Diabetic Retinopathy

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Introduction

Diabetes mellitus has become a major epidemiological problem across the world. Considering the micro-vascular complications that affect almost all organs in the body, the management of these patients can involve multiple specialties[1]. The eye is affected in a significant percentage of the patients and along with the kidney is an important cause of morbidity.

Epidemiology

It is estimated that there are about 135 million diabetics in the world in 1995. What is scary is the estimation that this number is likely to go up to 300 million by the year 2025[2]. Nearly a third of the patients are ignorant of their diabetic status. In Singapore the incidence of diabetes was 8.2% in 2004 and rose to 11.3% in 2010[3]. There seems to be significant difference among the ethnic races in Singapore, with Indians having the highest incidence[4].

In a pooled data analysis, global prevalence for any diabetic retinopathy was found to be 34.96%, that for proliferative disease 6.96% and for diabetic macular edema 6.81% - accounting for a prevalence of 10.2% of vision-threatening diabetic retinopathy[5]. Zheng et al have shown that among the migrant Indian population in Singapore, the risk of diabetes is 1 in 3 and that of retinopathy is 1 in 10[6]. They have also shown that 1 in 20 cases of bilateral blindness is due to diabetic retinopathy in this subset of Singapore population[7]. Similarly, 1 in 10 adult Malay diabetics were found to be at risk of vision-threatening diabetic retinopathy[8].

Pathogenesis and pathology

Non enzymatic glycation of sugars leads to formation of advanced glycation end products (AGEs). Increased polyol metabolism of glucose leads to altered signaling of pathways involving protein kinase C, nuclear factor kappa-B (NFK-B) and MAP kinase. These changes result in damage to retinal endothelial cells, pericytes, retinal pigment epithelial cells and neurons. Capillary basement membrane thickening and loss of pericytes takes place in the retinal vascular endothelium as the initial changes. The initial changes are characterized by the break down in blood retinal barrier, formation of microaneurysms etc. This is followed by closure of retinal capillaries leading to variable extent of ischemia. Proliferative retinopathy is characterized by formation of new blood vessels and fibrous proliferation.

The most important growth factor liberated is the vascular endothelial growth factor (VEGF) that has been found to be raised in both proliferative diabetic retinopathy as well as in diabetic macular edema. Other factors that may have a role to play in the causation of the diabetic retinopathy and its sequelae are the connective tissue growth factor (CTGF)[9], angioprotein (ang-2)[10], erythropoietin (Epo)[11], pigment epitheilium derived growth factor (PEDF)[12]. Matrix metallic proteinases, Intercellular adhesion molecules (ICAM 1), Insulin like growth factor (IGF 1), etc.

Clinical features

Diabetic retinopathy can be divided into background or non proliferative phase (NPDR) and proliferative phase (PDR). Macular edema can complicate both the non proliferative as well as proliferative phase. NPDR is characterized by presence of microaneurysms, retinal hemorrhages, dilated retinal veins, soft exudates (nerve fibre layer infarcts), intra retinal microvascular abnormalities (IRMA) and hard exudates (extra cellular lipid). The NPDR is sub divided into mild, moderate or severe. Mild NPDR is characterized by presence of only microaneurysms. The severe variety is characterized by the 4-2-1 rule i.e 4 quadrants of severe hemorrhages and microaneurysms, at least 2 quadrants of venous beading, and at least one quadrant of IRMA. Moderate NPDR falls between the two – more than just microaneurysms but less than the severe variety.

Macular edema

Macular edema is caused by leak from the incompetent retinal capillaries, microaneurysms, and IRMAs. Clinically it is characterized by retinal thickening with or without lipid exudation. Macular edema is classified into mild (some retinal thickening or hard exudates in posterior pole but distant from the centre of the macula); moderate (retinal thickening or hard exudates in posterior pole approaching the centre of the macula but not actually involving the centre) and Severe (Retinal thickening or hard exudates involving the centre of macula).

PDR

Proliferative diabetic retinopathy is characterized by proliferation of new vessels from retina (NVE) or from the optic disc (NVD). The onset of fibrosis and posterior vitreous detachment herald events such as pre retinal and vitreous hemorrhage, traction retinal detachment and sometimes combined traction and rhegmatogenous retinal detachment. The location and extent of the fibrovascular proliferation dictates the pathoanatomy.

Investigations

Fundus photography

Photographic documentation of the retina is done using standard fields. This not only serves as documentation but is an excellent way of screening large populations without the ophthalmologist having to visit the patients. Photography can be done at primary / family physician level and these pictures can be read by a centralized reading centre. Digital transmission of the photographs makes it easy to give the report in a few hours. Once abnormality is found, the patient can be referred to an ophthalmologist for physical evaluation.

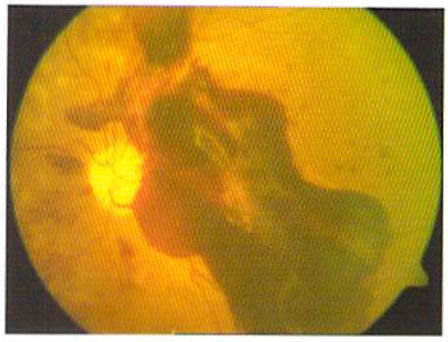

Figure 1 – Fundus picture of the left eye, revealing large areas of pre-retinal haemorrhage secondary to proliferative diabetic retinopathy.

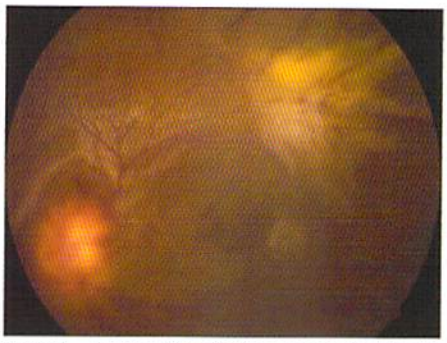

Figure 2 – Fundus picture showing advanced proliferative diabetic retinopathy with traction retinal detachment.

Fundus fluorescein angiography (FFA):

In this investigation, sodium fluorescein is injected intravenously and serial pictures of the retina are taken at close intervals. Normally this dye does not leak out of the retinal vessels. However in diabetic retinopathy, the dye leaks out of abnormal areas such as microaneurysms, IRMA, and new vessels and makes their presence easily detectable. The extent of retinal circulation can also be assessed and areas of capillary closure can be mapped. Presence of macular ischemia can be identified and this may have a bearing on the visual recovery following treatment for macular edema.

Optical coherence tomography (OCT):

OCT permits microscopic evaluation of the macula- almost to 3-4 micron resolution. It enables quantification of the amount of macular thickness and delineates subtle features such as foveal detachment, epimacular traction etc and is an excellent tool for follow up, after administering treatment for macular edema[13].

Ultrasonography:

In eyes with vitreous hemorrhage, ultrasonography permits the identification of any underlying retinal detachment. This evaluation would be important in deciding on when to operate.

Symptoms:

Sudden onset black spots are caused by mild to moderate vitreous hemorrhage while massive hemorrhage causes total loss of vision. Retinal detachment causes vision or field loss depending on its location. Macular edema produces more of visual acuity disturbance and difficulty in near activities. It must be stressed that diabetic retinopathy may remain asymptomatic till an advanced state is reached and hence the importance of screening.

Management:

Laser photocoagulation:

Laser photocoagulation is performed usually with green laser, although infra red laser can also be used for this purpose. The indications for laser photocoagulation are presence of new vessels (PDR) and macular edema. For new vessels, the treatment is administered as scatter treatment covering all quadrants of the peripheral fundus from the arcades up to equator and sometimes beyond. The burns are spaced one burn width apart and the treatment is usually delivered in 2 or more sessions. Macular edema is treated by focal laser to the leaky microaneurysms or IRMA within the macular area or as a grid pattern avoiding the central 300 microns of the retina around the fovea.

Additional (repeat) treatment may sometimes be done depending on the response. PASCAL laser is a recent innovation that permits more rapid scatter laser photocoagulation with relatively less pain and discomfort to the patient.

Treatment reduces the risk of severe visual loss in a majority of the cases[14].

Anti VEGF drugs:

The introduction of anti VEGF drugs such as Ranibizumab, Bevacizumab, and Pegaptanib sodium have revolutionized the approach to the treatment of diabetic complication of the eye. The intra vitreal administration of these drugs have become the preferred modality of treatment for macular edema with or without the laser photocoagulation[15,16,17]. Unfortunately the treatment efficacy is short lived (about 2-3 months) and hence there is need for repetition. These drugs have also been used for neovascularization of anterior segment and to reduce the vascularity of the fibrovascular tissue before surgery[18].

Intra vitreal steroid:

Triamcinolone acetonide is a drug that was found useful for macular edema when administered intra vitreally[19]. Recently long acting slow release devises (of dexamethasone) are available. These devices act for up to 6 months and hence eliminate the need for frequent injection as with anti VEGF drugs. However steroids in general have increased risk of glaucoma and cataract formation.

Vitreo retinal surgery:

Vitreo retinal surgery is recommended in cases with non resolving vitreous hemorrhage, traction retinal detachment involving the macula, traction- combined retinal detachment, pre macular fibrosis etc.

Follow up:

The first eye examination is recommended within 5 yrs of diagnosis if the patient is below 30 yrs of age, and when diagnosis of diabetes is made in patients over 30 yrs of age. Pregnant diabetics must have their eye examined within the first trimester.

If on first examination, there is minimal or no retinopathy, annual examination is recommended. In case of mild to moderate NPDR with no macular edema, a follow up after 6 months is recommended. In the presence of macular edema, severe NPDR, and PDR, the follow up is at about 3-4 month intervals.

Community health issues:

Control of blood glucose has been shown to delay the onset or progression of diabetic retinopathy in several studies[20,21,22]. Control of associated hypertension also has a beneficial effect[23]. In the treatment of diabetic macular edema, control of hyperlipidemia has been shown to have a beneficial effect[24,25]. Relevant to these facts is the observation of poor control of glycemia and blood pressure in the Malay population of Singapore[26].

Two studies from Singapore have shown the extent of negative impact that diabetic retinopathy has on the population, and specifically, the substantial difficulty in performing vision specific tasks on a daily basis[27,28].

Community health issues include increasing the awareness of this potential vision-threatening complication of diabetes, routine screening measures to facilitate early detection and timely management of diabetic retinopathy. Concurrently the importance of control of diabetes, hypertension and serum lipids should be highlighted to the population at large.

Associate Professor Lingam Gopal

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A/Prof Gopal completed his basic medical education from Andhra Medical College and did his postgraduate studies in ophthalmology from Postgraduate Institute of Medical Education and Research, Chandigarh, India. He did his fellowship in vitreoretinal surgery from Medical Research Foundation, Chennai and obtained the Fellowship of Royal College of Surgeons, Edinburgh.

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