow. It was well tolerated over 30 months of treatment, but in the dose used did not significantly reduce retinopathy progression. However, using it to reduce moderate visual loss by 30% and progression of macular oedema although the final results not yet known.

In conclusion, advances in the mechanistic understanding of diabetic microvascular complications are leading to novel therapeutic approaches. Some of these are now in trials. However their actual efficacies still await the results of these trials.

### Optic Nerve Repair & Regeneration

Presented by Prof NR Miller on 1 Oct 2003

We were fortunate to have Prof NR Miller with us for the neuro-ophthalmology symposium from 29th September to 4th October 2003.

It has long been thought that a mammalian retina is unable to regenerate due to the retina is considered a “hard” organ. However, recent experiments seem to indicate otherwise. In general, treatment for optic nerve injury aims to provide neuroprotection (prevention of ganglion cell death after damage) and neurorepair (restoration of nerve function after injury).

After injury, neuronal cells can undergo both necrosis as well as apoptosis. In recent experiments on mice which overexpress bid-2, 100% of retinal ganglion cells survived 1 month after optic nerve crush injury. Bcl-2 protein is thought to promote cell survival by antagonising the activation of specific cytochrome proteins (cytochrome Caspases) that cause apoptosis. The role of apoptosis is further demonstrated by the fact that surrounding retinal ganglion cells in monkeys which were not directly injured by trauma to the eye died. In order to prevent apoptosis, we need to eliminate substances that initiate apoptosis (eg. glutamate, nitric oxide) or provide substances that inhibit apoptosis.

The action of glutamate and its N-methyl-D-aspartic acid (NMDA) receptor is to increase intracellular calcium which leads to apoptosis via caspase and other pathways. Substances which may inhibit glutamate release or block its binding to NMDA and are currently under investigation include memantine, dazoxiben (MK801), SB203580, NBQX and DNXQ.

Nitric oxide has also been implicated in causing apoptosis. In fact intravitreal injection of nitric oxide synthase (NOS) can cause photoreceptor and ganglion cell death.

Although older patients have a higher risk of glaucoma, the risk of being injured from glaucoma is much higher in a younger patient. Risk not only varies with age but also with gender and race. The incidence of glaucoma is 3 times higher in African Americans as compared to the Caucasian population. Prof Quigley also gave us an insight on the patients for whom he had a lower threshold for starting treatment. Besides the patients with known risk factors such as thinner corneas, positive family history and myopia, he also tended to treat patients who cannot perform reliable fields, one-eyed patients, patients of a lower socio-economic status, patients with other ocular diseases and patients who are non compliant. His threshold for treatment is also dependent on the patient’s attitudes towards the condition. He would tend to treat people who are more worried about the condition progressing as opposed to a patient who is constantly worrying about the side effects of the medications.

He reminded us that before starting treatment, it is important to determine a patient’s baseline pressure from an average of 3 pressures on different days, so that target pressures can be set. Target pressures are also determined by the patient’s risk of field damage and progression.

“Screening should start with the families of glaucoma patients.” He also spoke of his experience with a community eye screening project in Baltimore. They found that people with eye diseases, especially glaucoma, access the health care system less frequently. He recommended that screening for glaucoma should start with relatives of glaucoma patients and not all patients. However, first degree relatives developing glaucoma is 10 times higher than the normal population.

Prof Quigley believes that smaller diameter discs also have a higher risk of being damaged from glaucoma as they have less reserve. Larger optic discs have more nerve fibres but they also have larger cup-disc ratios.

He further believes that glaucoma is at risk of being over-diagnosed as we become over-reliant on machines. We should always correlate the patient’s clinical status with the results from a visual field or other investigations such as the HRT. He cautioned against the patient’s own opinion of how well they are doing. His treatment is associated with 50% more cataract formation and could result in serious side effects (Coleman et al). He also reminded us that many of our patients are not putting their eye drops despite being given prescriptions for them. The main reason for this is failure to understand the disease condition.

He ended the talk by highlighting the public health impact of glaucoma in the US, where glaucoma care costs $1.43 billion/year.

### Key Learning Points

- Intracocular pressure of 21mmHg is no longer the magic number
- Not all glaucoma patients need to be treated
- Screening should start with the families of glaucoma patients

Written by Dr Alica How

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### Neuro-Ophthalmology

Presented by Dr Anita Chau, Dr Alan Fung & Dr Goein Tan on 20 Oct 2004

In neuro-ophthalmology, we are often referring to interesting cases that prove to be both a diagnostic and management challenge. A careful history, detailed clinical examination and appropriate neuro-imaging are important in the diagnosis of these cases. During our CME session, we presented 5 cases to illustrate these points.

**Patient 1** was a 63 year old Chinese male with a past medical history of hypertension, adult polycystic kidney and liver disease with a previous left thalamic cerebral vascular accident. He presented with an acute onset of bilateral blurring of vision for one day. Clinically he had decreased vision of 6/18 and V/L 6/30 and loss of color vision in both eyes, no relative afferent papillary defect (RAPD), and a left homonymous hemianopia visual field defect. However, inconsistent with the rapid history of onset, he was also noted to have bilateral pale discs. A CT scan showed an acute haemorrhage in the parieto-occipital region (Fig 1a). The patient was referred to the neurosurgeons for further management. But, what was the cause of the patient’s headache? More detailed history was obtained from his daughter who revealed that the patient had sustained a severe head injury at the age of 32 years. When he fell from a height and required emergency surgery performed. Our subsequent diagnosis was bilateral pale discs secondary to previous papilloedema or traumatic optic neuropathy. Retrospective review of the CT films showed a focal defect in left frontal bone possibly due to previous surgery (Fig 1b).

**Patient 2** was a 61 Chinese female with a history of hypertension and diabetes. Her medical history included parietal photoacoagulation in the left eye for diabetic retinopathy. She was asymptomatic, but was referred for a diabetic retinopathy review. The vision was decreased in the left eye with decreased colour vision in the left eye only. Both pupils were sluggishly reactive to light. Examination of the fundi showed bilateral pale discs with stable retinopathy and laser scars. There were no visual field defects. The CT scans of the brain were normal except that her ventricles were noted to be mildly enlarged (Fig 2). Once again what was the cause of the bilateral pale discs? A more detailed history was obtained from the patient and she revealed that she had undergone a ventriculo-peritoneal (VP) shunt for hydrocephalus of unknown cause 20 years ago. The patient was noted to have a right thalamo-cortical artery which was noted to be narrow. She had undergone a right carotid angiogram which showed a stenosis of 80% of the right carotid artery. She was referred for an urgent carotid endarterectomy and a significant improvement in her vision was noted.
years ago. The tube of the VP shunt could still be felt behind her right ear and the scalp scar was seen on careful examination. The diagnosis was post-papilloedema optic atrophy. Retrospective review of the CT scans showed the tip of the VP shunt in the lateral ventricles.

Our third and fourth cases were cases with bilateral swollen discs. These cases were discussed to illustrate how management can be complicated by the patients’ other systemic problems, and may sometimes require a multidisciplinary approach.

**Patient 3** was a 26 year old Indian female without any significant medical history or drug history who was diagnosed as having benign intracranial hypertension (BIH) after the relevant investigations. At presentation she had symptoms of blurring of vision in the left eye and headaches with tinnitus. Clinically, she had an inferior field defect in both eyes, more so in the left eye, and also a left RAPD (Fig 3a). She had bilateral swollen discs, with the left disc being also pale superiorly (Fig 3b). She had undergone a diagnostic and therapeutic lumbar puncture (LP) (opening pressure 28mm H2O) and was also treated with diamox to reduce her intracranial pressure with some improvement of her symptoms. She was found to be pregnant in March and had to stop diamox because of teratogenicity. Her left optic disc became less swollen but this was followed by progressive pallor, although the visual field of her left eye continued to show signs of improvement, and she remained asymptomatic. Her right disc also showed a gradual decrease in swelling. Our dilemma with the appearance of a meningioma (Fig 4c). There was no hydrocephalus. A diagnostic and therapeutic LP (opening pressure 33cm H2O) was performed and diamox was given to reduce the ICP with improvement of symptoms and a decrease in the disc swelling in both eyes (Fig 4b). Our diagnostic problem was whether the meningioma-like dural lesion involving the torcular was the cause of the transverse venous thrombosis, or whether this dural lesion was a metastatic lesion.

Our management challenge was that despite the chronic papilloedema, he had good optic nerve function. After discussion with neuroradiologist, neurosurgeons, oncologist and the patient, we decided to watch for further deterioration before offering a more permanent solution of a VP shunt as we thought that the lesion was unlikely to be a metastatic lesion.

**Patient 5** was shown to illustrate the importance of examining for multiple cranial nerve involvement to help localize the pathology. Our patient, a middle aged Chinese man, presented with diplopia from a fourth nerve palsy. He was also found to have loss of hearing (vestibular nerve abnormality) but had no other cranial nerve involvement. A CT scan showed a large acoustic neuroma as the cause of the fourth nerve palsy (Fig 5), and he was referred to the neurosurgeons for excision.

Currently phase 3 has been completed and subretinal injection was the only route of delivery which was found to result in uptake of a recombinant virus with subsequent expression of the associated protein (green fluorescent protein). The primate model is currently being considered for further studies on CNV as well as diabetes and myopia.

**Key Learning Points**

- Choroidal neovascularization can be induced effectively by a diode laser in monkeys.
- Subretinal injection of recombinant virus results in uptake and expression of the associated genetic material.
- The primate model of retinal disease could be considered for further studies on other retinal diseases.

Written by Dr Por Yong Meng

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**Novel Therapeutic Approaches in the Treatment of Diabetic Retinopathy**

Presented by Prof Lloyd Paul Aiello on 5 February 2003

Diabetic retinopathy (DR) is a spectrum of disease ranging from mild retinal changes with no visual deterioration to blindness. Recently, laser treatment has tremendously reduced the rate of visual loss. However, DR is still a major cause of loss of vision. Current laser treatments are not ideal and destroy the retina resulting in visual field loss and nyctalopia. Therefore novel approaches are being sought aiming for the following targets:

- Prevention of the development of PDR
- Preventing the onset or progression of macular oedema
- Preventing the progression of NPDR

Retinal ischaemia as well as multiple growth factors (e.g. VEGF, GH, IGF, TGF, HGF Pdgf, TgF) have been identified as potential causes of the various complications seen in DR. Blocking them may prevent complications even in the face of ongoing retinal ischaemia.
Welcome to the inaugural issue of the SNEC newsletter!

A lot of good research and clinical material are being presented at our CME programs. However it can be difficult for all of us to make it to these sessions. Hence this newsletter, which will come out quarterly.

In addition to providing a summary of the various topics that have been presented by some very distinguished speakers, including Optic Nerve Repair and Regeneration by Prof Neil Miller, Management of Glaucoma in the 21st Century by Prof Harry Quigley and Novel Therapeutic Approaches in the Treatment of Diabetic Retinopathy by Prof Paul Aiello, there will also be a photo quiz as well as accounts of our doctors' overseas HMDP experiences.

The articles are written by our Registrars as part of their Advanced Subspecialty training and by contributing these articles, we hope to sharpen their delivery and writing skills.

We also welcome contributions from you about your experiences, both social and work related, which you would like to share with our other readers.

Our Doctors on Overseas Fellowship Training in 2003

Dr Edmund Wong was on overseas fellowship training with the Joslin Diabetes Centre from 1 August 2002 to 31 July 2003. This centre conducts laboratory and clinical research in endocrinology, genetics, epidemiology, metabolism, islet cell transplantation and cell biology. Their pioneering work included the development of protocols in laser photocoagulation sessions, but the galactosemia disease and protocols enabling women with diabetes to safely have babies. More recently they demonstrated the role of VEGF in diabetic eye disease.

At the diabetes centre, the main supervisor was Dr LP A ello. Apart from clinical work, Dr Wong was involved in research training. The fellowship also included surgical vitreoretinal opportunities. Calls as first-on-call covered the Longwood area of Boston. During clinics, the importance of history taking was often stressed including inquiring about the occupation of the patient. Clinical findings were carefully documented and a treatment plan was formulated. He assisted in patient recruitment and evaluation, specimen collection and processing, and protocol writing.

Among research activities, the use of topical neopetane and its inhibitory effect on retinal leakage was investigated in animals. He learnt research techniques including retinal endothelial cell, RPC and pericyte cell culture and performing VEGF assays on ROP specimens. There was also a data club including pre-publication data under Dr George King. Current research projects encompass a wide breadth of topics including anti-permeability (PKC inhibitors), anti-angiogenesis and anti-proliferation treatments. At the Joslin Diabetes Centre, current research focuses mainly on protein kinase C inhibitors. Overall, our treatment of patients at SNEC seems very similar to that at the Joslin Centre. In terms of research, cultivating a research culture and being a core group of committed people seem much more important than the equipment. Time for research is important for work on major advances and the funding should not depend on financial remuneration.

Dr Ho Ching Lin was on overseas fellowship training with the Massachusetts Eye and Ear Infirmary (MEI) from 1 August 2002 to 31 July 2003. This centre, among many other achievements, was first to identify a drug for HSV and to discover the gene for RB and RR, and also identified the major resistance to aqueous outflow as being from the trabecular meshwork to Schlemm's canal. They also described the gonioscopic recognition of angle closure. Her main supervisor was David Walton, and the other supervisors were the in adult glaucoma service so she worked with included Lou Pasquale, Cindy Grosskreutz, and Janey Wiggs.

70% of her time during this 1-year clinical fellowship was spent in paediatric glaucoma and 30% in adult glaucoma. There were 7 Blue arc perimetry using the entoptic phenomenon was one of the experimental skills in investigating immunology. In particular, Dr Cheng wanted to start and complete a basic immunology study. To this end, he also had 5 basic science tasks dealing with basic immunology and involving an animal-handling unit.

One of the aims during this fellowship was to be exposed to bench work and to acquire basic skills in investigating immunology. In particular, Dr Cheng wanted to start and complete a basic immunology study. To this end, he also had 5 basic science tasks dealing with basic immunology and involving an animal-handling unit.

During the creation of a murine Experimental Autoimmune Uveitis (EAU) model with BIIIRIII mice, he learnt techniques including lymphocyte culture, proliferation assays, immunochromatography, immunofluorescence microscopy and the ELISA test-cytoine analysis. He also did a poster regarding the use of marijuana and the effects of cannabinoids on ocular cannabinoids are natural modulators of the immune system.

The locations of CB2 immune receptors were found to exist predominantly in areas of the body with a high density of lymphocytes such as the spleen and lymph nodes. CB2 receptors inhibit adenylate cyclase. The current study was investigating the potential immune modulating effect of 2 compounds and the effects were seen for histology and immunohistochemistry. Splenic and LN lymphocyte culture were also done.

Written by Dr Por Yong Ming

Choroidal Neovascularization

Work on Primates

Currently, the best model for understanding human disease is a non-human primate, an animal which is genetically closest to us. Only the primates have a retina with a similar architecture, vascular supply and equivalent neural tracts. Unfortunately, it is difficult to take care of them. In Singapore, we have the only AALAC (American Accrediting society for Large Animal facilities) accredited facility in Asia.

The Experimental Surgery unit was first established in SGH in 1982. This became the Dept of Experimental Surgery in 1989 whose aim was to provide research and training facilities with a bench to bedside concept. This was redeveloped from 12/01-10/02 according to AALAC standards for lab research and the primate facility was jointly developed with SERI. Currently the primate facility occupies 2 levels at SGH Block 9. One level is for large animal experiments and cadaveric dissection, and the other is for rodent and primate research.

New facilities for primate research include an ophthalmic examination room with slit lamp and fundus cameras and an operating theatre with operating microscope and General Anaesthesia setup. Labs also have been set up for pathology, biochemistry and microbiology as well as a behavioural unit. Currently, the primates used are crab-eating macaques (Macaca fascicularis). These fruit-eating animals have been used in the study of pathology, biochemistry and microbiology as well as a behavioural unit. Currently, the primates used are crab-eating macaques (Macaca fascicularis).

In addition, to provide a summary of the various topics that have been presented by some very distinguished speakers, including Optic Nerve Repair and Regeneration by Prof Neil Miller, Management of Glaucoma in the 21st Century by Prof Harry Quigley and Novel Therapeutic Approaches in the Treatment of Diabetic Retinopathy by Prof Paul Aiello, there will also be a photo quiz as well as accounts of our doctors' overseas HMDP experiences.

The articles are written by our Registrars as part of their Advanced Subspecialty training and by contributing these articles, we hope to sharpen their delivery and writing skills.

We also welcome contributions from you about your experiences, both social and work related, which you would like to share with our other readers.
PhotoQuiz
What do these pictures show? What is the likely cause?

Please send your entries to: cmenewsletter@snec.com.sg or fax to: (65) 6226 3395 Attention: Ms Chia Hui Yien
All winners will be notified by post and the answers will be published in the next issue.