

Oculopharyngeal Muscular Dystrophy

In Focus

Dear Readers

Oculopharyngeal muscular dystrophy (OPMD) is a form of muscular dystrophy that results from a mutation in the PABPN1 gene.

Although there are no treatments for OPMD — as yet — that address the underlying cellular or molecular abnormalities, there are surgical treatments for the main problems patients experience: droopy eyelids and difficulty swallowing.

This special section includes:

- *“Fast Facts” about OPMD*
- *An update on state-of-the-art research and disease management, with first-person stories from people with OPMD*
- *Information about genetic testing*

To learn more about OPMD, visit www.mda.org or call your local MDA office at (800) 572-1717.

Fast Facts

OPMD is a form of muscular dystrophy in which symptoms usually first appear between the 30s and 60s, and primarily involve the muscles of the upper eyelids and the swallowing muscles. As these muscles weaken, patients have difficulty keeping their eyes open and find that food and liquids are increasingly hard to swallow. As OPMD progresses, it can weaken the muscles of the limbs, particularly the legs.

The disease is more common in French Canadians, Jews of Central Asian descent (Bukharan Jews), and Hispanics living in New Mexico, than it is in the general population.

The underlying defect is a mutation in a gene on chromosome 14, identified in 1998 by an MDA-supported research team led by Guy Rouleau, who was then at Montreal General Hospital and McGill University in Montreal. (He’s now at the University of Montreal.)

The protein made from this gene is

called polyadenylate binding protein 1, or PABPN1. Because of the genetic defect in OPMD, the protein is slightly longer than normal, containing extra molecules of the amino acid alanine. The cellular and molecular effects of this lengthening of the PABPN1 protein are the subject of ongoing investigations. One effect is that clumps form in the nucleus of OPMD-affected muscle cells.

OPMD is dominantly inherited, meaning just one mutated PABPN1 gene, passed from one parent to a child, is sufficient to cause disease symptoms.

DNA testing for OPMD has been available for several years. Without DNA testing, it’s usually not possible to detect whether or not a person has inherited the OPMD gene defect until he or she reaches middle age.

MDA’s current commitment to research in oculopharyngeal muscular dystrophy (OPMD), as of July 22, 2009, is \$1,635,928, spread over 12 grants.

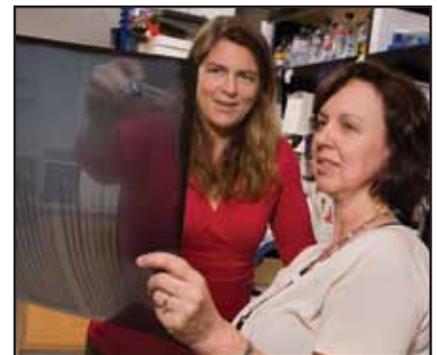
In Focus: Stopping a Long Protein from Shortening a Life

by Margaret Wahl

Seattle resident Ken Lang (see “Like a Frog,” page 8) says he knew a disease that impairs swallowing and speaking was a possibility for him, because his father, uncle and grandmother had been affected by such a disorder. “I first became symptomatic when I was about 51 or 52,” says Lang, now 62, “although I didn’t get an official diagnosis until about four years ago.” Now a writer and a dispatcher for a transportation company, Lang says his throat muscle problems gradually

increased until he couldn’t even swallow liquids and was having trouble speaking.

Carol Forde (see “Not Glad,” page 2), in Strum, Wis., also has a family history of insidious and specific muscle weakness, although earlier generations didn’t have a diagnosis. “I’m sure it goes back farther than my maternal grandmother, but all we knew was that my grandmother had really, really droopy eyelids, to the point where she would have to sit there with her elbow on the table and use her



Biochemist Anita Corbett (left) and molecular pharmacologist Grace Pavlath are studying OPMD at Emory University in Atlanta.

fingertips to hold her eyelids open,” says the 53-year-old technical writer.

The disease Lang and Forde are describing is oculopharyngeal muscular dystrophy (OPMD), a form of MD that runs in families and has a preference for weakening the muscles of the upper eyelid and the throat.

Until recently, not much more than that was known. But that’s changing.

A slightly longer protein

The underlying problem in OPMD is a remarkably small increase in the length of a protein known as PABPN1 (polyadenyl-

ate binding protein 1).

The increase in length is caused by a correspondingly small increase in the length of the gene for PABPN1, in the form of extra repeated sequences of the chemicals guanine, cytosine, guanine, or GCG. These repeated sequences are known as “GCG triplet repeats.” Each

Not Glad But Very Well Prepared

“We think my grandmother was French Canadian, but she didn’t really talk about her history a lot,” says Carol Forde. “I don’t think the doctor knew what she died of. He said it was pneumonia, but she might have aspirated [inhaled food or liquids into the lungs]. It was a different time. We just accepted it.”

But when her mother, Marjorie Sanderson, began experiencing some of the same symptoms many years later, the family was more concerned with diagnosis and treatment.

“My mother, before she retired, told me that people at work used to call her “sleepy” or “droopy” because she was developing ptosis [eyelid weakness].

“Then one day my mother was at a Penn State football game, and she noticed it was really hard for her to climb the steps into the bleachers.” Sanderson was in her late 50s and living on the East Coast at the time.

“The symptoms became more pronounced very, very slowly, and stairs got pretty hard for her,” Forde remembers. “But she was very active and very slim, and she did OK.” Eventually, a neurologist in New York identified the problem as OPMD.

“We had never seen my grandmother get really debilitated,” Forde says, “and we didn’t have reason to believe that my mother was going to have a really hard time. But it got to the point where the stairs were more

difficult for her. They had to buy one of those stair glides to go down into their basement, because that’s where the laundry was. She was probably in her mid- to late 60s.”

Some time after Forde and her new husband moved to Wisconsin in 1997, her parents followed. They were in their 70s, and Sanderson’s symptoms were getting worse. Forde and her mother visited the Mayo Clinic in Rochester, Minn., where Sanderson eventually underwent a frontalis sling procedure on her eyelids (for more on eye surgery procedures, see “Nips, Tucks and Lifts,” page 6).

Then, in September 2007, Sanderson suddenly died, at age 80. “This is hard for me,” Forde says, barely able to control her emotions. “She was home alone, and she choked on her lunch.”

Meanwhile, Forde’s own OPMD symptoms were progressing. At age 49, she looked in the mirror one day and saw her eyelids were drooping. It wasn’t long before her vision was affected, especially while driving at night. When she pulled up to a stoplight, the light would refract through her eyelashes. “It was like a light show,” she says. “I thought, ‘I really want to do something proactive about my eyelids.’”

In May 2007, Forde underwent a blepharoplasty on each eye with the same surgeon who had treated her

mother. “It provided some lift in my eyelids,” she says. “But, to be honest, I thought it would be more dramatic. I found I was still looking through my eyelashes.”

In July 2009, she underwent a Muller’s muscle conjunctival resection.

“My eyelid function is absolutely perfect,” Forde said, less than a month later. “I feel fine.”

So far, swallowing hasn’t posed a major obstacle for Forde, but she’s not complacent about it. “I do get stuff that sticks,” she says. “Maybe over the last four or five years, since I’ve started to notice it, there have been a couple of scary incidents.”

Recently, she’s begun having trouble walking up stairs.

“I’m not glad I have muscular dystrophy by any stretch of the imagination,” Forde says. “But with my mother having been very, very proactive about being diagnosed, and following the course of her progression, I feel like it’s not going to be wonderful, but I feel very well prepared.”



Carol Forde, after her blepharoplasty but before her Muller’s muscle conjunctival resection.

GCG triplet forms the instructions for a molecule of the amino acid alanine, a protein component. When there are extra GCG repeats, there are extra alanine molecules in the PABPN1 protein.

Why a tiny increase in the length of a protein should wreak such havoc in cells, affect muscle fibers in particular, and affect certain muscles more than others, is largely unknown, and several hypotheses are being tested.

Clumps in the nucleus

Normally, the PABPN1 gene, located on chromosome 14, contains six GCG repeats. Two PABPN1 genes are inherited by each person, one from the mother and one from the father. As few as eight, instead of six, GCG repeats, in one of the two genes, is enough to cause OPMD.

The molecular nature of OPMD “bears a superficial resemblance” to other so-called “triplet repeat” genetic diseases, such as myotonic dystrophy, says University of Rochester (N.Y.) neurologist Charles Thornton. “But in fact, whether there is really any overlap between the two in terms of what goes wrong, is unclear.”

Thornton co-directs the MDA clinic at the University of Rochester Medical Center, has had MDA support to study OPMD, and serves on MDA’s Medical Advisory Committee. “The size of the repeated sequence is much shorter than it is in other such diseases,” Thornton says, “and it doesn’t show changeability from one generation to the next, which is dramatic in some of these other diseases.”

On the other hand, the very small increase in the length of the gene causes the slightly longer protein to behave in a “different fashion” from normal, Thornton notes. “You can see that it forms clumps in the cell nucleus. But whether those clumps are closely connected with why people have muscle problems is still unclear.”

The abnormal clumps (also known

as “aggregates” or “inclusions”) are in the nuclei of muscle cells that carry the OPMD genetic abnormality. The extra length of the PABPN1 protein seems to cause it to fold improperly and clump up.

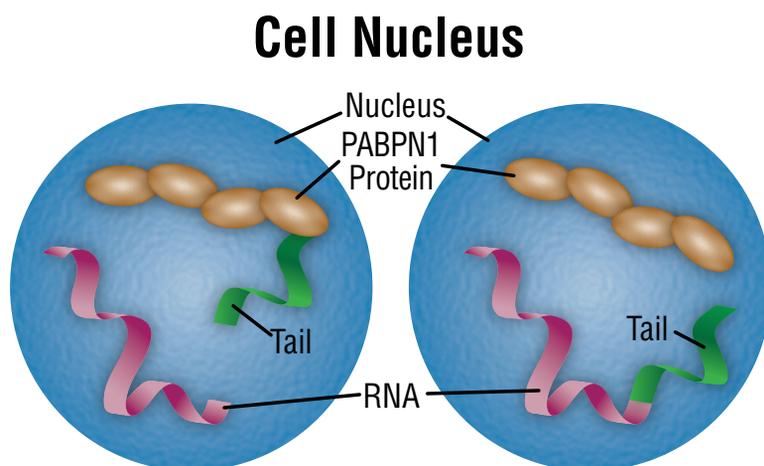
“The aggregates themselves could be toxic in some way,” says Anita Corbett, a molecular biologist at Emory University in Atlanta. However, she says, “as a full explanation for the disease, that’s losing favor.”

In fact, some recent studies have suggested that the clumping may actually *protect* cells that contain expanded PABPN1 protein molecules, at least up to a point, although that remains controversial.

A loss of PABPN1

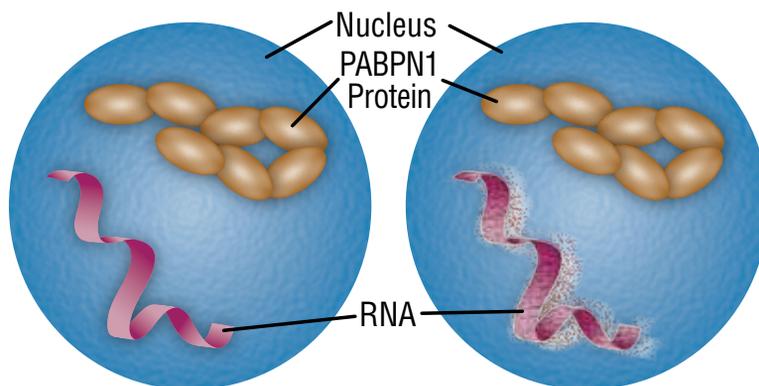
Corbett says there’s evidence to support the theory that depletion of PABPN1, because it’s “tied up in the aggregates,” also is a factor in the disease. She notes that normal-size, as well as extra-long, PABPN1 molecules, get trapped in the clumps, and that other proteins are trapped there, too.

A loss of PABPN1 function could have widespread effects on cells, Corbett says, because the protein appears to play a role in keeping pieces of genetic material stable in what can be a harsh cellular environment.



Evidence suggests that a normal function of the PABPN1 protein is to help attach a protective tail to pieces of RNA in cell nuclei.

OPMD-Affected Cell Nucleus



In OPMD, PABPN1 protein molecules that are slightly longer than normal, fold improperly, and form clumps. PABPN1, trapped in clumps, may fail to play its role in putting tails on RNA strands, leaving these strands vulnerable to destruction.

Surgery to Help Move Food Past Weak Throat Muscles

Starting with the tongue and moving down the throat and into the esophagus are a series of muscles that constrict and push food from the mouth to the stomach. The tongue and throat muscles weaken severely in OPMD, leading to choking, inhaling food into the lungs (“aspiration”) and lung infections (pneumonia). Speaking also can be adversely affected by weakening tongue and throat muscles.

Unfortunately, says Albert Merati, an associate professor in the Department of Otolaryngology-Head and Neck Surgery at the University of Washington Medical Center in Seattle, nothing can be done surgically to strengthen the weakening muscles. However, something *can* be done to weaken the resistance against which they have to push to get food past the throat and into the stomach.

The muscle that surrounds the throat just above the esophagus is known as the “cricopharyngeus,” or CP muscle.

Between swallows, the CP muscle is closed. When the constrictor muscles above it are active (imagine food moving through a snake), it relaxes and opens.

People have swallowing difficulties (“dysphagia”) if the constrictors are weak or any parts of the swallowing mechanism are not coordinated. In OPMD, Merati says, “it’s a matter of loss of strength in the constrictors that can’t be fixed. In this condition, the CP is the only thing we can operate on. The less obstruction there is, even in the absence of good pressure from above, the more easily stuff can go down.” (Imagine widening the narrow part of a funnel.)

There are a variety of procedures one can use to open the CP muscle, ranging from dilation with an instrument, to injections of a muscle-weakening substance, to cutting into the muscle.

Ultimately, if the throat muscles weaken enough so that food or liquids are inhaled into the lungs, the oral route for eating and drinking may have to be bypassed entirely and a tube inserted directly into the stomach.

Some procedures require general anesthesia, while others can be done using sedation or a local anesthetic.

(Muscle diseases in general can sometimes lead to unexpected reactions to inhaled anesthetics or muscle-relaxing medications, so the surgical team should be alert to monitoring the patient particularly carefully during and after surgery.)

CP dilation

The simplest procedure, Merati notes, is dilating the CP muscle with an instrument, known as “cricopharyngeal dilation.” It’s by far the most common treatment for dysphagia related to problems in the upper throat, but it’s temporary, lasting at most a year or so before it has to be repeated.

“It’s done casually in a lot of patients, because it’s convenient, and it’s low risk,” Merati says. If a gastroenterologist is already putting a scope down into the throat to see what the problem is, a dilating instrument can be inserted without adding much risk to the procedure, he notes.

Botox injections

The next step often is injections of botulinum toxin (popularly known as Botox, a brand name). Botulinum toxin, derived from a bacterium, is a poison that weakens muscle, and it can be injected into a muscle for this purpose. “The down side is, it’s temporary,” like the dilation procedure, Merati says, estimating the duration of its effect to be three to four months.

“Some patients who aren’t ready to commit to a permanent solution find it attractive,” he notes. “They can think of it as a trial run for a permanent operation, or they can keep getting Botox every now and then.” Merati says the procedure for Botox injections takes about 10 minutes, and most surgeons like to do it through the mouth, with the patient under general anesthesia.

Some doctors inject Botox through the skin in the throat area, which doesn’t require anesthesia, but Merati says the procedure isn’t as reliable. “If it gets in the wrong place, you can have all sorts of problems,” he notes.

CP myotomy

The definitive operation for OPMD-related dysphagia, and the one that Merati performs most often, is called surgical CP myotomy, which means cutting into the CP muscle.

The operation can be done with either a laser, through the mouth, or with a scalpel, through the skin. Either way, the CP muscle is cut, and its grip on the throat is permanently loosened, making it easier to

Pinning the tail on the RNA

“Cells are not a good environment for RNA,” Corbett says. (RNA is the genetic compound that’s made from DNA and from which protein molecules are then

produced.) Therefore, cells protect RNA by attaching a protective tail to it, which serves as a buffer. “The tail keeps the RNA molecules from being chewed up,” Corbett says.

PABPN1, it’s been found, is among the compounds that help put a tail

on RNA. The tails get shorter without PABPN1, Corbett says, although they’re not completely absent.

PABPN1’s role in RNA tail length and maintenance is pretty clear, at least in experiments in flies and mice. PABPN1 may also help RNA molecules move out

swallow. The operation requires about a 1.5-inch incision parallel to the collarbone on the left side of the neck and takes a half hour to an hour.

Merati says he's performed about 100 CP myotomies in his career, about 15 to 20 on OPMD patients. "About 90 percent of OPMD patients respond to surgery to some extent," he says, "and the majority do very well." Admittedly, he notes, about a third of people with OPMD will have some return of dysphagia symptoms three to four years after surgery, as their disease progresses.

G-tube insertion

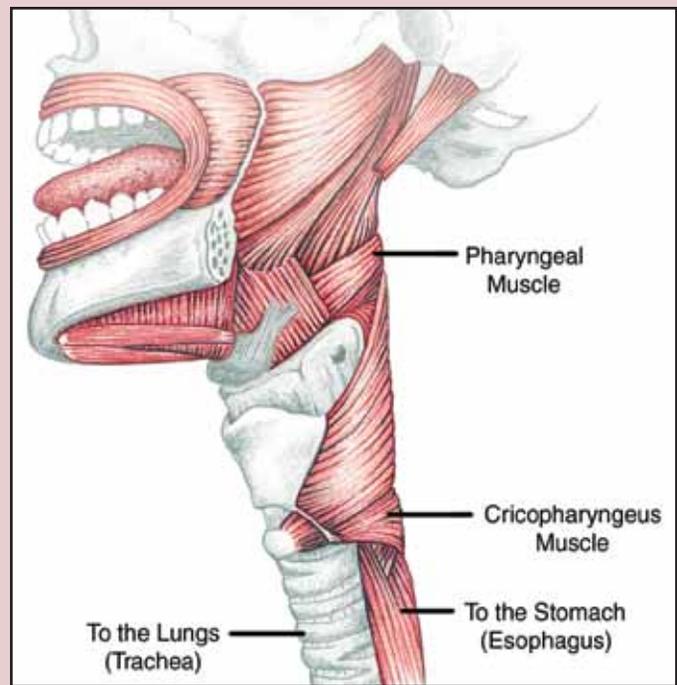
If a patient's swallowing muscles are so severely weakened by OPMD that food and drink can't be safely directed to the stomach, and instead routinely go down the trachea into the lungs, then a gastrostomy ("g") tube can be inserted. A g-tube goes directly into the stomach from outside the body, bypassing the oral route for swallowing entirely.

G-tube insertion is generally performed by a radiologist or gastroenterologist, Merati says. Avoiding eating and drinking entirely is a drastic, though sometimes necessary, step, Merati notes, adding that he often considers doing a CP myotomy even in people who already have g-tubes. In some cases, a myotomy can allow them to drink liquids, with care, even if they're getting most of their nutrition through the g-tube. At the very least, it allows them to safely swallow their own secretions.

Risks

The risk of eventual treatment failure and return of symptoms in a progres-

When throat muscles, such as the pharyngeal muscle, weaken, loosening the cricopharyngeus muscle with a surgical procedure or medication can ease swallowing in OPMD. When swallowing coordination becomes so poor that food and liquids are routinely misdirected to the lungs instead of the stomach, a gastrostomy tube in the stomach may be needed.



sive disease like OPMD is high, Merati notes. "Even if someone is 62 and has an operation and does well, eventually it may not continue to work, as the disease progresses."

Adverse events, though rare, may also occur. Paralysis of the vocal cords, damaging the ability to speak either temporarily or permanently, is estimated to occur about 1 to 3 percent of the time during a cricopharyngeal myotomy procedure, Merati says, although he's never seen it happen in his cases.

Another complication that Merati hasn't witnessed but which he notes is possible is a nonhealing wound in the neck through which food or liquid can drain. That, he says, can be fixed, but in the meantime, it can lead to a serious infection.

Gastroesophageal reflux — food or liquid coming up from the stomach into

the esophagus — can occur after the cricopharyngeal muscle has been weakened, Merati says, "because you've taken away one of the barriers to reflux." However, he says, it generally isn't a problem.

Finding a surgeon

Merati advises patients considering surgery to seek out a head and neck surgeon specializing in otolaryngology (the study of the ears and throat) or laryngology (the study of the throat) who has a lot of experience performing procedures to help with swallowing.

For help finding a surgeon in your area, check with the American Academy of Otolaryngology-Head and Neck Surgery at www.entnet.org or (703) 836-4444. Or, contact Albert Merati at amerati@u.washington.edu or (206) 598-4022.

of the nucleus into the main part of each cell, a necessary step before RNA can be used for protein synthesis, Corbett says, although that's less certain.

A preference for certain muscles

Grace Pavlath, also a molecular biologist at Emory, received MDA support from 2007 through June 2009 to collaborate with Corbett on a study of cellular mecha-

nisms underlying OPMD. She also serves on MDA's Scientific Advisory Committee.

Pavlath is particularly interested in why the clumping or loss of function of PABPN1 leads specifically to effects on muscle, since PABPN1 is found in virtually all the body's cells.

Nips, Tucks and Lifts for Droopy Eyes

“There are three ways to correct eyelid ptosis [drooping], and each relates to a different muscle that raises the lid,” says Elizabeth Bradley, a surgeon in the Department of Ophthalmology at the Mayo Clinic in Rochester, Minn.

In addition, she notes, some patients with OPMD and droopy eyes undergo an operation to remove extra skin around the lids.

With any of these procedures, patients typically receive local anesthesia and intravenous sedation, although general anesthesia can be used.

Blepharoplasty

Some patients with OPMD start with a “blepharoplasty” (plastic surgery on the eyelid), a procedure that’s often done in people who don’t have OPMD but whose eyelids have sagged with age. “If they have excess skin weighing down the lid, it’s an extra force the weak muscle has to counteract, and they may get some lid elevation if we take it off,” Bradley notes.

Levator advancement

The earliest procedure that directly addresses muscle action in the OPMD-affected eyelid is an operation on the “levator palpebrae superioris.” This muscle, a lifter of the upper eyelid, is the main muscle that raises the lid and one that weakens significantly in OPMD.

“When OPMD is still quite mild, we can often do surgery on that muscle,” Bradley says. “That’s called an ‘external levator advancement.’ We go through an external incision in the eyelid crease and tighten the muscle.” The procedure can be done under conscious sedation or general anesthesia.

Muller’s muscle resection

Muller’s muscle also plays a role in raising the lid, and it’s not affected in OPMD,

Bradley explains. Unlike the levator, which is a voluntary muscle, Muller’s muscle is under the control of the autonomic (automatic) nervous system. When the levator is very weak, tightening Muller’s muscle can increase lid opening by about 2 millimeters (0.08 inches).

To see whether an operation to shorten Muller’s muscle will be helpful, the patient is given an eye drop that makes it contract. If the eye drop helps significantly with eye opening, the patient is considered a candidate for a “Muller’s muscle conjunctival resection,” or MMCR. In this procedure, the muscle is shortened while the patient receives local anesthesia and conscious sedation.

The MMCR is an operation Bradley likes to perform when ptosis is too far advanced for a levator advancement but not yet maximally severe.

Frontalis sling

At the final stage of severe ptosis, the operation of choice is the “frontalis sling,” Bradley explains. The frontalis is a muscle in the forehead that’s not affected in OPMD.

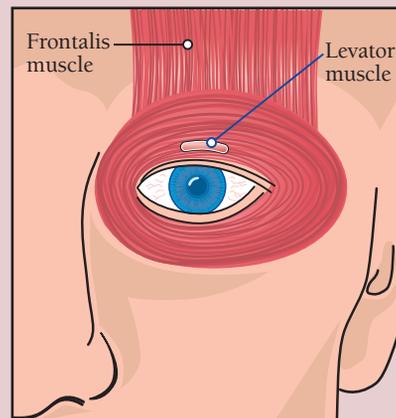
“When they have severe enough ptosis that we can’t do an MMCR and the levator is so severely affected that we would not expect improvement with a levator advancement, we do a frontalis sling,” Bradley says. “We put in a silicone sling that couples the frontalis muscle more directly to each eyelid. When they raise the forehead, the lids go up.”

Risks

There can be complications with eye surgery, Bradley notes.

It’s extremely rare, but there can be bleeding behind the eye, which can interfere with vision.

Anesthesia-related complications



In OPMD, the levator muscle weakens, causing the upper eyelid to droop. To offset this, a surgeon can remove excess skin from the upper eyelid; tighten the levator; tighten the nearby Muller’s muscle; or attach the frontalis muscle to the eyelid.

are not common in OPMD. However, theoretically, anyone with a muscle disease can have an unexpected adverse reaction to inhaled anesthetics or muscle relaxants, and the surgical team should be informed about the pre-existing condition.

In addition, eyelid muscle-tightening procedures can interfere with eye closure, leading to overly dry eyes.

And, Bradley says, 5 to 10 percent of the time, with any of these procedures, there’s a need to reoperate within the first two months after surgery, because the treatment hasn’t worked.

Most of the time, she says, the procedures, if properly performed and done at the right time in the disease progression, are effective, and patients tend to have “less discomfort than they had anticipated.”

Finding a surgeon

For help finding a surgeon who specializes in eyelid surgery, consult the American Academy of Facial Plastic and Reconstructive Surgery at www.aafprs.org or (703) 299-9291.

“In our MDA-funded work, we’ve been examining whether loss of PABPN1 affects myogenesis [muscle making],” she says. “We’ve taken cells from mice and used genetic technologies to eliminate PABPN1 to see whether that affects myogenesis. We’ve found that if you eliminate some of the PABPN1 in muscle cells, it causes problems for the functioning of these cells. We don’t get rid of 100 percent of the PABPN1, but we significantly lower the level of PABPN1 that’s normally present, and we clearly have problems with muscle-specific function,” she says.

Those experiments show that losing some of PABPN1’s function probably plays a role in OPMD, notes Pavlath. Clumps may be important, she says, “but we don’t think they’re the only thing that goes wrong in this disease.”

As for why the muscles of the throat and eyelids are particularly affected in OPMD, Pavlath says, “There are a number of reasons why it may be those muscles. Embryologically, the head and neck muscles develop differently from others. They utilize different genetic pathways, for instance, and they have different physiologic properties from other muscles.

“It’s possible that these particular muscles are more dependent on PABPN1 function than others and that muscle in general is more dependent on it than other tissues, such as the liver or skin.”

Late onset

In addition to its selective effects on certain muscle groups, OPMD also selectively affects older people, posing yet another set of research questions. “Muscles age,” Pavlath says, “and various properties of muscles change with age. It’s not known if different muscles age at a different rate, but some muscles may age differently. We get wise with age, but it doesn’t do great things to our organs.”

Troubling symptoms

“I would say the most troublesome aspect of OPMD is the difficulty with swallowing,” says Thornton.

Thornton routinely refers his OPMD patients to a speech and swallowing therapist (available through most MDA clinics) before referring them for surgery. He refers patients for surgery when swallowing becomes unsafe or very difficult.

A close second in causing trouble for patients is probably difficulty with eyelid weakness, Thornton says. “At a point in time where the problem is severe enough to interfere with a person’s vision, or if people are unhappy with their appearance,” he refers them to an eyelid surgeon. “Most of our patients get this at some point,” he says.

Another issue is fatigue. “Why it occurs I don’t understand very well,” Thornton says, “but fatigue is a big symptom with this disease. Muscles tire quickly with use, particularly the ones that show some weakness.”

A part of OPMD that’s not universal but can be quite hard to deal with, Thornton notes, is limb weakness, particularly in the legs but sometimes in the arms. “It’s not a uniform aspect of the disease,” he says, “but many people have this. In some people, it can be aggressive — surprisingly so. We don’t understand why some people have this to a much greater extent than others.”

As for activity and exercise, Thornton says, “We don’t know of information indicating that there’s much fragility of muscles in this condition, so that makes us less concerned about the possibility of doing damage to the muscles by working them hard. But even so, it’s sensible for people to tailor their activities and exercise for endurance, not power.”

Genetic testing

DNA-based testing for OPMD using a blood sample has been available for sev-

eral years. Your MDA clinic can steer you toward testing.

Next steps for scientists

Experiments in flies, worms, mice and cellular models of OPMD (all of which imperfectly mimic the human disease) have so far suggested some possible therapeutic avenues: helping cells resist a death spiral known as “apoptosis”; breaking up aggregates to free trapped proteins; raising the level of normal-length PABPN1 protein; and destroying abnormal PABPN1 genetic instructions or protein molecules.

In 2005, experiments showed mice carrying mutated PABPN1 genes and demonstrating some of the signs of human OPMD responded to doxycycline, an antibiotic used to treat infections in humans. The researchers speculated that the drug could be exerting its effect by reducing clumping and by working against apoptosis.

“There are some data showing that aggregates are the cause of the disease and that anti-aggregation therapies can help alleviate some of the effects,” Anita Corbett says. Whether the alleviation is the result of breaking up of the aggregates themselves or the release of necessary substances from their traps in these clumps, she says, isn’t known.

Another idea, notes Grace Pavlath, is that breaking up aggregates may make cells “more resistant to death signals” in general. (On the down side, Pavlath cautions that anti-cell-death strategies have been known to cause malignancies.)

Additional strategies also are being explored. If it becomes clear that loss of normal PABPN1 functions is central to OPMD, then increasing levels of this protein could be “potentially very important,” Pavlath says. She says one could envision various ways of doing that, such as putting in the protein itself or the gene for it, or by revving up protein production from the one normal copy of the gene

Like a Frog in Boiling Water

Ken Lang's OPMD symptoms began with swallowing problems, when he was about 50. "They were fairly mild at first," he says. "There were certain foods I could no longer eat," such as rice and ground beef. "I couldn't eat a hamburger. I couldn't swallow it. It would get stuck. I'd have to cough it up, or I'd feel a sensation of choking. Over the course of time, the symptoms got a little worse, and my voice started to go, which was a real bummer."

Lang, who's been a community organizer and radio personality, has relied on his voice a great deal. His father had also experienced trouble talking late in his life.

Despite knowing his family history, he managed to more or less ignore his symptoms until it was almost too late. "I was like a frog in boiling water," he says, referring to the hapless amphibian who's being cooked so slowly he doesn't notice there's a problem until it's too late. "I had all these things going wrong. I couldn't eat. I was losing weight. I just chalked it up to having muscular dystrophy." Had he postponed seeking medical atten-

tion any longer than he did, "it wouldn't have mattered," Lang says. "Some of my vital organs were shutting down."

At age 60, the 5-foot, 10-inch Lang weighed 103 pounds. "I was starving," he says. Eventually, he wasn't even able to swallow liquids.

Fortunately, he went to see throat surgeon Albert Merati at the University of Washington Medical Center in the nick of time. By the time he saw the doctor, Lang's throat muscles had weakened so much that a balloon-like pouch, known as a "Zenker's diverticulum," had formed. "This pretty much blocked me from eating, period," he says.

Lang underwent a surgical procedure called a cricopharyngeal myotomy, in which a tight muscle above the esophagus is loosened. The Zenker's diverticulum was repaired at the same time, although he had to undergo a revision of that repair later on.

"Since that time, not only is my voice back," says Lang, "but I have no swal-



Ken Lang, shown here at a friend's ranch in Washington state, says throat-muscle surgery saved his life.

lowing problems whatsoever."

The surgery, he says, "saved my life." His weight is now stable at 170. "It's a little heavy for me, but I'll take it."

While swallowing and speaking impairments have been Lang's main concerns with OPMD, he's also begun to experience some eyelid drooping, for which he's considering surgery, and noticeable weakness in his legs.

"I was a runner and a climber for many years," he says. "Those days are gone." But, he says, "my voice has gone back to being normal and strong, and I can eat anything."

that most patients have. (A few patients are unlucky enough to have inherited the genetic defect from both parents, and they tend to have severe OPMD.)

Targeting the extra repeats in the PABPN1 genetic instructions, Corbett notes, is yet another possible strategy, but a particularly difficult one. GCG repeats, in the PABPN1 gene and elsewhere, remain necessary to make alanine molecules, so targeting them would be problematic.

Getting rid of the abnormal PABPN1 protein itself, rather than the genetic instructions for it, could also be considered, she says, but the difference between the normal and the abnormal

PABPN1 protein is small, so weapons of protein destruction are likely to affect both.

"No one has made a mouse that lacks PABPN1" so far, Corbett says. However, eliminating this protein in flies is lethal, leading her to think that PABPN1 is probably necessary.

Charles Thornton is equally cautious about targeting mutated PABPN1, either at the gene or protein level. OPMD patients have two copies of the PABPN1 gene, "one good and one bad. Getting at the bad without harming the good is a challenge."

But, Thornton says, "the hopeful indication is evidence from several different research groups indicating that protein

clumping, or aggregation, may be a fundamental part of what causes the malfunction in muscles. If this is true, that's something that OPMD may share with other conditions, like Alzheimer's disease, that are much more common and are the subject of huge efforts by the pharmaceutical industry. It might be possible to import strategies into OPMD from these other fields." □