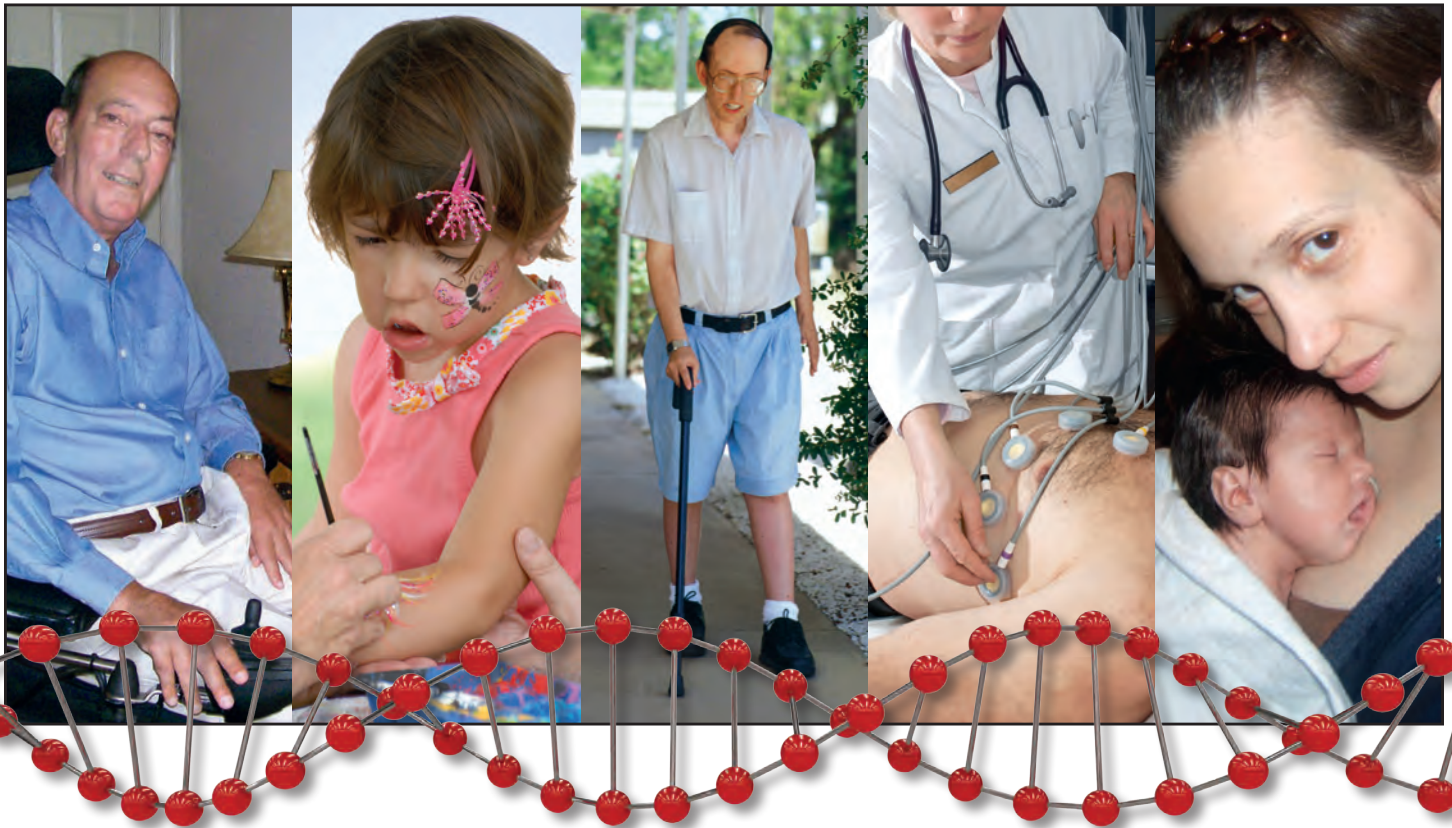


In Focus: Myotonic Muscular Dystrophy



by Margaret Wahl
MDA Medical and Science Editor

Myotonic muscular dystrophy is a challenging disease with diverse symptoms that can range from mildly difficult to life-threatening.

This series provides medical and scientific perspectives on types 1 and 2 myotonic dystrophy, and includes interviews with physicians, researchers and individuals and families affected by different forms of the disease.

(Note: MDA refers to myotonic muscular dystrophy by the acronym MMD, rather than the more common acronym DM (for dystrophia myotonica) because the Association also covers dermatomyositis, an inflammatory myopathy that goes by the abbreviation DM.)

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MMD: A Challenging and Multifaceted Disease

As far back as Carla Licon can remember, her mother had difficulty opening jars and walking long distances. Licon's mother wore ankle braces, and she also had an unusual symptom known as "myotonia," the inability to relax muscles, such as a clenched hand, at will.

Licon, who is 31 and lives in Victoria, Texas, thinks these symptoms started when her mother was in her 20s. Later, her mother's respiratory muscles weakened, leading to pneumonia, respiratory failure and her death at the age of 52.

The diagnosis was myotonic dystrophy, also known as myotonic muscular dystrophy and dystrophia myotonica, and abbreviated as either MMD or DM.

Licon's grandfather, a career military man, also had the disease. His MMD caused him to be put on light duty in his later years, and then to retire. He too died of pneumonia, before Licon was born.

When Licon was almost 17, she started noticing that her hands would start "locking up," and she began feeling tired. She explained it by saying she had worked too hard, but the symptoms gradually worsened. "It really didn't dawn on me until later that it was actually the muscular dystrophy," she says.

About a decade later, she began noticing leg cramps and spasms in her limb and abdominal muscles. Then things "seemed to go downhill pretty quick," Licon says. In early 2011, she had to leave her job at a phone company call center. "It got to where I couldn't work anymore," she says. "I couldn't function during the day. My hands would lock up, and I wasn't able to type in the notes that I needed to. On occasion my throat will kind of cramp up to where you can't understand anything I'm saying. I have to stop talking for a little bit and wait for it to get back to normal, and that's no good when you're on the phone all day."

Recently, Licon has had to move out of her apartment and into her future mother-in-law's home. "The apartment where we were living has stairs, and it was getting to where I was falling at least once a week," she says.

Adult-onset MMD1 affects multiple systems, organs

Licon has what's now known as adult-onset type 1 MMD (MMD1), a genetic disease that's caused by an expanded section of DNA on chromosome 19. The adult-onset form — sometimes called "classic" myotonic dystrophy and thought to be the most common type — has its onset in late adolescence or

young adulthood. It affects a number of body systems, although there is a wide range of severity.

The muscle-related symptoms include myotonia, for which the disease is named, and weakness, particularly of the face, neck, and limb muscles that are furthest from the center of the body (the distal muscles), such as the forearms, hands, lower legs and feet. Over time, all limb muscles can become weak.

Among the most serious effects of MMD1 are weakness of the breathing and swallowing muscles and dysfunction of the heart muscle, particularly the tissue in the heart that conducts electrical impulses from one part of the heart to another. (See page 6.)

The so-called "smooth" muscles of the gastrointestinal tract can be affected, causing diarrhea, constipation and abdominal pain. Other smooth muscles that line the hollow organs of the body, such as the uterus and gallbladder, can be affected as well, leading to obstetric complications and gallstones.

The lenses in the eyes almost always develop cataracts, which can be surgically removed when they interfere with vision. The cataracts are distinctive and have been described as resembling Christmas tree lights.

And then there are the effects on the brain, causing a range of symptoms, including learning disabilities, difficulty with decision-making, and what some psychologists have called an "avoidant" or "apathetic" personality type.

Excessive daytime sleepiness and chronic fatigue are among the most puzzling and troublesome of MMD1 symptoms, and their origin appears to be complex and probably related to the effects of the disease on the brain, limb muscles, respiratory system and heart, and perhaps to altered levels of testosterone and insulin. (For more, see page 14.)



Cataracts are very common in MMD. They can be detected by regular eye exams and can be surgically removed when they interfere with vision.



Babies born with congenital MMD1 are fragile at birth. They usually have trouble sucking and swallowing, and may need tube feedings and mechanical breathing assistance at first.

Congenital MMD1 threatens young lives, but children can improve

The most serious form of MMD1 — congenital-onset MMD1 — makes itself known at birth.

Babies born with congenital MMD1 have very weak muscles and lack of muscle tone (hypotonia). They appear floppy and have trouble breathing, sucking and swallowing.

There are always abnormalities in cognitive function, although intelligence can be in the normal range.

Speech and hearing difficulties often occur, and weakness of the eye muscles can cause vision problems. (Cataracts aren't a feature of congenital MMD during early childhood, but develop later, as they do in adult-onset MMD.)

In the past, many babies with congenital-onset MMD didn't survive, and death in the early months isn't uncommon even now. But with modern newborn intensive care units, these babies have a much better chance of survival.

With much support during the early years, children with congenital-onset MMD can thrive. Their muscles become stronger as they grow, and they usually walk and reach

major motor milestones.

Although some cognitive difficulties might not improve, most children can learn when given the right tools and environment. They often need help developing alternate means of communicating, so they can overcome the speech and writing difficulties caused by mouth, tongue and hand weakness.

Unfortunately, as children with congenital MMD approach adulthood, they start to develop the progressive features associated with the adult form of the disease. (For more, see page 9.)

Juvenile-onset MMD1 is 'somewhere in between' congenital and adult-onset forms

Some children develop MMD1 during their preschool or school years, although they aren't born with symptoms of the disease. These children do not have the severe medical problems of babies with congenital-onset MMD1. However, cognitive difficulties can be serious, presenting challenges in school and social life.

The cognitive aspects of juvenile-onset MMD1 may overshadow the muscle aspects of the disease, although eventually, the muscle weakness will become apparent as well. The heart can be affected and needs attention.

Children with juvenile-onset MMD1 need lots of medical, educational and psychosocial support as they move toward adulthood. (For more, see page 12.)

DNA expansion on chromosome 19 underlies MMD1

In 1992, multiple research teams, some sponsored by MDA, simultaneously identified what's now known to be the root cause of all forms of MMD1 — an expanded area of DNA on chromosome 19.

The area contains hundreds to thousands of repeated sequences of cytosine, thymine and guanine — or CTG — three DNA components. These CTG repeats are normal components of a gene known as DMPK, but the usual number of repeats ranges from three to 37. In people with MMD1, the CTG sequence

is repeated at least 50 times.

At the lower end of the expansion range (about 50 to 80 repeats), symptoms may be very mild or nonexistent. Cataracts are common, but they often don't lead to an MMD diagnosis.

In general (but not reliably), the more pronounced the symptoms and the earlier the disease begins, the more repeats there are. The "classic" disease range (for adult-onset MMD1) is often between 100 and 500 repeats. Children born with the congenital-onset form can have thousands of CTG repeats.

And, in general (but again, not always), the number of repeats expands when the chromosome 19 gene mutation is passed from parent to child, and this expansion correlates with more severe symptoms and earlier disease onset. (The phenomenon of a disease getting worse and starting earlier as it's passed from generation to generation is called *anticipation*.)

The congenital-onset form of the disease is found almost exclusively when the transmitting parent is the mother.

It should be noted that the number of repeats changes with time (generally expanding with age) in the tissues of an affected person, and it can differ in different tissues, such as blood cells and muscle cells. Therefore, the number of repeats depends on which tissue is sampled and the age of the person at the time the sample is taken. This means repeat number is not necessarily an accurate predictor of disease onset or severity; its main use is to unequivocally determine which individuals have MMD1 and which do not.

DNA and RNA expansions in MMD1 and MMD2

Neurologist and neurophysiologist John Day was at the University of Minnesota at the time and was seeing patients in the MDA clinic in Minneapolis. (He's now in California, heading Stanford University's neuromuscular disease program and MDA clinic.)

"When I came to Minnesota in 1992, I worked with a family my predecessor had already identified as having myotonic dystrophy," Day recalls. "The genetic test had just become available for what turned out to be



Neurologist John Day heads Stanford University's neuromuscular disease program and MDA clinic. He's had a long-standing interest in myotonic dystrophy.

myotonic dystrophy type 1. So I said, 'That's great. Why don't we send off the genetic test just to confirm things?' It came back negative, which I thought was curious.

"Then within a week or two, a woman came into the clinic from a different family. She was pregnant, and she said her father had myotonic dystrophy and she wanted to know if she carried the genetic mutation."

Day asked her if she ever had problems releasing her grip on objects, and she said, "You mean like when I was driving down here today, and I couldn't let go of the steering wheel?"

Strongly suspecting MMD, Day sent her blood to be tested — and her test also came back negative. "I thought, 'That's good, but what the heck is going on?'" Day says. "I had thought she was affected. She had weakness and grip myotonia, and her father clearly had myotonic dystrophy. But here was a second family that was genetically negative."

By 1993, Day had seen two or three more families who appeared to have MMD but whose DNA tests were negative, and doctors in Germany were reporting similar families.

Day talked to Laura Ranum, a neurogeneticist at the University of Minnesota who, with Day and neurologist Ken Ricker in Germany, would soon become involved in tracking down the origins of what eventually would be called type 2 myotonic dystrophy (MMD2). (Ranum, who has received several

MDA research grants to study MMD, has since relocated to the University of Florida.)

In 2001, a team that included Ranum and Day and was funded in part by MDA announced the surprising findings: MMD could be caused by either of two genetic mutations — the CTG repeat expansion on chromosome 19 that had been identified in 1992, or a newly identified CCTG repeat expansion on chromosome 3 in a gene called ZNF9.

The number of CCTG (cytosine, cytosine, thymine, guanine) repeats in an MMD2-causing expansion averages 5,000, while the normal number is less than 50. The average repeat expansion in MMD2 is therefore much larger than in MMD1.

MMD2 is, in general, a somewhat milder condition than MMD1, although it shares features with that disorder. Both are characterized by myotonia, cataracts, defects in conduction of cardiac impulses, and an initial pattern of weakness that affects the muscles that flex the neck and fingers.

MMD2 has been called proximal myotonic myopathy, or PROMM, because the initial symptoms often involve difficulty arising from the floor or a low chair because of progressive weakness of hip musculature — the proximal muscles. This is in contrast to MMD1, where weakness of distal muscles in the hands is often an early symptom.



Laura Ranum, a neurogeneticist at the University of Florida, is a longtime MDA research grantee with a special interest in myotonic dystrophy.

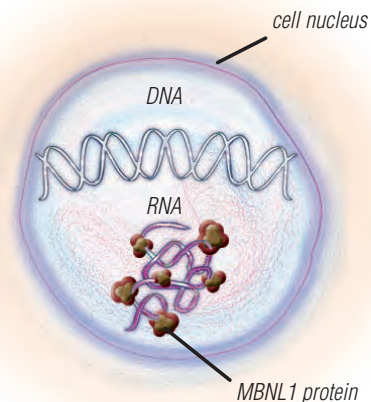
There are differences in the pattern of weakness between MMD1 and MMD2, but current nomenclature emphasizes the similarities in the two diseases, Day says.

One difference between the forms of MMD is that no congenital form of MMD2 has been seen so far. "I think the safest thing to say at this point is there's no evidence of a congenital form" in MMD2, Day says.

And MMD2 does not seem to appear at an earlier age or to increase in severity with each generation, as MMD1 does.

Mild or moderate cognitive impairment can occur in both forms of the disease, Day says. Major cognitive impairment, such as

DNA and RNA Expansions in MMD1 and MMD2



The nerve and muscle cells of people with MMD1 and MMD2 have expanded sections of DNA, which are converted to expanded sections of RNA. The RNA traps a protein called MBNL1 and has other toxic effects on the cells.

that sometimes seen in congenital-onset MMD1, has been reported in some individuals with MMD2, but, Day notes, it could be merely a coincidence and not directly related to the MMD2 genetic mutation.

Tiredness and fatigue occur in MMD2, but the extreme sleepiness that can occur in MMD1 does not seem to be common in MMD2. "Clearly, more research is necessary to clarify this point," says Day.

Similarly, in MMD2, Day says, cardiac problems are present at a higher rate than in the general population, and they can be very severe and life-threatening in some individuals, but they're not as "predictably present" as in MMD1.

Families with MMD1 and MMD2 come to doctors' attention for different reasons, Day notes. "What brings all too many people with MMD1 to clinical attention is that they have a child in the family who has congenital-onset disease," Day says. "Unfortunately, very few people with adult-onset or mild MMD1 receive an accurate diagnosis unless their child, niece or nephew is identified as having congenital-onset or juvenile MMD1."

Because there is no known congenital form of MMD2, he says, many with this disease come to clinical attention only after they reach 30 or 40 years of age and start having proximal leg weakness. (Adult MMD2 patients are often misdiagnosed as having an inflammatory myopathy or another muscle disorder, and the correct diagnosis can be missed for years.)

MMD2 may be MMD1 minus the 'developmental' aspects

Day's way of looking at the two forms of the disease is that MMD1 has a "variable but potentially profound developmental defect"

that can produce problems in infancy or childhood, while MMD2 does not appear to have this developmental component.

The scope and degree of developmental abnormalities (those that start early in life) vary in MMD1, Day notes. There can be weakness of all muscles, including those involved in breathing and swallowing; or weakness primarily of the muscles of the

“An interesting and currently unresolved question is why the CTG expansion in MMD1 can cause both the early developmental and later progressive problems, but the CCTG expansion in MMD2 either does not cause any developmental changes or causes them to such a minimal extent that they escape routine detection.”

head and face, changing their shape and affecting speech; and there can be effects on brain development, potentially causing cognitive or behavioral abnormalities.

Day says, "These developmental problems can be incredibly profound and come to light at birth; or they can be moderate and show up during childhood; or they can be minimal and only be identified incidentally on examination of affected adults."

He says some people with MMD1 who come to the attention of doctors as adults may not have had any medical problems until

recently, but close examination may uncover a thin face and high-arched palate, indicating muscle weakness of these areas during early life. And careful testing may reveal cognitive features that reflect developmental aspects of the disease.

"A major distinction between the two forms of myotonic dystrophy is that MMD1 has this developmental component, which can be variably severe from person to person, but which we do not recognize at all in MMD2," Day says. But, he says, in either form of MMD, there is a later-onset, progressive component starting in or near adulthood that affects skeletal muscles, the heart, brain, eyes and other organs in a very similar way.

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Where the research is headed

Several MDA grantees are working on strategies to block or destroy the repeat expansions in MMD1 and MMD2. Small molecules, such as pentamidine, and a strategy known as antisense are in development. (See page 16 for more.)

For videos covering some of the main research goals in MMD, see Myotonic Muscular Dystrophy Research Update for Families on the MDA website at mda.org/IDMC8. □

Cardiac Care in MMD: Lack of Symptoms May Mask Deadly Problems

In MMD1, scarring of the conduction system of the heart may prevent signals from the upper chambers (atria) from being transmitted to the lower chambers (ventricles), so that people with the disease may be unaware of dangerously fast atrial heart rhythms. Unfortunately, the first symptom they experience can be a stroke, instead of a rapid heart rate.

In 2006, Ron Hayes was a 54-year-old executive at Procter & Gamble in Cincinnati when he began noticing some weakness in his hands. “I was trying to clean my glasses,” he remembers, “and my thumb couldn’t push the spray.” A visit to a hand surgeon resulted in a referral to a neurologist and ultimately to a diagnosis of adult-onset MMD1.

Ron Hayes, a retired executive who lives in Denver, didn’t learn he had MMD1 until late middle age. He was in his mid-50s when cardiac testing revealed he needed a pacemaker immediately. Today, he enjoys golf and time spent with his children and grandchildren.

A DNA test of Hayes’ blood cells revealed 131 CTG repeats, consistent with the mild end of the MMD1 spectrum. In fact, Hayes had been active in sports in high school and had a football scholarship in college.

His son, Doug, had been diagnosed with MMD1 in 2001, at the age of 22, but with



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very different disease manifestations from his father’s. (See page 12 for more.) Meanwhile, before the hand weakness, the only significant event in Hayes’ health history had been cataract removal in his mid-40s.

Hayes’ diagnosis came fairly quickly, probably because of the family’s awareness of the disease. Many people with MMD, even today, go through what’s referred to as a “diagnostic odyssey,” as they visit doctor after doctor for seemingly unrelated symptoms.

In 2008, after he had retired and moved to Denver, Hayes’ MDA clinic physician sent him to a cardiologist, who fitted him with a Holter monitor, a device that continuously records an electrocardiogram (EKG) for at least 24 hours while the wearer goes about his normal daily routine.

The Holter monitor revealed that electrical signals were moving through Hayes’ heart more slowly than normal, a problem known as a conduction disturbance. The immediate insertion of a pacemaker was recommended, and Hayes didn’t argue. His brother suspected of having MMD but without a diagnosis, had died suddenly, probably of cardiac causes.

Today, Hayes plays golf and enjoys time spent with his children and grandchildren. He still has hand weakness and some weakness in his lower legs and takes medication to counteract afternoon sleepiness.

MMD, he says, “is not the end of your life” — but he realizes it might have been had he not sought cardiac care.

His advice: “Look at what you can still do, and don’t assume you can’t do things — but see a cardiologist.”

Scarring impairs conduction of electrical impulses

William Groh is a cardiac electrophysiologist at the University of Indiana’s Krannert Institute of Cardiology. Groh has a special interest in the cardiac complications of MMD1 and receives MDA support to study them.

Although his formal research has focused on MMD1, Groh also sees people with MMD2 in his practice.

“My experience is that the severity of heart involvement is significantly less in MMD2,” he says. “But if they develop issues, it seems to be along the same lines. I don’t think that there have ever been real good studies [of the cardiac aspects] in MMD2. Case reports of individual patients with problems aren’t going to tell you what’s going on in terms of the whole population.”

By contrast, for more than a decade, Groh and his colleagues have studied more than 400 MMD1 patients drawn from some 20 MDA clinics. Unlike most studies by cardiologists, Groh’s study didn’t confine itself to patients who were referred for cardiac evalu-



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ations because they had developed signs or symptoms.

"We took all comers," he says. "We followed all of those patients, and we were able to determine cardiac risk factors."

Cardiac disease in MMD1, Groh says, is nearly always conduction disturbance, resulting from the gradual replacement of the heart's conductive tissue with scar tissue, a process known as cardiac fibrosis.

"It's the conduction [of electrical signals that move through the heart] that appears to be first disturbed in patients with myotonic dystrophy," Groh says.

Conduction disturbance can lead to abnormal heart rhythms called arrhythmias. Arrhythmias that are too slow sometimes require a pacemaker that delivers regularly timed electrical impulses to bring the heart rate up to normal.

When the heart rhythm is too fast, an implantable defibrillator can deliver an electrical shock to restore a normal heart rhythm. (These are sometimes called implantable cardioverter-defibrillators, or ICDs.)

Although fibrosis seems to particularly affect the heart conduction system, the entire heart muscle can be affected as well, says Groh. However, he notes, only rarely do people with MMD1 develop abnormalities in the heart tissue responsible for the pumping of blood, a condition known as cardiomyopathy.

Actual heart failure (partial or complete failure of the pumping mechanism) is uncommon in people with MMD, Groh says. "If they do develop it, it tells us that the heart

is really significantly affected. We see that in only a small percent of our population."

Rather, Groh summarizes, "We think the underlying problem is fibrosis and abnormalities in the heart that seem to specifically and primarily affect the conduction system, the specialized tissue that allows for electricity to flow through the heart. It leads to a higher risk of arrhythmias, and a small percentage of patients develop cardiomyopathy."

The most serious arrhythmias are those that cause the lower chambers of the heart — the ventricles — to stop beating or to beat too slowly to sustain life; or to beat in a fast, uncoordinated and ineffective way.

Both these fast and slow ventricular arrhythmias can lead to sudden death, and people with MMD1 unfortunately are at increased risk for that.

Normally, electrical impulses travel via specialized conduction pathways from the sinoatrial node to the atrioventricular node and then throughout the heart, in an orderly fashion.

In MMD1, these conduction pathways are disrupted by scar tissue, leading to heart rhythm abnormalities.

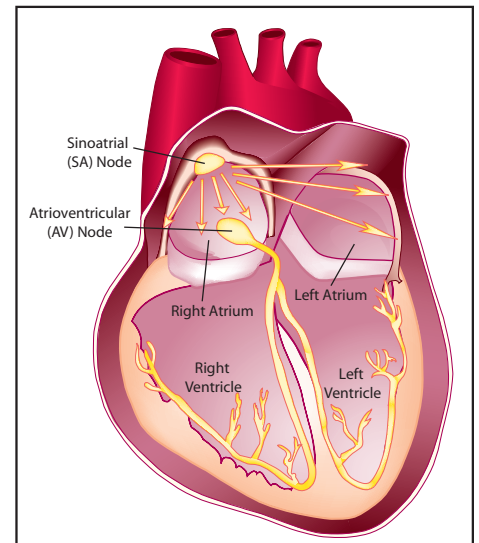
Less often, people with MMD1 develop problems that affect the heart's pumping mechanism, a condition known as cardiomyopathy.

Atrial fibrillation may go undetected

About 10 percent of people with MMD1 in Groh's study developed atrial fibrillation, a rapid, uncoordinated contraction of only the heart's upper chambers (the atria,) which normally route blood from the circulation to the ventricles, which then pump it around the body.

It's a serious problem, because the turbulent blood flow it causes can lead to clots and strokes. Although generally not considered as serious as a ventricular arrhythmia, Groh believes it's an indicator that fibrosis, which is progressive, is under way in the heart.

"Patients with myotonic dystrophy are getting atrial fibrillation in their 40s and 50s at a rate of about 10 percent," he says, while in people without MMD, "we see that frequency in people in their 70s and 80s. So it's an early degeneration of the heart."



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Early, yes, but associated with increasing age. Children born with congenital-onset MMD1 typically don't develop heart problems while they're young, Groh says. "If they develop them, they don't start until their 30s."

EKGs predict risk

Regular EKGs can pick up conduction abnormalities in MMD1 and MMD2.

Groh's research has shown that a good screening test for atrial fibrillation and other arrhythmias is the EKG. "It's a simple test, it's a cheap test, and it can be done by your general doctor or a cardiologist," Groh says. "It's a helpful test to predict who's going to develop heart problems."

He recommends that everyone with MMD1 get an EKG at diagnosis, to establish a baseline to which future EKGs can be compared. He prefers to have a new patient undergo 24-hour EKG monitoring as well as a simple "snapshot" EKG, and also to have an echocardiogram, an imaging study that reveals the structure of the heart.

A normal screening EKG, 24-hour EKG and echocardiogram are very reassuring, Groh notes. The usual recommendation is to repeat the EKG every year, and more often if symptoms appear. But Groh says some patients with normal EKGs may need a new



Regular EKGs can pick up conduction abnormalities in MMD1 and MMD2.

one only every two or three years.

Groh recommends similar screening for MMD2 patients. However, he says, “The likelihood that the results will show no evidence of cardiac disease will be higher in MMD2 than in MMD1, and then screening can be done every two years or so, depending on the EKG and symptoms.”

Symptoms important but potentially confusing

Watch out for “palpitations” (the feeling that the heart is beating hard, fast and irregularly), severe lightheadedness, fainting or significant shortness of breath, Groh says.

But, he cautions, symptoms can be confusing in people with MMD. “Patients with advanced myotonic dystrophy have respiratory issues,” he notes, “so some of those symptoms, such as shortness of breath, might not necessarily reflect cardiac problems.”

Another source of confusion, Groh notes, is that atrial fibrillation, dangerous in itself and a marker of progressive cardiac fibrosis may not give rise to any symptoms at all in people with MMD1.

In people without MMD, a very rapid or irregular heart rate in the atria is conducted to the ventricles. The heart rate in the ventricles, normally 60 to 100 beats per minute, is increased to about 150 beats a minute, which

generally causes feelings of discomfort, such as palpitations, that prompt medical attention.

But, Groh says, “Because atrial fibrillation tends to coexist in myotonic dystrophy patients with conduction disease, it’s often not conducted to the ventricles. So people may have a resting [ventricular] heart rate in the 70 to 80 beats per minute range and may have no symptoms at all. That can be dangerous, because there’s a higher risk of stroke with atrial fibrillation. The first symptom they might present with might be a stroke, instead of symptoms of a rapid heart rate.”

Many ways to treat cardiac arrhythmias (with caveats)

Treatment of the cardiac arrhythmias that occur in MMD1 also poses some special challenges. For example, there are several medications used in the general population to treat arrhythmias that may be dangerous in people with MMD.

Drugs known as beta blockers, which have indirect effects on arrhythmias, and more potent anti-arrhythmic drugs, such as amiodarone (Cordarone) or sotalol (Betapace, Sotalax, Sotacor), are sometimes prescribed for people with MMD, Groh says. However, he worries about this.

“One of the problems with those medications is that they all have the potential for making conduction disease worse” because they dampen the transmission of electrical signals in the heart, Groh cautions.

In general, he says, if someone with MMD “has symptomatic arrhythmias, and they’re going to be treated with one of these anti-arrhythmic drugs, they should have either a pacemaker or a defibrillator in place to protect them from the worst rhythm disturbances, which could be life-threatening.”

If the source of the rhythm disturbance can be pinpointed, a technique called ablation (destruction of tissue by heat or cold) can sometimes solve the problem. In this procedure, a catheter — the “ablator” — is introduced into the heart, usually through a vein.

This type of intervention is particularly useful in a type of fast arrhythmia to which people with MMD1 are prone, Groh says. In this type of abnormal heart rhythm, the conduction of impulses through the heart is slowed so much that the electrical impulses

loop around and re-enter the tissue, paradoxically leading to a heart rhythm that’s too fast. “Conduction is so slow that the tissue becomes excitable again and allows the impulse to re-enter,” says Groh. The ablation procedure destroys the re-entry loop.

When it comes to electronic devices, Groh’s research has led him to believe that an implantable cardioverter-defibrillator (ICD), which can protect against both slow and fast arrhythmias, may be better than a pacemaker, which protects only against slow arrhythmias. (All defibrillators have a backup pacemaker.)

Although the superiority of ICDs over pacemakers in MMD is suggested by his research, it needs to be confirmed in a trial comparing the two interventions, he says. “In our study, nearly half the patients that had pacemakers died during the follow-up period. A significant percentage of that population had sudden, unexpected death, and I think that speaks to the protection that the defibrillator can give over the pacemaker.”

Decisions about devices: To prevent or treat?

Ultimately, decisions about treatment, including the use of potentially lifesaving devices, rests with the individual with MMD — or on occasion, a parent or guardian (although it’s very rare for children with MMD1 to have significant heart involvement).

Some people are eager to receive a device as a preventive measure, even if the degree of fibrosis or arrhythmia isn’t yet severe enough to cause problems. Others reject the idea, and Groh respects that choice as well.

“Some of my patients, after I explain this to them, say to me, ‘Dr. Groh, you’ve gone through this with me, and I’ve decided that I only want a pacemaker or defibrillator if it’s absolutely necessary right now; I don’t want a prophylactic pacemaker or defibrillator.’”

That, however, doesn’t mean they should ignore their hearts. Groh would like to establish an online cardiac resource for people with MMD. “I’d like to set up a website that will provide further information to patients and physicians, one that would allow EKGs to be put on the website so we could review them. This is something I’d really like to do in the future.” □

Energy, Dedication, Hope Help Parents of Children with Congenital MMD1

Newborns with congenital-onset MMD1 are often fragile and may need mechanical ventilation to assist their breathing and a feeding tube for nutrition.

Concern about Cody Beam started right away. "About 12 minutes after he was born, he quit breathing while my husband was holding him," recalls Cody's mother, Tina Beam, of Arlington, Wash.

Cody, born at Providence Regional Medical Center in Everett, Wash., was "very floppy and couldn't swallow," Tina recalls. He was whisked away to the neonatal intensive care unit, where he was placed on a ventilator, and then transferred to Seattle Children's Hospital when he was a week old. He stayed there another three weeks.

"They checked him out for everything," Tina says. "They checked his eyes, his heart and lungs, and his feet, because they were turned in. I think he's seen just about every doctor there — ear, nose and throat, cardiology, pulmonary. There was a lot going on."

The Beams were fortunate to get a DNA-confirmed diagnosis — congenital-onset type 1 myotonic dystrophy (MMD1 or DM1) — within a month, a relatively short time compared to what many families experience.

Tina and Cody both have MMD1

Tina learned that she too has MMD1, although until Cody was born, she wasn't aware of the disease in herself.

"The only thing I have is I'm weak in my hands," she says, "but I also have worked for many years on a computer, so I never thought anything of it. I just assumed that my hands were weak from being on the computer all day."

A rocky first year, but then things turned around

Cody came home from the hospital when he was about a month old, with a feeding tube down his nose and supplemental oxygen.

The nasogastric (nose-to-stomach) tube was later replaced with a standard gastrostomy tube, which goes directly into the stomach from outside; and then with a type of gastro-

stomy tube that can be detached between feedings (the brand name is MIC-KEY feeding tube), leaving a permanent interface on the abdomen that looks like the seal on a beach ball.

The first year was rocky. Cody had trouble breathing and "absolutely couldn't eat anything," Tina recalls. His feet were put into casts to straighten them. The future looked uncertain.

But, says Tina, "About the time he turned a year old, everything turned around."

One night, when Cody was about a year, the family was having vanilla pudding for dessert, and Cody was "adamant that he wanted my pudding," Tina says. "We had tried rice cereal before that, but he wouldn't eat it. I thought, Well, I'll try this; it's just a little bite. And he kept wanting more, and he was swallowing it, and nothing came back up. We tried the rice cereal again the next day, and he just didn't want it. We found out that he just didn't like rice cereal!"

At 2 years and 4 months, Cody "does eat quite a bit by mouth but not enough to sustain himself," Tina says, so he gets two supplemental tube feedings during the day and one at bedtime.

His breathing has stabilized so much that he's slept in his own room without oxygen or a monitor since shortly after he turned 2, in August 2011.

"We started taking him off [the oxygen] a little bit at a time," Tina says. When he was about 4 months old, he was able to stay off it for periods of time during the day, and by the end of his first year he was only on it during the night.

Cody's motor skills also have been improving. At about 18 months, he began



Newborns with congenital-onset MMD1 are often fragile and may need mechanical ventilation to assist their breathing and a feeding tube for nutrition.

crawling on his hands and knees, and he's now starting to walk, with support. (Most children can walk unaided before 18 months.)

"He will walk holding onto our hands," Tina says, "but he's on his toes. We've been trying to work on that. He can use a walker and walk just fine too. But he won't walk on his own. He'll hold onto the bed or the couch and walk around it or down the side of it. But his speed in walking, holding onto our hands, has gotten good enough that I wouldn't be surprised if he takes off on his own soon."

Cody's vision and hearing have checked out fine, as has his heart function. He's had two echocardiograms and two 24-hour EKGs



Cody Beam, shown here at age 2, started improving after his first year.

with a Holter monitor. "They'll check it every year," Tina says.

Meanwhile, she's optimistic about Cody's cognitive and social development. "They haven't really tested it," Tina says. "But as far as we're concerned, he's sharp as a tack. I can almost say anything to him — 'Close the door, open the door, close the cupboard, put that back, put that down, give it to me' — and he knows exactly what I'm talking about and will do it. If you say 'Get ready to go,' he'll get his coat. As far as we're concerned, he understands."

Cody's speaking vocabulary is limited to "uh-oh" and "yee-hah" (the average 2-year-old can say sentences of two to four words), but his speech therapist thinks that may be a problem with the oral muscles more than it is a cognitive deficit and has recommended that he begin learning sign language.

The Beams have just started that, and so far, Tina says, "it seems to be going OK." (Unfortunately, many children with congenital-onset MMD have very weak hands and can't use conventional sign language.)

His social development is progressing fairly normally as well, including tantrums typical of 2-year-olds and decided preferences for certain people and things.

He's starting to recognize the doctor they see about his feet, and "he doesn't like him," Tina says. "Anybody else, he's pretty good with. For a long time, he didn't like anybody. If you weren't Mom or Dad, you weren't good enough. He would just cry and cry. But he's finally starting to warm up to Grandma. It's about time, because she was starting to get her feelings hurt."

(Temper tantrums, fear of strangers and showing affection to familiar people usually emerge at around 18 months. Cody's development is somewhat delayed, but definitely moving in the right direction.)

Doing 'amazingly well,' with lots of help

Family life has certainly changed since Cody's birth. Tina is no longer working outside the home because of Cody's special needs and therapy appointments, which take place one to three mornings a week.

Reading the story of Liz Trumpy (see *Great Expectations: Pregnancy and Childbirth*

with *Neuromuscular Disease, Quest*, July-September 2010), shortly after Cody's diagnosis "just kind of gave me hope" that progress was possible for her son, Tina says, and much progress has been made.

"We don't do everything for him," she says. "We make him do it. That's the only way they're going to get better. If they can do it, you just have to force them."

With Cody, a Binky (pacifier) is the most reliable motivator. "To get him to stand up and get something off the counter, the Binky is a big motivator," Tina says. "We did the same thing when we first got the walker. We would sit in front of him, and if he tried to crawl to us, we'd put him back and say, 'If you use the walker and come to me, you can have your Binky.' He'll do anything for that Binky."

She says, "He does amazingly well considering what we started with. It sounds like a lot, because he can't eat just anything and he can't talk and he can't walk, but when you consider what we started with, we're fine with it."

Florida family also had scary first year with their baby

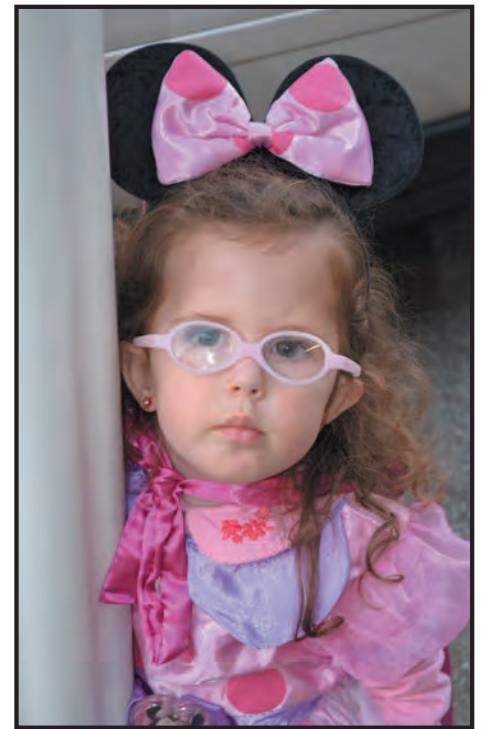
Elizabeth Conte in Jacksonville, Fla., tells a similar story about her daughter, Kate, now 2½.

"About 18 hours after she was born, she had some breathing complications and some other things. She wasn't eating well, and her blood sugar dropped, and we ended up with a trip to the neonatal intensive care unit at Wolfson Children's Hospital in Jacksonville."

Kate stayed in the NICU for about two weeks. Meanwhile, Elizabeth, still recovering from a Caesarean delivery, also had to care for her older child, Charlie, then 2.

"That complicates it all, when you're trying to balance between a child that misses you at home and a new baby you don't know what's going on with," she says.

Newborn Kate was "very floppy and didn't move a whole lot, but they got her breathing under control," her mother recalls. "We left the NICU not really knowing what was wrong with her. We just knew that she had taken several tests for different things. It was about the age of 3 months when we got the DNA test result back, and it was positive for myo-



Kate Conte at age 2½, dressed as her favorite character, Minnie Mouse. Like Cody Beam, she began making steady progress in her second year.

tonic dystrophy."

The Contes learned that Kate had congenital-onset MMD1 and that Elizabeth herself was probably affected.

Elizabeth says they had "no idea it ran in the family. I'm one of six children, so for us that was a huge thing." She remembers going home feeling devastated.

"We lived for about the next week in complete depression around my house. No one smiled, no one laughed. It was just horrible. Then my husband and I were eating dinner one night, and I said, 'I can't do this anymore. I cannot live like this. I'm a positive person. I can't live in this kind of dreariness anymore.' He said, 'I'm feeling the same thing. Let's make a change.' So we did.

"We decided we were going to research and find out everything we could about the disease; that we were going to be proactive and find the best treatments we could for her. We knew it was genetic, and we knew I probably had it, but we didn't know much more than that."

Elizabeth and her husband, David, quickly educated themselves, through MDA and other sources, such as the book *Myotonic Dystrophy: The Facts* (Oxford University Press, 2009), which was written for families by renowned medical geneticist Peter Harper.

Elizabeth, who taught kindergarten and first grade for 10 years, says she now stays home full time because of Kate, whom she got involved in a Florida-based early intervention program called Early Steps as soon as possible.

"The first year of life was very slow, very tedious," Elizabeth recalls. "She didn't make a whole lot of progress very quickly. Finally, after she turned a year old, she was able to sit up on her own and stay in a sitting position without falling over. And then once we got to that, the trunk tone increased, and she made great progress after that.

"But the first year was really tough. We had a lot of choking episodes, a lot of chest infections, and we ended up in the hospital several times."

Kate has exceeded her parents' expectations

"She started walking right around the age of 2. She's still not fully where she should be developmentally for her age, but she is so much farther than we ever thought she was going to be," Elizabeth says.

"She's eating and drinking, and she's doing well with that. We have very little choking now. She has an occupational therapist, a speech therapist and a physical therapist. Right now, she's attending two mornings a week of a little preschool program, and she's loving it and is doing well. I just had a conference with her teacher, and she was so pleased that Kate can get around her environment without falling.

"She can say some words, but she's very limited in her speech. She's learned a lot of sign language from a video called 'Signing Time,' and she uses it all the time to communicate with us, which is really helpful." (Signing Time markets DVDs that teach sign language to babies and children; they're about \$20 each.)

Not just about Kate

Elizabeth, 35, has no MMD1 symptoms at all, but the Contes worry about her future. She hasn't had a DNA test, but since her father and daughter both have had positive

test results for MMD1, doctors have told Elizabeth that she must be affected. "He said, 'You're the link in between, so we know you've got it.'"

Elizabeth also believes some of her siblings may be affected, but her greatest concern is for her son, Charlie. "We're not having him tested," she says, although she knows there's a 50 percent chance that he's inherited the MMD1 gene defect from her. "We watch," Elizabeth said. "We know some of the signs of the childhood-onset form, but we haven't seen anything yet." It's not something they like to think about.

"I think probably the most devastating

"We decided we were going to research and find out everything we could about the disease; that we were going to be proactive and find the best treatments we could for her. We knew it was genetic and we knew I probably had it, but we didn't know much more than that."

blow was not just that I have a daughter that has an issue, but that I have an issue and everybody else — we don't know if they have it or not."

Her advice to others: "Be knowledgeable. I would definitely say read, read, read, because you can never learn enough about it. There's always something new coming."

After extensive self-education, Elizabeth says, "this makes sense to me now. I understand why this and that, and the things we need to look out for. Because of that, I feel like we're on top of Kate's medical condition all the time. And when I go in, I feel like I have valuable information to share at each visit with each specialist."

Baby with congenital MMD1 often a wake-up call

Having a child with congenital-onset MMD1 remains a common way for the disease to be recognized in a family, says Stanford University neurologist John Day. Even when an adult with MMD1 has serious symptoms (not the case for Tina Beam or Elizabeth Conte), they're often not connected to MMD until an affected baby is born.

Day recalls a woman who needed cataract surgery at age 25 and had a cardiac arrest requiring an implanted defibrillator at age 28, but whose underlying MMD1 was unrecognized until her first child was born with congenital MMD1.

"Unfortunately, those of us teaching medical students have too often provided them with an inaccurate image of muscular dystrophy that is at odds with adult-onset MMD," Day says. "Because the clinical features of MMD are so tremendously variable in adults, and the increase in disease severity between parents and their children can be so marked, the existence of MMD in parents is all too often obscured until an affected child is correctly diagnosed."

Although the prognosis for babies born with congenital MMD1 has improved with neonatal intensive care, therapies during early childhood and special education, the disease still has profound consequences and can be life-threatening, especially in the early months.

Day says better awareness by doctors of the signs and symptoms of adult-onset MMD1 — such things as early cardiac abnormalities, early and unusual cataracts, grip myotonia and weakness that can be subtle — is needed to help families make informed decisions and help parents and professionals prepare for the possible birth of a baby with special needs. □

Juvenile-Onset MMD1 Can Cause Cognitive, Behavior Challenges

Young people with MMD1 often need a lot of guidance and support as they move into adulthood.

Ron Hayes didn't get a diagnosis of type 1 myotonic dystrophy (MMD1 or DM1) until he was 54, long after he had enjoyed academic and athletic success in high school and college, had earned a master's degree in public health, had married and had children, and had established himself in a career.

Getting an MMD1 diagnosis had some implications for Ron's life, particularly as it illuminated the cause of his hand weakness and prompted an important consultation with a cardiologist.

But the story for his son, Doug, has been very different.

Asperger-like syndrome

Doug Hayes received a diagnosis of juvenile-onset MMD at the age of 22, after a long history of difficulties that started in his pre-school years and didn't seem to have much to do with muscle disease. Juvenile-onset MMD begins during childhood, but well after birth.

Before the MMD1 diagnosis, his condition had been called Asperger syndrome, a disorder characterized by significant difficulties in social interaction and restricted, repetitive patterns of interests and behavior.

At 32, Doug lives at home with his parents and doesn't have a job. "He's had a series of minimum wage jobs," Ron says, "but he loses them because he can't get there



Young people with MMD1 often need a lot of guidance and support as they move into adulthood.

on time and has poor communication skills and slurred speech. He can't live on his own. He's been in college since he was 18, but he has no degrees."

Cognitive and behavioral difficulties can occur in adult-onset MMD1 and in congenital-onset MMD1, but in juvenile-onset MMD1, they can be the most prominent aspect of the disease. In fact, muscle symptoms may go unnoticed for a long time in young people with juvenile-onset MMD1, while parents and teachers focus exclusively on school problems.

Teen's mother reframed expectations for her son

Suzette Ison's 17-year-old son, BillyDean, began showing some worrisome signs when he was 5, but didn't receive a diagnosis of juvenile-onset MMD1 until he was 10.

Suzette, a nurse who works for an insurance company in Indianapolis, began noticing that her son's social development in his early school years wasn't the same as that of her daughters.

"I had one doctor tell me that boys mature later," she recalls. "I had heard that, too, so I kept going with that. But then we got to 9, 10 years old, and things just seemed to get worse."

Suzette, 45, switched from a hospital-based job to a more flexible one to be more available to her son.

Originally, Suzette thought her long-term goal was "getting him to be able to advocate for himself," she says. "I thought that was going to be possible. I thought I could educate BillyDean to be able to take care of himself, but I didn't understand at that time the real challenges of MMD."

Until recently, she had hoped BillyDean would be interested in attending modified college classes, but she has accepted that his interests lie elsewhere.

"My girls were both interested in college and all that, and I'm seeing now the difference," she says. She's planning to buy some land out in the country and build a home with an attached living area for BillyDean, so that he can live "independently, in his own area, but staying by me, so we can still work together."

Suzette wants to be sure that BillyDean gets to his medical appointments and into programs that he needs. But if she can buy land out in the country, she says, he can help take care of the land and work with animals.

"There's an animal shelter not too far from there. He has a service dog, and he loves animals. He could get a job at the animal shelter, maybe part time because of his fatigue. He would be good at that, because he's interested in that. I don't know how much he would make, but that would be something he could do."



Suzette Ison (right) plans to build a home with an attached area for her son, BillyDean (left), where he can live semi-independently.

Planning and processing difficulties most common problems in MMD1

"When you talk about myotonic dystrophy type 1, the most common cognitive deficits are problems with visual-spatial processing, the ability to look at puzzles or move things around in space," says Nicholas Johnson, a neuromuscular medicine fellow at the University of Rochester who is conducting research related to quality of life in MMD1 and MMD2, and to brain chemistry in MMD1.

The other common problem area is executive functioning, or the ability to plan ahead, he says.

"In mildly affected individuals, they might not have any cognitive problems, or they may just have limited problems with visual-spatial processing or executive function.

"But when individuals are more severely affected, that's where you can see some changes in their overall cognition, a kind of global cognitive impairment where they may have had difficulty in school or may have needed some special education."

Muscle weakness doesn't always correspond to cognitive impairment. Emma Ciafaloni, an associate professor of neurology and pediatrics and co-director of the MDA Clinic at the University of Rochester in New York, remembers a patient with MMD who was an excellent pianist but for whom playing became more and more difficult.

"It wasn't for motor reasons," Ciafaloni says. "His hands were perfectly strong. I think it was more the cognitive processing."

An 'avoidant' personality noted in some with MMD1

Johnson says there are also certain personality characteristics that are associated with MMD1.

"Neuropsychologists would put that under the rubric of avoidant personality disorder," he says, referring to a disorder characterized by pervasive social inhibition and avoidance of social interaction.

On the milder end of the scale, the "MMD1 personality" may merely describe



A supportive family can make a big difference in the life of a young person with MMD1.

someone who doesn't like crowds and doesn't interact as well with other people as most people do.

However, Ciafaloni cautions that what may appear to outsiders to be apathy may sometimes more accurately reflect difficulty making decisions.

What may appear to outsiders to be apathy may sometimes more accurately reflect difficulty making decisions.

"They may look like they don't care, but they may be having a hard time organizing and processing and deciding what to do next," she notes.

Family and professional support helpful

A supportive family can make a big difference in the life of a young person with MMD1.

People with MMD who have family members who are involved in their care are "better off in terms of functioning in the community," Ciafaloni says. "If they're loners, then it becomes more of a problem."

A neuropsychologist can be helpful in identifying the areas where an individual has deficits and then setting up some compensatory tools, she notes.

But, says Johnson, "One of the problems with this particular issue is that it's relatively imperceptible to the patients themselves.

Sometimes people will say they feel a little foggy or they don't feel like they can quite process things as fast as other people — but in general, it's really not something that they particularly struggle with."

Family members, such as spouses and parents, may be the ones who notice this more.

Problems less profound and less common in MMD2

As with most aspects of MMD, cognitive and personality characteristics associated with type 1 occur in type 2, but not as often and not as profoundly. "Maybe it's too simplistic," says Ciafaloni, "but it seems like MMD2, for the vast majority, is a milder version of MMD1." □

Excessive Daytime Sleepiness Can Be ‘Debilitating’ in MMD1 and MMD2

Thirty-two-year-old Doug Hayes has struggled with some of the cognitive and social features of type 1 myotonic dystrophy (MMD1 or DM1) most of his life. But there’s something else that’s contributed to his difficulties with jobs and schooling: daytime sleepiness. Doug recently had a job scanning documents, his father says, but his daytime sleepiness interfered.

One doctor prescribed Adderall [an amphetamine-based stimulant], to help Doug stay awake, but he had to stop taking it when his liver started showing signs of damage. Now, Provigil (modafinil, a wakefulness-promoting medication), while not quite as effective, is helping him to some extent. “He pays more attention,” his father says.

For Jenefer Hopson, also 32, MMD1 symptoms began during adolescence. Hopson lives in Rochester, N.Y., and she has been able to work, marry and have a child. However, sleepiness has been a problem, especially in her adult life.

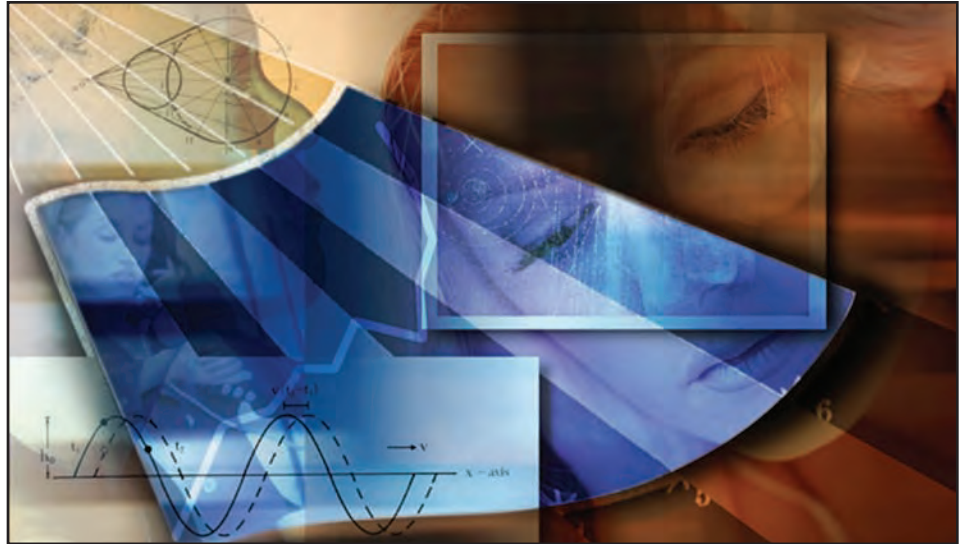
“If I worked early in the morning and got out at noon or 1 o’clock, then it was OK,” she says. “But if I worked past 1 o’clock, I could run into issues. I would fall asleep at work.”

She’s now home with her baby and still has trouble staying awake. “It depends what I do during the day,” Hopson says. “If I just sit around and don’t do anything, I can stay up a little bit longer. But if I’m out running around doing errands, I’ll come home three hours later and be ready for a nap.”

Not taking that daytime nap — by taking stimulant medications — would cause her to fall into such a deep sleep at night that she feared she wouldn’t hear the baby if he needed her.

Respiratory muscle weakness can contribute to somnolence

BillyDean Ison, age 17, began showing signs of excessive daytime sleepiness in his early school years. “He was falling asleep continually,” his mother says, “including when he had plenty of sleep.



Staying awake through the day can be a challenge for people with MMD1 and MMD2.

In BillyDean’s case, the sleepiness may be at least in part due to another MMD1-associated problem — respiratory muscle weakness.

“He retains carbon dioxide,” his mother says. “We’ve worked with BiPAP [bilevel positive airway pressure] at night for a long time, but he hasn’t been able to tolerate it.”

Excessive sleepiness also can occur in MMD2

People with MMD2 can experience daytime sleepiness as well. “I could fall asleep at my desk at work with no problem at all,” says Krista Schulz, a 47-year-old Web designer at the University of Connecticut, whose MMD2 was diagnosed when she was in her early 40s.

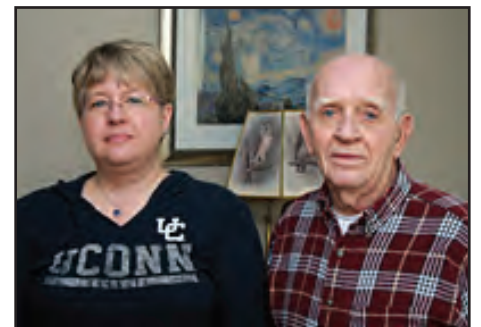
“Even when I’m driving, I get so tired,” Schulz says. “I’ve had to pull over sometimes on the way home from work because I was so tired. I’ve tried lots of coffee. I’ve even tried NoDoz [caffeine pills].”

Schulz sleeps well at night, and so far she has not experienced any breathing or heart problems. But the fatigue and sleepiness persist.

Karen Raymond of Frederick, Md., knows what that’s like as well. Now a 50-year-old facilities security officer, she started having symptoms in her early 40s that eventually led to a diagnosis of MMD2. Fatigue and sleepiness play a big role in her life.

“I don’t know if people can really understand how difficult it is,” she says. Starting in her 40s, she says, “I was feeling so overwhelmingly tired that it was difficult to get through the day. It’s very hard to explain to somebody just what I mean by that. I could be speaking to somebody and about fall asleep. I would be at my desk at work and sitting at my computer doing something one minute and nodding off the next.

“For a while, my husband and I were carpooling, which was good, because he drove, and I would sleep. Then he retired, which left me driving, so I couldn’t sleep in the car on the way home anymore, and that became a problem. I had never been one to feel sleepy while driving, and all of a sudden it was to the point where I was sleepy, and I didn’t have that far to drive.



Krista Schulz and her father, Arthur Schulz, both have MMD2. Krista, a Web designer, has gotten so sleepy while driving home from work that she’s had to pull off the road.

"It was just awful. I would come home from work and say, 'Sorry, I have to lie down and take a nap.' Every day." These days, she's become "quite adept at power napping," although she believes she sleeps well at night.

"Now I just do it all the time," she says of her power naps, which generally last 20 minutes to an hour and a half. "I think, 'Oh, I'd better go and take my nap now, because if I don't, I'm going to be in trouble.' I can just sit down and close my eyes, and I'll be sound asleep. It doesn't matter what I'm doing."

Provigil seemed to help for a time, but it may have exacerbated her migraine headaches. Now, Raymond says, with her migraines under better control, she's going to give Provigil another try.

People with mild muscle weakness can have debilitating sleepiness

The excessive daytime sleepiness seen in MMD1 and to a somewhat lesser extent in MMD2 has been a long-standing interest of neurologist Emma Ciafaloni, co-director of the MDA Clinic at the University of Rochester Medical Center in New York.

In 2003, Ciafaloni received a two-year MDA research grant to study excessive sleepiness — hypersomnolence — in MMD.

"I think the problem of hypersomnolence in myotonic dystrophy is extremely intriguing and also unique for any of the neuromuscular disorders," Ciafaloni says. "I think that what triggered my interest was the fact that, sometimes, patients who have a very mild form of myotonic dystrophy in terms of the muscle involvement can be extremely debilitated functionally by the sleep disorder."

Possible causes of hypersomnolence in MMD

"It's not just one type of sleep disturbance that these patients have," says Ciafaloni. "We can see the whole spectrum in different patients, or even different types in the same patient."

Ciafaloni says the spectrum ranges from classic obstructive sleep apnea, meaning periodic breathing cessation during sleep due to upper airway obstruction; to a type of hypersomnolence that very much resembles narcolepsy, a disorder of the brain that involves

excessive daytime sleepiness and sudden attacks of sleep.

"It makes it very challenging to treat," Ciafaloni says, "but I also think that it is a potentially treatable aspect of the disease and therefore it's important to try to figure out exactly which type each patient has."

Ciafaloni's research and experience have led her to believe that the hypersomnolence of MMD can be a combination of:

- inadequate breathing due to weakness of the diaphragm muscle;
- obstructive sleep apnea due to collapse of the upper airway musculature; and
- disrupted sleep-wake cycles originating in the brain.

She believes each person with MMD can have any one of those things or any combination of them.

"Overall, excessive daytime sleepiness is probably present in about 50 percent of the patients," she says. "This has repercussions on their functioning and fatigue and is a difficult part of the disease."

When it comes to treatment of hypersomnolence, a good diagnosis is essential, Ciafaloni says.

"I think it's very important, with myotonic dystrophy being such a multisystem, multi-organ disease, to really have a team approach and be very proactive in addressing all the issues. It's important to really get the help of sleep specialists to try to treat the hypersomnolence. We're fortunate here [at the University of Rochester] because many of our sleep specialists are interested in myotonic dystrophy, but I would encourage patients to proactively seek screening and help if they feel that their sleep is not right or they feel excessively fatigued during the day."

Medications, ventilation, habit changes can be combined

If the diagnosis is a more central (brain-related) hypersomnolence, Ciafaloni generally prescribes the wakefulness-promoting medication Provigil, or the closely related Nuvigil (armodafinil).

"We do try modafinil quite a bit," she says. "It was originally used for narcolepsy, but it's now used for many more indications, even just general fatigue and hypersomnolence. That's something that we use frequently and



Neurologist Emma Ciafaloni, co-director of the MDA Clinic at the University of Rochester Medical Center (N.Y.), has had a long-standing interest in the excessive daytime sleepiness associated with MMD.

that the sleep specialists recommend in these patients, as well as older stimulant medications, such as Ritalin or Adderall, or even a combination of these.

"If nighttime sleep is being interrupted by breathing difficulties, daytime sleepiness often results. If the breathing interruptions during the night are caused by collapse of the upper airway tissues and musculature (obstructive sleep apnea), then CPAP — continuous positive airway pressure — is prescribed, Ciafaloni says.

But if nighttime breathing is insufficient mostly because of weakness of the diaphragm muscle, then the preferred treatment is BiPAP (a registered trademark of Philips Respironics), in which air is delivered at one pressure for inhalation and another for exhalation. Sleep-disordered breathing of mixed origin is tricky to treat, she acknowledges.

Neuromuscular disease specialists, sleep specialists and psychologists, who can help people change their sleep habits and establish a more beneficial sleep cycle, all have a role to play, she says.

Even so, treatment may not work.

"Sometimes compliance is not great," Ciafaloni says. "Sometimes it's just because these interventions that usually help in regular sleep apnea don't help these patients, so they stop using them. Sometimes CPAP just doesn't improve the symptoms as much as it would in sleep apnea without myotonic dystrophy."

Often, it's a combination of medication, habit changes, and CPAP or BiPAP that helps, she says. "It's usually not just one thing fixing it." □

MMD Research: Seeking to Free Proteins from a 'Toxic Web'

The complex and multifaceted disease known as **myotonic muscular dystrophy (MMD)** — also known as **dystrophia myotonia (DM)** — was the subject of an In Focus report in the April-June 2012 Quest.

Experimental strategies hold the potential to markedly improve the outlook for people with myotonic muscular dystrophy (MMD, also known as dystrophia myotonia or DM).

So far, most research is focused on type 1 MMD (MMD1 or DM1), which is caused by an expanded stretch of DNA on chromosome 19. However, experts say many of the same strategies in development for type 1 will likely apply to type 2 MMD (MMD2 or DM2), for which the underlying cause is an expanded stretch of DNA on chromosome 3.

Expanded DNA leads to the creation of expanded and toxic RNA, which causes

problems for cells mainly because it traps and disables important proteins. (The expanded RNA has other effects as well, and these differ between the two types of MMD.)

Therefore, an important goal in MMD research is to free cellular proteins — particularly one called muscleblind 1 or MBNL1 — from their RNA web. Different researchers are approaching this goal with slightly different strategies.

Three researchers, multiple approaches

Thomas Cooper at Baylor College of Medicine in Houston is using molecules called antisense oligonucleotides to attract an enzyme that destroys toxic RNA and frees proteins such as muscleblind 1

(MBNL1). (See “Targeted Destruction,” page 17.)

Matthew Disney at Scripps Research Institute in Jupiter, Fla., is using small molecules designed in his laboratory to free proteins from weblike toxic RNA. (See “Blocking Harmful Interactions,” page 18.)

And, Charles Thornton is using both antisense oligonucleotides and small molecules to either destroy toxic RNA or separate it from cellular proteins. (See “Multiple Strategies Make Sense,” page 20.)

Cellular Proteins Resemble Bees in a Hive



Bees in a hive have various jobs.

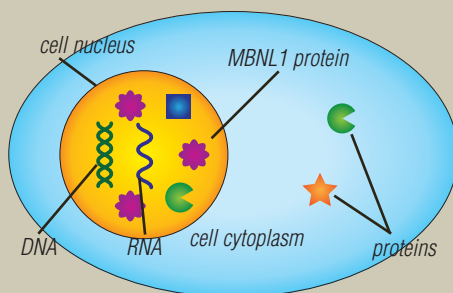


Bees caught in a spider web can't perform their jobs.



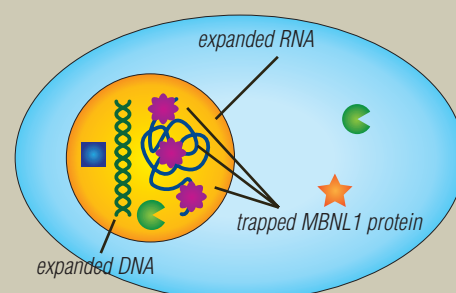
Bees freed from the spider web can resume their normal duties.

Normal cell



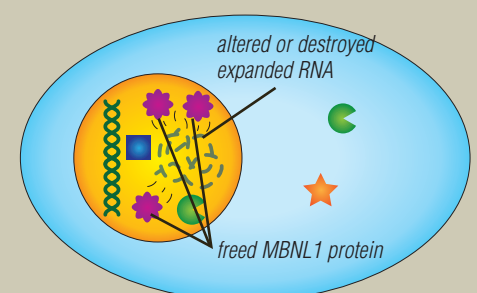
Proteins in a cell have various jobs, some in the nucleus and others in the cytoplasm.

MMD-affected cell



The genetic mutations that cause MMD1 and MMD2 cause an expansion of DNA and RNA. Proteins, particularly MBNL1, get caught in the expanded RNA web.

Treated MMD-affected cell



Several strategies in development to treat MMD1 and MMD2 involve freeing proteins, particularly MBNL1, from the web of expanded RNA so that they can resume their normal duties.

MMD Research: Targeted Destruction



Thomas Cooper, M.D.

Affiliations: Baylor College of Medicine, Houston

Strategy: Using antisense oligonucleotides to attract an enzyme that destroys toxic RNA in MMD1-affected cells

degrade [destroy] the RNA with the CUG repeat expansion. That's the approach that we've been using and that's been funded by MDA.

Q: How does the antisense oligonucleotide that you're using destroy the expanded RNA?

A: It doesn't do it directly. It attracts an enzyme called RNase H that destroys it.

Q: How does that work?

A: RNase H is in the cell nucleus, and its usual function is to seek out and destroy RNA that's paired with DNA. That type of RNA needs to be short-lived, so the cell wants to get rid of this hybrid molecule.

“We saw the amount of RNA that contains the expanded repeats decrease by 50 percent in the mouse muscles that got the treatment compared to the muscles that didn't get it.”

The antisense oligonucleotide that we put in as a potential therapy is modified DNA. It's specifically designed to bind to CUG repeat expansions in RNA. When it does that, the resulting construction looks to the cell like a DNA-RNA hybrid — something it wants to destroy.

Q: How do you keep the antisense from sticking to normal-length stretches of CUG repeats in the RNA?

A: It's specifically designed to bind preferentially to stretches of RNA that contain more than the normal number of CUG repeats. In our laboratory experiments, we've found that the antisense oligonucleotides we're using had no effect on stretches of RNA containing 12 CUG repeats, the average number found in non-MMD1 cells.

Q: When the RNase H enzyme comes in, does it take out the whole strand of RNA instructions, or just the CUG repeat-containing part?

A: Our antisense molecules, which we're calling CAG gapmer antisense, contain 14 or 16 nucleotides. Those 14 or 16 nucleotides stick to the CUG repeats, and that short piece of RNA will be degraded by the RNase H.

We now have two shorter RNA strands: The free ends where we clipped out that small piece with the CUG repeats are now exposed. RNA is fairly unstable, once you break it. There are other enzymes in the cell that will quickly jump on those free ends and degrade them.

Q: Could destroying the whole RNA strand cause a problem?

A: Probably not. Remember that, in MMD1, there is one normal gene for the protein known as DMPK and one abnormal one, with the CUG repeat expansions, in each cell nucleus.

Theoretically, we're only destroying the DMPK instructions that contain the CUG repeat expansions, leaving the

ones without the expansions alone.

Evidence suggests we don't need too much DMPK protein, so it's likely that enough of it can be made from the instructions that aren't expanded and won't be targeted.

Thomas Cooper, a professor in the Department of Pathology and Immunology at Baylor College of Medicine, is a longtime MDA research grantee who has current MDA support to develop oligonucleotide-based therapies for myotonic muscular dystrophy (MMD, also known as DM).

Margaret Wahl, MDA's medical and science editor, talked with Cooper about his research.

Background note: *In type 1 myotonic dystrophy, there is an abnormally expanded stretch of chemical sequences known as CUG repeats in the genetic instructions for the DMPK protein. Antisense oligonucleotides are specific chemical sequences designed to home to other specific chemical sequences, such as CUG repeats.*

Q: What's the goal of using antisense oligonucleotides in MMD? Is it to block the interaction between the CUG repeats and other molecules, or to degrade these repeats?

A: It's both. There are different approaches. One is to block the interaction of the CUG repeats with a protein called muscleblind 1 [also called muscleblind-like protein 1 or MBNL1], freeing up muscleblind 1 to carry out its normal functions.

The second approach, which is a different kind of antisense oligonucleotide, is to

Q: What did you see when you injected CAG gapmer antisense oligonucleotides into a leg of a mouse with an MMD1-like condition?

A: This mouse contains pieces of DMPK RNA with 960 CUG repeats. We saw the amount of RNA that contains the expanded repeats decrease by 50 percent in the mouse muscles that got the treatment compared to the muscles that didn't get it.

We also saw a 40 percent reduction in abnormal clumps of RNA stuck to muscleblind protein.

And we saw a partial restoration of correct RNA splicing, a crucial step needed for protein synthesis, in the treated muscle fibers. A normal function of muscleblind 1 is to participate in the splicing process, so we believe at least some muscleblind 1 was freed from its RNA trap to do this.

Q: Do you think this same approach would work for type 2 myotonic dystrophy, where there's a CCUG repeat in the RNA?

A: Yes, I think it would probably work the same way for type 2, although we've only tested it in mouse and cell models of type 1.

Q: What are some caveats with this approach?

A: One important caveat is that we don't know to what extent our mouse model — or any mouse model — really mimics the human disease. These mice are probably expressing a lot more RNA than would be expressed in any human cell. But expressing huge amounts of RNA might not be the right thing to do. The question you have to ask is, are you reproducing what's happening in the human disease?

Q: Do you think this type of treatment is something we're likely to see during the lifetime of anyone who has myotonic dystrophy today?

A: Several labs are producing promising results with antisense oligonucleotides. I hate to be overly optimistic, but I have to say, I'm very enthusiastic. □

MMD Research: Blocking Harmful Interactions



Matthew Disney, Ph.D.

Affiliations: Scripps Research Institute — Florida, Jupiter, Fla.

Strategy: Using laboratory-designed small molecules to block interactions between toxic RNA and protein in MMD1-affected cells

Myotonic dystrophy is thought to be a disease in which abnormal RNA folding plays an important role, and I'm particularly interested in RNA folding and misfolding. My training in RNA biophysics has had a great influence on our efforts in developing myotonic dystrophy therapies.

Q: How has your background as a biochemist and biophysicist influenced your approach to developing myotonic dystrophy therapies?

A: We've been studying what types of folds the toxic RNA in myotonic dystrophy adopts, and we've been comparing these folds to those adopted by other cellular RNA molecules that we do not want to target.

By using this information, we've leveraged

our ability to design and synthesize small molecules that can potentially bind to just the toxic RNA folds seen in myotonic dystrophy.

Q: So, you're attempting to target only the toxic RNA repeats and not other RNA repeats?

A: Right. It remains to be seen if you can do this and how well you can do this. The approach that we've put forward is that our designed compounds specifically tar-

Matthew Disney is an associate professor in the Department of Chemistry at the Scripps Research Institute in Jupiter, Fla. He has MDA support to design small molecules that target the toxic RNA that underlies myotonic muscular dystrophy (MMD, also known as DM).

MDA Medical and Science Editor

Margaret Wahl talked with Matthew Disney about his work.

Background note: RNA is derived from DNA and is the chemical step between DNA and protein synthesis. In MMD, the RNA is abnormally expanded.

Q: Your background is a bit different from that of some of the other researchers working on myotonic dystrophy. Are you coming at this challenge not so much as an expert in MMD, but as a biochemist with a special interest in RNA?

A: Yes. I have a background in biochemistry with a focus on the physical properties of RNA.

“Myotonic dystrophy is thought to be a disease in which abnormal RNA folding plays an important role.”

get the expanded repeats of [the chemical sequence] CUG in myotonic dystrophy type 1 and the expanded repeats of [the chemical sequence] CCUG in myotonic dystrophy type 2.

We're targeting multiples of these repeats in a row, not a single copy of the repeat or just a few copies of the repeat. We think that by only targeting many repeats in a row, the compounds should have fewer off-target effects in cells and — although this has to be seen down the road — fewer side effects.

Q: You mentioned type 2 as well as type 1 myotonic dystrophy. Are you working on both?

A: It's interesting that you ask that. When we first got interested in myotonic dystrophy drug targets, we designed compounds for type 2. However, there weren't adequate cell and animal models of MMD2 in which to test these, so we switched to type 1. But, yes, we're optimistic about type 2.

Q: Your goal in targeting the repeats is to block their interaction with other molecules in the cell?

A: That is our goal.

Q: So you're not trying to destroy the repeats or the whole RNA strand, as some other strategies are attempting to do?

A: Right. The reason we don't want to destroy the repeats is that the RNA attached to the repeat may have some physiological function. If you destroy the CUG repeats in type 1 myotonic dystrophy, for example, you may affect the DMPK messenger RNA [genetic instructions for the DMPK protein] that the CUG repeats are attached to.

We've demonstrated that when we target the CUG repeats in the DMPK instructions with our small molecules, our designer compounds, these instructions are no longer stuck in the cell nucleus. They can get out of the nucleus and into the cytoplasm of the cell, where they have to go for the DMPK protein to be made.

Q: Why do you think the RNA can get out of the nucleus once you've targeted it with one of your small molecules?

A: It's because the small molecules are binding to the CUG repeat RNA and stopping large proteins from sticking to them. It turns out that the protein sticking is what keeps that DMPK messenger RNA stuck in the nucleus. If we can dislodge the large proteins, then the messenger RNA can leave the nucleus.

Q: How do your small molecules compare to other small molecules in development to treat myotonic dystrophy?

A: Our compounds have RNA-binding modules that are separated by what we're calling spacers. We think by making small molecules with spacers, they will go to and recognize RNAs that fold up into a long hairpin shape and not the ones that don't. [It's believed that the CUG repeats in MMD1 cause the RNA to fold into a shape that looks like a hairpin.]

I think it remains to be seen how one can target these expanded repeats specifically with a small molecule. But if I were to bet I'd put my money on a modularly designed compound like the one we've designed that targets the expanded repeats in MMD1, as opposed to a traditional small molecule that might recognize just one repeat.

Q: What kinds of chemicals are you using to target CUG or CCUG repeats?

A: We've made derivatives of things like antibiotics, and we've made some other compounds that are similar to some known drugs. The bis-benzimidazoles are one class we're working on.

Q: Are those the ones you're calling H molecules?

A: Yes.

Q: What have you seen in the laboratory with these molecules?

A: In cells that have an MMD1-type defect, we've seen that the designed compounds are capable of correcting three key features of the disease: the binding of cellular proteins to the CUG repeats; the retention of DMPK RNA in the cell nucleus; and the creation of potentially cell-damaging clumps of RNA and proteins in the nucleus.

All three of those defects were corrected in cell models of MMD1. The cellular proteins were released from the CUG repeats, allowing them to do their normal jobs; the DMPK messenger RNA was able to leave the cell nucleus and be used for synthesis of DMPK protein; and there were fewer RNA-protein clumps.

Q: Have you done any experiments with these compounds in mice?

A: Yes. The animal studies were done in collaboration with Charles Thornton. (See page 20 for more.) We wouldn't have been able to do them without him.

Charles' lab injected our compounds into their MMD1 mice. These mice have expanded CUG repeats in the actin gene, not the DMPK gene.

We saw correction of the MMD1-associated defects in chloride ion channels and calcium ion channels, which are required for controlling muscle contraction and relaxation. We think that's because MBNL1 [muscleblind-like protein 1] and possibly other proteins, which are needed for correct synthesis of these channels, were freed from the CUG repeats to do their usual jobs.

So far, that's all we've looked for, and that's all we've seen, but we're extending those studies.

We're also going to see if oral dosing of these compounds in the mice is effective.

Q: Do you think you'll reach the heart with these compounds?

A: Yes.

Q: And the brain?

A: I'm not so sure. That remains to be seen. Here at Scripps, we have a distribution, metabolism and pharmacokinetics facility, where we can test compounds to see their distribution very quickly and potentially optimize them if need be.

These drug discovery facilities are a major advantage that we have here at Scripps. They set us apart from more traditional academic institutions and make us uniquely positioned to potentially advance compounds from the lab to the patient.

Q: How does your strategy compare to, say, some of the antisense oligonucleotide strategies being developed for myotonic dystrophy?

A: The antisense strategies are much further along in development than the small molecules, and some have been shown to reduce myotonia [the prolonged contraction of muscles associated with myotonic dystrophy].

But the advantage of small molecules is that they're tried-and-true therapeutics. Most FDA-approved drugs are small molecules. There are only maybe one or two antisense oligonucleotides that have been approved by the FDA [U.S. Food and Drug Administration].

Small molecules are easier to manufacture than antisense oligonucleotides, and they may get into targeted tissues and cells more easily.

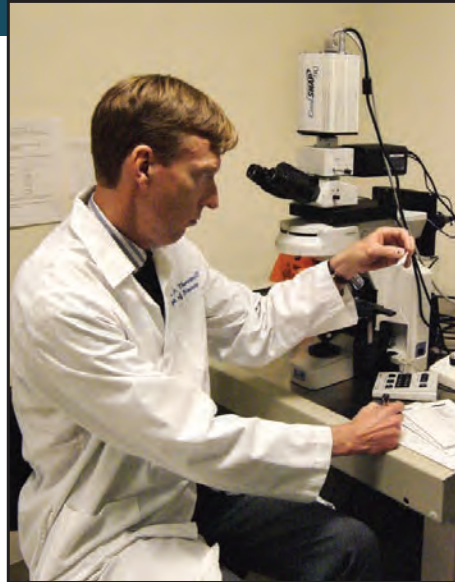
Also, they can often be delivered orally. Aspirin, for instance, is a small molecule. It would be hard to envision an antisense molecule being orally available. It would be much easier to envision a small molecule being orally available.

And finally, antisense compounds are pretty costly to make. The thought is that a small molecule will be easier to make and easier to produce in large quantities, and therefore cheaper.

Q: How big is an antisense oligonucleotide compared to a small molecule of the type you're developing?

A: Antisense oligonucleotides are 10 to 50 times the size of a small molecule like ours. □

MMD Research: Multiple Strategies Make Sense



Charles Thornton, a professor of neurology at the University of Rochester (N.Y.), has received MDA support for research in myotonic muscular dystrophy (MMD, also known as DM) and other neuromuscular diseases. He's currently developing antisense oligonucleotides and small molecules for MMD. Thornton also co-directs the MDA Clinic and directs the MDA/ALS Center at the University of Rochester Medical Center.

Margaret Wahl, MDA's medical and science editor, talked with Charles Thornton about his research.

Background note:

The underlying cause of type 1 MMD is an abnormal expansion of repeated CUG chemical sequences in the genetic instructions for the DMPK protein. The underlying cause of type 2 myotonic

Charles Thornton, M.D.

Affiliations: University of Rochester (N.Y.)

Strategies: Using antisense oligonucleotides to attract an enzyme that destroys toxic RNA in MMD1-affected cells

dystrophy is an abnormal expansion of repeated CCUG sequences in the genetic instructions for the ZNF9 protein.

Q: When designing a therapy for type 1 or 2 myotonic dystrophy, is it better to interrupt the interactions between the CUG or CCUG repeats and protein molecules, or to destroy the repeats?

A: I think the important point is that there's strength in diversity, having different ways to come at the problem. MDA is supporting several research groups that are using

“I think the important point is that there's strength in diversity, having different ways to come at the problem. MDA is supporting several research groups that are using different technologies to develop a treatment for the disease.”

different technologies to develop a treatment for the disease.

All of them are showing progress in one way or another in terms of having some of the intended beneficial effects when they're tested in cells growing in a dish or in a mouse that has some characteristics of myotonic dystrophy.

There might even be a reason to think that

these things, if tried together, might have a stronger effect than if tried individually. That hasn't been tested yet, but it could be tested, down the road. There eventually

could be combination therapies.

It's too early now to say which of the strategies in development is the best method. They all should be moved forward as efficiently as possible.

Q: Are you hopeful about antisense as a strategy for MMD?

Note: *Antisense oligonucleotides are molecules designed to target a specific chemical sequence, generally to block it or destroy it.*

A: I'm not going to tell you what I'm going to vote for — small molecules or antisense. If I had to make a guess, I think the first one that will be tested in clinical trials is likely to be antisense because there are some shortcuts in the development process for that kind of drug.

Q: Are there different kinds of antisense that are being tried?

A: Yes. There are different research groups that are trying different types of antisense. They come in different chemical flavors.

Antisense is a chain, and the types of antisense are different in terms of the chemical makeup of the parts that join the chain together — what people call the backbone or framework of the chain.

One approach is to use antisense as a guide molecule that shows an enzyme called RNase H where to make a cut in RNA. You pick the RNA that you want to cut, you design an antisense to couple with it, and then the RNase H cuts the target.

Note: *RNA is a chemical derived from DNA that can carry genetic instructions for protein synthesis and can play other cellular roles. Abnormal expansions in the RNA for the DMPK protein underlie MMD1, and abnormal expansions in the RNA for the ZNF9 protein underlie MMD2.*

Q: A few years ago, you were experimenting with an antisense compound called CAG25 in a mouse with expanded CUG repeats and an MMD1-like condition.

A: Yes. When we did that, CAG25 was not making a cleavage in the target. It was binding to the RNA repeats, the toxic RNA, but not causing cleavage of it.

Q: What did you hope the CAG25 construct would do?

A: The CAG25 molecule, which resembles RNA, was designed to bind to CUG repeats, and to keep cellular proteins like MBNL1 [muscleblind-like protein 1] from getting stuck on the repeats.

Q: And did it do that in the mice?

A: Yes. The mice had toxic RNA with expanded CUG repeats in their muscle tissue. They were given injections of CAG25 into one leg muscle and injections of an inactive substance into the corresponding

“After the treatment, we saw large reductions of the toxic RNA, elimination of myotonia, normalization of a process called RNA splicing, and no evidence of harmful side effects.”

muscle on the other leg.

In the CAG25-injected muscles, the MBNL1 protein was freed up, which allowed it to do its normal job in the cell. The muscles treated with CAG25 showed several improvements in structure and function compared to the untreated muscles. In fact, myotonia — the prolonged muscle contraction seen in myotonic dystrophy — was eliminated in the treated mouse muscles.

Note: *For more on CAG25, read “MMD Research: ‘Bright’ Prospect” at quest.mda.org.*

Q: But you've also used the type of antisense that attracts RNase H, which destroys the expanded RNA?

A: Yes. That's the gapmer antisense work we presented at the International Myotonic Dystrophy Consortium in late 2011. That work was a joint effort with Isis Pharmaceuticals and Genzyme [now part of Sanofi].

Antisense can be RNA-like, or it can be DNA-like, or it can be constructed so that it's hard to say which it's like.

CAG25 is more RNA-like, but the gapmer antisense that we talked about at the conference is more DNA-like — and that's what RNase H is looking for. The job of RNase H is this: Show me where you've got DNA bound to RNA, and that's where I'll try to cut the RNA.

Actually, we didn't target the RNase-H-attracting antisense directly to the CUG repeats in our experiments. We targeted it to a part of the RNA strand that doesn't have the repeats.

An RNA molecule is like a long strand, and if you make a cut anywhere along it, so that it's no longer intact from head to tail, there's machinery inside cells that recognizes that and gets rid of the fragments that are generated by the cutting.

Picture a long piece of spaghetti. Put food coloring over one part of it, towards one end, and call that the expanded CUG repeats: That's the toxic part. If you take a knife and cut that spaghetti at any other place, the entire strand — including the part with the CUG repeats — will be unstable and easily nibbled up by other substances in the cell.

Note: *For more on the 2011 consortium, see “International MMD Consortium Includes Professionals, Families” at quest.mda.org.*

Q: If they nibbled up the DMPK RNA, would that be a problem?

A: That's an important question about the safety of this approach. There's a possibility that the amount of DMPK protein made by the cell would go down even further than it already has. It's already somewhat reduced, and it might be further reduced, which might cause symptoms. Based on

animal studies, we're not expecting that that would have strong effects, but we have to monitor this carefully.

Q: What happened to the MMD1 mice that got this gapmer antisense treatment that doesn't target the CUG repeats but causes destruction of the whole RNA piece?

A: The treatment showed some striking effects. We injected the antisense under the skin — systemically — so that it could circulate throughout the body. We gave the antisense injections twice a week for one month. We checked on the mice as early as one week after the injections, or as long as one year later.

After the treatment, we saw large reductions of the toxic RNA, elimination of myotonia, normalization of a process called RNA splicing, and no evidence of harmful side effects. RNA splicing is a process that MBNL1 participates in, so we assume that MBNL1 was free to do its usual job. A very surprising observation was that the antisense was still active up to one year after the last injection.

Q: You've also experimented with a small molecule called pentamidine to block the interaction between CUG repeats and MBNL1 protein. Can you tell us more about that?

A: Yes. That study was directed by Andy Berglund, a biochemist at the University of Oregon. We helped out with the testing in mice.

Together with Dr. Berglund's group, we found that pentamidine counteracted some of the effects of the abnormal genetic instructions in mice with an MMD1-like

disease. The molecule appeared to inhibit MBNL1-CUG interactions, and there was improvement in some RNA splicing patterns. It was a partial effect, but it was an important start.

A big drawback with pentamidine is that it's fairly toxic. It would have to be chemically modified before it could be considered as a candidate for treating myotonic dystrophy.

That said, it's good to push forward on several different fronts at the same time. Several other groups of chemists are hav-

“I would say that the hope that drives us every day is the possibility of having people take medication that will actually make them feel and function better.”

ing success also.

Note: For more on pentamidine, read “MMD Research: Disrupted Disease Process” at quest.mda.org.

Q: Have you tried any of these strategies in type 2 myotonic dystrophy, where you have CCUG repeats causing the problem?

A: Not yet, but we're eager to do so.

Q: Do you think they would work similarly?

A: It's a little bit different, but I suspect that a similar approach could be used in myotonic dystrophy type 2 to good effect.

Q: Would you expect an antisense-based drug to get into the brain, which also can be affected in myotonic dystrophy?

A: It will have to be specifically put there. There is a therapeutic trial under way in which this type of compound is being delivered into the spinal fluid, for a condition other than myotonic dystrophy, and it's able to reach many parts of the brain. At first glance, this idea doesn't seem very practical, but I suspect that it might prove to have some important advantages.

Q: Would this type of compound get into the heart?

A: It's too early to know, but I think there are reasonable prospects that this could also work in the heart.

Q: If someone who is, say, 30 years old with type 1 myotonic dystrophy were to be treated with something that blocked or destroyed CUG repeats, how do you think it would affect him or her? Would it actually reverse symptoms?

A: I'm glad you asked that question, because I think that's really uppermost in people's minds. I would say that the hope that drives us every day is the possibility of having people take medication that will actually make them feel and function better. From the experiments that have been done in animals, it's not unrealistic to think that that's a possibility, but we don't really know yet. □