Corneal Stem-Cell Transplantation

A transparent and avascular cornea is essential for maintaining useful vision. It is covered by stratified epithelium which is responsible for maintaining a smooth ocular surface as well as for providing a barrier against environmental stress. The most superficial cells are regularly shed from the surface of the eye and replaced by new cells that are ultimately provided by corneal epithelial stem cells located in the limbal area of the peripheral cornea (Figure). Although stem cells of the corneal epithelium are never depleted under physiologic conditions except in certain conditions such as chemical injuries, thermal injuries, the Stevens-Johnson syndrome, and ocular Pemphigoid which can cause destruction of the limbal epithelium. The loss of stem cells from the corneal epithelium leads to invasion of the cornea by vascularized conjunctival epithelium and causes blindness that can not be treated by standard corneal transplantation.

Conical renewal and repair are mediated by the stem cells from the limbus. No doubt, allogenic corneal transplantation (keratoplasty) restores transparency temporarily, but eventually the conjunctival cells begin to invade and resurface the cornea. The only way to prevent this invasion is to restore transparency through grafting of autogenous limbal stem cells.

In 1989, Kenyon and Tseng reported the successful transplantation of a limbal autograft obtained from the healthy eye in the treatment of severe unilateral ocular-surface disease. For patients with bilateral disease, Tsai and Tseng, followed by Pfister and Tsubota et al., reported the transplantation of corneal epithelial stem-cell allografts obtained from donor tissue. Modification of the technique by the use of amniotic membrane as a substrate replacement and eye drops containing autologous serum as a tear replacement has permitted new approaches to the treatment of even end-stage cicatrical diseases with complete loss of stem cells and tears. Such severe diseases have been considered contraindications to surgery because of the extremely poor prognosis of patients treated with corneal transplantation.

Although preliminary reports of the transplantation of corneal epithelial stem cells are promising, yet a study reporting the eventual disappearance of donor-derived limbal cells in the recipient has raised many questions about the feasibility of this technique. Long-term efficacy and complications of the transplantation of corneal epithelial stem cells as a treatment for severe disorders of the ocular surface have been examined. As a result to avoid the complications, the surgical procedure has been designed to remove all abnormal tissue invading the ocular surface and the corneal stem cells are provided by transplantation of limbal allografts from the cadaveric donors. Amniotic membranes has also been used as a replacement substrate when underlying stromal tissue had been destroyed. These are used in the reconstruction of the ocular surface to facilitate epithelialization and to reduce inflammation and scarring, which may compromise the success of limbal transplantation.

Human limbal cell cultures (keratinocytes) generate holoclones (a protein) capable of proliferation and is required to permanently replace the massive epithelial defects. They are identified through the expression of P63 transcription factor, which sustains the proliferative potential of producing the limbal stem cells by regulating their mitotic division through C/EBP8 (mitotic strains). To determine the number of
holoclones by clonal analysis is a cumbersome procedure. In contrast, quantitative immunodetection of P63, a marker of holoclones is straightforward and can be performed before grafting. The outcome of limbal stem cell transplantation has been judged to be successful in 76% of the eyes. (Graziella Pellegrini Ph.D., from Italy)

It has been observed that the most common causes of limbal stem cell deficiency are 97.3% chemical burns (87% unilateral and 12.5% bilateral) as reported in the literature i.e., Alkali 80%, Acid 15%, thermal 3%, and others (infection and irradiation).

The corneal limbal stem cell transplantation is a very promising technology, which is not a new surgical procedure in our country. We have a very few ophthalmic centers in Pakistan having undertaken this procedure with great success. It is a matter of pity that they have not encouraged the young ophthalmologists
to undertake limbal stem cell transplantation as a regular procedure on their list. Similarly, we also know that a very few surgeons have ventured amniotic membrane graft, but hardly anyone has reported his experience in the scientific journals. In our country where we have alarming rate of corneal blindness, there is a great paucity of available donor material. Sometime back we started Keratoplasty in sixties. We mostly depended on Sri Lankan donor material, but in our humble experience, as discussed above, the results remained unsatisfactory in most cases. In fact, every case was subjected to corneal grafting because limbal stem cell transplantation was hardly introduced at that time. In our country we know that there are plenty of corneal blindness due to road accidents, blast injuries, chemical burns, irradiation and inflammation, etc etc. We need to undertake such procedures of limbal cell and corneal transplantation on larger scale as a routine on our list at least in major and teaching institutions; this will help to reduce the incidence of blindness in our society and will mitigate the human sufferings in terms of socio-economic conditions in order to bring them in the main stream of life as a normal person.

As technology becomes more important in all spheres of life, it is only those countries that can use the technology efficiently and profitably, will prosper. If a country cannot adapt technology to its local needs it will fall further behind. Globally speaking, Finland—such a small country with a population equivalent to 1/3 rd of Karachi, ranks number one in the world in terms of research and development than any other nation. Similarly, Sweden and USA ranks amongst the first five nations as the most technologically savvy nations. Israel ranks number 17 in the graph of 25 such nations, while Pakistan stands nowhere in the list of technologically advanced nations, it is a matter of pity.

Take an example of a country like Saudi Arabia where ophthalmic sciences have progressed by leaps and bounds, the corneal grafting, limbal cell transplantation, amniotic membrane graft and allied research has been taken as a routine almost in every teaching hospital. Their research-oriented work is regularly published in Saudi Ophthalmic Society Journal (published from U.K.) with highest quality of research articles. In this context, we therefore, advise and hope that our ophthalmologists especially the upcoming youngsters will change their outlook and undertake these procedures as a routine work.

REFERENCES

Dr. Inam ul Haq Khan, FCPS
Consultant Ophthalmologist & Associate Editor
E. Mail>ophthalmologyupdate@gmail.com
Cell: 0333 5158885

لا يُقدّر أعجوب في العالم كله
لكنك قدمت إلينا كنزًا للأجيال
أتول
ABSTRACT:
Objective: This study was undertaken to clarify controversial role of glucose-6-phosphate dehydrogenase with regard to oxidative stress. Retinopathy was considered as a marker of oxidative stress.
Subjects & Methods: Glucose-6-phosphate dehydrogenase (G6PD) is associated with oxidative stress caused by obesity. This study was undertaken to assess the activity of G6PD with regard to retinopathy. Retinopathy was considered as an indicator of underlying oxidative stress. Degree of retinopathy was compared to the activities of G6PD. It was a cross sectional study. A total of 80 adults in age bracket of 25-40 years (20 with risk for developing diabetes, 20 diagnosed diabetics, 20 metabolic syndrome patients and 20 controls) were selected among ambulatory patients and people, who came to get their fasting blood sugar checked at laboratory of Combined Military Hospital Lahore. This study was approved by the ethical committee of the University of Health Sciences Lahore. Anthropometric parameters of oxidative stress were assessed through detailed medical history and clinical examination. Blood G6PD activity was assessed through commercially available G6PD kit. Fundoscopy was performed by an eye specialist to assess the degree of retinopathy. Fundoscopic findings were correlated with G6PD activities.
Result: Patients with hypertensive retinopathies appear to have G6PD activities towards higher side. Patients with diabetic retinopathies appear to have G6PD activities towards lower side.
Discussion: • Role of glucose-6-phosphate dehydrogenase (G6PD) in fighting oxidative stress is controversial.
• We studied G6PD activities and correlated them to retinopathies.
• In patients with hypertensive retinopathies G6PD activities appeared to be on the higher side of spectrum of G6PD activities.
• In patients with non-proliferative retinopathies G6PD activities appeared to be on lower side of spectrum of G6PD activities.
Conclusion: This study was undertaken to clarify controversial role of glucose-6-phosphate dehydrogenase with regard to oxidative stress. It appears glucose-6-phosphate dehydrogenase activities are up regulated in scenario of hypertensive retinopathies. Whereas in diabetic retinopathies G6PD activities appear to be down regulated.
Keywords: Glucose-6-phosphate dehydrogenase (G6PD), Pentose Phosphate Pathway (PPP), Reduced Nicotinamide Adenine Dinucleotide (NADPH), NADPH Oxidase (Nox), Retinopathies, Oxidized glutathione (GSSG), Reduced Glutathione (GSH)

INTRODUCTION:
Diabetic retinopathy is a major reason for blindness globally. The capillaries of retina are lined with endothelial cells, which are supported by equal number of pericytes. Together these comprise the blood retinal barrier. Pericytes provide tone to vessels. In diabetes the ratio of endothelial cells to pericytes is altered from 1:1 to 4:1. Blood vessels of retina have tight junctions which protect them against leakage. Sustained hyperglycemia damages the tight junctions and protection against leakage is lost. Fluid or blood seeps into retina causing retinal swelling. The basement membrane thickens, blood flow is changed. Pericyte ghosts and acellular capillaries result because of accelerated apoptosis of pericytes and endothelial cells. In retina leukostasis is increased as leukocytes become less deformable, thus further compromising endothelial function. Progressive dysfunction ultimately causes capillaries to die prematurely with resultant ischemia followed by new vessel formation and ultimately retinal detachment which leads to blindness. Biochemical abnormalities believed to be responsible for development of retinopathy appear within two months after induction of diabetes in rats. Histopathologic changes of retinopathy become manifest, within a year in rats and within decades in humans. Small number of apoptotic capillary cells in diabetic retina may lay the foundation of acellular capillaries and pericyte ghosts. However these histopathologic changes are silent as they do not produce any clinical signs. The first clinical signs are appearance of microaneurysms. With disease progression the endothelial cells in

Financial Support: None. Two glucose-6-phosphate dehydrogenase kits were provided by University of Health Sciences Lahore, through funds for research.

Received: July’2012 Accepted: Sep’2012
an attempt to repair the damaged vessel start multiplying on inner side, ultimately blocking the capillaries with resultant ischemia and new vessel growth. New capillaries start sprouting from surface of retinal veins towards center of eye with no pericyte support. This culminates in retinal detachment leading to blindness. Thus irreversible cellular events which take place in clinically silent initial phase of diabetic retinopathy have late structural consequences.

Now coming to biochemical basis of these changes. Free radicals in low concentrations are required for normal signaling processes and for maintenance of redox potential for pathways of cell proliferation and apoptosis. However excess generation or decreased neutralization of free radicals causes oxidative stress at cellular level. This oxidative stress leads to complications like retinopathies. Metabolic toxicities which lead to excess production of reactive oxygen species (ROS) by mitochondria. These pathways augment redox stress with excess ROS. This results in retinal tissue injury. Diabetic complications are caused by toxic effects of increased insulin, increased glucose, high blood pressure, deranged lipid profile, increased cytokines and growth factors. In presence of all these irritants redox stress adds fuel to fire.

A tripeptide comprising of gamma-glutamyl-cyteinyl-glycine called glutathione plays an important role in neutralizing free radicals. When glutathione neutralizes free radicals it itself becomes oxidized written as (GSSG). GSSG cannot further neutralize any free radicals unless it is reduced again to GSH form. Reduced form of Nicotinamide Adenine Dinucleotide (NADPH) reduces oxidized form of glutathione and the cycle of neutralization of free radicals continues. Source of NADPH is the pentose phosphate pathway (PPP) of glucose metabolism. In PPP an enzyme glucose-6-phosphate dehydrogenase (G6PD) plays key role in NADPH generation. During production of pentose phosphates by PPP under influence of G6PD, NADPH is produced. In this scenario NADPH appears vital for fighting oxidative stress by continuous replenishing of GSH.

But some researchers believe that G6PD derived NADPH instead of replenishing GSH, gets diverted to NADPH oxidase (Nox) pathway. Nox pathway causes generation of superoxide anions which exacerbate oxidative stress. If this is so, then G6PD deficiency should protect against oxidative stress. But contrary to claims about exacerbation of oxidative stress by “G6PD derived NADPH”, in a recent study by Cappai G. et al., it was concluded that G6PD deficiency accelerates micro vascular complications of diabetes. How G6PD deficiency accelerates damages caused by diabetes, out weights its protective effects. This may imply that G6PD plays positive role in fighting oxidative stress, otherwise G6PD deficiency should play positive role due to decreased diversion of, NADPH generated by PPP, to superoxide anion generation pathway.

But results are conflicting, quite contrary to findings of Cappa G. et al, Matsui et al demonstrated that G6PD deficiency is beneficial, as lower levels of superoxide anion caused by G6PD deficiency, lead to decreased aortic lesion growth in apolipoprotein E(-/-) mice. Further studies are required to clarify controversial role of G6PD with regard to oxidative stress.

SUBJECTS & METHODS:
Fundoscopy provides a simple and non-invasive way to assess damage done to retina by diabetes or hypertension or any other cause. Pupils of patients were dilated by atropine eye drops and fundoscopy was performed by an eye specialist. The retinopathies were defined according to the classification of retino-pathies by international council of ophthalmology. Blood samples were drawn by venipuncture of the cubital vein from each individual after an overnight fast. All samples were taken between 8 and 10 a.m. as they were to be analyzed for fasting blood sugar and fasting samples should not be taken later than 10 am because then gluconeogenesis starts. 5ml blood was collected in K3EDTA tubes as whole blood for determination of the levels of G6PD. Blood was transported to University of Health Sciences Lahore at 2°C-8°C. Within four hours of sample collection the blood was tested for G6PD using G6PD kit code BCS 180955 (50 tests) by bcs Biotech S.p.A. The kit consisted of three bottles containing: Solution A (hemolysis solution), Solution B (Drabkin’s solution) and Solution C (Reaction mix for G6PD).

First of all hemolysate was prepared by pipetting 380 µL of solution A (hemolysis solution) and 20 µL of whole blood was added to it. Then in second test tube 245µL of solution B (Drabkin’s solution) was added, and 20µL of hemolysate was added to it. Spectrophotometer (OPTIMA SP – 300 spectrophoto-meter) was calibrated with air, then reading was performed at 540nm against a Drabkin
blank, reading was noted when reaction became linear at approximately 2 minutes. Hb concentration was calculated by multiplying absorbance by 33.6. For G6PD determination 250 µL of solution C (reaction mix for G6PD) was added to third test tube and 20 µL of hemolysate was added. Absorbance was read at 340 nm. Absorbance (A1) was read after 3 minutes and second absorbance (A2) was read after one minute of the first absorbance. The G6PD was calculated individually for each subject using the formula:

\[ \text{G6PD} = \left( \frac{\text{UI/dL}}{\text{gHb/dL}} \right) \text{ or } \text{G6PD} = \frac{\text{UI}}{\text{Hb}} \]

Enzymatic Unit (UE): is the amount of enzyme that makes the transformation of 1 µmole of substratum per minute per ml at 37°C under optimal conditions.

\[ \text{UI/dL} = \frac{\text{OD} \times 1000 \times \text{volume of assay mixture µL} \times \text{dilution factor} / \varepsilon \times \text{optical pathway} \times \text{sample volume µL}} {\varepsilon \times \text{optical pathway} \times \text{sample volume µL}} \]

**Example:**

1. Dilution factor is:
   Volume of assay mixture / sample volume = 265/20 = 13.2
2. Optical pathway is 1 cm.
3. Volume of assay mixture = 265 µL
4. \( \varepsilon \) (wave length 340 nm) = 6.22 µL / ml cm

**Sample 2**

G6PD = 9.0 / 0.63 = 14.3U/gHb

**Sample 3**

G6PD = 9.0 / 0.68 = 13.2

**RESULTS:**

**Fundoscopic Findings**

Figure 1: Distribution of Retinopathies among Study Groups

Figure 1 shows the results of fundoscopic examination for all subjects. It can be seen that none of the subjects from control group had apparent retinopathy. In high risk group 80% had no apparent retinopathy and 20% had grade 2 hypertensive retinopathy. Among diabetics 60% had no apparent retinopathy, 5% had bilateral healed chorioretinitis, 5% had grade 1 hypertensive retinopathy, 5% had grade 3 hypertensive retinopathy, 5% had moderate non proliferative diabetic retinopathy, 10% had moderate non proliferative diabetic retinopathy with superimposed grade 3 hypertensive retinopathy.
According to figure 2, G6PD activities were mainly distributed in range of 5 to 13 U/gHb. With some values as low as 3 and as high as 15 which can be considered outliers. No apparent retinopathy appears to be distributed in the whole spectrum of G6PD activities. All grades of hypertensive retinopathies lie in range of 7-15U/gHb of G6PD. Moderate non-proliferative retinopathy lies in G6PD activity range of 11U/gHb. Whereas moderate non-proliferative retinopathy with superimposed grade 3 hypertensive retinopathy corresponds to G6PD activity range as low as 7U/gHb. Severe non-proliferative retinopathy is distributed in range of 5-9 U/gHb of G6PD activity.

**DISCUSSION:**
Early histopathologic changes of retinopathy are silent as we can see that 80% subjects in high risk group have no apparent retinopathy on fundoscopic examination. For normal cellular functions ROS are produced continuously in all cells. However, pathological conditions emerge when either there is excess production of ROS or there is inefficient removal of ROS. During normal oxidative metabolism ROS are eliminated by an efficient scavenging system. Increased oxidative stress in diabetes is postulated to cause retinopathy. Decreased tissue concentration of low
molecular weight antioxidants as glutathione is one of the causes of oxidative stress. For moderate non-proliferative retinopathy with superimposed grade iii hypertensive retinopathy and severe non-proliferative retinopathies G6PD activities appear to be concentrated towards lower side, which may imply that G6PD is unable to supply NADPH for replenishment of reduced form of glutathione. Thereby contributing to oxidative stress or the greater the oxidative stress, the lesser the activity of G6PD. Key events in pathogenesis of retinopathy include: hyperglycemia and altered redox homeostasis and resultant oxidative stress. Animal studies have demonstrated that oxidative stress not only plays part in development of retinopathies but also in resistance of retinopathy to reverse after correction of glycemic control. This resistance is due to accumulation of damaged molecules and ROS that are not easily removed. Therefore reduced glutathione is of crucial importance because it acts as ROS scavenger and maintains redox hemostasis. Its levels are decreased in retina in diabetes, and enzymes responsible for its metabolism are compromised.

CONCLUSION:
Our findings of low levels of G6PD in non-proliferative retinopathies suggest that low activities of G6PD augment oxidative stress due to non-availability of GSH. For hypertensive retinopathies the G6PD activities appear towards higher side of spectrum which may be due to diversion of NADPH derived from G6PD into NADPH Oxidase pathway, where NADPH instead of replenishing GSH is diverted into pathway for production of superoxide anion. More efforts are needed to clarify these gaps in knowledge.

REFERENCES:
INTRODUCTION:

Recently the relationship between low vision and blindness has been clearly understood. If blindness and low vision is not considered as an important health problem, they will have deep effects on the quality of life for many people.

Great efforts have been made to promote prevention of the most common causes of blindness through the public health approaches and international organizations. It is estimated that 0.85% of the world’s population has a corrected visual acuity in the better eye of less than 3/60, with an increase of 1-2 million each year and approximately 80% of visually impaired persons live in developing countries.

Rehabilitation services for the visually impaired persons in Sudan are actually very weak and limited. The number of blinds in Sudan was estimated to be 517,680. However, in the whole country there is one actively teaching institute “Elnur Institute” at Khartoum North established in 1960 as special primary school for blind children. It covers only the basic stage using simple tactile and auditory systems in teaching. The secondary stage should be attended in ordinary schools by using the hearing sense only. In 1970 the Sudan National Association of the Blind (SNAB) was founded in Khartoum North. The aim of SNAB is to gather blinds for educational, vocational, recreational, and occupational integration.

However, 0.6% of blinds in the whole country receive the rehabilitation services through this centre. This percentage cover blinds living nearby the building of SNAB and those who are aware and able to reach it.

METHODS:

Voluntary samples of 100 subjects registered in the blind centre were invited for eye examination. A verbal consent was obtained from subjects, those agreed the protocol. Examination was done using portable equipments and devices that are similar to those found in the low vision clinics. The data included; a questionnaire of personal data, visual acuity, minimum eye examination, refraction, low vision devices assessment, and observation of mobility were evaluated. The results showed that 39% had functional vision which could be improved with low vision devices. The trend of causes is similar to that found in most developing countries.

RESULTS:

The group age ranges from 18 to 62 years of whom 66 were males and 34 were females.

Table 1

<table>
<thead>
<tr>
<th>Characteristics of the group</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of blindness Since Birth</td>
</tr>
<tr>
<td>40%</td>
</tr>
<tr>
<td>Previous treatment Surgery</td>
</tr>
<tr>
<td>30%</td>
</tr>
</tbody>
</table>

In addition 55% of subjects reported that they had no family history of blindness and 45% of the group declared an evidence of positive family history.

ABSTRACT

Objective: This study aimed to give information about the causes of blindness and the effects on the visual function and mobility among a sample group in the blind center in Khartoum state. Clinical examinations were performed for visually impaired voluntary sample of 100 subjects from Sudan National Association of the Blinds (SNAB). Functional testing of visual acuity, anterior segment examination, refraction, low vision devices assessment, and observation of mobility were evaluated. The results showed that 39% had functional vision which could be improved with low vision devices. The trend of causes is similar to that found in most developing countries.

Key words: Visual impairment, Visual acuity, Causes, Mobility.
Table 2
Cross-tabulation of vision in Two Eyes (Horizontal right eyes and vertical left eyes) in the group

<table>
<thead>
<tr>
<th></th>
<th>&lt;3/60</th>
<th>CF</th>
<th>HM</th>
<th>PL</th>
<th>No PL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3/60</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>CF</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>HM</td>
<td>6</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>PL</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>17</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>No PL</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>6</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15</td>
<td>14</td>
<td>18</td>
<td>27</td>
<td>26</td>
<td>100%</td>
</tr>
</tbody>
</table>

31% of subjects were dependent on sighted guide of their relatives, 20% use white cane and 49% use their hands as feelers for searching. Six eye problems identified the main causes of blindness as 28% Corneal opacities, 23% Glaucoma, 20% Retinitis pigmentosa, 9% Optic atrophy, 5% Choroido-retinal degenerations, and 3% Cataract. However, other different causes included; 4% Congenital microphthalmia, 2% Trauma (phthisis bulbi), 2% Inflammatory (phthisis bulbi), 2% of Cortical blindness, 1% Coloboma of iris and Optic atrophy, and 1% Congenital anophthalma.

**DISCUSSION:**

The result clearly shows that the prevalence of low vision in the blind center was significantly high. The personal history of subjects showed 40% of the group assumed to be affected since birth while 14% of blindness occurred during adult life. This was probably demonstrated that most of visual disorders were associated with genetic factors. Nearly all subjects included in this study had eye care service before or during their registration in the blind center. The data in Table 01, showed that 34% in this group had no medical intervention. This is probably due to either their condition was not treatable or there was no outcome from treatment. 45% of the blind group had reported a family history of visual problems among siblings. However, this proportion of positive family history is significantly higher. The parental consanguinity was present in almost the entire group. This was confirmed by the study of Sid Ahmed which reported 92% in SNAB and Elnur Institute have shown parental consanguinity. A study by Kotb, et al in Saudi Arabia at school of blinds, showed that 89% of children were blind from genetically diseased or congenital disorders attributed to parental consanguinity. Generally, the trend of hereditary ocular problems will be predicted to continue unless an effective genetic counseling is to be adapted to the population.

In this group, although 57% had detectable residual vision but no evidence of good visual behavior during daily activities. No doubt a profound visual impairment has a severe impact on mobility and many subjects included in this study were unable to visually detect some hazards at a safe distance.

All types of refractive errors were found in this study, but hypermetropia is more dominant. A significant number of subjects have shown no fundus reflex to be evaluated by the retinoscope.

**CONCLUSIONS**

There is a high need for researches in nearly all areas of visual impairment (low vision and blindness) and services, particularly to address with respect to quality of life through the effectiveness of:

1. Identification of those in need of low vision services at community level.
2. Psychological, social, and counselling impact of visual impairment.
3. Orientation and Mobility (O&M) training programs.

**REFERENCES**

Outcome of Pediatric Cataract Surgery at Al-Ibrahim Eye Hospital, Karachi

Abdul Rashid Shaikh MS¹, Yawar Zaman FRCS², Abdul Sami FCPS³
Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Karachi

ABSTRACT

Objective: To determine the outcome of pediatric cataract surgery at Al – Ibrahim Eye Hospital

Subjects and Methods: A Randomized Control Trial (RTC) was carried out at Al-Ibrahim Eye Hospital from January 2010 to June 2011. A total of 120 eyes of 96 patients were selected from the hospital OPD by simple random sampling. Patients were equally divided into two surgical groups. Group “A” patients underwent extra capsular cataract extraction with posterior chamber intraocular lens implantation combined with posterior capsulectomy only. Group “B” patients had same procedure along with anterior vitrectomy.

Results: Out of 60 eyes in group A, Best Corrected Visual Acuity (BCVA) at the end of six months; 6/6-6/18 in 43.3% eyes, 6/24-6/60 in 26.7% eyes and 16.7% eyes had visual acuity of less than 3/60, while BCVA of 8 children was not recorded on Snellen chart due to age less than three years. Intra ocular inflammation in group-A, 26.7% eyes had mild, 46.7% eyes had moderate, 10% eyes had severe inflammation and 16.7% eyes developed pupillary membrane. While in group-B, 43.3% eyes had mild, 46.7% eyes had moderate, 5.0% eyes had severe inflammation and only 5.0% eyes developed pupillary membrane. Out of 60 patients in group “A” Posterior Capsule became opacificed; Grade I in 63% eyes, Grade II in 16.7% eyes and Grade III in 20% eyes. While in group-B remained grade I in 93.3% eyes, Grade II in 3.33% eyes, and Grade III in another 3.33% eyes. The p value = 0.01867164 is very significant.

Conclusion: The outcome of pediatric cataract surgery was better in patients undergoing extra capsular extraction and IOL implantation with posterior capsulectomy combined with anterior vitrectomy than those who underwent extra capsular extraction and IOL implantation with only posterior capsulectomy.

Key words: Congenital cataract, Developmental cataract, Primary Anterior vitrectomy, Posterior Capsule Opacification, Visual Axis Obscuration

INTRODUCTION

Congenital and early developmental cataract is common ocular abnormality and is an important cause of significant visual impairment in childhood. Many different techniques have been advocated for the treatment of pediatric cataract e.g needling, linear extraction, and intra capsular extraction. Now a days one of the common surgical techniques is extra capsular cataract extraction and IOL implantation with posterior capsulectomy and anterior vitrectomy. This advent in surgical technique today have improved the removal of pediatric cataracts and decreased the post operative complications. This study was conducted to determine the outcome of pediatric cataract surgery at Al – Ibrahim Eye Hospital.

SUBJECTS AND METHODS

A Randomized Control Trial (RTC) was carried out at Al-Ibrahim Eye Hospital from January 2010 to June 2011. A total of 120 eyes of 96 patients were selected from the hospital OPD by simple random sampling. Inclusion criteria were children with congenital and developmental cataract with age 2 to 14 years of either gender. The purpose and nature of the procedure was explained to the parents. A written informed consent was obtained. Patients were divided equally into two surgical groups. Group “A” who underwent extra capsular cataract extraction with posterior chamber Intraocular Lens implantation combined with posterior capsulectomy. (ECCE+PC IOL+PPC) only Group “B” who under went Extra capsular cataract extraction with posterior chamber intra ocular lens implantation combined with posterior capsulectomy and anterior vitrectomy. (ECCE+PC IOL + PPC +AV)

A detailed antenatal, birth and postnatal history was taken including the history of any systemic disease. A full ocular examination including, visual acuity
measurement, IOP measurement was done. Patient underwent investigations i.e. Complete blood count, ESR, RBS as a preparation for general anesthesia. Pupillary dilatation was achieved with topical tropicamide 1% and phenylepherine 2.0% eye drops. Surgical procedure performed was extra capsular cataract extraction followed by posterior chamber intraocular lens implantation. Next step was either being pars plana anterior vitrectomy and pars plana posterior capsulectomy or only posterior capsulectomy as defined by the randomization.

After general anesthesia, surgical area was cleaned with povidone-iodine 10%. Eye was meticulously draped with sterile draping. All patients operated through limbal approach. Anterior capsulorhexis was performed with cystotome. Cataract was aspirated by irrigation/aspiration cannula. Posterior capsulectomy was performed by either cystotome or vitreous cutter. In surgical Group “B” anterior vitrectomy was also performed. A posterior chamber IOL was implanted in all patients. Surgical wound was secured by 10/0 nylon suture(s). Subconjunctival Gentamicin +Dexamethasone were injected at the end of procedure. Eye closed and sterile pad +/- bandage was applied. Intraocular inflammation was graded according to the following criteria:

1. Mild inflammation 5 – 10 cells
2. Moderate inflammation 11 – 20 cells
3. Severe inflammation 21 – 50 cells
4. Organized pupillary membrane:

Exudative membrane covering the pupillary zone

Posterior capsule opacification was graded according to following criteria.

**Grade I:** No central posterior capsule opacification is seen in the central visual axis.

**Grade II:** Posterior capsule opacification is present in the central visual axis but on fundoscopy with direct ophthalmoscope, there is a mild obscuration of fundus detail.

**Grade III:** Posterior capsule opacification is present in the central visual axis but on fundoscopy with direct ophthalmoscope, there is a marked obscuration of fundus detail. No structures can be identified

**DATA ANALYSIS**

Data was analyzed by SPPS. 16.0. frequencies and percentages were calculated for all qualitative variables including gender, age groups, visual acuity, inflammation grading and PCO grading between two groups. The hypothesis was tested by Chi-square. “p” value of less than 0.05 was taken as significant.

**RESULTS**

In this study there were total of 120 eyes (n=120) of 96 patients, 12 (12.5%) patients had bilateral cataract. They were divided into two groups. In Group-A there were 60 eyes (n=60) who underwent extra capsular cataract extraction, posterior chamber intraocular lens implantation combined with posterior capsulectomy(ECCE+PC IOL+PPC) only. In Group-B there were 60 eyes (n=60) who underwent extra capsular cataract extraction with posterior chamber intraocular lens implantation combined with posterior capsulectomy and anterior vitrectomy. (ECCE + PC IOL + PPC + AV).

In Group-A, Mean ±SD of age was 9.1 ±4.2 years, while in group-B, Mean ±SD of age was 10.5 ±3.2 years. In group-A, out of 60 patients, 50 (83.33%) were male and 10 (16.7%) were female, while in group-B 42 (70%) were male and 18 (30%) were female. Table-1

**Best Corrected Visual Acuity (BCVA) at the end of six months for group-A, 26 eyes (43.3%) had visual acuity of 6/6-6/18, 16 eyes (26.7%) had visual acuity of 6/24-6/60, 10 eyes (16.7%) has visual acuity of less than 3/60 while visual acuity for 8 eyes (13.3%) was not recorded. Best Corrected Visual Acuity (BCVA) at the end of six months for group-B, 52 eyes (86.7%) had visual acuity of 6/6-6/18, 6 eyes (10%) had visual acuity of 6/24-6/60, while visual acuity for 2 eye (3.33%) was not recorded. Table-3**

Intra ocular inflammation in group-A, 16 eyes (26.7%) had mild, 28 eyes (46.7%) had moderate, 6 eyes (10%) had severe inflammation and 10 eyes (16.7%) developed pupillary membrane. While in group-B, 26 eyes (43.3%) had mild, 28 eyes (46.7%) had moderate, 3 eyes (5.0%) had severe inflammation and only 3 eyes (5.0%) developed pupillary membrane. Table-2

When these results were subjected to statistical analysis by chi square test, they were significant, with...
The treatment of an infant or child with a cataract requires different decision processes and modifications in surgical procedures compared with the treatment of an adult with a cataract. The developing visual system, growth and anatomic differences in the eye and related structures, and psychosocial differences between children and adults contribute to the differences in management.

The adult eye is fully developed, and the visual pathways are mature. Management after cataract surgery is principally a process of optical rehabilitation to achieve restoration of vision. In children, however, the eye and the visual pathways are developing, and the operation to remove a cataract is only the first step in a long process aimed at promoting normal development of the visual system and achieving the best possible visual acuity in the affected eye or eyes. Treatment of congenital cataract remains a challenge. It is resource demanding, difficult and requires a dedicated joint effort by parents and the medical profession. Yet a good result is of utmost importance both for the individual patient and socio-economically.

Even with the best possible conditions treatment of patients with congenital cataract is a challenging task, sometimes rewarding but most of the time full of pitfalls and unexpected problems, glaucoma being the most serious threat10,11.

In our study there were total of 120 eyes (n=120) of 96 patients, 12 (12.5%) patients had bilateral cataract. Patients were randomly divided into two surgical groups. The mean age of patients in our study was similar in both groups i.e. 9.1±4.2 years and 10.5±3.2 in group A and B respectively. This helped us in comparing the two groups with respect to visual acuity, postoperative inflammation and PCO. Regarding gender distribution there was male preponderance in both groups. This may be due to the fact that, the health problems of female members of the family are overlooked in developing countries. Hence their referral to tertiary eye care facilities is poor. Regarding postoperative visual acuity, at final follow-up BCVA of 6/6 to 6/18 (0.0-0.5 logMAR) was achieved in 65% eyes. In Kuk-Hyoe’s12 series of 92 eyes with congenital cataracts, 51.7% eyes achieved BCVA of >0.5 logMAR at last visit. Laurence C Lesueur13 from Purpun University Hospital France reported that out of 107 paedriatic cataract surgeries 90% of pseudophakic eyes regained visual acuity of >0.5 logMAR, which is better than our results.

On comparing the two groups, 85% eyes in group B achieved BCVA of 6/6-6/18 as compared to 43% eyes in group A. This shows that anterior vitrectomy along with posterior capsulectomy results in much improved visual outcome. Samin Hong14 mentioned the similar finding in his study in which he removed the posterior capsule and anterior hyaloid face. He was able to achieve near normal visual acuity in 77.78% eyes after surgery.

In children, any intraocular surgical procedure especially cataract can results in higher postoperative inflammation than adults15. This is due to weak or immature blood-aqueous barrier and decreased fibrin clearing capacity of trabecular meshwork. It can be related with surgical technique due to trauma to adjacent structures. In our series moderate postoperative inflammation (11–20 cells in anterior chamber) was seen in 46.7% of eyes (grading of the inflammatory cells was performed on slit lamp with a 2mm long and 1mm wide slit beam with maximal light intensity and magnification). Similar observation was reported in Ozkurt’s16 series in which he observed moderate postoperative inflammation in 47% eyes in non-heparin used group. In our study severe postoperative inflammation (21-50 cells) and organized
pupillary membrane was observed more in group A. This shows reduced postoperative inflammation after anterior vitrectomy in combination with posterior capsulectomy. Luo Y\textsuperscript{17} also observed a significant difference of postoperative inflammation between the two groups.

At the end of six months PCO of grade II and III was observed in 36.7\% eyes in group A, where as in group B it was only seen 6.7\% eyes. Luo Y\textsuperscript{17} in his study showed 76.1\% and 11.8\% in group A and group B respectively. This supports our finding that anterior vitrectomy in combination with posterior capsulectomy is advantageous in younger patients concerning after-cataract formation. Kugelberg\textsuperscript{18} also reported the benefits of anterior vitrectomy in reducing the incidence of PCO.

Hence Primary posterior capsulectomy with anterior vitrectomy is associated with a low opacification rate of posterior capsule. It provides the clear optical media for immediate postoperative retinoscopy. It minimizes the possibility of secondary surgical procedures. In addition, anterior vitrectomy keeps the vitreous face posterior to the plane of the iris, reducing the possibility of posterior synechiae and making an iridectomy unnecessary. Therefore, it is recommended for children undergoing cataract surgery.

CONCLUSION

The outcome of pediatric cataract surgery was better in patients undergoing extra capsular extraction and IOL implantation with posterior capsulectomy combined with anterior vitrectomy than those who underwent extra capsular extraction and IOL implantation with only posterior capsulectomy.

REFERENCES

Role of Avastin in Retinal Angiomatous Proliferation

Shafqatullah Khan Marwat, FCPS1, Muhammad Tariq Khan FCPS2

ABSTRACT

Purpose: To evaluate the short-term efficacy and safety of intra-vitreal Avastin (IVA) injection in patients with retinal angiomatous proliferation (RAP).

Methods: Seven eyes of 5 patients with RAP were included in this study. All of the eyes evidenced stage-2 RAP lesions, except for one eye with a stage-3 lesion. IVA (1.25 mg/0.05 cc) injections were conducted at 4 to 6-weeks intervals. Complete ocular examinations were performed and analyzed at baseline and upon the follow-up visits. Angiographic results and Optical Coherence Tomographic (OCT) findings were also analyzed before and after the IVA injections.

Results: Seven eyes were studied in 5 patients who had undergone IVA injection. Partial (in 3 eyes) or complete (in 4 eyes) regression of RAP was noted after IVA injection in all of the studied eyes. Visual acuity improved in 5 of the eyes, and was stable in 2 of the eyes. One eye evidenced severe intraocular inflammation after IVA injection and a subsequent development of new RAP, which was controlled with repeat IVA injection.

Conclusions: This treatment was effective over 6 months, stabilizing or improving visual acuity and reducing angiographic leakage. These short-term results suggest that IVA injection may constitute a promising therapeutic option, particularly in the early stages of RAP.

Keywords: Intravitreal Avastin injection, Retinal angiomatous proliferation

INTRODUCTION

Retinal angiomatous proliferation (RAP) is a variant of neovascular age-related macular degeneration, originating from the retinal vasculature. Some authorities prefer the term ‘retinal anastomosis to the lesion (RAL)’ as they believe that the choroidal neovascularization (CNV) lesion precedes the development of an anastomosing retinal vessel to this lesion. Also the terminology like ‘deep retinal vascular anomalous complex’ and ‘retinal–choroidal anastomosis’ has been used in literature. Yannuzzi et al. introduced the term ‘retinal angiomatous proliferation (RAP)’ to describe a vascular process that these authors believe originates within the neurosensory retina. 1 Although direct laser photocoagulation, photodynamic therapy (PDT), surgical removal of the lesion, surgical excision of the retinal feeder vessels, intravitreal triamincolone acetonide, periocular anecortave acetate and transpupillary thermotherapy (TTT) have previously been reported as therapeutic modalities for RAP, 2-4 the recurrence or progression of RAP lesions after these modalities are not infrequent occurrences and hence none of these treatment strategies are completely effective for RAP. It was reported in an experimental mouse study that excessive vascular endothelial growth factor expression may trigger the growth of new vessels toward the sub-retinal space from the deep retinal capillary plexus, and the new vessels were shown to enlarge and form a complex with other vessels. 5-7 This occurs in a fashion similar to the evolution of RAP, and suggests the possibility that anti-vascular endothelial growth factors (anti-VEGFs) may be utilized as a treatment for RAP. We hereby describe the short-term effectiveness and safety profile of intravitreal Avastin (bevacizumab), a full-length recombinant monoclonal antibody for vascular endothelial growth factor A, delivered via injection into patients with RAP presenting at our settings.

MATERIALS AND METHODS

Seven consecutive eyes of five patients who had undergone IVA injections for the treatment of RAP were included in this series. The study group was comprised of one man and four women. The mean age in the study group was 67.6 years. The diagnosis of RAP was predicated on the results of fluorescein angiography (FA). Six eyes were verified to have stage-2 RAP lesions,
in accordance with the classifications established by Yannuzzi et al. The remaining eye was confirmed to have a stage-3 RAP lesion. All the eyes were subjected to IVA as an initial treatment. Both eyes were involved in all five patients, but IVA was not considered to be an appropriate treatment modality in the fellow eyes of 3 subjects with disciform scarring. Measurements of best-corrected visual acuity, slit lamp examinations, fluorescein angiography, and optical coherence tomography were conducted in all patients. The median pre-treatment visual acuity was 6D60 (Table).

Avastin (Bevacizumab) 1.25 mg in 0.05 ml was injected into the superior pars plana area, 3.5 mm apart from the corneal limbus, using a 29-gauge needle, and the location of injection was then changed in the following sequence: 10 o’clock, 12 o’clock, and 2 o’clock, in order to avoid repeated injections at the same location. IVA injection was initially conducted at 4 weeks and then afterward at 6-weeks intervals. Slit lamp examination and funduscopy were conducted on the same day of, but prior to the consequent IVA injections. Optical Coherence Tomography and Fluorescein Angiography was conducted at first presentation before injections and then at the last follow up in order to determine the quantity of leakage and regression of the RAP lesion. Bevacizumab was injected up to 7 times. The mean follow-up duration after the initial IVA injection was 7.6 months (range 6–12 months).

RESULT

On angiographic examinations conducted at the last follow up visit, partial (3 eyes) or complete (4 eyes) regressions of RAP and significant reductions of the hyper-fluorescent lesions were noted in all of the study eyes. On the optical coherence tomographic examinations, a reduction in the central macular thickness, as well as a complete resolution of sub-retinal fluid and/or retinal pigment epithelial detachment were noted in all of the eyes on the final visit. Five eyes evidenced better visual acuity and 2 eyes evidenced stable visual acuity. Median BCVA at the last visit had improved to 6D18-P. The visual results of the individual eyes are provided in the Table.

In one case (patient #5 in the Table) the patient was found to have severe intraocular inflammation detected two days after the fourth IVA injection. The bacterial culture of the vitreous specimen revealed no growth. The intraocular inflammation subsided as the result of intra-vitreal antibiotics and topical and systemic steroid treatments. Two weeks after the inflammation settled, the angiogram indicated a new RAP lesion. However, the RAP lesion regressed with repeated IVA injections. Otherwise, no injection-related complications were detected.

DISCUSSION

In all cases, stable or improved vision, reductions of central thickness on optical coherence tomography, and partial or complete obliterations of RAP on angiography were noted. Our results indirectly confirms the idea that vascular endothelial growth factor contributes to the development of RAP. As the majority of our cases evidenced stage-2 RAP with pigment epithelial detachment, IVA appears to work, at least in lesions of up to stage-2. Although the previous studies show the recurrence or progression of RAP lesions after photodynamic therapy or laser ablation being not infrequent occurrence, the development of such occurrences appears to be reduced as a consequence of IVA.

CONCLUSION:

Although the number of cases in this study was rather small and the follow-up time was limited, IVA appears initially to constitute an effective treatment, which can improve the prognosis of RAP. IVA should be considered as a therapeutic option, particularly in

### Table

<table>
<thead>
<tr>
<th>Pt. No</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Eye</th>
<th>RAP stage</th>
<th>No. of IVA inj.</th>
<th>VA (Pre-inj)</th>
<th>VA (Post-inj)</th>
<th>Follow-up (months)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>72</td>
<td>R</td>
<td>2</td>
<td>4</td>
<td>6D 36</td>
<td>6D18</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>2</td>
<td>4</td>
<td>6D 60</td>
<td>6D60</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>67</td>
<td>R</td>
<td>2</td>
<td>3</td>
<td>6D 24</td>
<td>6D12</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>2</td>
<td>4</td>
<td>4D 60</td>
<td>6D12</td>
<td>8</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>64</td>
<td>L</td>
<td>2</td>
<td>3</td>
<td>6D 18</td>
<td>6D9</td>
<td>9</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>65</td>
<td>L</td>
<td>2</td>
<td>3</td>
<td>6D 24</td>
<td>6D24</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>70</td>
<td>R</td>
<td>2</td>
<td>7</td>
<td>4D60</td>
<td>6D60</td>
<td>12</td>
<td>Severe intra-ocular inflammation &amp; recurrence</td>
</tr>
</tbody>
</table>

RAP=retinal angiomatic proliferation, IVA= intravitreal Avastin injection, VA=visual acuity
cases in which RAP is diagnosed in an early stage.

REFERENCES
Safety and Efficacy of fixed Combination of Dorzolamide & Timolol Maleate in Primary Open Angle Glaucoma*

Amna Adil Hasni FCPS¹, Intizar Hussain FCPS, FRCS²
Shabana Chaudhry FCPS FRCS³, Muhammad Mueen Bhatti⁴, Shamshad Ali⁵

ABSTRACT

Objective: To evaluate the safety and efficacy of fixed combination of topical dorzolamide and timolol maleate, in primary open angle glaucoma (POAG).

Materials and Methods: This descriptive case series study was carried out at department of ophthalmology, Services Institute of Medical Sciences & Services Hospital, Lahore. 64 eyes of 50 patients fulfilling the inclusion criteria were enrolled during the study period of 3 months. One drop of topical fixed combination of timolol maleate and dorzolamide were administered twice daily in the affected eye. Baseline intraocular pressure was recorded and during the follow up at week 1, 4, 8 and 12, the efficacy of the drug was evaluated by percentage change in intraocular pressure (IOP) from the base line value. The safety was evaluated on the basis of symptoms and signs experienced by the patients.

Results: There were 21 male and 29 female patients with age ranging from 51 to 76 years. The IOP reduction percentage ranged from 12% to 27% with mean of 18.3%. On instillation of drug, 14% of the patients experienced burning of eye, 8% had itching, 12% had stinging of eyes and 30% complained of bitter taste. Only 6% of the patients had ocular sign of conjunctival hyperaemia. None of the patient had intense symptoms to discontinue the drug.

Conclusion: Topical fixed combination of timolol maleate and dorzolamide is safe and effective in lowering the IOP in eyes of patients of POAG.

Key words: POAG, IOP, Fixed combination of timolol maleate and dorzolamide

INTRODUCTION

Primary open-angle glaucoma (POAG) is the most common type of glaucoma. It is a chronic slowly progressive optic neuropathy characterized by cupping of the optic nerve head, associated with characteristic pattern of visual field loss and IOP more than 21 mm Hg. It is usually bilateral but can be asymmetric.

The goal of the glaucoma treatment is to preserve the visual function and to lower the IOP below the level which can cause nerve damage. Powerful IOP-lowering medications are currently available that allow many patients to achieve their IOP-lowering goals with a single medication. Despite the substantial IOP lowering possible with mono-therapy, many patients may need to use 2 or more medications to reach a target IOP sufficiently low to prevent further visual deterioration. Because of the inconvenience and possible confusion caused by multiple bottles for patients using adjunctive therapy, fixed combination products have been introduced over the past several years. Medications that are combined and placed in one bottle have a benefit of convenience and improve compliance and also reduce cost.

Timolol maleate is the most common beta blocker used for treatment of POAG. Studies have been conducted on the IOP lowering effect of various drugs, showing that timolol, a beta blocker causes 25% IOP reduction when used as a first line mono-therapy. The studies determined that timolol suppresses the aqueous humor production, decreases the IOP and increases the retinal blood flow.

Carbonic anhydrase is an enzyme in the ciliary body which is required for the secretion of aqueous humour. By inhibiting this enzyme there is a decrease in the aqueous humor secretion by ciliary epithelium. The commercially available topical Carbonic anhydrase inhibitor (CAI) is dorzolamide and brinzolamide. These drugs have good corneal penetration, and are water soluble. These agents reduce IOP from 14 to 17%. When a beta blocker is used in combination with topical carbonic anhydrase inhibitor, additional 15% of IOP reduction occurs. Adverse effects of topical CAIs are burning and stinging of eyes on instillation, corneal allergy, corneal punctate keratitis and bitter taste. This study was carried out to evaluate the safety and efficacy of fixed combination of topical dorzolamide and timolol maleate, in primary open angle glaucoma.
MATERIAL AND METHODS

This descriptive case series study was carried out at the Department of Ophthalmology, Services Institute of Medical Sciences & Services Hospital Lahore. Patients included fulfilled the following criteria:

- Patients of either gender within age of 50-80 years.
- Baseline IOP > 21 mm Hg.
- Old patients with the diagnosis of POAG in one or both eyes using antiglaucoma medication.

Exclusion Criteria:

- H/O of hypersensitivity to dorzolamide or timolol.
- H/O ocular allergy within 6 months.
- Argon laser trabeculoplasty within 3 months.
- H/O chronic or recurring inflammatory ocular disease.
- H/O ocular surgery within 6 months.
- Asthma, COPD, heart block or impaired renal function.
- Patients showing side effects within first week to an extent that the drug has to be discontinued.

Washout period for previously prescribed medicines:

- Prostaglandins — 4 weeks.
- Beta blockers and alpha agonist — 2 weeks.
- Miotics and carbonic anhydrase inhibitors — 5 days.

Patients fulfilling the inclusion criteria were enrolled in the study with written informed consent. The risks and benefits of the treatment were explained to the patient. Baseline IOP was recorded before the start of medication, or after the completion of washout period, in case of old patients of POAG. During the 3 months of treatment period, 1 drop of fixed combination of 0.5% timolol maleate and 2% dorzolamide was administered twice daily in the affected eye. The side effects of the drug occurring during the study were dealt appropriately. The efficacy and safety was evaluated at the end of 3 months of follow-up even if IOP was significantly reduced within 3 months.

The first follow-up was conducted at the end of the first week and then successive follow-up at the end of the 4th, 8th, and 12th weeks. At every follow-up IOP was measured with an applanation tonometer twice at 9:00 am and 2:00 pm and the mean was taken as final value. The efficacy was analysed on the basis of percentage reduction of IOP from the baseline value. Frequency of side effects like burning, bitter taste and means and standard variation for continuous variable age was calculated.

RESULTS

64 eyes of 50 patients were included in the study. There were 37 right eyes and 27 left eyes. Age range of the patients was from 51 years to 76 years with mean age of 63 years ± 6.951 years (Table 1). There were 21(42%) male and 29(58%) of female patients. The baseline IOP range was from 22 mmHg to 29 mmHg with mean value of 24.59, Table 2 shows the range of IOP in both eyes with minimum and maximum values along with the mean, among the age groups of the study population.

The drug showed significant reduction of IOP at first follow-up and the IOP lowering effect was sustained throughout the study period. Changes in IOP from the baseline ranged from 4 mm Hg to 6 mm by the end of week 12. The minimum percentage change of IOP from the baseline was 12.5% and the maximum change was 27%, with the mean value of 18.3%. The IOP continued to drop between the week 1 and week 4, however the reduction in IOP stabilised by month 1 and was essentially maintained through month 3 (Fig. 2).

The safety of the drug was evaluated on the basis of side effects which patients experienced. Out of the study population 28 patients experienced the adverse effects. Only 6 patients had complaint of more than one side effect, 7 patients experienced burning, 6 experienced stinging, 4 complained of itching and 3 patients of the study population had sign of conjunctival hyperaemia in the first week of instillation of the drops. The commonest side effect experienced by the patients was bitter taste which occurred in 30% patients of the study population (Figure 3). Among all these side effects, none of them had intensity to the extent to discontinue the topical medication. Topical artificial tear drops were advised to the patients experiencing burning, stinging and itching to make the eyes more comfortable.

### Table 1: Age Distribution of Patients

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-60</td>
<td>17</td>
<td>34%</td>
</tr>
<tr>
<td>61-70</td>
<td>22</td>
<td>44%</td>
</tr>
<tr>
<td>&gt;70</td>
<td>11</td>
<td>22%</td>
</tr>
</tbody>
</table>

### Table 2: Baseline IOP Analysis in mmHg

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>No of eyes</th>
<th>IOP Range</th>
<th>Mean IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>22</td>
<td>26</td>
<td>23.11</td>
</tr>
<tr>
<td>61-70</td>
<td>28</td>
<td>29</td>
<td>23.89</td>
</tr>
<tr>
<td>&gt;70</td>
<td>24</td>
<td>29</td>
<td>26.18</td>
</tr>
</tbody>
</table>
comfortable. Topical artificial tears have no effect on IOP level. There were no other local or systemic side effects of drug in any patient of the study group.

**DISCUSSION**

POAG is a chronic progressive disease and in most of the patients, frequently, more than one medication is required to achieve adequate control of IOP. There are several potential benefits of fixed-combination medications as compared with using the individual components separately. These include a reduction in the total number of drops and preservative instilled per day, cost savings, improved tolerability and compliance and avoiding the washout effect resulting from rapid instillation of multiple drops. Attempts have been made to develop effective fixed combinations of glaucoma medications. In recent years, fixed combinations of drugs have gained wide acceptance all over the world. Over the period of time it has proven that fixed combinations are safe and effective in lowering the IOP. These are also convenient and cost effective.

The evaluation of additive effect of timolol with rest of the antiglaucoma drugs has been the study of interest over the past two decades. Initial studies which used prostaglandin analogues combined with beta blocker showed additive effect on IOP reduction of up to 13-14% from the baseline value in patients of POAG. Varma and Hwang described that the IOP lowering efficacy of fixed combination of latanoprost, a prostaglandin analogue and timolol is greater than their mono-therapy regimen.

There are various other studies, done in past two decades which prove the additive effect of beta blocker and CAI. When comparison of the percentage of IOP reduction in a group of patients receiving the combination of timolol and dorzolamide was done to those receiving the individual drugs as monotherapy, it was evident that the fixed combination was superior in controlling IOP and reduction was greater on average in the combination group than in the dorzolamide and timolol groups. The combination was well tolerated and was convenient for the patients to use. In our study we have also evaluated the IOP lowering effect of fixed combination of timolol maleate and dorzolamide in eyes with primary open angle glaucoma. In comparison to the previous studies done on fixed combination drugs, we have not compared the efficacy of the combination drug with the mono-therapy, or their concomitant administration. Hutzelmann et al studied the comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol to the administration of dorzolamide and timolol. It was a randomised, double masked and multicenter study. Out of 299 patients 151 received the topical fixed combination of 2% dorzolamide / 0.5% timolol. Efficacy of the fixed combination was determined on the basis of reduction of IOP from the baseline, which was -3.8 mmHg to -5.8mmHg in the combination group. The percentage change was from 14.6% to 23.3%. In the
Safety and Efficacy of fixed Combination of Dorzolamide & Timolol Maleate in Primary Open Angle Glaucoma

Dorzolamide is effective in lowering IOP by 18.3% from the baseline value, in patients of POAG. It is a safe topical anti-glaucoma medication with mild local side effects and no significant systemic complications.

REFERENCES
9. Sherwood MB, Craven R, Chou C, Dubiner H B, Batoos Singh A L, Schiffman R M, Whitcup SM. Twice daily 0.2% Brimonidine - 0.5% Timolol fixed combination therapy versus monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension. Arch Ophthalmol 2006; 124: 1230-1238.
INTRODUCTION

Age-related macular degeneration (AMD) is a progressive late onset disease affecting central vision. It is the leading cause of irreversible blindness among older adults, affecting one in three people aged 75 or older, and with the aging population the problem is increasing.1,2

The number of individuals affected by age-related macular degeneration is expected to increase by 50% by the year 2020.3 Current treatment options by endothelial growth factor (VEGF) inhibitors – anti-VEGF therapy are limited to the late stage of the disease, when central vision is already under great threat, and even new treatments make little impact on the rate of blindness. Monthly intravitreal anti-VEGF injections with systemic exposure to anti-VEGF will be replaced by new drugs taken in a non-invasive way. Statins are the most commonly used lipid lowering drugs. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that statins may be useful in the prevention and treatment of age-related macular degeneration.

Key words: Irreversible vision lost, age-related macular degeneration, prevention, non-invasive treatment, lipid lowering drugs.
Age-Related Macular Degeneration: What else we can do?

suggestions that statins may be useful in the prevention and the treatment of age-related macular degeneration.

MATERIALS AND METHODS

Age-Related Macular Degeneration: Statins use in Prevention & Treatment

The association between the use of statins and age-related macular degeneration has been evaluated in many clinical studies; however the results have been contradictory.

Data from large population-based studies, including previous analyses from the Blue Mountains and Beaver Dam studies and a large study conducted in a health organization in Israel have not found a protective association between statin use and AMD. Kaiserman, N., et al. stated that statin use is not reducing the risk for wet AMD.

RESULTS

In another new analysis using data from the Beaver Dam Eye Study in Wisconsin, statin use at the 10-year examination was not associated with the subsequent incidence of early or late AMD, or progression of AMD at the 15-year examination. Data from new case-control study confirmed also that use of statins was not associated with newly diagnosed exudative AMD. The study had 80% statistical power to detect a protective effect of 0.70, but it cannot exclude a smaller effect.

Hall, N.F., et al. reported a significantly lower frequency of AMD (defined broadly as all types and severities) among statin users relative to non-users. The OR reported in that study was 0.14, 95% CI 0.02-0.83. The limitations of the Hall, N.F. et al. have been addressed in detail and include the small sample size and the cross sectional design. Martin-Du Pan, R.C. confirmed that statins are well tolerated and they could reduce the risk of macular degeneration. Data from cohort study of patients with bilateral large drusen within a multicenter, randomized, clinical trial are not consistent with a strong protective effect (risk ratio, ≤ 0.85) of statins on the development of advanced AMD among these patients. Baghdasarian, S.B., et al. in a cross-sectional analysis have found that AMD was less common among statin users than nonusers (4% (1/27) vs. 22% (76/352); p=0.02).

Chuo, J.Y., et al. evaluated the effect of lipid-lowering agents in the development of AMD through a meta-analysis of observational studies, estimating the pooled relative risk (RR) for all eight studies, and also for seven studies examining the use of statins, for those RR was 0.70 (95% CI, 0.48-1.03). The authors concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing AMD, although clinically significant effects cannot be excluded. Etminan, M., et al. in the observational study have found a slightly higher risk of developing AMD among statin users. Observational studies evaluating treatment effects are subject to range a biases, bringing to heterogeneity of findings. Drobek-Slowik, M., et al. in case-control study revealed statin use may be a protective factor against AMD. Treatment indication and compliance biases, which refer to distortion of associations resulting from known and unknown differences in participant characteristics, prescribed the treatment and the treatment actually taken, are difficult to quantify and may also vary in magnitude between the studies.

There is evidence that the pattern, prescription, and type of statin usage have changed in the last decade. Furthermore, there is evidence that not all statins are equally effective for lipid lowering. In a meta-analysis, atorvastatin displayed two to four times the potency of simvastatin in reducing total cholesterol levels. Thus, it is likely that the type and dosage of evaluated statins are different.

DISCUSSION

The beneficial effect achieved by the treatment of endothelial dysfunction in chronic cardiovascular diseases is already an evidence belonging to the basic treatment of the disease. Given the fact that the vascular system is uniform and consubstantial both physiologically, patho-physiologically and in terms of therapy, and that it plays a key role in AMD, endothelial dysfunction should be treated and type of statin usage have changed in the last decade. Furthermore, there is evidence that not all statins are equally effective for lipid lowering. In a meta-analysis, atorvastatin displayed two to four times the potency of simvastatin in reducing total cholesterol levels. Thus, it is likely that the type and dosage of evaluated statins are different.
actually taken, the succession of prescription refills during the observation periods among the majority of statin users suggests that these medications were actually being taken. Finally, this study population was limited to older males and the results should only be considered generalizable to males aged 50 and older.

McGwin, G. Jr., et al., in the case-control study of 871 AMD cases and 11,717 controls after adjusting for the confounding influence of age, gender, and race, revealed a statistically significant relationship between AMD and use of cholesterol-lowering medications (OR, 0.79; 95% CI, 0.63-0.99). The results of this study add to the growing body of evidence that cholesterol-lowering medications may reduce the risk of developing AMD.

In the latest analysis of the Blue Mountains Eye Study in Australia, while controlling for age and other factors, statin users at baseline and at the five year followup had a 67% lowered risk of indistinct soft drusen, a key late AMD precursor lesion, at the 10-year examination. Statin use, however, as stated by authors, was not related to the incidence of late ARMD or other early ARMD signs. This large population-based study as an observational study evaluating treatment effects is subject to a range of biases which were discussed earlier. Wilson, H.L., et al. (35) in a retrospective consecutive case series investigated the relationship between statin and aspirin use and the risk of choroidal neovascularization (CNV) in patients with AMD.

Age-related macular degeneration disease status and time of onset of CNV was compared between patients treated or not treated with statins for at least 6 month. Of CNV subjects, 20% used statins, compared with 38% of dry AMD subjects without geographic atrophy and 33% of controls with geographic atrophy (hazard ratio = 0.51, 95% confidence interval (CI) = 0.31-0.86, p=0.01). The general consensus is that therapy with statins or aspirin is significantly associated with decreased rates of CNV. The strength of this study (35) is the use of main outcome measure, represented by angio-graphically evident CNV, and also the diagnosis, which was based on review of fundus photographs and fluorescein angiograms in masked fashion. The latest experimental study conducted by Sagara, N., et al., evaluated the effect of specific statin-pitavastatin on CNV in rats and have also advocated the use of pitavastatin in preventing CNV development in AMD patients, based on claims that the therapeutic dose of pitavastatin for human hypcholesterolemia effectively suppressed experimental CNV in rats. The authors reported that pitavastatin-treated rats had significantly less fluorescein leakage, evaluated by masked observers; reduced thickness of CNV and decreased gene expression of VEGF. These encouraging results should be confirmed in clinical trials. Schmeer, C., et al. have recently advocated the use of statins in retinal eye diseases, based on their anti-apoptotic, anti-proliferative effects, besides lipid-lowering and anti-inflammatory properties. The authors presented evidence for the role of heat shock proteins (Hsps) as target of statin-mediated neuroprotective effects in ocular diseases.

The general consensus is that a randomized trial of statin use in AMD patients is warranted. Wong, T.Y., Rogers, S.L. also advocated initiation of a randomized controlled trial. The authors estimated the required sample size, described clinically relevant endpoints, and concluded that only 1,704 participants are needed for a five-year trial to evaluate the effects of statins on slowing AMD progression by 25% or more (relative risks RR of 0.75 or lower), assuming a cumulative progression rate of 6% for the placebo group.

CONCLUSION

In conclusion, there are potentially multiple biological bases for the protective effect of statins on the risk of AMD. With regard to the potential for a lipid lowering effect, cholesterol is a ubiquitous component of drusen in normal and AMD eyes. With regard to the potential for pleiotropic effects, many of the same processes that occur in the atherosclerotic intima, probably also occur in AMD. Neovascularisation is a major complication in both conditions. Therefore, angiogenesis is potential point of statin modulation. Taken into account that not all statins are equally effective, the challenge for future laboratory research will be to determine the best type and dosage of statins and also to determine which processes are modulated by statins in vivo and therefore are primarily responsible for the apparent beneficial effects observed in the previous studies.

Clearly, further observational studies cannot adequately address many unanswered questions. It is time to conduct a randomized controlled trial to provide direct evidence of the effectiveness of specific type statin in lowering the incidence and progression of AMD.

New intervention as statins usage to prevent the development of age-related macular degeneration and its progression remain an important strategy to limit the morbidity of this significant public health problem.

REFERENCES

INTRODUCTION:
Anemias are a group of hematologic disorders manifesting in a decrease in the number of circulating red blood cells and/or a decrease in the amount of hemoglobin (Hb) in each cell. A low Hb (at sea level) is <13.5 gm/dl for men and <11.5 gm/dl for women. Fundus lesions can be the accompanying symptom in anemias or thrombocytopenia. The exact mechanism of these fundus abnormalities is not completely understood.

CASE REPORT
59 years old male presented with one day history of deterioration of vision after blood transfusion. He was a known chronic case of internal hemorrhoids for the last 3 years and developed bloody diarrhea couple of days back, as a result of which his Hb dropped to 2 gm/dl. His condition was worsened by acute renal failure and pulmonary edema. He was transfused 6 bags of blood after which his Hb raised upto 9.5 gm/dl. There was no accompanying thrombocytopenia.

On presentation his BCVA was CF and IOP was 12 mmHg OU. There was no APD, ocular motility was full OU and anterior segment slit lamp examination was within normal limits. On fundus examination extensive preretinal, intraretinal and subretinal hemorrhages were seen in both eyes. Many of the hemorrhages showed white centers (Roth spots). Soft exudates and venous tortuosity was also visible. Despite peripapillary hemorrhages optic disc seemed to be normal. A differential diagnosis of diabetic retinopathy, hypertensive retinopathy, valsalva retinopathy, anemic retinopathy and leukemias was considered. On the basis of history, clinical examination and lab reports a diagnosis of anemic retinopathy was made.

DISCUSSION
Anemia is a low Hb due to a decreased red blood cell (RBC) mass. It may be due to reduced production or increased loss of RBCs. Symptoms common to all anemias are weakness, fatigue, dyspnea, palpitations etc.

Transient retinal hemorrhages associated with anemia from gastrointestinal hemorrhage were first described by Ulrich in 1883. Retinal changes in anemias are usually non specific and rarely of diagnostic importance and may closely simulate diabetic or hypertensive retinopathy. Carraro et al in their study of 226 patients observed the retinopathy in 28.3% of the patients, fundus lesions being closely associated with severe anemia (Hb < 8 gm/dl) and severe thrombocytopenia (PLT < 50 x 10^9/L). Among patients with concomitant anemia and thrombocytopenia the incidence of retinopathy was 38%. It is seen that duration and type of anemia do not influence the occurrence of retinopathy. These lesions usually resolve in a period of 4-6 weeks with the correction of anemia and recommended management is just to wait and observe.

REFERENCES

Correspondence: Dr. Khalid Masood Ashraf FCPS, LRBT Eye Hospital, G. T. Road, Mandra, District Rawalpindi. Ph. 0321 5007919, E-Mail: kmashraf70@yahoo.com
DETERMINANTS OF THE CURRENT DENGUE PANDEMIC

The global burden of dengue is large; an estimated 50 million infections per year occur across approximately 100 countries, with potential for further spread. The primary vector, *Aedes aegypti* mosquito, has become widely distributed across tropical and subtropical latitudes. It emerged from Africa and spread into Asia through commercial exchanges in the 18th and 19th centuries, and has spread globally with the advent of increased travel and trade in the past 50 years. In addition, the geographic range of a secondary vector, *A. albopictus*, has dramatically expanded in recent years. Globalization of trade, in particular the trade of tires from used vehicles, is thought to explain the dispersal of eggs and immature forms of these arboviral vectors into new territories. Endemicity has also been facilitated by rapid urbanization in Asia and Latin America, resulting in increased population density with an abundance of vector-breeding sites within crowded urban communities and the areas surrounding them. Dengue infections in Africa remain largely unquantified, but recent outbreaks suggest that substantial parts of the continent may be at risk for increasing dengue transmission. More surveillance is required to assess the true burden of disease.

Vector control, through chemical or biologic targeting of mosquitoes and removal of their breeding sites, is the mainstay of dengue prevention, but this approach has failed to stop disease transmission in almost all countries where dengue is endemic. Antigenic diversity of the dengue virus is important, since the lack of long-term cross-immunity among the four virus types allows for multiple sequential infections.

The diagnosis should be considered in any patient presenting with fever that has developed within 14 days after even a brief trip to the tropics or subtropics, including those regions where dengue has not traditionally been considered an endemic disease.

VIROLOGIC FEATURES

Dengue is caused by one of four single-stranded, positive-sense RNA viruses also referred to as serotypes of the genus flavivirus. Infectious virus and the virus-encoded soluble nonstructural protein 1 (NS1) are present in blood during the acute phase, and high-level early viremia and NS1 antigenemia have been associated with more severe clinical presentations. The detection of NS1 is also the basis for commercial diagnostic assays.

Dengue viruses exist in two environments: the urban or endemic setting, where humans and mosquitoes are the only known hosts, and forested areas, where transmission of mosquito-borne viruses occurs between non-human primates and, rarely, from these primates to humans. Within each dengue virus serotype, multiple genotypes comprise phylogenetically related sequences. Subtle antigenic differences exist between genotypes of the same serotype, but these may not be clinically relevant, since human infection with one serotype is believed to confer long-lived serotype-specific immunity, but only short-lived cross-immunity.
between serotypes. The dynamics of dengue viruses within urban and endemic populations are complex, involving the birth and death of viral lineages. Although dengue has emerged in multiple new territories over the past 40 years, the viruses themselves are paradoxically “local” in their evolutionary histories, suggesting that the global dispersal of dengue virus has occurred in relatively infrequent “jumps,” most likely by the movement of viremic humans to new geographic settings with a suitable vector and a susceptible population.

**IMMUNOPATHOGENESIS**

Epidemiologic studies have identified young age, female sex, high body-mass index, virus strain, and genetic variants of the human major-histocompatibility-complex class I–related sequence B and phospholipase C epsilon 1 genes as risk factors for severe dengue. Secondary infection, in the form of two sequential infections by different serotypes, is also an epidemiologic risk factor for severe disease. Mechanistically, increased risk in secondary infection is thought to be linked to antibody-dependent enhancement of virus infection in Fc receptor–bearing cells and the generation of a large infected cell mass in vivo. A consequence of a large virus-infected cell mass is a physiological environment in tissues that promotes capillary permeability; however, this hypothesis is based on temporal associations between immunologic markers and clinical events, without evidence of a direct, mechanistic link to causation.

**PATHOPHYSIOLOGY OF ENDOTHELIAL DYSFUNCTION**

There is no evidence that the virus infects endothelial cells, and only minor nonspecific changes have been detected in histo-pathological studies of the microvasculature. Although no specific pathway has been identified linking known immunopathogenic events with definitive effects on microvascular permeability, thrombo-regulatory mechanisms, or both, preliminary data suggest that transient disruption in the function of the endothelial glycocalyx layer occurs. This layer functions as a molecular sieve, selectively restricting molecules within plasma according to their size, charge, and shape. Hypo-albuminemia and proteinuria are observed during dengue infection; proteins up to and including the size of albumin are preferentially lost; this is consistent with a small but crucial change in the filtration characteristics of the glycocalyx. Both the virus itself and dengue nonstructural protein 1(NS1) are known to adhere to heparan sulfate, a key structural element of the glycocalyx, and increased urinary heparan sulfate excretion has been detected in children with severe infection.

**DIFFERENTIAL DIAGNOSIS AND DISEASE CLASSIFICATION:**

Although most dengue virus infections are asymptomatic, a wide variety of clinical manifestations may occur, ranging from mild febrile illness to severe and fatal disease. The differential diagnosis is broad and varies as the disease evolves. During the febrile phase, it includes other arboviral infections as well as measles, rubella, enterovirus infections, adenovirus infections, and influenza. Other diseases that should be considered as part of the differential diagnosis, depending on the clinical picture and local disease prevalence, include typhoid, malaria, leptospirosis, viral hepatitis, rickettsial diseases, and bacterial sepsis.

Patients were previously classified as having either dengue fever or dengue hemorrhagic fever. In particular, there was concern regarding the requirement that all four specific criteria (fever lasting 2 to 7 days, tendency to hemorrhage evidenced by a positive tourniquet test or spontaneous bleeding, a platelet count of less than 100×10^9 per liter, and evidence of a plasma leak based on changes in the hematocrit and pleural effusions) be met to support a diagnosis of dengue hemorrhagic fever — such that some patients with clinically severe disease were categorized inappropriately. With the recent revision of the World Health Organization (WHO) dengue classification scheme, patients are now classified as having either dengue or severe dengue. Patients who recover without major complications are classified as having dengue, whereas those who have any of the following conditions are designated as having severe dengue: plasma leakage resulting in shock, accumulation of serosal fluid sufficient to cause respiratory distress, or both; severe bleeding; and severe organ impairment. It is hoped that this system will prove more effective for triage and clinical management and will improve the quality of surveillance and epidemiologic data collected globally.

**Clinical Manifestations:** After an incubation period of 3 to 7 days, symptoms start suddenly and follow three phases — an initial febrile phase, a critical phase around the time of defervescence, and a spontaneous recovery phase.

**Febrile Phase:** The initial phase is typically characterized by high temperature (ε38.5°C) accompanied by headache, vomiting, myalgia, and joint pain, sometimes with a transient macular rash. Children have high fever but are generally less symptomatic than adults during this phase of the illness. Mild hemorrhagic manifestations such as bruising, particularly at venipuncture sites and a palpable liver are commonly noted. Laboratory findings include mild-to-moderate thrombocytopenia and leukopenia, often with a moderate elevation of hepatic amino-transferase levels.
This phase lasts for 3 to 7 days, after which most patients recover without complications.

Critical Phase: In a small proportion of patients, typically in children and young adults, a systemic vascular leak syndrome becomes apparent around the time of defervescence, evidenced by increasing hemoconcentration, hypoproteinemia, pleural effusions, and ascites. Initially, physiological compensatory mechanisms are up-regulated in an attempt to maintain adequate circulation to critical organs, resulting in narrowing of the pulse pressure when loss of plasma volume becomes critical. If the pulse pressure narrows to 20 mm Hg or less, accompanied by signs of peripheral vascular collapse, dengue shock syndrome is diagnosed and urgent, although careful, resuscitation is required. Systolic pressure may remain normal or even elevated at this time, and the patient may appear deceptively well, but once hypotension develops, systolic pressure decreases rapidly and irreversible shock and death may follow despite aggressive attempts at resuscitation. During the transition from the febrile to the critical phase, between days 4 and 7 of the illness, it is crucial for the clinician to be aware of warning signs that clinically significant vascular leakage may be developing in the patient. These signs of impending deterioration include persistent vomiting, increasingly severe abdominal pain, tender hepatomegaly, a high or increasing hematocrit level that is concurrent with a rapid decrease in the platelet count, serosal effusions, mucosal bleeding, and lethargy or restlessness. (Fig:1)

Hemorrhagic manifestations are most common during this critical period. In children, clinically significant bleeding occurs only rarely, usually in association with profound and prolonged shock. However, major skin bleeding, mucosal bleeding (gastrointestinal or vaginal), or both may occur in adults with no obvious precipitating factors and only minor plasma leakage. Moderate-to-severe thrombocytopenia is common, with nadir platelet counts below 20×10⁹ per liter often observed during the critical phase, followed by rapid improvement during the recovery phase. A transient increase in the activated partial-thromboplastin time and a decrease in fibrinogen levels are also frequently noted. However, the coagulation profile is not typical of disseminated intravascular coagulation, and the underlying mechanisms remain unclear. Infrequently, other severe manifestations, including liver failure, myocarditis, and encephalopathy, occur, often with minimal associated plasma leakage.

Recovery Phase: The altered vascular permeability is short-lived, reverting spontaneously to a normal level after approximately 48 to 72 hours, and is concurrent with rapid improvement in the patient’s symptoms. A second rash may appear during the recovery phase, ranging from a mild maculopapular rash to a severe, itchy lesion suggesting leukocytoclastic vasculitis that resolves with desquamation over a period of 1 to 2 weeks. Adults may have profound fatigue for several weeks after recovery.

Diagnostic Tests: Laboratory diagnosis of dengue is established directly by detection of viral components in serum or indirectly by serologic means. The sensitivity of each approach is influenced by the duration of the patient’s illness. (Figure 4) During the febrile phase, detection of viral nucleic acid in serum by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay or detection of the virus-expressed soluble nonstructural protein 1 (NS1) by means of enzyme-linked immunosorbent assay (ELISA) or the lateral-flow rapid test is sufficient for a confirmatory diagnosis. For primary infections in persons who have not been infected previously (which is typical in the case of most travelers), the diagnostic sensitivity of NS1 detection in the febrile phase can exceed 90%, and antigenemia may persist for several days after the resolution of fever. The sensitivity of NS1 detection in the febrile phase is lower in secondary infections (60 to 80%), reflecting an anamnestic serologic response due to a previous dengue virus or related flavivirus infection.

Serologic diagnosis of dengue relies on the detection of high levels of serum IgM that bind dengue virus antigens in an ELISA or a lateral-flow rapid test; IgM can be detected as early as 4 days after the onset of fever. IgM seroconversion between paired samples is considered a confirmatory finding, whereas detection of IgM in a single specimen obtained from a patient with a clinical syndrome that is consistent with dengue is widely used to establish a presumptive diagnosis. Commercially available IgM tests with acceptable performance characteristics have recently been identified. In addition, patients with secondary infections mount rapid anamnestic antibody responses in which dengue virus–reactive IgG may predominate over IgM. In clinical settings where methods of molecular detection (e.g., RT-PCR) are not available, investigation for elevated levels of dengue virus–reactive IgM or soluble NS1 in serum is a pragmatic diagnostic approach in a patient in whom dengue is suspected.

Management

Currently, no effective antiviral agents to treat dengue infection are available, and treatment remains supportive, with particular emphasis on careful fluid management. Patients who have no complications and are able to tolerate oral fluids may remain at home with
The kinetics of viremia in a patient with secondary dengue, the timing of common complications, and possible mechanistic causes are shown. Early in secondary infection (or primary infection of infants), antibody-dependent enhancement is thought to increase in vivo concentrations of virus. Antibody-dependent enhancement is linked to the presence of non-neutralizing or subneutralizing levels of dengue virus–reactive IgG induced by a primary infection, or acquired passively in newborns. A large infected cell mass results in elevated concentrations of acute-phase response proteins, cytokines, and chemokines; generation of immune complexes; and consumption of complement and release of split products. The activation, proliferation, and secretion of cytokines in tissues by memory T lymphocytes recognizing conserved and altered peptide ligands are postulated to add to the inflammatory milieu during secondary infections. Collectively, the host immunologic response is thought to create a physiological environment in tissues that promotes capillary permeability when the viral burden is in rapid decline. However, the exact mechanisms are unclear. Interactions between dengue nonstructural protein 1 (NS1) and the surface glyocalyx layer may result in release of heparan sulfate into the circulation, thereby altering the filtration characteristics of the layer and resulting in leakage of proteins. Loss of essential coagulation proteins probably plays a major role in the development of the typical coagulopathy, which is usually manifested as an increase in the partial-thromboplastin time accompanied by low fibrinogen levels but with little evidence of procoagulant activation. Heparan sulfate may also function as an anticoagulant and contribute to the coagulopathy.

**Figure 1. Immunopathogenesis of Severe Dengue in Secondary Infections.**

The kinetics of viremia in a patient with secondary dengue, the timing of common complications, and possible mechanistic causes are shown. Early in secondary infection (or primary infection of infants), antibody-dependent enhancement is thought to increase in vivo concentrations of virus. Antibody-dependent enhancement is linked to the presence of non-neutralizing or subneutralizing levels of dengue virus–reactive IgG induced by a primary infection, or acquired passively in newborns. A large infected cell mass results in elevated concentrations of acute-phase response proteins, cytokines, and chemokines; generation of immune complexes; and consumption of complement and release of split products. The activation, proliferation, and secretion of cytokines in tissues by memory T lymphocytes recognizing conserved and altered peptide ligands are postulated to add to the inflammatory milieu during secondary infections. Collectively, the host immunologic response is thought to create a physiological environment in tissues that promotes capillary permeability when the viral burden is in rapid decline. However, the exact mechanisms are unclear. Interactions between dengue nonstructural protein 1 (NS1) and the surface glyocalyx layer may result in release of heparan sulfate into the circulation, thereby altering the filtration characteristics of the layer and resulting in leakage of proteins. Loss of essential coagulation proteins probably plays a major role in the development of the typical coagulopathy, which is usually manifested as an increase in the partial-thromboplastin time accompanied by low fibrinogen levels but with little evidence of procoagulant activation. Heparan sulfate may also function as an anticoagulant and contribute to the coagulopathy.
instructions to return to the hospital immediately if bleeding or warning signs suggestive of vascular leakage develop. However, our practice is to evaluate these patients daily in a medical clinic with a complete blood count to monitor hematocrit and platelet values. Development of any warning sign indicates the need for hospitalization and close observation, with judicious use of parenteral fluids in patients with inadequate oral intake or a rapidly increasing hematocrit. If the condition progresses to the dengue shock syndrome, prompt fluid resuscitation to restore plasma volume is imperative, followed by ongoing fluid therapy to support the circulation at a level just sufficient to maintain critical organ perfusion. Isotonic crystalloid solutions should be used, and isotonic colloid solutions should be reserved for patients presenting with profound shock or those who do not have a response to initial crystalloid therapy. To limit the risk of the development of fluid overload, parenteral fluid therapy should be kept to the minimum required to maintain cardiovascular stability until permeability reverts to a normal level.

Blood transfusion can be lifesaving for patients with severe bleeding that compromises cardiovascular function, but it should be undertaken with care because of the risk of fluid overload. Platelet concentrates, fresh-
frozen plasma, and cryoprecipitate may also be needed depending on the coagulation profile. However, at present, there is no evidence that prophylactic platelet transfusions are of any value in patients who do not have clinically significant bleeding, even when thrombocytopenia is profound. The use of prophylactic platelet transfusions is increasing in countries where dengue is endemic, but given the associated clinical risks and the financial costs, controlled trials need to be performed before this becomes established as the standard of care. In patients with severe dengue infection, adjuvant therapy, including vasopressor and inotropic therapies, renal-replacement therapy, and further treatment of organ impairment, may be necessary.

The establishment of a therapeutic pipeline and the design of randomized, controlled trials of drugs targeting the virus or the immune response are recent developments. Recent trials have assessed chloroquine, oral prednisolone, further trials of statins and other antiviral drugs are planned. Currently, there is no evidence in favor of the use of any specific therapeutic agent for dengue. Ideally, patients with severe dengue infection should be treated in dedicated high-dependency units where frequent clinical observations by experienced staff with immediate access to repeated hematocrit measurements can ensure that fluid therapy is carefully titrated as needed. In such circumstances, mortality of less than 1% is achievable among patients with shock, and the need for ventilatory support and intensive care is minimized.

New Approaches to Targeting the Vector: New vector-control approaches include the release of genetically modified male mosquitoes that sterilize the wild-type female population, thereby reducing egg output and the population size of the next generation that would be available for potential transmission of the dengue virus. An alternative strategy involves

---

**Figure 4. Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection.**
Detection of viral nucleic acid, nonstructural protein 1 (NS1), or IgM seroconversion is a confirmatory finding in patients in whom dengue is a possible diagnosis. Day 0 is the first day when the patient noted any symptom during this illness. ELISA denotes enzyme-linked immunosorbent assay, and RT-PCR reverse-transcriptase polymerase chain reaction.
embryonic introduction of strains of the obligate intracellular bacterium wolbachia into A. aegypti. Strikingly, wolbachia-infected A. aegypti are partially resistant to dengue virus infection and can invade natural A. aegypti populations, suggesting the possibility of induction of widespread biologic resistance to dengue viruses in A. aegypti populations.

**Vaccines:** The leading dengue vaccine candidate, Chimeri Vax (Sanofi Pasteur), is a tetravalent formulation of attenuated yellow fever 17D vaccine strains expressing the dengue virus prM and E proteins. It has been difficult to develop a vaccine for dengue that is safe and elicits balanced neutralizing antibody responses to all four serotypes. However, in the past 5 years, remarkable progress has been made, and multicenter phase 2–3 clinical trials that are designed to determine the efficacy of this three-dose vaccine are under way. Data on immunologic correlates of immunity are lacking. Long-term follow-up of vaccines will be essential to understand whether waning vaccine-elicited immunity predisposes recipients to more severe outcomes on subsequent natural infection. Other candidates in early phases of clinical development include vaccines containing live attenuated dengue viruses and recombinant subunit vaccines.

**Future Directions:** The field of dengue research has been invigorated over the past decade, fueled by the growing recognition of the burden of disease coupled with the prospect of a dengue vaccine. However, no vaccine can be an immediate global panacea, and efforts to improve treatment through application of existing best practices in triage and fluid management, along with efforts to develop new antiviral or other therapeutic drugs, must continue. Similarly, innovative approaches to preventing transmission of the virus, such as through modification of mosquito populations, should be fostered. An improved understanding of the current epidemiology of the disease and the potential for its future spread would also assist policymakers in allocating resources to combat this global public health challenge.

**REFERENCES**

The number of ophthalmologists in practice and training worldwide: a growing gap despite more than 200,000 practitioners

Dr. Serge Resnikoff, 16 A quai du Seujet, Geneva, 1201, Switzerland; William Felch, Tina-Marie Gauthier, Bruce Spivey

To assess the current number of ophthalmologists practicing worldwide in 2010 and to create a system for maintaining, collecting and improving the accuracy of data on ophthalmologists per population, ophthalmologists performing surgery, growth rate of the profession, and the number of residents in training. Between March 2010 and April 2010, the International Council of Ophthalmology emailed a standardized survey of 12 questions to 213 global ophthalmic societies. Missing data and additional information were gathered from direct correspondences with ophthalmologist contacts. The total number of ophthalmologists reported was 204909. Data are presented for 193 countries. Information was obtained from 67 countries on the number of ophthalmologists doing surgery, entering practice, leaving practice, rate of growth and resident training. The survey results show that despite over 200000 ophthalmologists worldwide, there is currently a significant shortfall of ophthalmologists in developing countries. Furthermore, although the number of practitioners is increasing in developed countries, the population aged 60+ is growing at twice the rate of the profession. To meet this widening gap between need and supply, it is necessary to aggressively train eye care teams now to alleviate the current and anticipated deficit of ophthalmologists worldwide.


Breakthrough in Understanding Macular Degeneration

Dr. Jayakrishna Ambati
Professor of Physiology and Professor
Vice-Chair of Ophthalmology and Visual Sciences
University of Kentucky

Dr. Jayakrishna Ambati, has made a major breakthrough in the “dry” form of age-related macular degeneration known as geographic atrophy (GA). GA is an untreatable condition that causes blindness in millions of individuals due to death of retinal pigmented epithelial cells. Dr. Jayakrishna Ambati, Professor of Physiology, and Professor and Vice chair of Ophthalmology and visual sciences at UK, is a leader in the field of macular degeneration research. In human eyes with geographic atrophy there is a deficiency of the enzyme DICER1, leading to accumulation of toxic AluRNA molecules in the retinal pigmented epithelium.

The Cell paper shows that when these RNAs build up in the eye they trigger activation of an immune complex known as the NLRP3 inflammasome. In turn, this leads to the production of a molecule known as IL-18, which causes death of retinal pigmented epithelial cells and vision loss by activating a critical protein known as MyD88.

Importantly, Ambati and colleagues found evidence that activity of the inflammasome, IL-18, and MyD88 were all increased in human eyes with GA. They then showed that blocking any of these components could prevent retinal degeneration in multiple disease models. The researchers are excited that blocking these pathways could herald a new potential therapy for GA, for which there is no approved treatment.

Ambati is working with iVeena Pharmaceuticals, Inc. of Salt Lake City to commercialize therapies for geographic atrophy.

Nature, 2011; DOI: 10.1038/nature09830
Profile of
An Ophthalmologist par Excellence

Prof. Dr. Marianne Levon Shahsuvaryan
M.D., Ph.D., D.Sc., (Yerevan), Republic of Armenia
— A committed Teacher, a Surgeon and a Researcher

Practicing ophthalmology is a privilege and ophthalmologists are intimately familiar with the rewards and personal satisfaction, their efforts bring.

Prof. Marianne Shahsuvaryan, a doyen of Ophthalmology in the Republic of Armenia, is currently holding a chair of Ophthalmology at Yerevan State Medical University & Chief of Malayan Ophthalmologic Centre, Yerevan. She was attracted to Ophthalmology by her family particularly her mother, Dr. Svetlana Bakhshinova, a renowned ophthalmologist and Associate Professor in the Department of Ophthalmology at the National Institute of Health in Yerevan.

Dr. Shahsuvaryan is also the Medical Training Director of Armenian Eye Care Project (AECP) and Chief Executive of the National Ophthalmology Society of Armenia. As an ophthalmologist, she finds “great satisfaction” in helping patients and restoring their vision. She believes, “these goals will be achieved through continuing educational programs. Prevention works best when it is introduced from the Primary Health Care level, which will eventually contribute to AECP’s larger mission — to eliminate preventable blindness in Armenia.”

Born in Yerevan in 1966, Shahsuvaryan, is the only child of her parents, who enjoyed drawing, knitting, crocheting, macramé, writing poetry and stories right from the very childhood. She received her early education at secondary school, Yerevan in 1983. At a younger age, Shahsuvaryan shared the excitement of eye surgery through the experiences of her mother, and got enrolled as a medical student at Yerevan State Medical University. She completed her Diploma in Medicine with Honors in 1989 and post-graduation in Ophthalmology at the Central Physicians Advancing Training Institute, Moscow, Russia. She accomplished her Ph.D., thesis in 1996 on the subject of “new possibilities of forecasting in neo-vascular glaucoma and pathogenesis-based treatment in retinal vein occlusion” at Yerevan and D.Sc. thesis in 2003 on the subject of “new aspects of early diagnosis, medical treatment and prophylaxis in retinal vein occlusion” at Yerevan. She also attended short-term fellowship at the Moorefield’s Eye Hospital, London and Leuven University, Belgium in 2000.

As far as her experience is concerned, she has worked as general ophthalmologist from 1991 to 1995 at 8th Hospital, Yerevan till 2005 and as Associate Professor of Ophthalmology at State Medical University from 2005-07. She was elevated to the chair of Professor in 2007. She has attended 18 International Ophthalmic conferences and presented scientific papers. She has the credit of publishing 85 original articles in national and international Journals. She has authored many Ophthalmic books, naming: Comprehensive Eye Examination; Essentials of Ophthalmology; Handbook of Practical Ophthalmology; Emergency in Ophthalmology; The Red Eye: Telling the Truth about a Danger and Ophthalmology Text Book.

Her other activities include her responsibilities of implementing the USAID/AECP Global Development Alliance Program in the medical education and training arena for International Develop-ment to integrate primary ophthalmologic health care in Armenia. In addition an important aspect of her work is to analyze and assess the country’s environment in view of general ophthalmic education. Shahsuvaryan shares her knowledge with others, which she considers, is important for her own professional development. Self-education allows her to treat patients based on modern scientific findings and technologies. She is also the Fellow of the Armenian Ophthalmological Association and Armenian Medical Association.

As her name ‘Shahsuvaryan’ depicts in Persian as “Shahsuvar”- a riding princess. She is a real riding princess in the field of ophthalmology, possessed with a charming personality and unwavering determination to revolutionize the existing system of teaching. She is committed to provide state-of-the-art technology to the emerging field of Ophthalmic sciences. She is transcending an arduous journey towards perfection which is the ultimate aim of her life. Moreover, she is a champion for ameliorating the plight of visually handicapped. In fact, she is an institution, a university within herself who carries a mission for every minute of her life. We wish her enough strength and vigor to continue serving her people and the profession to her best. ………………… Editor in Chief
PUPIL-INVOLVING THIRD CRANIAL NERVE PALSY: think the worst first:

A pupil-involving third cranial nerve palsy is one of the true emergencies in neuro-ophthalmology. That’s because it may signal an aneurysm, which could rupture and lead to a subarachnoid hemorrhage—a potentially fatal event. The third cranial nerve supplies several of the extraocular muscles and the levator muscle as well as the ciliary muscle and iris sphincter. Thus, disorders of this nerve may have varied presentations, including ptosis, diplopia, ocular movement disturbances, and pupillary abnormalities. The ophthalmologist’s time-critical task is differentiating between compressive—possibly indicating an aneurysm—and non-compressive etiologies for third cranial nerve palsy.

The pupil’s lessons. The classic “rule of the pupil” states that when aneurysms compress the oculomotor nerve, the iris sphincter will be impaired, leading to a sluggishly reactive or dilated pupil. If the pupil is entirely spared in the setting of a complete ophthalmoplegia and ptosis, the oculomotor nerve palsy is usually due to a local infarction. But the rule does not apply if the extra-ocular motor palsy is incomplete; it must be applied with caution to patients who are less likely to have vasculopathic risk factors or in whom an inflammatory or neoplastic cause is likely.

To further confound the rule, posterior communicating artery (PCOM) aneurysms may present initially with normal pupils. Conversely, pupillary involvement can occur with vasculo-pathicoculomotor palsies, demonstrating anisocoria usually 1 mm or less but sometimes as great as 2.5 mm. In addition, both intracranial aneurysms and vasculo-pathicoculomotor palsies may cause severe headache, further confusing these two entities. We always think of the worst first when it comes to third cranial nerve palsies, whether the pupil is involved or not.

Other possible causes of third nerve palsy with pupil involvement include:

- Giant cell arteritis (GCA)
- Pituitary apoplexy
- Demyelinating disease (e.g., multiple sclerosis)
- Midbrain infarction
- Oculomotor nerve schwannoma/meningioma
- Brain metastasis
- Trauma
- Ophthalmoplegic migraine
- Myasthenia gravis may also mimic a third cranial nerve palsy, but the pupil will never be involved.

DIAGNOSING THIRD CRANIAL NERVE PALSY:

Whether you assess the patient yourself or refer to a neuro-ophthalmologist, documentation of an acute
or progressive process is critical. An acute headache pointing to a possible aneurysmal leak or rupture. This, along with stiff neck, nausea, and loss of consciousness, is a typical finding for a subarachnoid hemorrhage.

**Ocular examination.** With all new patients, a standard history and exam, including checking eyelid position and evaluating the pupils—for symmetry, size, reactivity, and presence of a relative afferent pupillary defect—before administering mydriatic drops. The ophthalmic exam must also include investigating the ‘real estate’ in and around the third nerve. This includes checking ocular motility to evaluate the fourth and sixth cranial nerves, as well as assessing corneal sensitivity and facial sensation innervated by the fifth nerve. With complete third cranial nerve palsy, the eye has complete ptosis and is ‘down and out,’ moving only in the direction of the spared oculomotor nerves. (Fig. 1).

**Blood tests.** Dr. Vaphiades recommends tailoring blood tests to the clinical situation. For example, you may need stat creatinine (to rule out impaired renal function before ordering a computed tomographic angiogram (CTA); stat ESR, blood CP, metabolic panel including glucose, and C-reactive protein (for suspected GCA); or cholesterol/triglycerides (for suspected vasculopathic cause).

**Imaging.** If we suspect an aneurysm, we order an emergent CTA adding that he usually schedules same-day neuroimaging even for vasculopathic suspects. Concern has been raised about the cost-effectiveness of imaging all such patients. He said that if third nerve palsy is partial in any way, he strongly recommends neuroimaging, including brain magnetic resonance angiography (MRA) or CTA. For patients with a complete motor third nerve palsy, including complete ptosis and normal pupil, imaging remains controversial. His preferred imaging modality is CTA; in particular, its maximum intensity projection (MIP) images not only show the vascular supply, but also reveal the brain better than a conventional CT scan because of its thin slices and excellent resolution. With this technology, it’s almost like you’re getting two studies in one. Dr. Vaphiades reserves non-contrast MRA for patients who are pregnant, have impaired renal function, or can’t tolerate the contrast dye used for CTA.

**Further testing as needed.** CTA should detect aneurysms as small as 3 mm in size, if CTA results are equivocal, the next step is a lumbar puncture to check for blood in the cerebrospinal fluid and conventional digital subtraction angiography—the gold standard for confirming the presence of an aneurysm.

**MANAGING THIRD CRANIAL NERVE PALSY**

---

**Complete third-nerve palsy.** (1) A 20-year-old man with a compressive right pupil-involving third cranial nerve palsy from a right PCOM aneurysm. The right eye is “down and out” with complete ptosis and a fixed, dilated pupil. (Arrows indicate direction of gaze.)
If the diagnosis is an aneurysm, the patient is immediately admitted for neurosurgical clipping. After the surgery, both neuro-ophthalmology and neurosurgery may follow the individual on an outpatient basis.

The clinician must be able to quickly determine whether the patient has arteritic anterior ischemic optic neuropathy (AAION) or non-arteritic anterior ischemic optic neuropathy (NAION). NAION does not require immediate treatment or a specific intervention. AAION, however, is associated with giant cell arteritis—an ophthalmic emergency in which a missed diagnosis can be devastating.

The single most important task in evaluating a new case of anterior ischemic optic neuropathy is to recognize the 10 percent or so of patients who have an arteritic condition. These patients have about a 75 percent risk of going blind in the other eye within days if it is not recognized and treated. To avoid that worst-case scenario, if you have a high suspicion of giant cell arteritis, you should send the patient to the emergency room for the lab workup and, potentially, immediate parenteral steroid treatment.

DISTINGUISHING AAION FROM NAION

The ophthalmologist must go through a series of steps to rule out AAION. The arteritic form is more common among lightly pigmented individuals and rarely occurs in people younger than age 50 or 55 (the mean age is 70). He added that the patient may present with generalized malaise or muscle pain, but the most important additional signs are jaw claudication, headaches, and scalp tenderness. If these are present in any form in the patient’s history, they raise the stakes much higher for arteritic ischemic optic neuropathy. However, that about 25 percent of AAION patients have no prodromal symptoms.

In contrast, the mean age for NAION is 60. NAION arises with no warning and no prodrome, either systemic or ocular. With these patients, one moment they are fine, but the next moment they have a problem. They often have some risk factors, including diabetes and possibly elevated lipids and hypertension—but diabetes is the only generally accepted risk factor. Five AAION findings listed the key findings that point to a diagnosis of AAION:

- Severe vision loss to counting fingers or worse
- Chalky white swelling of the optic nerve (Fig. 3; compare with hyperemic swelling in NAION, Fig. 4)
Evidence of retinal ischemia (i.e., cotton-wool spots or retinal artery occlusion)
- Abnormalities in perfusion of the choroid on fluorescein angiogram
- Abnormal exam of the temporal artery under the skin of the scalp

These are the five things we think about when we look at these patients.

**Three tests for patients over 50.** Every patient with anterior ischemic optic neuropathy who is over age 50 should have three stat laboratory tests: ESR, C-reactive protein, and platelet count. “Generally, elevation of any two of these increases the likelihood of arteritic ischemic optic neuropathy a great deal, When in doubt, the ophthalmologist should not hesitate to treat the patient with steroids while he or she is trying to figure this out. If the suspicion is high, we would prefer that the patient be on steroids, even if unnecessarily, for up to four days while waiting for the test results. Biopsy if indicated. The history, exam, and laboratory findings determine whether the patient should have a biopsy of the temporal artery. Dr. Volpe emphasized that steroid treatment should not be delayed while waiting for a biopsy because treating the patient for several days will not affect the biopsy’s accuracy.

**MANAGING AAION**

General ophthalmologists can certainly diagnose AAION and initiate treatment, but they may want to involve a neuro-ophthalmologist in decision making about biopsy and chronic steroid use. Once the diagnosis is established, he said, it is not unreasonable for an ophthalmologist to work with a rheumatologist to manage a patient with giant cell arteritis.

**WHAT ABOUT PATIENTS WITH NAION?**

The non-arteritic form currently has no specific treatment, although some experts will put patients on systemic steroids, particularly if the condition is progressive. Identification of risk factors such as diabetes, hyperlipidemia, and hypertension, as well as a history of sleep apnea. A controversial issue is whether they had used erectile dysfunction drugs around the time of their event. Although the association is unproven, if they did use ED drugs, most of us will prefer that the patient be on steroids, even if unnecessarily, for up to four days while waiting for the test results. Biopsy if indicated. The history, exam, and laboratory findings determine whether the patient should have a biopsy of the temporal artery. Dr. Volpe emphasized that steroid treatment should not be delayed while waiting for a biopsy because treating the patient for several days will not affect the biopsy’s accuracy.

**MIMICKING CONDITIONS**

Certain conditions can mimic anterior ischemic optic neuropathy. In a younger patient, for example, the profile for ischemic optic neuropathy overlaps that of optic neuritis. The same is true for neuroretinitis and other inflammatory or infiltrative conditions. As soon as the case seems to be progressing, involves pain, or is associated with atypical disc findings, a more detailed workup is indicated, including an MRI scan and blood workup for systemic inflammation and multiple sclerosis.

**HORNER SYNDROME: Red Flags for Systemic Disorders**

The patient who presents with a droopy eyelid, miosis, and anhidrosis on one side is probably not in danger of losing vision. But those telltale signs of Horner syndrome are red flags for possible underlying malignancy, stroke, or aneurysm. More commonly, though, the underlying cause is benign. Previous neck or open heart surgery or cluster headaches, for example, might have caused damage along the sympathetic nerve pathway and triggered Horner syndrome. But with Horner, the physician must always suspect the worst.

**DIAGNOSING HORNER SYNDROME**

Horner syndrome results from a lesion somewhere along the pathway of a paired three-chain nerve in the sympathetic nervous system. The physician’s job is to find that lesion. The first step is to recognize the syndrome. The classic presentation includes ptosis, anhidrosis on the affected side, and pupil dilation lag after abrupt reduction in illumination (the affected pupil is much slower to dilate). But it’s possible to misdiagnose Horner syndrome as Adie’s tonic pupil, physiologic anisocoria, a reaction to topical brimonidine, or pseudoexfoliation syndrome. Testing with 0.5 percent apraclonidine in both eyes will help confirm the diagnosis: In Horner syndrome, the affected pupil will dilate and the eyelid will sometimes elevate in response to apraclonidine, while the unaffected eye will change minimally, if at all. In infants six months of age or younger, cocaine testing should be used instead because apraclonidine can penetrate the blood-brain barrier and cause respiratory depression.

**IDENTIFYING THE UNDERLYING CAUSE**

**History.** Once Horner syndrome is confirmed, Dr. Kardon tries to establish the date of onset, sometimes resorting to family pictures. Is it new or has it been there for years? The new ones are more worrisome. A history also includes questions about head or neck trauma, such as accidents or surgery that might have damaged the sympathetic nerve.

**Localizing the lesion.** Most patients with Horner syndrome get an MRI. But unless it’s an emergency, Dr. Kardon prefers to wait until he has run a second pupil test, this time with topical hydroxyamphetamine. (If cocaine was used to diagnose Horner, three days should elapse before the hydroxyamphetamine test. With apraclonidine, testing can be done the next day.) The hydroxyamphetamine test differentiates between Horner caused by damage along the first or second
nerves in the chain (preganglionic Horner) and that caused by a lesion in the last nerve in the chain (postganglionic Horner). If the location is preganglionic, the affected pupil will dilate, but if postganglionic, the pupil will not change.

This distinction makes it easier to pinpoint where to direct the imaging. Some doctors order an MRI covering the entire sympathetic pathway. The problem with that is it costs more, because you’re imaging a larger area of real estate. It also makes it uncertain where to look on an MRI. If the lesion is small and you’re not sure where along the chain to focus, it can be missed during reading of the scan. That’s why we use the hydroxy-amphetamine test.

A case in point. The case of a 52-year-old woman who came to Dr. Kardon after developing Horner syndrome, highlights the importance of the hydroxyamphetamine test (Fig. 5). She had previously been diagnosed with a benign cavernous sinus meningioma that caused a sixth nerve palsy with double vision. This history suggested that the new Horner syndrome was caused by a lesion along the postganglionic sympathetic nerve at the site of the meningioma. But it wasn’t. The hydroxyamphetamine test showed it was in a preganglionic location. So we imaged her. Our image showed that she had a metastatic breast cancer, which had not yet been diagnosed.

WHAT’S THE WORST IT CAN BE?

Malignancy. Everyone’s concerned about neuroblastoma when they see a child with this syndrome. Although it’s treatable, it can be deadly if not diagnosed early. In adults, Horner may be caused by tumors occurring along the sympathetic chain, including lung tumors, thyroid cancers, and metastatic tumors.

Stroke. The first nerve of the three-nerve chain travels along the brain stem, the lower part of which is the medulla. Horner syndrome may signify a stroke in the lateral part of the medulla. These patients can be walking and talking, and it’s not always obvious that they have a stroke.

Vascular dissection. A patient may present with pain on the side of the face that can go into the ear or jaw and is sometimes mistaken for a toothache. But there could be a carotid dissection—a tear in the artery causing bleeding that compresses the postganglionic sympathetic fibers. A carotid dissection may cause a small clot to form, which can break off and lodge in the brain. Patients should be carefully monitored for signs of stroke.

Aneurysm. This potentially lethal vascular problem may occur in the carotid artery farther up in the brain. As the aneurysm expands, it may compress the nerves and cause a sixth nerve palsy and Horner syndrome. Patients may present with double vision and Horner.

WHEN NOT TO WORRY TOO MUCH.

Cause unknown. Sometimes you don’t discover the underlying cause, for example, a problem may be localized to the preganglionic nerves, but the imaging is negative. In such cases, Dr. Kardon reassures the patient that he’s not seeing the cause, the patient is followed for at least another year to make sure nothing else crops up to make us want to reimage the patient.

A happy ending. A 50-year-old man slipped and fell on a dock. Prior to the trip he had a checkup and was declared fit. But the morning after the fall, he...
noticed that his right eyelid was drooping. He also experienced pain on the right side of his face that was so severe and returned home he went to his dentist, who extracted a tooth. But the pain persisted, as did the droopy lid. After noticing a change in his pupil, he saw Dr. Kardon. An MRI revealed a right carotid dissection, probably related to his fall. Dr. Kardon put the patient on antiplatelet medication to reduce the chance of clot formation. The man weathered the episode without a stroke, and the pain eventually resolved.

**Bottom line.** Be vigilant in making the diagnosis and looking for the underlying cause. Even if the actual syndrome doesn’t cause much dysfunction, it’s a red flag that something serious may be going on.

**PITUITARY ADENOMA: Recognize the Visual Field Patterns**

Before the advent of MRI and sophisticated hormonal blood tests, pituitary adenomas were often diagnosed by the ophthalmologist. Depending on the patient’s complaint—headache, hormonal changes, or visual disturbance—the initial diagnosis may be made by a neurosurgeon, an endocrinologist, or an ophthalmologist. Ultimately, however, the three specialties work together to treat the patient. Often the finding is incidental, as, for example, when an MRI is ordered for a headache or injury. Or the patient may present with a hormonal problem. Then the ophthalmologist gets involved to determine if vision is affected. The good news is that pituitary adenomas do not grow quickly, and they’re usually benign. They don’t spread. They don’t kill you. But they can disturb vision and even lead to blindness by putting pressure on the chiasma or other parts of the visual system in that area, such as the optic nerve and optic tracts. Visual field testing is essential. Automated perimetry is a must. It is also important to assess visual acuity, pupils, and optic disc appearance. Bitemporal defect is a classic finding. But remember that pituitary tumors can present in more ways than just the classic bitemporal visual field defect. For example, in a non-classic visual field, one side may look bad, while the other side shows only a mild defect (Fig. 6). It’s still a bitemporal field defect, but not complete. The asymmetry can throw people off. In some cases, one might even see a unilateral temporal defect if the compression is occurring at the distal optic nerve just before the chiasma (Fig. 7).

Another variation of visual field sometimes seen in pituitary adenoma is the so-called “junctional scotoma,” or anterior chiasmal syndrome (Fig. 8). In this situation, there is central loss of vision due to optic nerve compression in one eye and temporal loss in the other eye due to chiasmal compression. An ophthalmologist could miss the diagnosis by not recognizing that these unusual visual field presentations may be related to pituitary tumor. In such cases, especially if the eye looks healthy, it’s tempting to do nothing and tell the patient to return in six months. But it is warned that a delayed diagnosis may lead to serious vision problems.

**Seek out hormonal disturbances.** If the visual field isn’t a slam dunk. It is advised asking questions related to hormonal dysfunction. Because the pituitary gland controls most of the body’s endocrine functions by

secreting various hormones, any physical changes related to hormonal disturbance may help confirm the diagnosis. For example, an elevation of the hormone prolactin can cause galactorrhea (inappropriate lactation) in women and impotence in men. Elevated growth hormone can cause fingers, hands, and feet to grow. We ask about changes in ring size, shoe size.

Masqueraders. Of course, any compression on the chiasm or other parts of the visual system can affect vision. So you must consider a diagnosis of any other tumor, an aneurysm, or a demyelinating plaque related to MS. “MRI will rule those out,” (Fig. 9).

MANAGING PITUITARY ADENOMA

If the ophthalmologist discovers the tumor, the next stop is referral to a neurosurgeon. Not all pituitary adenomas need to be removed; medication, radiation, and watchful waiting are other management options. If a tumor isn’t removed and isn’t causing visual problems (tumors smaller than 10 mm typically don’t affect vision), Dr. Golnik repeats the visual field test every six months, as the tumor can grow. If it doesn’t change for a year or two, I switch to an annual exam. If the tumor is removed, the ophthalmologist follows up with postoperative perimetry. If the tumor isn’t completely removed, the patient needs subsequent perimetry at regular intervals.

Visual prognosis. Patients often ask, Will my vision get better? If OCT shows a loss of the nerve fiber layer, the answer is no. But in other cases, vision may return rapidly. For example, tumors that produce prolactin can be shrunk with medications, including bromocriptine and cabergoline. Vision can improve dramatically in a week or two, from nearly blind to 20/20. But timing is everything—the visual outcome depends on how long the tumor has been pressing on the chiasma or optic nerve. The main issue for the ophthalmologist is to recognize some of the non-classic visual field patterns, because prognosis for visual recovery depends on the timeliness of diagnosis.

REFERENCE:

(This article is a guide for postgraduates and does not need many references . . . .  Editor)
CONGRATULATIONS

Dear Prof. Yasin Durrani

I am writing to express my deep gratitude to you for sending me the printed copy of your excited journal, which reached me safely and which I have read with great interest as usual, particularly your editorial on ‘Diabetic Retinopathy–Current Concept’ available online earlier. You have chosen not only the topic of permanent interest, but also the latest hot update on DR-neurovascular origin of it, which is very knowledgeable for wide auditorium of Ophthalmology Update’s readers, taken into account the latest publication in Aug 2012. My congratulations!

Taking this opportunity I would like one more time to thank you very much for publication of my paper and also for your kind cooperation. Wishing you continued fruitful work and prosperity. Warmest regards,

Prof. Marianne Shahsuvaryan Ph.D., D.Sc.
Republic of Armenia

Dear Prof. Durrani,

RECOGNITION OF OPHTHALMOLOGY UPDATE BY HEC

I heartily congratulate you and others who have worked hard towards the approval of the Ophthalmology Update by the Higher Education Commission of Pakistan. I became aware of Ophthalmology Update couple of years ago and was very impressed and happy to find very high quality contents which are very informative and much needed by the ophthalmologists for their every day practice and research work. It is all due to your extreme dedication and hard work. We are very grateful for bringing a Pakistani ophthalmic journal to international standards and making Pakistan proud of it. God bless you.

Sincerely,
Syed S. Hasnain M.D.
in the disc, whereas the severing of the smaller blood vessels will result in hemorrhages at the disc margin and characteristic whitish pallor, devoid of inflammation in the disc. The severing of the nerve fibers results in more sinking of the disc since the nerve fibers also provide anchorage to the optic disc as roots do to a tree. The cascade of sinking disc and severing of the nerve fibers will become self-propagated and will continue until all the nerve fibers are severed at the scleral edge and the optic disc is totally destroyed.

It may be difficult to give accurate stages to the glaucomatous disc since the sinking and severing of the nerve fibers is a continuous process. However, a glaucomatous disc may be divided into three stages. In the early stages there will be increased visibility and prominence of the border area of the disc. Temporal area of the disc sinks first due to its inherent temporal tilt. Temporal area will appear sunken and shallow due to severing and depletion of the nerve fibers and pale due to severing of the vasculature. Temporal vessels will appear sloping on the surface of sunken area. As the severing of the nerve fibers progresses, the excavation will eventually obliterate the physiological cup by the production of superior and inferior notching of the physiological cup and corresponding visual field defects will appear. We may start noticing nasal shifting of the blood vessels due to severance of temporal nerve fibers.

Analogy: if we cut the roots of the tree from one side, the tree will shift towards the opposite side. This may be called an intermediate stage of glaucoma. Other signs appearing in the glaucomatous disc are peripapillary atrophy, which is more likely due to destruction of blood vessels of circle of Zinn-Haller which supply the border tissue. Another characteristic feature is the bald appearance around the disc due to severance of smaller blood vessels.

In the later stages, an entire disc area will appear pale and excavated. Blood vessels will be kinking more due to the underlying depletion of the nerve fibers. The entire rim of the scleral opening will become visible due to extreme thinning of the RNFL. At the end-stage, the entire disc will appear excavated. Smaller blood vessels would have disappeared after their severance whereas the larger blood vessels are left hanging on the scleral rim. Histology of the end-stage glaucomatous disc reveals a large empty bean-pot; therefore it cannot be a deeply cupped disc as widely believed, but a left over area after the severance of entire RNFL.

In summary, the optic disc may be sinking (herniating) in the scleral canal. As a result, the nerve fibers, along with blood vessels, are being continuously severed resulting in empty spaces (excavation) and the characteristic whitish pallor of the optic disc. If we keep these aforementioned events in mind, then the diagnosis of glaucoma not only becomes easy but we would also know, based on the amount of sinking, kinking of the blood vessels, excavation and pallor, the every stage of a glaucomatous disc. I am certain that my colleagues would find this method so easy and convincing that they may not need cup/disc ratio or DDLS or anything else for evaluation of the disc for glaucoma.

REFERENCES:

Syed S. Hasnain M.D.
General Ophthalmology
Porterville, California, USA
Email: hasnain40@sbcglobal.net

19th Annual Hyderabad Ophthalmic Conference 2012
to be held from 9th, 10th & 11th November, 2012 at Hotel Indus, Hyderabad.

Theme: Current Trends in Ophthalmology

Please contact:
Prof. Dr. Khalid Iqbal Talpur
General Secretary
OSP Hyderabad
& Secretary
Organizing Committee

Phone: 0300-3049951
E-mail:khalid_talpur@hotmail.com
Grapes play a pivotal role in preventing innumerable health disorders and can be used as home based remedies for several ailments. Grapes are a popular snacks as well as a refreshing addition to vegetable salads, giving a sweet tart flavor. They are usually found in nature in various colors, due to presence of anthocyanins. The colors are crimson, black, dark blue, yellow, green, pink and orange (popularly known as ‘Sunder Khani’ grapes), originally from Sultana grapes of Turkish origin. Dried grapes are known as raisins, we call them *Kishmish or Mewa*, popularly used during winter as dry fruit to thwart the effects of cold, providing instant energy to the body. These are usually eaten raw. Grapes are the primary source of 71% of red and white wine; 27% are used as fresh fruit and 2% as dried fruit. Apart from that they are also used for making jams and jellies.

Grape seed extract can be used for treating high blood pressure, asthma, cancers and increases nitric oxide in the blood which prevents blood clotting there by reducing the chances of heart attack. The anti-oxidants present in the grapes prevent the oxidation of LDL cholesterol which blocks the blood vessels. Grape seed oil is used in salads, dressings, as flavored oil, marinades, baking, in sun-burn lotions, massage oil, lip balm, hair medications, body creams and hand creams. Raisins are extremely nutritious, help in many disorders, including constipation, acidosis, anemia, fever, eye care, generalized weakness and gaining weight. Grapes are rich source of Vitamin A, C, B6, folic acid, essential minerals like potassium, calcium, iron, phosphorus, magnesium and selenium. Ripe grape juice is an important home-made remedy for migraine. Grapes are considered as laxative food and very effective in overcoming chronic constipation, dyspepsia and indigestion as it contains organic acid, sugar and cellulose. The anti-oxidants present in grapes also provide the needed boost to our immune system. A recent study has shown that purple colored concord grape juice help in preventing the breast cancer.

Resveratrol, a beneficial polyphenol present in grapes reduces the level of amyloidal beta-peptide in patients with Alzheimer’s disease and stalls the neurodegenerative process in the brain. Additionally grapes can prevent the age related macular degeneration by over 36%, if 3 serving are taken a day. The flavonoids present in the grapes have an anti-oxidant effect and reduce the damage caused by free radicals in cases of cataracts and age related problems like cardiovascular diseases and cancer.

Red grapes have strong antibacterial and antiviral properties and can protect us from infections especially poliovirus and herpes simplex virus. Grapes contain a compound called *Pterostilbene* which has the capacity to reduce cholesterol level. Saponins present in grape’ skin can also prevent the absorption of cholesterol. Thus, grapes play an important role in preventing innumerable health disorders and can be used as home based remedies for several ailments.
Instructions to the Authors

All materials submitted for publication should be sent to the journal ‘Ophthalmology Update’. Articles/research papers which have already been published or accepted elsewhere for publication should not be submitted. A paper that has been presented at a scientific meeting, if not published in full in proceeding or similar publication may be submitted. Press reports of meetings will not be considered as breach of this rule.

Ethical Aspects: If articles, tables, illustrations or photographs, which have already been published, are included, a letter of permission for republication (or its excerpts) should be obtained from the author(s) as well as the editor of the journal where it was previously published.

Material for Publication: The material submitted for publication may be in the form of original research, a review article, short communications, a case report, recent advances, new techniques, review on clinical/medical/ophthalmic education, a letter to the editor, medical quiz, Ophthalmic highlights/update, news and views related to the field of medical sciences. Editorials are written by invitation. Report on Ophthalmic obituaries should be concise. Author should keep one copy of the manuscript for reference, and send three copies (laser or inkjet) to the Managing Editor, Ophthalmology Update through E-mail/CD or by post in MS word. Photocopies are not accepted. Any illustrations or photographs should also be sent in duplicate. Authors from outside Pakistan can also e-mail their manuscript. It should include a title page, E-mail address, fax and phone numbers of the corresponding author. There should be no more than 40 references in an original/review article. If prepared on computer, a CD should be sent with the manuscript.

Dissertation/Thesis Based Article: An article based on dissertation submitted as part of the requirement for a Fellowship can be sent for publication after it has been approved by the relevant institution. Dissertation based article should be re-written in accordance with the instructions to authors.

References: References should be numbered in the order in which they are called in the text. At the end of the article, the full list of references should give the names and initials of all authors in Vancouver style based on the format used by the NLM in Index Medicus. It verify the references against the original documents before submitting the article.

Peer Review: Every paper will be read by at least two staff editors of the editorial board. The paper selected will then be sent to one or more external viewers.

Abstract: Abstract of original article should be in structured format with the following sub-headings: Objective, Design, Place and duration of Study, Patients & Methods, Result and Conclusion.

Introduction: This should include the purpose of the study or observation should be summarized.

Methods: Study design and sampling methods should be mentioned. The selection of the observational or experimental subjects (patients or experimental animals, including controls) should be described clearly. The methods and the apparatus used should be identified and procedures described in sufficient details to allow other workers to reproduce the results and references to established methods. All drugs and chemicals used should be identified precisely, including generic names, doses, routes of administration.

Results: These should be presented in a logical sequence in the text, tables and illustrations. Only important observations should be emphasized or summarized.

Discussion: The author’s comments on the result, supported with contemporary references, including arguments and analysis of identical work done by others. Brief acknowledgement may be made at the end.

Conclusion: Conclusion should be provided under separate heading and highlighting new aspects arising from the study. It should be in accordance with the study.

Copyright: Material printed in this journal is the copyright of the publisher of Ophthalmic Newsnet/Ophthalmology Update and may not be reproduced without the permission of the editor/publisher. The publisher only accepts the original material for publication with the understanding that except for abstracts, no part of the data has yet been published or will be submitted for publication elsewhere before appearing in the journal. The Editorial Board makes every effort to ensure the accuracy and authenticity of the material printed in the journal. However, conclusions and statements expressed are the views of the authors and do not necessarily reflect the opinions of the Editorial Board. Publishing of advertising material does not imply an endorsement by the Ophthalmic Newsnet/Ophthalmology Update.

Address for Correspondence: The Chief Editor, Ophthalmology Update, 267-A, St: 53, F-10/4, Islamabad, Pakistan. E-mail: ophthalmologyupdate@gmail.com