Abstract

The first part of the article describes various factors increasing the risk for angle closure glaucoma, such as older age, female sex, being Asian, having blood relatives with glaucoma, having smaller eyes (far-sightedness) and individual features of the eye. It emphasizes that angle closure glaucoma is more a disease of higher than normal eye pressure than is open angle glaucoma. The author explicates in comprehensible anatomic details the process, mechanism and first means of treatment of angle closure, specifics of hyperopic eyes, the nature of pupil block.

In the next part of the article the author answers the most pressing question for all glaucoma patients: will I be blind? He explains that though glaucoma presents a real threat to the vision of anyone who develops it, if a person continues to follow the standard care instructions, there is a good chance that he will preserve much of his sight until the end of his life. At the same time the author emphasizes the irreversibility of the vision loss and the importance of adhering with the treatment program, describes several characteristic signs and symptoms of glaucoma, and gives a brief account of the anatomical reasons behind them. Vision loss statistics is also presented.

The next section forms of definitive treatment for glaucoma are discussed. Today restoring the lost vision still remains a future hope, however, present treatments can slow the process so much that no meaningful loss might occur in the person's lifetime. Successful glaucoma surgery can lower eye pressure to a safe level, but it is important to keep having doctor's exams regularly even when successful surgery has been done. The other kind of successful treatment for most persons with glaucoma is to take daily eye drops indefinitely. Several hypothetic ways of prolonging the effect of glaucoma medicine are discussed, such as long-lasting drugs and virus particles carriers. Current neuroprotection therapy research and the initial steps of nerve cell replacement are also mentioned.

The last part of the article gives an account of genetic background of glaucoma and present research of genetic risk factors, and underlines the importance of intrafamilial information sharing and regular glaucoma check-ups.

KEY WORDS: glaucoma, angle closure glaucoma, risk factors, intraocular pressure, follow-up examination.
Factors increasing the risk for angle closure glaucoma

- Older age (again)
- Female sex (that’s different)
- Being Asian
- Having blood relatives with it
- Having smaller eyes (far-sightedness)
- Features of how internal eye structures behave (iris, choroid)

As with open angle glaucoma, older persons are more likely to have angle closure. We have seen people in their twenties with the disease, but that is very rare. The rate peaks around age 60 or so, at least in part because the natural tendency is for eyes to get shorter (slightly smaller) with time. By contrast with open angle glaucoma, angle closure affects women probably 50% more often than men. The reasons for this aren’t completely settled, but we do know that women have smaller eyes and that is one of the contributors.

For reasons that aren’t yet fully understood, Asian persons have a lot more angle closure than everyone else in the world, though it may be that east Indians also have a greater risk. Asians don’t have more of the other risk factors; at least present research says that their eyes don’t have more of the other contributing factors, such as more persons with smaller eyes. Asian eyes look a little different from Europeans because they have different eyelid structure, not because their eyes themselves are a different size. The contribution of

family history (genetics) to angle closure is real, but not as well studied as for open angle glaucoma. No actual mutations or DNA code mistakes in particular genes are known that are associated with angle closure yet. Without question, however, if your mom (or another close blood relative) had it, you are at least somewhat more likely to have angle closure as well.

Angle closure glaucoma is more a disease of higher than normal eye pressure than is open angle glaucoma. As discussed in a previous section, the process of angle closure means that the iris moves to block the trabecular meshwork, raising eye pressure and causing damage. This can happen either suddenly (an acute angle closure crisis) or more commonly as a silent but on-going process that gradually plugs up the meshwork with iris stuck to it, leading to a chronic disorder. The dominant reason for the iris to block the meshwork is that it starts out close to the outflow area in the first place in smaller eyes. Smaller eyes are often “far-sighted” (hyperopic). Persons with hyperopia develop the need for eyeglasses in mid-life and become unable to read print without glasses earlier than everyone else. When we measure the length of their eyes, they are shorter than average, with crowding of the structures together. This slows the movement of aqueous humor from where it is produced behind the iris (at the ciliary body) through the pupil (between the iris and lens) and into the front chamber (anterior chamber) of the eye. Because the block of aqueous movement is at the pupil, doctors call it pupil block. If there were an opening in the iris, the fluid couldn’t be blocked — so the
first treatment for angle closure is to make a hole where there isn’t one naturally. This is done in the office with a laser, pretty painlessly, with only eyedrop anesthesia.

More detail about the risk of developing angle closure glaucoma and treatment or no treatment for suspects for angle closure is included in the section “Why isn't glaucoma either there or not there — what makes you an angle closure suspect?”

Will you go blind?

Take Home Points

- Odds of going blind are low
- Once damage happens it can’t be fixed
- Relatively more blindness from angle closure than open angle glaucoma
- We must prevent damage before it happens
- Adherence with the treatment program improves your chances

If you are like many persons that we have cared for, one of the first thoughts you have when presented with the knowledge that you have glaucoma is: will I be blind? The good news is that if you are not blind at this time, there is a very good chance that you will never be blind, at least from glaucoma. It is true that glaucoma is the second leading cause of blindness in the world after cataract. And, it presents a real threat to the vision of anyone who develops it. But from scientific studies all over the world and among persons just like you, we can say that the vast majority of persons who know that they have glaucoma, and who continue to follow the standard care instructions, will arrive at the end of their lives still reading and seeing well enough to enjoy life from both eyes.

Once we are adults, we don’t grow any new cells in our brain. Since glaucoma kills nerve cells that are truly part of the brain, it is not surprising that once vision is lost from glaucoma, it cannot be restored. The nerve cells that are dead were part of an intricate network in the retina and had a long fiber stretching inches up into the brain to begin a visual process that is more complex than we can even imagine now. Our best hope for the glaucoma patient, and the goal of treatment, is to save the vision that is left. We can do that to such an extent that most of those with glaucoma will live normal visual lives. Research in our laboratories and in others is presently working very hard to find ways to restore lost vision from glaucoma and other diseases, but at present nothing can be done to return vision that has been lost from glaucoma.

Actual statistics show that about 5% of European-derived persons with glaucoma will lose the ability to read standard print in both eyes from open angle glaucoma. The number is 3 times higher among African-Americans. And, it is also 2-3 times higher for those with angle closure glaucoma. But, many of this small percentage who become blind are those who were nearly blind before they found out that they had glaucoma.

A famous glaucoma specialist from Boston, Morton Grant, wrote about his many years of seeing and studying glaucoma. He concluded that those few patients who did badly and lost their vision from glaucoma were most often those who didn’t follow care instructions or who came to the doctor too late. For the persons in that group, we have included a section “What does low vision treatment have to offer?”

Again, looking at real statistics, about 15% of glaucoma patients will lose the ability to read in one eye. That is a tragedy for them and hurts their ability to do some things that require vision to see in 3 dimensions, what is called depth perception. Having lost one eye, one is more likely to knock over the salt shaker at dinner, or to stumble on stairs and curbs. Glaucoma damage decreases the contrast sensitivity of the vision system, so what seemed like a black and white page of print before is now more grey and white. Glare is more of a problem for the glaucoma patient. And, you must develop methods to adjust to changes in lighting when moving from bright sunshine to dark interiors, or the other way around. Each of these effects is due to the loss of some ganglion cells from the retina in the eye.

Glaucoma is most likely to affect one eye much more than the other. We don’t know why this is, since both eyes have seemingly been exposed to the same environment, diet and use. My mom went to the orthopedic surgeon with pain in her right knee. She asked the doctor: “why is my knee hurting?” and he answered: “Well, Mrs. Quigley you’re 80 years old.” She said: “The other knee’s 80, too, and it doesn’t hurt!” But, it turns out to be fortunate that glaucoma affects one eye more, since damage mostly in one eye with the other eye unaffected leaves the person pretty functionally normal. Our research at the Glaucoma Center of Excellence has been instrumental in showing how glaucoma affects persons’ lives in the real world. Those with one eye that is largely intact can do most daily activities as well as persons with two good eyes. While they must maintain a higher level of alertness, driving and walking are largely done just as well and safely by early and moderate glaucoma patients as their equal aged brothers and sisters with two good eyes.

The areas of vision affected by glaucoma are fortunately not in the center part of our world where we read and watch televisions and computers. The zones where the early dying nerve cells see the environment are in the middle areas, not the center and not at the extreme outside of our peripheral vision. Since the brain normally gets input from both eyes about every place in our immediate world, as long as one eye is providing the picture of a zone, the brain isn’t missing anything. This explains something that puzzles patients when they see their visual field testing from each eye. The doctor shows them black areas (areas where the eye cannot see) in one eye, yet as far as the patient is concerned there are no such black areas or missing spots in their real world when they are looking with both...
eyes. That’s good for continuing to function normally, but it is one reason why people don’t notice their own glaucoma damage until very late in the injury process. If the left eye still sees what the right eye is missing, damage in the right eye is not noticed. And, the damage happens so slowly that the person has time to adjust to the change without realizing it is happening. When we measured those with severe glaucoma damage in both eyes on a walking course, the person bumped into things more and walked more slowly than those of the same age. When we asked them if they had any trouble walking, they said: “No” — because they had realized gradually that walking had become more difficult, but had taken it for granted that it was due to old age.

There is very active research to determine what effects glaucoma has on important activities of daily living. We often hear from patients that they are having more difficulty with reading, for example. When we measure their acuity on the letter chart on the wall, they have normal 20/20 vision. Perhaps the subtle loss of nerve cells near the central vision, or other effects of glaucoma, do actually impair reading. We have determined that glaucoma patients can start reading at a normal pace, but slow significantly within 15-20 minutes. Glaucoma patients also give up driving earlier than persons of the same age without vision problems. Driving a car is a vital personal activity that determines in many ways the ability to live independently in our society. We need to determine which patients should, in fact, stop driving, and which ones can continue to do so safely.

While it is true that most glaucoma patients don’t get to a stage of severe vision loss, there is a slow worsening of vision function in some glaucoma patients with time, even when appropriate treatment is given. This worsening is so minor in the majority that we can feel confident they will not be impaired in their lifetime. But, a minority of those with glaucoma progressively worsens at a rate much greater than the rest. For the slow progressors, standard treatment is perfectly sufficient, while for the rarer ones with more aggressive disease, treatment must also be aggressive. As we deal with the examining techniques and treatments for glaucoma in the next sections, it will become clearer that “one size doesn’t fit all” for glaucoma treatment. Some need only regular examinations and don’t even need pressure lowering therapy, while others must undergo surgery to save vision. But, whichever group one falls into, vision should be able to be saved with a good program jointly agreed to by doctor and patient.

Can glaucoma be cured?

Take Home Points

- There is presently no cure
- Successful treatment can stop meaningful vision loss
- Nerve cell replacement research has taken initial steps

When she was 90 years old, my wonderful Grandma Mamie told me she was having trouble putting on pullover sweaters because her shoulders had arthritis. “Harry,” she asked, “you’re at that medical school Johns Hopkins, when is my shoulder going to get better?” I had to help her understand that we weren’t going to cure her shoulder, but we could buy her button-up sweaters. An important part of helping persons with glaucoma is to channel that hopefulness that Mamie expressed into flexibility to deal with what they’ve got. (Mamie kept winning at Bingo and playing bridge for some time afterward).

In this section, we’ll discuss two forms of definitive treatment for glaucoma, one may happen in the future, and one is what we can do now. The future hope is to restore vision that has been lost. That can’t presently be done. The present treatments can slow the process so much that no meaningful loss occurs in the person’s lifetime. Successful glaucoma surgery can lower eye pressure to a safe level (Operations for glaucoma). Such surgery can last for many years without need for any eye drops or medicines. But, since there are some surgery eyes that start needing medicine or more surgery again later, it is important to keep having doctor’s exams regularly even when successful surgery has been done. So, checkups will be needed, just as they are for other serious illnesses where a remission has been produced, to be sure it doesn’t come back. For now, we have several ways to lower eye pressure to really slow vision loss from glaucoma.

As described already, the successful treatment for most persons with glaucoma is to take daily eye drops indefinitely. Several laboratories and companies are presently working on a variety of ways that the medicine for glaucoma could be given only once or twice per year. These approaches will probably include placing the medicine as a deposit under the surface of the eye or even inside the eye in the doctor’s office under sterile conditions. This may sound scary, but for another eye disease called age-related macular degeneration, inside the eye injections every month are already proving to be a sight restoring method that older persons find easy to tolerate. This could really increase the number of those with glaucoma who no longer need to take eye drops every day.

There are several things that could be placed on or in the eye that could help. Some would be drugs in a long-lasting formula that lower eye pressure. Others would be carriers made from modified virus particles that get inside the eye cells in the front or back of the eye. Once inside these viral carriers fool the cells into thinking that the DNA they carry should be translated like a normal gene and the substance that is produced is made by the cell as if it were a natural molecule. The Glaucoma Center of Excellence team has already tested several such molecules that slow glaucoma damage in animal models of glaucoma. Ideally, one injection of such a viral carrier would last for years to protect the
eye. This may sound like Star Wars, but one eye disease called Leber's congenital amaurosis has already been helped dramatically in human eyes by this type of approach. People with that disease have the fortunate situation that when the viral carrier was injected, they actually saw better. This insertion of DNA is called gene therapy, and there are active research programs to use this approach for glaucoma.

Gene therapy is only one of the things now being included in the approach called neuroprotection research for glaucoma. This type of treatment, when it becomes available, will involve any method that keeps nerve cells alive longer — and preserves the vision that the person has at that time. But, gene therapy and neuroprotection will not restore lost vision. In general, these methods do not try to lower eye pressure, but rather they make the eye or the nerve cells less likely to suffer from the effects of eye pressure and the other negative things that glaucoma does. We now have more than a dozen types of potential neuroprotective drugs that have been shown to work in this way in mice, rats, and even monkeys. One full trial of a drug called Memantine in over 1,000 patients was conducted to see if the pill would slow the rate of peripheral visual loss in glaucoma patients. The drug didn’t work well enough to be recommended for patients with glaucoma, but some large drug companies are actively researching this area. A very small study tested whether one of our existing eye drops for glaucoma has additional benefit as a neuroprotectant. Unfortunately, the data require confirmation before we can be sure what was found. When we talk to glaucoma patients and their families, there is often a wonderful hopefulness that adding some treatment to the standard approaches will be helpful. Consideration of the things that are called “alternative therapies” is given in section Are there treatments other than lowering eye pressure?

Standard glaucoma treatment has been shown to slow the progress of the disease in the majority of patients to such an extent that they never become more impaired than they are at the time they discover they have the disease. That isn’t a cure, but it is a comfort. But, for those who have very significant vision loss from glaucoma, the hope is that we will find a way to restore vision. For some eye problems, there are actual improvements to be expected from treatment. Cataract surgery means that the lens inside the eye has become clouded. Surgery is commonly done to remove the foggy lens and replace it with an artificial one. Cataract surgery routinely restores normal vision to those for whom cataract was their only problem. Yet, in glaucoma, the loss of vision is due to death of the nerve cells called ganglion cells. These cells do not replace themselves as our skin cells do, for example.

So, to be able to restore vision, we must put back a lot of nerve cells. And, they can’t just be thrown into the retina, they have to go in the places where previous ones lived. And, they have to link up on one end with the other retinal nerve cells they normally get information from, as well as to grow a fiber along those 2 inches up to the brain, and link up with the partner cells in the next relay station. And, the connections (synapses) need to be made in a way that produces useful vision images, without messing up the existing connections for the parts of vision that haven’t been lost from glaucoma already.

As you can see, that’s a lot of “And”s. But, 10 years ago, I held a meeting of scientists in which all the group talked about was how impossible it would ever be to restore vision in glaucoma. My lab and other research groups went to work and since then we’ve accomplished some of the initial steps. First, we know where we can get the nerve cells that we need — we can get them from your own eye. Within every eye are cells that made lots of daughter cells during life in the womb, then when the eye was “finished”, they went to sleep and stopped dividing. They’re alive, in the front part of the eye (the ciliary body), where we can get some out (surgically) without hurting the eye. Thousands of new cells can be made from such a piece of removed tissue, and the beauty is that they are your cells, so there shouldn’t be a problem with rejection. That’s when someone else’s tissue is put into you and is attacked and killed since it’s foreign.

These new cells from inside the eye are called progenitor cells. They went pretty far toward becoming eye cells during development prior to birth, then they stopped developing and stayed quietly in the eye, waiting to be turned back on. Why don’t we want to use stem cells, which you have probably read about? Scientists call something a stem cell when it can turn into many different things, like a bone cell, an ear cell, or a heart muscle cell. Stem cells are present in fetuses at an early stage after fertilization and we have learned a lot about development from them. But, there are ethical and practical issues involved in their use when they come from unborn fetuses. Other “stem cells” have been produced by treating adult cells in special ways. For these and for fetal stem cells, we would have to convince the stem cell that it wants to be an eye cell. Instead, the approach we have taken is to start with a progenitor cell that already had begun to be an eye cell. Furthermore, stem cells come from a different person and the body’s attempts to reject them would need to be treated.

Progenitor cells from the eye and from some other tissues (like the bone marrow where blood cells start) have been tested as replacements in the eye and there are some positive results. Progenitor cells have been convinced to move into the retina of animal eyes and have lived there for brief periods. No one has yet succeeded in finding a way to take the next steps: getting the synapse connections wired up to the existing cells in the retina and growing a fiber up to the brain. We have plans that hopefully will beat those problems. But, more work is needed and no therapy will be available for a number of years.
How can you help your family avoid glaucoma damage?

Take Home Points

- Tell your family about your glaucoma and have them get good exams
- Specific gene mutations have been found explaining a few glaucoma cases
- There are no standard gene tests that help most patients now
- Present genetic research may provide new tests in the future

Several years ago, we did a study that asked 100 glaucoma patients to give us permission to call all their relatives and ask about glaucoma. We called 300 adult relatives of our patients and asked them what they knew about glaucoma, whether they knew they had a relative with it, if they knew it runs in families, and how often they had eye exams. Our results were disappointing. A lot of the family members did not know that they were at greater risk. The patients often hadn’t told family members they have glaucoma. Some people aren’t that close to family, and other patients said that they didn’t think telling family members would lead them to do anything. “You know how grown kids are, they don’t listen to me when I tell them to get eye exams”, said one older patient.

Even worse, among the family members, more than half had never had a visual field test. Almost all of them said that they get their eyes “checked” every year, but they weren’t getting the best test for finding glaucoma. We can’t tell if that was because their eye doctor was choosing not to do the test or if he/she didn’t know that the patient had a family history of glaucoma.

We tell every glaucoma patient to have all adult relatives (mother, father, sisters, brothers, adult children) go once a year to an eye doctor and say the following exact words: “My mom has open angle (or angle closure) glaucoma and I want a test of my angle and a visual field test.” This makes sure that the correct tests are done and repeated every year. If you don’t have glaucoma at age 40 or 50, it can still develop later, increasingly after age 60. It may be that glaucoma severity is also inherited, meaning that if you have a family member with severe vision loss from glaucoma, you are more likely to have that, too. People can’t really be sure that their grandmother really had glaucoma without seeing the actual records from past doctors’ exams. Having old records is very valuable.

It’s one thing to say that a disease “runs in families” and quite another to know how the specific gene defects underlie the inherited tendency. Each gene functions like a recipe, telling the cell the ingredients needed to make a protein that your body needs. People have about 20,000 distinct genes, and scientists have only recently started to understand how some of them work. However, the process of looking for the “bad” genes has taught us some valuable lessons in medicine in the last 30 years. First, there is not one single gene that explains why people get a common disease. Glaucoma, like other complex disorders, has genetic factors, environmental factors, and other contributing features, so simple answers like a mistake, called a mutation, in one gene will not explain why most people get the disease. Second, when a defect in one gene is found in persons with a disease, there are often several areas of the same gene that can have mutations or changes that alter what the gene makes. If there is a mistake in the recipe, the protein can come out wrong, and there are many places where a mistake could be made. So, even within the same gene that is defective, it can malfunction in different ways in different people. Third, the disease-causing aspect can be how much product a gene makes rather than a defect in the gene code sequence for the molecule being made. Fourth, there are genetic disorders in which it takes two “hits” or gene defects in separate genes for the abnormality to happen (this is probably true for exfoliation syndrome).

Hunting for genetic risk factors can be done by one of two approaches. Scientists look at the DNA of families with many members who have the disease, in a test called linkage analysis. They look for pieces of DNA that are linked to the presence of disease. In this method, the family relationships are very helpful for finding the gene, so the larger the family and more complete the information about who had the disease, the better. This method works best with rare mutations that greatly increase someone’s chances of getting the disease. The other method, called an association study, doesn’t use family information. In these studies, scientists compare the DNA of people who do or don’t have the disease and again look for pieces of DNA more frequently associated with disease than you would expect by chance.

For open angle glaucoma, several likely zones in the human genome have been found, with 3 that have now been pretty well established to contribute to a small number of cases. Genes for the protein molecules called myocilin and optineurin are defective in certain subgroups of persons with open angle glaucoma. Myocilin mutations lead to high eye pressure at the age of 20 to 30 in families with this defect. Myocilin’s action, when abnormal, seems to block up outflow of aqueous humor. Optineurin mutations are said to be more common in those with glaucoma at lower eye pressure. One hypothesis for how it causes damage is to make ganglion cells more sensitive to dying. For the subgroup with exfoliation syndrome, there are differences in a chemical coded by the LOXL1 gene, whose function relates to the supporting tissues in the eye.

One might think that genetic testing of blood samples might be a good thing to do, to determine if you have one of these defects. Practically speaking, however, the chance that the average glaucoma patient has one of the known mutations is really very low. The tests are very expensive (thousands of dollars per gene tested) and are not done in routine labs. Having the specific mutation or the variation in a particular zone (called a single nucleotide polymorphism or SNP) doesn’t mean that you have a 100% chance of glaucoma. So, at this time, it is only in research studies that gene testing has value.

To be continued in the 3-d part.