UPDATE ON MANAGEMENT OF RETINAL / MACULAR DEGENERATION

Dr. (Mrs.) Manju Lalwani; Dr. Ajay Dudhani, MS, DNB, FCPS, DOMS

Overview Macular Degeneration

Age-related macular degeneration (ARMD) is a degenerative condition of the macula (the central retina). It is the most common cause of vision loss in the United States in those 50 or older, and its prevalence increases with age. AMD is caused by hardening of the arteries that nourish the retina. This deprives the sensitive retinal tissue of oxygen and nutrients that it needs to function and thrive. As a result, the central vision deteriorates.

Macular degeneration varies widely in severity. In the worst cases, it causes a complete loss of central vision, making reading or driving impossible. For others, it may only cause slight distortion. Fortunately, macular degeneration does not cause total blindness since it does not affect the peripheral vision.

Difference between wet and dry macular degeneration? AMD is classified as either wet (neovascular) or dry (non-neovascular). About 10% of patients who suffer from macular degeneration have wet AMD. This type occurs when new vessels form to improve the blood supply to oxygen-deprived retinal tissue. However, the new vessels are very delicate and break easily, causing bleeding and damage to surrounding tissue. Patient with wet macular degeneration develop new blood vessels under the retina. This causes hemorrhage, swelling, and scar tissue but it can be treated with laser in some cases. Dry macular degeneration, although more common, typically results in a less severe, more gradual loss of vision. The dry type is much more common and is characterized by drusen and loss of pigment in the retina. Drusen are small, yellowish deposits that form within the layers of the retina.

CAUSES OF MACULAR DEGENERATION

Genetics, age, nutrition, smoking, and sunlight exposure may all play a role.

SIGNS AND SYMPTOMS

- Loss of central vision. This may be gradual for those with the dry type. Patients with the wet type may experience a sudden decrease of the central vision.
- Difficulty reading or performing tasks that require the ability to see detail
- Distorted vision (Straight lines such as a doorway or the edge of a window may appear wavy or bent.)

Detection and Diagnosis

Eye physicians usually diagnose AMD.Vision Testing, Amsler grid test, ophthalmoscopy, fundus photography and fluorescein angiography are some common tests performed during a retinal exam.

Treatment

There is no proven medical therapy for dry macular degeneration. In selected cases of wet macular degeneration, laser photocoagulation is effective for sealing leaking or bleeding vessels. Unfortunately, laser photocoagulation usually does not restore lost vision, but it may prevent further loss.

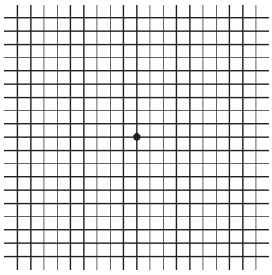
Recently, photodynamic therapy has proven to be effective in stopping abnormal blood vessel growth in some patients with wet AMD. This new type of laser treatment is far less damaging than laser photocoagulation and is the treatment of choice in many cases. Early diagnosis is critical for successful treatment of wet macular degeneration. Patients can help the doctor detect early changes by monitoring vision at home with an Amsler grid. Nutrition and macular degeneration Several recent studies have indicated a strong link between nutrition and the development of macular degeneration. It has been scientifically demonstrated that people with diets high in fruits and vegetables (especially leafy green vegetables) have a lower incidence of macular degeneration. More studies are needed to determine if nutritional supplements can prevent progression in patients with existing disease.

Tips for AMD patients

If you've been diagnosed with AMD, making a few

simple lifestyle changes could have a positive impact on the health of your retina.

- Monitor your vision daily with an Amsler grid. By checking your vision regularly, changes that may require treatment can be detected early.
- Take a multi-vitamin with zinc. (check with your eye physician for a recommendation). Antioxidants, along with zinc and lutein are essential nutrients, all found in the retina. It is believed that people with AMD may be deficient in these nutrients.
- Incorporate dark leafy green vegetables into your diet. These include spinach, collard greens, kale and turnip greens.
- Always protect your eyes with sunglasses that have UV protection. Ultraviolet rays are believed to cause damage to the pigment cells in the retina.
- Quit smoking. Smoking impairs the body's circulation, decreasing the efficiency of the retinal blood vessels.
- Exercise regularly. Cardiovascular exercise improves the body's overall health and increases the efficiency of the circulatory system.
- These are a few tips to make reading easier:
- Use a halogen light. These have less glare and disperse the light better than standard light bulbs.
- Shine the light directly on your reading material. This improves the contrast and makes the print easier to see.
- Use a hand-held magnifier. A drugstore magnifier can increase the print size dramatically.
- Try large-print or audio books. Most libraries and bookstores have special sections reserved for these books.
- Consult a low vision specialist. These professionals are specially trained to help visually impaired patients improve their quality of life. After a personalized consultation, they can recommend appropriate magnifiers, reading aids, practical tips, and many resources.
- Use a bright reading light
- Wear your reading glasses if appropriate



- Hold the chart approximately 14-16 inches from your eye
- Cover one eye
- Look at center dot
- Note irregularities (wavy, size, gray, fuzzy)
- Repeat the test with your other eye
- Contact ophthalmologist if you see any irregularities or notice any changes

I) MEDICAL THERAPY

A. Antiangiogenessis therapy

a) Thalidomide : The Amdats study

It has long been known tumours release chemicals that cause general destruction of healthy tissue. One of the most potent of these chemicals, tumour necrosis factor alpha I appears in.

This could explain thaliolomides apparent effectiveness in treating a variety of conditions. Though it is well established that thalidomide causes phocomelia (lack of limb development) in pregnancy for patients of non child bearing age its chief side effects seen to be mild drowsiness and reversible nerve changes in the extremities.

Researchers also observed some effect retarding the growth of new blood vessels that tumour require for growth.

As pertains in AMD researchers also found to be inhibit blood vessel growth in.

If growth of vessels from the choroid to retina could be inhibited it could help revent wet AMD.

THE AMDATS STUDY

Studies on patients with AMD are being conducted to determine whether thalidomide can inhibit the growth

of choroidal vessels into the retina. That cause wet AMD.

There are 2 studies involved

a) Determine thalidomides preventive potential

b) Determine thalidomide's potential to prevent recurrence in patients initially successfully treated with laser for wet AMD.

In both aims of the study, patients receiving thalidomide will take 100 mg/day for the first two weeks, increase to 200 mg/day in the third week and continue at hat level for 50 more weeks.

If the study demonstrates positive results the trial will probably be expanded to patients at more centers.

b) Troponin

Troponin is one of the newer generation antiangiogenesis factors.

In animal studies, anti angiogenic product troponin I appeared to inhibit blood vessels formation in an animal eye model of retinal neovascularisation.

A single intraocular injection of Troponin significantly ($p < 0.0005$) inhibited retinal angiogenesis in this models.

c) Angiotensin and Endostatin

Angiotensin and Endostatin are naturally occuring human proteins that inhibit angiogenesis. In mice they have been reported to prevent tumour growth due to their angiogenesis properties.

They are in research and will lead to a powerful, safe class of angiogenesis factors. No attempts have yet been reported regarding their study related to the eye.

d) PKC 412

A new anti angiogenesis agent called PKC 412 has halted abnormal growth of retinal blood vessels which cause vision loss in macular degeneration.

PKC 412 has completely stopped the growth of blood vessels in experimental animal models and human clinical trials will hopefully begin.

PKC 412 blocks chemicals in the body that faster new blood vessels growth (angiogenesis), causing vision loss in the macula. The drug promises to be an effective treatment for wet macular degeneration, the most devastating form of the disease effecting about 10% of MD patients.

e) Macugen

The drug is injected by needle directly into the eye to treat ARMD.

A study showed that macugen improved or stabilized vision in 33% of the 1,200 patients tested compared with 23% of the placebo ground that reported the same result.

B. Phototrop

Patients in the early stages of ARMD have shown a significant improvement after treatment with phototrop, a compound of acetyl-L-carnitine, highly concentrated amega-3, and co-enzyme A10.

A double blind, placebo controlled study showed that phototrop is effective in restoring mitochondrial and retinal functions in ARMD patients.

C. Nutritional supplements

Lutein is a dietary carotenoid found primarily in leafy green vegetables such as spinach.

The significance of tutein is that it, along with the related carotenoid zeaxanthin, are dominant pigments found in the macula.

It is felt that these yellow pigments (lutein) may sere to filter blue light from reaching the retina. Which has been established as a major cause of potic damage to the retina.

Furthermore, carotenoids are well known to have antioxidant properties. The outer reitna's photo receptor layer with its high proportion of poly-unsaturated fatty acids, is subjected to constant photochemical insults leading to oxidation and free radical formation.

Carotenoids may play a role in preserving normal and retinal and vascular function.

Supplemental "billberry" may be effective at preventing capillary leakage in conditions such as diabetic macular oedema as well as in macular degeneration.

D. Carbon –dioxide

AMD patients are benefiting form a new combination drug therapy being tested. The therapy involves a combination of medicines which includes carbon

dioxide, an element which dilates the blood vessels in the retina for the maintenance of proper blood flow.

It is the diminished circulation of these vessels that can cause the photoreceptor cells to deteriorate, leading to macular degeneration and loss of central vision.

Certain combinations of chemicals called "carbonic anhydrase inhibitors" given as eye drops is tricking the eye into maintaining its carbon dioxide while supplying important nutrients.

Reports have shown that 60 out of 65 patients have shown dramatically improved vision.

E. Echothiophate (ECHO) Therapy

A topical drop of ECHO can restore lost visual acuity in some cases of chronic retinal degeneration. Research has shown that ECHO appeared to increase the capability of the few surviving tumors, endowing this reduced population with enhanced stimulus potential.

For best absorption the drug must be administered before a good night's sleep.

F. Anecortave acetate

A modified steroid, anecortave acetate, developed by Alcon laboratories, actually inhibits abnormal vessel growth (neovascularisation) in patients with exudative (wet) macular degeneration.

The drug has a remarkable ability to supress the new vessel growth, which is the leading cause of vision loss in patients with wet macular degeneration.

The ongoing study analysed patients with similar abnormal vessel growth on their corneas. All patients demonstrated a total shut down of neovascularisatin of the cornea.

In wet macular degeneration, vision loss occurs when the breakdown of the basement membrane in the retina allows an opening for new vessels (neovascularisation) to grow up through the membrane and leak fluid into the overlying layers of the retina.

This fluid and blood eventually scars, leaving the patient with a dark grey or black distortion in their vision.

Alcon laboratories hopes that anecortave acetate will be the compound to inhibit growth of these vision robbing, abnormal vessels and would be a big step towards reducing the amount of legal blindness in AMD patients.

Although preliminary data suggests that Anecortave acetate is a safe compound the study is ongoing and safety is, as with only new drug therapy a concern.

II) LASER PHOTOCOAGULATION / DRUSEN LASERING

Published reports indicated pretreatment of the retina with laser photocoagulation in cases where aging spots were seen may help prevent the dry and wet form of macular degeneration.

These aging spots similar in appearance to aging spots on the skin are known to be loosely associated with macular degeneration. Low intensity argon laser a infrared diode lasers are use.

III) PHOTODYNAMIC THERAPY

Pretreatment with specialized chemicals preferred absorbed in abnormal new blood vessels and are sensitive to certain types of laser may allow more effective eradication of these vessels in the wet from of AMD.

IV) PRISMATIC INTRAOCULAR LENS

Using a specially designed intraocular lens one research effort has attempted to shift the focused rays of light outside the scared center.

This potentially allows the eye to recover vision with a "new center". While using a new region of the retina for central vision will not allow very sharp vision in return, restoring central acuity in any manner potentially improves quality of life and visual function.

V) GENETIC THERAPY

It is clear genetics plays a significant role in AMD. Progress is steadily being made forwards identifying which genes are responsible.

However, it will be several years until that identification is completed and optimistically several more before we devise a method for gene replacement or modification that is successful.

While axokine and other survival factors show great promise, it is not yet clear how these agents will be delivered to the retina. The retina is protected from direct exposure to the blood supply, making it difficult

for most drugs to reach photoreceptor cells. Therefore, survival factors cannot be delivered systemically VVA a pill on an intravenous injection.

Presently, injection into the eye is the most effective to deliver survival factors. Although eye injections are relatively safe, they are not the ideal way to deliver drugs.

Researchers are working to develop more effective drug delivery methods to the retina.

Gene therapy is the delivery of a gene or genetic information to retinal cells to achieve a therapeutic effect.

The gene therapy, in research has been used to deliver the gene that produces the survival factor known as basic fibroblast growth factor (bFGF) to retinal cells.

In addition to preserving vision in animal models with retinal degeneration the bFGF gene also produced this survival factor for long periods of time.

Although further work is needed, gene therapy may offer a more effective, long term drug delivery method than injection.

VI) MICROCURRENT STIMULATION THERAPY

MCS is a form of electrical acupuncture involving microcurrent stimulation applied at points around the eyes and elsewhere on the body.

Expectations are that the stimulation will boost the cells ability to rid themselves of waste products and raise the levels of nourishment and oxygenation by increasing blood flow.

After approximately seven office visits during the first tow weeks of treatment, the patient continues self treatment by purchasing a portable microcurrent machine.

Even in the absence of approved trials, some eye care professionals are promoting it as a safe and effective method for treating macular degeneration, retinitis pigmentosa, Stargardts disease and other retinopathies that lead to partial or total blindness.

VII. IMPLANTABLE MINIATURE TELESCOPE (IMT)

The importance miniature telescope (IMT) is being tested for use in AMD and other forms of macular degeneration.

The telescope is implanted into the eye into the same position that an intraocular lens would be placed after a cataract extraction (patients in the study have their cataract of lens removed).

It changes the images upto three times but only in the center.

The peripheral vision of that eye is eliminated by the placement of the telescope. In clinical trials, the implant is placed in the better eye.

The IMT is a microsized precision telescope, about the size of a pea, that is designed to magnify the images onto the retina. By magnifying images, it is hoped the blind spot caused by macular degeneration can be reduced in size; allowing for better central vision and associated function in daily activities.

The IMT is implanted by an ophthalmologist in an outpatient procedure.

The implanted eye provided magnified central vision. The non-implanted eye provides peripheral or "side" vision for mobility and navigation.

Since the IMT is implanted inside the eye, natural eye movements are used to scan the environment and leading materials.

It is not a cure –instead it is a method for projecting larger, brighter images to the retina.

VIII. PROTON BEAM RADIATION THERAPY FOR MACULAR

DEGENERATION

External from radiation therapy is being studied as a possible treatment for wet AMD.

In this type of treatment, xrays are directed at the eye, targeting the abnormal blood vessels under the macula. A potential advantage of radiation therapy is that is could possibly be used to treat a broader range of cases than the 10% to 15% that can be treated with laser therapy.

Some early studies have shown that the radiation therapy may limit or even reduce the growth of abnormal blood vessels under the macula. Some results suggest that people with wet AMD who are treated with radiation may have less vision loss that those who are not treated.

However, other studies have not been able to show that the treatment has any benefit.

Some researchers are also concerned about whether treating the eye with radiation may cause permanent damage to the cells in the retina, optic nerve, and lens, resulting in increased vision loss.

At this time, radiation therapy has not been shown to be an effective treatment option for people with ARMD. Not enough research has been done to understand the possible benefits and possible harmful effects of this treatment. More clinical trials and research are needed to determine whether people with wet AMD can benefit from this treatment.

IX. MACULAR TRANSLOCATION / RELOCATION SURGERY

A very intricate form of surgery on the central reina or macula has been dramatically effective in a few cases of wet AMD. Patients in sudden drop in vision caused by subretinal blood have had the macula literally moved off the region of bleeding underneath.

A few reported cases of dramatic success dating back to 1995 suggest. This treatment may play a role in cases of wet AMD treated before bleeding has caused permanent scarring of the forea.

The rational for foveal translocaiton is to relocate the sensory retina (fovea) onto the healthier retinal pigment epithelium.

Photocoagulation is the only treatment proven to be effective thus for in reducing the risk of severe visual loss form a CNVM due to myopic macular degeneration.

However, when photocoagulation is applied to the fovea, patients, experience an immediate decrease in visual function after treatment. There are various other options to treat subfoveal CNVM including radiation interferon and others, but none of these modalities cure the disease process at the fovea. Surgical excision and photodynamic therapy are currently being evaluated in prospective, randomised, muticenter clinical trials.

CASE REPORT

The surgical technique was, after conventional retrobulbar block, the following : Isolation of 3 rectus muscles and a 6mm cresent shaped scleral resection was performed in the 120^0 centered in the supero-temporal quardrant. Lately a variation has been performed placing 5-0 nylon mattress sutures in partial thickness covering the same area. The sutures were not tied until vitreous surgery was completed. A 3PPPV with detachment of posterior hyaloid to equatorial region was then performed. Peripheral breaks and lattice degeneration was treated using diode laser endophotocoagulation. Retinal detachment is created trans-retinal with a 40 gauge cannula. The cannula was placed outside of the temporal –superior arcades and BSS was slowly injected using a viscous fluid injector. Additional injections were made in the inferior arcade and temporal to the macula in order to obtain a bullous temporal RD. In some cases retina was manipulated to produce a complete sensory retinal separation from the RPE extending from the optic nerve to the or a serrata. A small air bubble was injected to avoid retinal incarceration when instruments were removed. Then intraocular pressure was lowered and the pre-placed scleral sutures were tied.

Finally, a fluid-air exchange was performed filling more than 50% of vitreous cavity with air subretinal fluid is not drained.

Sclerotomies and conjunctiva are sutured. Proper head position is recommended and then laser green photocoagulation applied in the CNV when retina is completely reattached.

IX. MICROELECTRONIC RETINAL IMPLANTS

Background

Microelectionic retinal implants are an example of research underway to restore some vision to those with severe vision loss by replacing a defect or missing link along the visual path way.

Microelectronic retinal implants in development include subretinal devices, designed to replace photoreceptors in the retina, and epiretinal devices, designed to communicate directly with the ganglion and bipolar and cells.

The purpose of both types of implants is to restore some vision by electrically stimulating functional neurons in the retina.

The implants are being developed to help people with degenerative disease of the retina such as retinitis pigmentosa, and macular degeneration.

All retinal implants require an intact optic nerve pathway to allow then to function.

Research into the results of electrical stimulation of the retinal surface showed that sensation to light could be produced and that retinal neurons are preserved after death of photoreceptors in retinitis pigmentosa.

Devices have been tested for feasibility and biocompatibility in animals.

Technology

There have been two approaches to creating microelectronic retinal implants.

The subretinal device or implant is a microelectrode assay powered by approximately 3,500 microscopic solar cells. The implant, called the "Artificial Silicon Retina®"; is 2mm in diameter and 0.001 inch in thickness. Dr. Alan Chow, an ophthalmologist, and Dr. Vincent Chow, co-founders of Optobionics®; co-operation developed the implant.

The premise of the design is the current generated by the device in response to light stimulation will alter the membrane potential of overlying neurons and thereby activate the visual system.

The epiretinal implant differs from this approach. An epiretinal device consists of several systems. The components will include a camera for image acquisition, image processing electronics, a telemetry system to provide power and data to the implanted subsystems, implanted electronics for signal decoding and stimulus generation, and an electrode array for delivery of change to the retina.

In another research, an epiretinal device includes the use of a miniature laser to provide power and signal to the implanted photodiode array.

The array will convert incident light into electrical current. Another component of the implant, the stimulation chip, will control the distribution of current.

Development of retinal implants hope that the devices will restore the ability to distinguish between light and dark and to see dim outlines and shapes for patients blind from retinal degenerative diseases.

Results

There are no reports in the peer reviewed literature of retinal implants in humans.

According to a company report, two patients had smaller versions of the Optobionics corporations microelectronic retinal device implanted. These two patients and a third who received on implant the following day, had almost all their vision because of retinitis pigmentosa.

Their surgery was undertaken as a first step in feasibility and safety studies in humans required by US FDA before any clinical trials can be undertaken.

The third patient received an implant the following day at a nearby hospital.

There were no reported complications from the surgery.

Retinal implants are at a very early stage of development. Additional basic research to prove the concept and clinical trials to demonstrate safety and effectiveness will probably take several years to complete.

XI. RETINAL CELL TRANSPLANTATION PHOTORECEPTOR CELL

Cell transplantation is one way of limiting the progress of retinal degeneration in animal models of binding diseases such as RP and AMD.

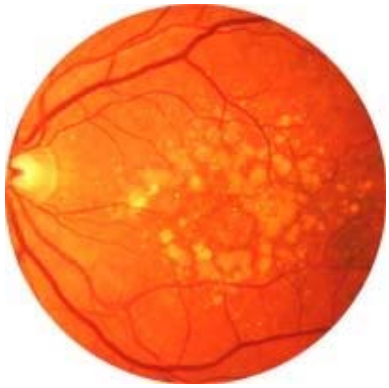
Here a human RPE cell line was transplanted into the subretinal space of a rat model and showed, using head tracking to moving stripes and pattern discrimination in conjunction with single – unit cortical physiology, that cortically mediated vision can be preserved with this treatment.

The researchers used cells which developed spontaneously from human eye, thus avoiding the ethical issue of taking cells from immature fetuses.

Contact Details :
Dr. (Mrs.) Manju Lalwani
Pramukhswami Eye Hospital
Near Rly. Stn., Chunabhatti (E),
Mumbai - 400 022.
Tel. : 2405 5151 / 2405 5252

Dr. Ajay Dudhani
Zen Eye Centre
Tel. : 2604 7107

This example demonstrates what a patient with advanced macular degeneration sees.



Drusen