



MYOTONIC DYSTROPHY FOUNDATION

Toolkit



MYOTONIC
DYSTROPHY
FOUNDATION

TABLE OF CONTENTS

Part 1: Introduction	1
Letter from the Executive Director	1
About the Myotonic Dystrophy Foundation	3
Empowerment: Shannon Lord’s perspective	4
Paradigm for working together: dream big	6
Myotonic Dystrophy Foundation Medical and Scientific Advisory Committee	8
Part 2: Information for People and Families with DM	11
Understanding myotonic dystrophy	11
How DM affects your body	12
Types of myotonic dystrophy	13
Genetics of myotonic dystrophy	17
Living with DM	19
Resources for individuals and families	23
MDF video academy — list of educational videos	24
Glossary	26
Key milestones in myotonic dystrophy	33
Part 3: Information for Medical Professionals	35
Overview	35
Genetic causes of myotonic dystrophy	37
Multisystemic features of myotonic dystrophy	46
Part 4: Resources for Medical Professionals	71
DM1 health supervision checklist	72
Practical suggestions for the anesthetic management of a myotonic dystrophy patient	73
Occupational therapy suggestions for the management of a myotonic dystrophy patient	81
Role of physical therapy in the assessment and management of individuals with myotonic dystrophy	91
Medical References	100

PART I: INTRODUCTION

LETTER FROM THE EXECUTIVE DIRECTOR



Dear Reader,

Welcome to the Myotonic Dystrophy Foundation (MDF) and our **MDF Toolkit**. Whether you are reading this page because you are new to myotonic dystrophy (DM), or have been dealing with this complex condition for many years, you are probably well aware of the challenges it presents.

At MDF we are committed to helping you and others like you navigate the challenges of DM. Comprehending the mechanics of myotonic dystrophy can help you manage your condition and actively work with your doctors. To that end, we've put together this information package with the guidance of the MDF medical and scientific advisory committee members, who are the leading experts on myotonic dystrophy and who together have devoted over one hundred years to the research and treatment of DM.

Some of the helpful pieces you'll find inside the **MDF Toolkit** are:

- **Valuable information** compiled by MDF to educate individuals and their families, as well as detailed resources for medical providers.
- **Myotonic Dystrophy: The Facts**. An easy-to-understand book for individuals and families written by the geneticist, Dr. Peter Harper, a preeminent expert on DM.
- **Medical Alert Card**. A wallet-sized identification card for affected individuals to carry with them to alert medical providers about the condition, and especially the dangers of anesthesia.
- **Medical History Sheet**. A document to record treatments, medications and health conditions that affected individuals can share with their providers.
- **Information** about becoming a member of MDF, how to find additional news and resources via our website (www.myotonic.org), our online Community Forum (www.community.myotonic.org) and other opportunities for community support and involvement.

At MDF, it is our mission to educate families and medical providers about DM, in order to improve the quality of life of people living with the disease, and to maximize efforts focused on treatments and a cure for DM. Again, welcome to the MDF community. We look forward to working with you in the fight against myotonic dystrophy, and supporting your efforts to live better with DM, now and in the future.

Best wishes,

A handwritten signature in black ink, appearing to be 'Molly White'. The signature is stylized and includes a long horizontal line extending to the right.

Molly White

ABOUT THE MYOTONIC DYSTROPHY FOUNDATION



MYOTONIC DYSTROPHY FOUNDATION

The Myotonic Dystrophy Foundation (MDF) is a non-profit organization founded by families living with myotonic dystrophy (DM) in 2007. Through education, advocacy, and research, MDF is committed to enhancing the quality of life of people living with myotonic dystrophy, and maximizing efforts focused on treatments and a cure for DM.

Based in Menlo Park, California, MDF partners with, and complements the work of, the Muscular Dystrophy Association (MDA), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDCP), and other governmental, academic and philanthropic agencies.

The MDF website (www.myotonic.org) serves as an information clearing-house for families affected by myotonic dystrophy, physicians and other medical providers, as well as the research community. The MDF online Community Forum (www.community.myotonic.org) is a community-led site where individuals and groups interact, share information and stories, ask questions and find support. The MDF team includes the staff, the Board of Directors, made up of business and governmental leaders and many individuals whose families have been impacted by the disease, and the MDF Medical and Scientific Advisory Committee, a group of leaders from academic, clinical, and governmental organizations.



Shannon Lord was the founding chairman of MDF and a board member from 2006 to 2009. She has the mild form of DM1 and her two grown sons have childhood onset DM. She has been a speaker, advocate, and fundraiser for the myotonic dystrophy cause for nearly 10 years, and was responsible for the participation of American family members at the International Myotonic Dystrophy Consortium in 2005. The Myotonic Dystrophy Foundation evolved from that meeting, with Shannon at its helm.

Empowerment: Shannon Lord's perspective 20 years after diagnosis

After learning of your diagnosis of myotonic dystrophy, you probably can't quite believe it's true. A sense of denial might overcome you for a while, and slowly, ever slowly, the reality starts sinking in. You may become angry and blame others. Then you try to bargain: if only ...then maybe. Finally, sadness and depression consume you and you feel frustrated and hopeless. If you allow this process to progress, eventually it is possible to arrive at a place of acceptance. These are the steps of grieving often described in the field of psychology.

It is important to grieve, to go through this natural process – *through* being the only preposition with integrity. If you try to skirt by, around, over or under it, you will continue to feel sadness and grief as much as you try to quell your feelings. Support groups or counseling can help you navigate *through* this process. A very important step is learning to ask for help.

Over time you might come to realize that you are not the disease. You, the person with DM or a family member of someone with the disorder, are so much more than that. It is important to learn to accept this inherited disease - over which you had no control - and consciously make choices to do things that make you feel good, that give you joy: Garden. Paint. Play your favorite CD. Go to a good movie. Run. Ride your bike. Eat nutritious meals. Feed the birds. Maintain a sense of humor if at all possible.

It is also important to tell your story to those who will listen, whether family and friends, therapist or support group. Over time, if you tell your story enough times to those who listen, you will begin to realize that the sadness and loss start to diminish. At some point you might even come to realize that you can assume some control over your attitude about what has befallen you.

It is important to assume responsibility for taking the best care of yourself.

- Learn as much as you can about DM and teach your family.
- Write down questions for your doctors and take them with you to your appointments.
- Share the “Information for Medical Professionals” section in this booklet with your providers—many of them will not know as much as you.
- Assume responsibility for guiding the treatment process for yourself or family member. Your doctor might never have treated a patient with this disorder.
- Acknowledge your talents and run with them!

Some DM families, after coming to grips with their diagnosis and needing to do something, have derived tremendous pleasure – and success – in working to raise money to help researchers find a treatment or cure for their family disease. At a time when government funding has been cut back tremendously, these families are thinking of creative ways to continue to advance research with contributions from the private sector. While knowing they are unable to cure themselves or their loved ones, they can control these fundraising efforts to help expedite the next best thing: scientific research by the experts. And the organizers of these events feel great in the process! Some of us find that our greatest rewards often come through giving – our time, our talents, and our resources.

One individual decided to ride his bicycle to and from work every day – 32 miles round trip – for up to 5,000 miles in his 40th year, and sought pledges from family and friends of \$20 per mile, raising over \$100,000 in the process. A stunning success! Another person organized a bake sale at his office and asked colleagues to contribute baked goods. With the sale of cookies and cakes, and a few extra donations thrown in, he raised over \$700. These people are putting their creativity to work, achieving great success, and reaping totally unexpected personal rewards from the satisfaction and support they receive. In the process they are helping move research closer to a cure.

Even after you have grown accustomed to the idea of having DM and are feeling stronger, you will find yourself riding the wave of sadness from time to time. It is natural to feel that way, so don't try to deny those feelings; allow them, and know that soon the wave will reach shore again and you'll be back on solid ground. As time marches on, the period between the waves will grow farther and farther apart.

Remember: Asking for help is a sign of strength, not weakness. You do not have to travel this path alone.

Shannon Ford

“PARADIGM FOR WORKING TOGETHER: DREAM BIG”

Eric Wang, Ph.D.

Harvard-MIT Health Sciences and Technology
MDF Fund-A-Fellow Postdoctoral Fellow
Myotonic Dystrophy Family Member



“My name is Eric Wang, and it’s an incredible honor for me to serve as an advocate for myotonic dystrophy, both as a researcher who studies myotonic dystrophy, and as a person who grew up seeing the effects of DM every day. I have watched how it has impacted both the affected and unaffected members of my family.

When I look back on the past 15 years of my life, there was a clear turning point in my relationship with DM, how it affected my family, and how I dealt with this fact. Throughout junior high school and high school, I watched my dad gradually lose fine motor control, lose the ability to get up and down stairs, and go through several close calls with severe falls and heart function. In college, I remember how every time I came home for holiday breaks, I would notice how my dad looked a bit different each time, as a result of his muscle wasting. The disease impacted me and my entire family in a negative way, and in general we felt helpless as to what we could do to slow down the effects of this terrible disease.

After college, I worked in a lab where I studied cardiovascular biology. During that time, I applied to graduate school, and had to choose the area of research where I wanted to do my PhD. I consulted other students in the lab about interesting research areas, and there was one particular evening that really served as a Eureka moment for me. I was having dinner with another student in the lab, and I remember it very vividly. We were in the basement of John Harvard’s Pub in Cambridge, Massachusetts. I remember that we both ordered a mushroom swiss burger – it was a good burger – and not because of how it tasted – it was so good because that night, a light bulb went on in my head. It was there that my friend suggested that I study DM, to be – quote – a “champion” of the disease. In a way, the idea was extremely obvious – to use my biology training to study a disease that runs in my family – but for some reason I have never considered it seriously. I think it was partly due to a narrow way of thinking – thinking that I couldn’t make a significant difference. This narrow way of thinking is something that I would like us all to transcend in some way.

That night, my journey of empowerment began – I later found David Housman at MIT, who, with other members in this audience, found the gene for DM1 in 1992, and also sought out Chris Burge, an expert in computational biology and the study of gene regulation, whose recent entry in the DM field has already led to advances in our understanding of DM. I also sought

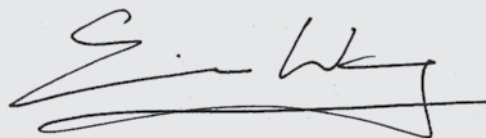
out leaders in the DM field, who have served as informal mentors to me over the past five years – and let me tell you – the DM field is absolutely remarkable for its collegiality, drive, and focus. As a result, with their help, I have been able to make contributions to the field that will hopefully have an impact down the line.

Investigators, we need to bring other people into the field who have complementary expertise that we will need – this means your colleagues who study other aspects of biology, our industry partners, and those in regulatory bodies. To conquer this disease, we will need, as many have described over the past few days, to work together as a team, and together with patients.

DM families – many people go through life not finding that thing that drives them, that thing they live, or die, for. Obviously, DM in my family has been a curse – because of its terrible effects – but on the other hand DM has given me an incredible purpose in life – a challenge and obstacle to overcome – through which we will all do our best to prevail and become better people. I urge you to take a moment to imagine a world in which you or your family still has DM, but you aren't limited by practical or financial concerns. What would that world look like? Is it a world in which all doctors know about DM? Is it a world in which most people on the street understand what a DM patient looks like and what their needs are? Is it a world in which teachers at school know how to deal with the needs of a DM child? Is it a world where genetic testing is free? What can we do together to get closer to that world? This, I think, is the adjustment in thinking that we should all make – to dream big, and of course, to later come back to reality, but to have the courage to dream.

Progress in the DM field has been phenomenal but we have not yet reached the end of the road. There will be hills and valleys, and numerous storms to weather. We need to be prepared for these moments but must also be prepared for the inevitable day when therapies are a tangible reality. We must organize so that we can move forward carefully yet deliberately, with a passion tempered by prudence. We need to support and encourage one another, so that we can get through all of these experiences in one piece, and we must make it our goal to continue pushing on in spite of all odds.

We will overcome this disease, but it will need to be a group effort – in the way that DM has served as a paradigm for disease of RNA toxicity – let's show the world our paradigm for how to work together to cure a terrible disease.”

A handwritten signature in black ink, appearing to read "Jim Wang". The signature is fluid and cursive, with a long horizontal stroke at the bottom.

Speech transcript, 2011 MDF Annual Conference

MYOTONIC DYSTROPHY FOUNDATION MEDICAL AND SCIENTIFIC ADVISORY COMMITTEE



Tetsuo Ashizawa, M.D.

Executive Director of the McNight Brain Institute and Professor and Chairman of the Neurology Department at the University of Florida, Dr. Ashizawa graduated from Keio University School of Medicine in Tokyo in 1973. He completed his internship in Medicine in Pittsburgh, a residency in Neurology at Baylor College of Medicine in Houston, and a fellowship in Neuromuscular Studies and Neurochemistry with the Muscular Dystrophy Association at Baylor. While at Baylor he assisted one of several teams around the world in locating the *DMPK* gene for myotonic dystrophy. He has received numerous research awards and grants, especially for myotonic dystrophy and ataxia. In 1997, he and Dr. Claudine Junien co-founded the International Myotonic Dystrophy Consortium (IDMC), a biennial scientific meeting where physicians and scientists convene to focus on the cause and ultimately a viable treatment or cure for DM. Dr. Ashizawa has published numerous articles on myotonic dystrophy in medical and scientific journals. For more information on Dr. Ashizawa, visit the University of Florida website (<http://mdc.mbi.ufl.edu/ufmdc-team/tetsuo-ashizawa-m-d>).



John W. Day, M.D., Ph.D.

Dr. Day relocated to Stanford University as Professor of Neurology, Pediatrics and Pathology in 2011 in order to build a comprehensive center for understanding and treating muscular dystrophy, serving as Director of Stanford's Neuromuscular Medicine Program in the Department of Neurology and Neurological Sciences. Dr. Day remains an active member of the University of Minnesota collaborations he helped forge as Director of Minnesota's Paul and Sheila Wellstone Muscular Dystrophy Center. He is working to integrate California and Minnesota resources with the international network of myotonic dystrophy research to assure that this most-common form of muscular dystrophy is conquered as soon as possible. Dr. Day attended medical school at the University of Minnesota, graduating in 1977. He attended graduate school at Albert Einstein College of Medicine and completed his internship in Internal Medicine in New York. He did his residency in Neurology and a fellowship in Clinical Neurophysiology and Neuromuscular Disease at the University of California in San Francisco. In 2001, along with Laura Ranum, Ph.D. and team, he participated in the identification and genetic characterization of myotonic dystrophy type-2 caused by a mutation on the third chromosome. He has published numerous articles on myotonic dystrophy in professional journals and is currently conducting a brain-imaging study of affected individuals. For further information on Dr. Day, visit the Stanford University website (http://med.stanford.edu/profiles/John_Day/).



Richard Lymn, Ph.D.

Dr. Lymn is a bio-physicist who has dedicated his entire career to muscle research. After majoring in math at the Johns Hopkins University, he attended graduate school at the University of Chicago, where he made groundbreaking discoveries on the chemical steps producing muscle force that have become the major basic authority on that topic. After graduate school, he worked at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England correlating chemical and structural changes during muscle contraction. He continued his studies of molecular changes during muscle force generation at the National Institutes of Health (NIH).

Dr. Lymn left active research to become a health scientist administrator at NIH, where he created a muscle biology program of grants and contracts that grew to a budget greater than \$70 million. He detected areas that needed enhancement and implemented initiatives in new fields. In 2005 he organized the Burden of Muscle Disease conference at NIH, which focused on three muscular dystrophies, including myotonic dystrophy. Dr. Lymn left NIH after nearly thirty years leading federal efforts to further the understanding of muscle biology and to guide the research process. He continues to foster research on muscular diseases, collaborating with researchers and private groups. For further information, see www.lymnfoundation.org. The non-profit Lymn Foundation was founded in 1999. Grants were first awarded in 2006 to recognize the students and researchers under age 35 who show promise in contributing to the knowledge of muscle biology and muscle disease. For further information on Dr. Lymn visit the Lymn Foundation website (http://www.lymnfoundation.org/Richard_W_Lymn_Profile.html).



Darren Monckton, Ph.D.

Dr. Monckton is Professor of Human Genetics (Institute of Molecular Cell and Systems Biology) at the University of Glasgow. After graduating from the University of Bath with a B.Sc. in Biochemistry, he went on to complete his Ph.D. at the University of Leicester investigating genetic instability at the minisatellite repeat loci used in DNA profiling. He then received a Muscular Dystrophy Association Fellowship to move to Baylor College of Medicine, where he first began working on myotonic dystrophy type 1. After completing his fellowship at the MD Anderson Cancer Center he moved to the University of Glasgow, where he established his

own group. He is internationally recognized for his work in understanding the molecular turnover and role of tandemly repeated DNA sequences in the human genome and their relationship to inherited disease, with a specific focus on the CTG repeat within the gene associated with myotonic dystrophy type 1. Over the past 15 years, Dr. Monckton has contributed to many publications on genetic instability, has been awarded numerous grants, and is a sought-after presenter at myotonic dystrophy-focused conferences around the world. He also serves on many advisory boards and committees. For further information on Dr. Monckton, including his research interests, visit the University of Glasgow website (http://www.gla.ac.uk/news/media/expertsdirectory/medicalveterinaryandlifesciences/name_56481_en.html).



Richard Moxley III, M.D.

Dr. Moxley is Professor of Neurology and Pediatrics, Division of Medicine, at the University of Rochester in Rochester, New York and Director of the Wellstone Muscular Dystrophy Center. After graduating from Harvard and the University of Pennsylvania Medical School, he completed his internship in Pennsylvania and then a Heart Disease and Stroke Control Program at NASA Headquarters. He completed his residency in Neurology at Harvard Medical Center and his fellowship in Medicine at Johns Hopkins University. He completed a postdoctoral NIH special fellowship in Endocrinology and Metabolism at Johns Hopkins.

In addition to the directorship of the Wellstone Muscular Dystrophy Center, he is Associate Chairman of the Department of Neurology at Strong Memorial Hospital, and formerly Director of the EMG/Nerve Conduction Laboratory at Strong Memorial Hospital. With support from the NIH he initiated the National Registry for DM and FSHD (facioscapulohumoral dystrophy, another form of muscular dystrophy), a tool investigators can use to incorporate affected DM family members into their research. He has published numerous articles on myotonic dystrophy in professional journals, and serves on many advisory boards and committees. Dr. Moxley has carried out an investigation of mexiletine, a medication that relaxes myotonia, or muscle stiffness, and is currently conducting a clinical trial of SomatoKine in individuals with myotonic dystrophy. For further information on Dr. Moxley, visit the URM website (<http://www.urmc.rochester.edu/people/?u=23115880>).



Charles Thornton, M.D.

Dr. Thornton is Professor of Neurology at the University of Rochester. He, along with Dr. Moxley, is a Co-Director of the MDA clinic at URM. He received his B.A. and medical degree from the University of Iowa. His internship in Internal Medicine was carried out in the University of California Los Angeles-San Fernando Valley Program. He finished his residency in Neurology in 1985 at Oregon Health Sciences University, and a fellowship in Neuromuscular Disease at Strong Memorial Hospital in Rochester in Experimental Therapeutics. He has received a number of grants for DM research and has published numerous results in

professional journals. He is now beginning to focus on the treatment phase of research for myotonic dystrophy. For further information on Dr. Thornton, visit the URM website (<http://www.urmc.rochester.edu/people/?u=20909840&s=researchers>).

PART 2: INFORMATION FOR PEOPLE AND FAMILIES WITH DM

UNDERSTANDING MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) is a genetic disorder that affects many parts of the body. There are different types of DM, and some cause more serious problems than others. There is currently no cure for myotonic dystrophy, but there is a lot you can do to improve the quality of your life, by taking part in your care and actively managing your symptoms. New discoveries about the disorder and how it can be treated are coming to light almost every day, but in general myotonic dystrophy is not well understood by the general medical community. It is important that you learn as much as you can about your condition so you can talk to your doctors, and educate the people around you. Stay up to date on new developments so you can ensure that you get the best care possible.

OTHER NAMES FOR MYOTONIC DYSTROPHY

- **Dystrophia myotonica (DM).** Latin name and most common abbreviation
- **Steinert's disease.** Named after one of the people who identified the disease. Sometimes called Curschmann-Batten-Steinert syndrome
- **Myotonic muscular dystrophy (MMD).** Name and abbreviation sometimes used
- **DM1.** Common abbreviation for myotonic dystrophy type 1
- **DM2:** Common abbreviation for myotonic dystrophy type 2
- **Proximal myotonic myopathy (PROMM).** Term sometimes used for DM2

HOW DM AFFECTS YOUR BODY

Myotonic dystrophy is a very complicated condition. The symptoms and disease progression can vary widely. The affects can be quite different even among members of the same family, so it is difficult to predict just how the disorder will affect you and your family. One person may only have mild muscle pain or cataracts that develop in later years, while someone else with the condition may be born with serious breathing problems.

The most common effects of DM are muscle problems, including muscle weakness (myopathy), trouble relaxing a muscle (myotonia), and muscle wasting that gets worse over time (atrophy). However, it is misleading to think of DM as only a muscle disorder because it also affects many other body functions, including the heart, lungs, and gastrointestinal (GI) system. The disorder can also cause problems with cognitive function, personality, and vision. Not everyone with DM will have all or even most of the possible symptoms.

Body system	Possible Effects
Skeletal muscles	<ul style="list-style-type: none"> • Muscle weakness (myopathy) • Muscle stiffness and trouble relaxing a muscle (myotonia) • Muscle wasting that gets worse over time (atrophy) • Severe muscle weakness and delayed development in newborns and infants
Cardiac system	<ul style="list-style-type: none"> • Heart rhythm problems (arrhythmias) • Enlarged heart muscle • Low blood pressure • Sudden death
Respiratory system	<ul style="list-style-type: none"> • Breathing problems in newborns • Frequent lung infections • Aspiration of food or fluids into airways • Inability to breathe in enough oxygen • Sleep apnea
Gastrointestinal (GI) system	<ul style="list-style-type: none"> • Difficulty swallowing • Pain and bloating after meals • Constipation, diarrhea, irritable bowel syndrome, gastrointestinal reflux • Gallstones • Enlarged colon
Brain and central nervous system (CNS)	<ul style="list-style-type: none"> • Difficulty with thinking and problem-solving • Emotional and behavior problems • Excessive daytime sleepiness • Nerve damage in feet and hands
Reproductive system	<ul style="list-style-type: none"> • Small testes, low sperm count, low testosterone • Higher risk of miscarriage and stillbirth; early menopause • Problems with pregnancy and delivery • Newborn complications
Hormones	<ul style="list-style-type: none"> • Insulin resistance • Premature frontal balding in men
Immune system	<ul style="list-style-type: none"> • Lower levels of antibodies in bloodstream
Tumors	<ul style="list-style-type: none"> • Higher risk of benign skin tumor (pilomatrixoma)
Vision	<ul style="list-style-type: none"> • Cataracts • Damage to the retina • Drooping eyelids (ptosis)

TYPES OF MYOTONIC DYSTROPHY

- **DM1.** This is the most common form of the disease and the one with the most severe effects. At least 1 in 8,000 people worldwide have DM1, although the number may be far greater. There are three categories of DM1, categorized by when symptoms of the disease first appear:

Congenital: Presents life-threatening issues at birth

Childhood onset: First signs are usually intellectual disability, and learning disabilities

Adult onset: Characterized by distal muscle weakness, wasting, and stiffness.

- **DM2.** The second type, DM2, was discovered in 2001. It is still unclear how many people have this type of the disease, which is also known as proximal myotonic myopathy (PROMM). DM2 is a milder form of myotonic dystrophy that comes on in adulthood. The most common symptom is muscle pain that comes and goes. Other possible types of DM, caused by different genetic mutations, are currently being investigated.

Form of Myotonic Dystrophy	Gene affected	Repeat Count		
		Healthy	Pre-mutation	Affected
DM1	Dmpk (dystrophia-myotonica protein kinase) gene on chromosome 19	<37 repeats	38 – 49 repeats	50 – >4000 repeats
DM2	Znf9 (zinc finger protein 9) gene on chromosome 3.	10 – 26 repeats	27 – 74 repeats	75 – >11,000 repeats

Testing and diagnosis for DM

Making an initial diagnosis starts with a complete family history and physical examination. A person will also undergo a battery of medical tests, depending on the symptoms he or she is having. A key element of the evaluation is electromyography (EMG). This procedure detects the presence of myotonia in a high proportion of people with DM1 or DM2. When test results point strongly toward a diagnosis of myotonic dystrophy, the disorder can be confirmed by genetic testing.

The genetic test requires a blood sample from the patient. The DNA is extracted from the blood sample and analyzed to see if that person has the mutation that causes myotonic dystrophy. Prenatal testing, where the DNA of the fetus is checked for the presence of the myotonic dystrophy mutation, is also available.

Diagnosis of myotonic dystrophy is not difficult once the disorder is suspected. However, the path to a correct diagnosis of myotonic dystrophy can be long and complex, and delays in diagnosis are very common. It can typically take over 6 years to reach a diagnosis of DM1 and up to 11 years to confirm DM2.

Genetic testing

Genetic testing (also referred to as DNA testing) is a definitive diagnostic of whether or not a person has DM. DNA, the genetic material in the nucleus of cells, is isolated from a sample of blood or other tissue, and then analyzed to determine whether or not a specific mutation is present.

Genetic testing is available for DM1 using standard DNA diagnostic protocols (PCR and southern blot) to confirm the presence of DM.

Genetic testing is also available for the diagnosis of DM2 using standard DNA diagnostic protocols. However, in some cases the repeat expansion for DM2 may be too large for PCR testing. In those instances, southern blot techniques are used for diagnosis.

Reasons to consider genetic testing

Genetic testing can be beneficial in the following situations:

- A confirmed diagnosis can eliminate the need for additional medical tests and reduce anxiety about the cause of symptoms.
- People with DM should be educated about the dangers of anesthesia and alert their doctors if they should need surgery.
- Couples can make family planning decisions based on their genetic risk.
- Mothers with DM1 can have special monitoring during pregnancy and prepare for risks involved for a child born with congenital DM.

Obstacles to getting a diagnosis

Since the symptoms of DM often mimic more common diseases, many potential causes need to be ruled out through medical testing. Medical professionals are often unfamiliar with DM since they see these cases so infrequently. Selection of the appropriate genetic test may not be obvious since there are more than thirty genetically distinct forms of muscular dystrophy. In the case of myotonic dystrophy, diagnosis is complicated even further by the variability of the disease. Some of the confounding issues include:

- **Myotonic dystrophy can take multiple forms that affect a broad spectrum of systems.** Individuals may visit several different specialists for disparate symptoms, such as an ophthalmologist for blurred vision, a gastroenterologist for stomach pain, and a cardiologist for an abnormal heartbeat. These individual physicians may not be aware of their patient's full range of problems and therefore may not be able to put the pieces together for an accurate diagnosis.
- **The severity of symptoms can vary greatly, even within the same family.** Quite often individuals go to their primary care physician with a variety of complaints, most so general that the doctor never suspects any serious problem. As a result, a correct diagnosis may be delayed until the disease has progressed significantly.

Managing DM

Myotonic dystrophy symptoms tend to worsen gradually over several decades. While no treatment exists that slows the progression of myotonic dystrophy, management of its symptoms can greatly improve quality of life. Taking steps early to prevent or treat problems as they come up can help avert complications.

Treatment	Symptom
Medications	
Anti-diabetic drugs	<ul style="list-style-type: none"> • Treat high blood sugar levels • Manage mild diabetes symptoms
Anti-myotonic drugs (such as mexiletine)	<ul style="list-style-type: none"> • Control myotonia that impairs normal activities
Nonsteroidal anti-inflammatory drugs	<ul style="list-style-type: none"> • Manage muscle pain
Wakefulness-promoting agents	<ul style="list-style-type: none"> • Control excessive daytime sleepiness
Rehabilitative therapy	
Physiotherapy	<ul style="list-style-type: none"> • Treats muscle weakness, myotonia and contractures
Speech therapy	<ul style="list-style-type: none"> • Helps with swallowing and pronunciation issues
Psychiatric therapy	<ul style="list-style-type: none"> • Addresses behavioral and psychological issues (such as attention deficit, depression and anxiety disorders)
Individualized support	<ul style="list-style-type: none"> • Helps with learning disabilities and cognitive delays
Devices	
Assistive devices (such as neck braces, arm and foot braces, canes, walkers, scooters, and wheelchairs)	<ul style="list-style-type: none"> • Ensure safe navigation
Eye crutches	<ul style="list-style-type: none"> • Support droopy eyelids (ptosis)
Pacemaker or implantable cardioverter defibrillator (ICD)	<ul style="list-style-type: none"> • Address irregular heartbeat issues
Incentive spirometry and cough assist devices	<ul style="list-style-type: none"> • Improve respiratory function
Continuous positive airway pressure (CPAP) device	<ul style="list-style-type: none"> • Ensure respiratory sufficiency
Surgery	
Orthopedic surgery	<ul style="list-style-type: none"> • Correct gait issues and contractures
Cataract removal	<ul style="list-style-type: none"> • Improve vision
Eyelid surgery	<ul style="list-style-type: none"> • Correct droopy eyelids

Regardless of the form of DM or the severity of symptoms experienced by a patient, individuals with myotonic dystrophy can have severe reactions to anesthesia and should be monitored carefully whenever anesthesia is administered. For more information, please refer to our anesthesia guidelines.

Management of congenital, childhood-onset, and pregnancy

The congenital and childhood-onset of DM appear earlier in life with more severe symptoms. Therefore they present more and different management challenges than the adult onset forms of the condition. Pregnancy in affected mothers poses serious complications for both the mother and the newborn, often requiring intensive intervention.

GENETICS OF MYOTONIC DYSTROPHY

Myotonic dystrophy is an inherited disease that is passed from one generation to the next through a faulty gene. It is not caused by an infectious agent such as a virus or bacteria.

How genes work

DNA is the genetic material found in the nucleus of nearly every cell. A gene is a stretch of DNA that carries a set of instructions on how a protein should be made. These proteins carry out the functions of the body. Scientists estimate that humans have about 25,000 different genes. For example, there are genes that control eye color, genes that make proteins to break down food in the stomach, and genes that encode enzymes that regulate how cells grow.

When the DNA of a gene is altered, a mutation is said to have occurred. Some mutations have little effect on how the body functions. Others are more serious, causing the production of defective proteins that result in disease symptoms.

How myotonic dystrophy is inherited

Both DM1 and DM2 are passed from parent to child by *autosomal dominant* mutations. This means that the faulty gene is located on one of the chromosomes that does not determine sex (autosome) and that one copy of the mutated gene is enough to cause the disease (dominant). Because the gene is not located on the X or Y sex chromosomes, it can be passed to male and female children with equal frequency.

In nearly all cases, patients with DM have one normal copy of the DM gene and one copy with the mutation. This means an affected parent has a 50% chance of passing on the mutated gene to an offspring. Individuals who receive the mutated gene will have the disease, although they may not show symptoms for many years. Children that do not inherit the mutated gene will never develop DM.

A recent study suggested that all affected individuals can be traced back to just one or two people who had the original mutations, thousands of years ago. Unlike some genetic diseases, for example, the types of genetic changes that come from exposure to radiation or toxic chemicals, the mutations causing DM do not occur spontaneously.

Causes of DM

In patients with myotonic dystrophy, there is a problem with a particular gene that causes it to convey faulty instructions. This mistake results in the symptoms of DM. The two forms of myotonic dystrophy are caused by mutations in different genes. Although DM1 and DM2 show similar symptoms, the two forms have fundamentally different origins. Scientists are currently looking into the possibility that there may be additional forms of DM caused by mutations at different sites.

- **DM1.** The genes responsible for myotonic dystrophy type 1 (DM1) are found on chromosome 19. Each chromosome consists of a long chain of chemicals that form the units of DNA. These units are called nucleotide bases. The disease is characterized by stretches of DNA (abbreviated CTG) on the *DMPK* (dystrophia-myotonic protein kinase) gene that are repeated several times. It is sometimes referred to as a *trinucleotide repeat disease* because of the repetition of these three DNA base pairs. In healthy people, there are between 5 and 37 repeats of the CTG sequence. People with myotonic dystrophy type 1 have expanded repeats which can contain anywhere from 50 to more than 4,000 repeats of the CTG sequence.
- **DM2.** The genes responsible for myotonic dystrophy type 2 (DM2) are found on chromosome 3. The repeat sequences contain stretches of DNA in which four chemicals (abbreviated CCTG) on the *Znf9* (zinc finger protein 9) gene are repeated. As in DM1, the disease occurs after the number of repeats exceeds a certain threshold. Healthy individuals will have fewer than 75 CCTG repeats. People with DM2 can have anywhere between 75 and 11,000 repeats.

Distinctive genetic mechanisms in DM

Myotonic dystrophy is one of the most complex disorders known. In addition to the incredible variability of clinical symptoms, the disease also has several unique mechanistic features:

- **Autosomal dominant inheritance.** The genes for DM1 and DM2 are dominant, meaning that a person can inherit the disease even if only one parent carries the gene. Also, a child has the same risk of inheriting DM regardless of whether it is the father or the mother who carries the gene.
- **Variable penetrance.** This term refers to the fact that the number and severity of DM symptoms varies widely among people with the disease. This is true even among people with the same subtype, and among individuals in the same family.
- **Somatic mosaicism.** A key characteristic of DM is that different cells in different tissue types will show varying numbers of genetic repeats. This is due at least in part to the fact that the number of repeats changes, is different in different cells and increases in number throughout the lifetime of the individual. Thus, the number of repeats reported in a diagnostic test will depend on how old the individual was when sampled, which tissue was tested and then, will only measure the average number of repeats.
- **Anticipation.** The number of repeats in the DM genes tends to increase with each affected generation. As a result, the symptoms of the DM1 appear earlier in life and are more severe in each successive generation. These changes are often dramatic. For example, a person whose only symptom was cataracts that appeared later in life can have a child with life-threatening symptoms present at birth. This effect indicates that the number of times the gene sequence is repeated has a bearing on the severity of the disease symptoms. Anticipation appears to be less pronounced in DM2.
- **Transmission of congenital form through mother.** The most severe form of myotonic dystrophy (congenital myotonic dystrophy: DM1) is almost always passed to the child from an affected mother. Scientists think that this occurs because the number of repeated sequences expands greatly during the process when the egg cells are created.

What to expect

Myotonic dystrophy is a progressive or degenerative disease. Symptoms tend to worsen gradually over several decades. While no treatment exists that slows the progression of myotonic dystrophy, management of its symptoms can greatly improve patient quality of life. Early intervention can reduce or avert complications that sometimes arise.

DM2 tends to be less severe than DM1 and has less impact on life expectancy. DM1 is much more variable and the prognosis for an affected individual is difficult to predict. Some people may experience only mild stiffness or cataracts in later life. In the most severe cases, respiratory and cardiac complications can be life threatening even at an early age. In general, the younger an individual is when symptoms first appear, the more severe symptoms are likely to be.

However, prognosis is as variable as the symptoms of this disease. How myotonic dystrophy affects one individual can be completely different from how it manifests in another, even for members of the same family. It is impossible to predict how the disease will affect any one individual.

DM as a family disease

Because of the inherited nature of DM, a diagnosis in one individual has implications for other family members. Questions arise about whether or not the affected person should tell family members who show no symptoms. If the person does share the positive diagnosis of myotonic dystrophy, the family must then decide whether or not to be tested. Because the mutation can be present with few or no symptoms, family members who are affected may not be aware that they have myotonic dystrophy.

Concerns about asymptomatic testing

There are three explanations as to why some individuals with myotonic dystrophy might not show symptoms of the disease:

- Symptoms may be so mild these individuals do not realize they have the disorder.
- They may have a late onset form of the disease and do not yet exhibit symptoms.
- They may carry a pre-mutation (a form of the mutation that is less extensive than that seen in patients who display symptoms). These individuals are not likely to develop disease symptoms, but their children are at risk of inheriting the mutation and having the disorder.

Testing when symptoms are not present is not as straightforward. Some problems that may arise from a diagnosis of DM include:

- Difficulties in obtaining insurance, such as health, disability, and life
- Prejudice in the workplace or elsewhere
- Impact of being diagnosed with a disorder when no cure or treatment capable of slowing the progression of myotonic dystrophy currently exists

Family planning with DM

Individuals with myotonic dystrophy may have concerns about starting a family because of the risks of passing the disease to their children. Discussing family planning issues with a genetic counselor can help individuals make an informed decision.

Multiple diagnostic options exist for patients who are considering having children. These include:

- **Preimplantation genetic diagnosis (also known as PGD).** This is the diagnosis of a genetic condition before pregnancy. This form of testing is done on a woman's eggs using in vitro fertilization. Unfertilized eggs are taken from the woman by a doctor and are fertilized outside the womb in a laboratory. The embryos are tested for DM at the 6 to 8 cell stage. Only non DM-affected fertilized eggs are implanted into the uterus.
- **Prenatal diagnosis.** Parents wishing to find out during pregnancy whether their fetus has inherited the myotonic dystrophy gene can undergo prenatal testing. Two types of tests are available:

Amniocentesis. This procedure involves removing a sample of fluid from the womb that contains skin cells shed by the fetus. The cells are then grown in the lab to provide DNA for testing. The test is typically done 15 weeks into the pregnancy and can take 2-3 weeks for results to become available.

Chorionic villus sampling (CVS). The doctor removes a piece of tissue from the edge of the placenta using a needle inserted through the abdomen or vagina. The sampled tissue contains the same genetic information as the fetus; the DNA is isolated and tested for the presence of the myotonic dystrophy mutation. The test can be done in the first trimester (generally around 10 weeks into the pregnancy) and results are typically available within 1-2 weeks.

Mothers who have DM1 should be closely monitored during pregnancy because they have a higher risk of having a child with congenital DM1. In these cases, excessive amniotic fluid (hydramnios) can accumulate, which can usually be seen during ultrasound examination. Decreased fetal movement is frequently noted. Also, breech presentation and weak uterine contractions can cause long or difficult deliveries, often resulting in Caesarean births.

Newborns with congenital myotonic dystrophy require immediate intensive medical support. Delivery at a medical center with high-risk neonatal support may be recommended. Regardless of whether or not testing is done, individuals with a family history or symptoms of myotonic dystrophy should inform their obstetrician so the medical team can prepare for the possible complications seen with these children.

Working with your doctor

Because of the range of systems affected, people with DM may see multiple specialists who are unaware of the full spectrum of issues experienced by a person with the disorder. Informed patients often know more about the various aspects of DM than any single specialist they see. This variability in symptoms presents unique challenges in both the diagnosis and management of the disease. Therefore, it is important for individuals with DM and their families to learn as much as they can about the disease and its symptoms.

Multi-disciplinary teams are often needed to provide comprehensive, coordinated clinical care. By taking an active role in diagnosis and management of their condition, people with DM can aid this process and help make sure that potential complications are detected and managed at the earliest stages.

Symptoms and specialists in DM management

Medical specialist	Complaint
Primary Care Physician	Exhaustion, inability to sleep well, excessive daytime sleepiness, feeling faint
Pediatrician	Hypotonia (also known as floppy baby syndrome) or child with learning and behavioral problems
Ophthalmologist	Blurry or dimmed vision (possible cataracts), eye muscle weakness, droopy eyelids (ptosis)
Cardiologist	Abnormal heartbeat, heart damage (cardiomyopathy), fainting spells
Pulmonary Specialist	Chronic respiratory problems, sleep apnea, frequent chest colds that do not go away, aspiration pneumonia caused by swallowing issues
Endocrinologist	Insulin resistance, benign thyroid mass
Dermatologist	Benign tumors associated with hair follicles (pilomatrixoma)
Gastroenterologist	Chronic diarrhea, constipation, unexplained stomach pain, gallstones, swallowing problems
Urologist and Reproductive Endocrinologist	Ectopic pregnancies, low testosterone, infertility, miscarriage, stillbirths
Psychiatrist	Depression, personality abnormalities such as excessive apathy, socialization issues, and attention deficit
Neurologist	Nerve and muscle complaints including weakness, stiffness, and chronic muscle pain, cognitive development delays, reduced executive function
Anesthesiologist	Respiratory failure before and after general anesthesia
Orthopedic Surgeon	Foot deformities, curvature of the spine
Podiatrist	Gait issues and muscle weakness
Plastic Surgeon/Oral Surgeon	Jaw and mouth bone deformities that disturb chewing and speech
Audiologist	Hearing loss
Speech Pathologist	Delayed or impaired speech, swallowing difficulties
Physical Therapist	Gait irregularities and muscle weakness

Finding support

Support can come from family, friends, churches, psychotherapists, and healthcare professionals, as well as other members of the DM community who live with the disease and have life experiences similar to those you experience. MDF is comprised of families living with myotonic dystrophy and we welcome you to join our support family.

Most likely you fit into one of the following categories:

- I am living with myotonic dystrophy.
- I am a parent caring for a child, young adult or adult living with myotonic dystrophy.
- I am a spouse caring for a husband or wife living with myotonic dystrophy.
- I am a non-affected family member of a person living with myotonic dystrophy.
- I am a grandparent and the genetic link to myotonic dystrophy in the family.
- I am a widow/widower of an individual who lived with myotonic dystrophy.
- I am a friend of a person living with myotonic dystrophy.

As individuals, family members, and friends of people with DM, it is important to learn to manage the symptoms of myotonic dystrophy to maintain the best possible quality of life. Support groups can help you to understand the physical as well as the psychological and emotional aspects of the disease. These groups also allow you to build alliances with other individuals in similar positions and promote learning and sharing. In the process of giving support to others, you will receive support in return. As you share your experiences with others, be mindful that the symptoms of myotonic dystrophy affect each individual differently, even those in the same family.

As most families coping with the disease know, finding a local support group can present a challenge. There are support groups coordinated through different organizations, but they are not specifically focused on myotonic dystrophy. Because of this, many homegrown support groups have sprung up in the United States, around the world, and on the internet.

The Myotonic Dystrophy Foundation Community page (www.myotonic.org) provides links to support groups, activities, and discussion forums in your area. You should also visit the MDF Community Forum (www.community.myotonic.org), where you'll find over 2,000 people looking for information, sharing support and making connections online.

RESOURCES FOR INDIVIDUALS AND FAMILIES

BOOKS

Myotonic Dystrophy – The Facts, by Prof. Peter Harper, published by Oxford University Press, 2002.

A hundred-page book written for families living with myotonic dystrophy, written in easy-to-understand language. A good place to begin educating yourself. Available on-line at oup.org/usa or amazon.com.

Myotonic Dystrophy – Present Management, Future Therapy, edited by Prof. Peter Harper, published by Oxford University Press, 2004. A 240-page book written by DM experts from around the world, geared to medical professionals. Highly technical descriptions; great book to own in order to take to medical appointments as specific symptoms arise.

Myotonic Dystrophy, 3rd Edition, by Prof. Peter Harper, published by W.B. Saunders, 2001. A 400-page book on DM written for medical professionals. Highly technical descriptions.

Disabled and Challenged: Reach for Your Dreams, by Terry Scott Cohen and Barry M. Cohen, published by WishingUwell Publishing, 2005. A 130-page book written by a young adult with myotonic dystrophy along with his father, a psychologist.

Genetic Instabilities and Neurological Diseases, 2nd ed., by Robert D. Wells and Tetsuo Ashizawa, published by Elsevier Academic Press, 2006. Highly technical descriptions.

Helping Friends: Helpful Hints for Persons Living with Myotonic Muscular Dystrophy, published by The Myotonic Dystrophy Assistance and Awareness Support Group (MDAASG). A helpful guide by a Los Angeles-based group for families dealing with DM. The guide is downloadable from the MDF website (<http://www.myotonic.org>).

MEDICAL JOURNALS

PubMed

PubMed is a searchable database of published scientific research articles maintained by the National Library of Medicine. This site is designed for researchers and clinicians and contains journal articles about research in myotonic dystrophy. View their online tutorials on the use of the site. Visitors can search terms such as myotonic dystrophy, Steinert's disease, proximal myotonic myopathy, and PROMM to find articles about research into myotonic dystrophy. www.ncbi.nlm.nih.gov/s

GROUPS AND ORGANIZATION

A variety of organizations exist in the United States and around the world to support people living with myotonic dystrophy. For more information and links to organizations in your area, go to the MDF website (<http://www.myotonic.org>) and enter "find support" in the search field in the upper right hand corner of the web page.

MDF VIDEO ACADEMY

LIST OF EDUCATIONAL VIDEOS – VIEW AT WWW.MYOTONIC.ORG

1. **Myotonic Dystrophy: A 40 Year Perspective**, Peter S. Harper, M.D., University Research Professor (Emeritus), Cardiff University
2. **The Spirit of Difference**, Rick Guidotti, Director, Positive Exposure
3. **DM 101: Introduction to Myotonic Dystrophy**, Darren Monckton, B.Sc., Ph.D., University of Glasgow
4. **DM 101: Genetics and Biology Joint Q&A Session**, Katharine Hagerman, Ph.D., University of Rochester Medical Center (2 videos)
5. **DM 101: Clinical Research Q&A Session**, Nicholas Johnson, M.D., University of Rochester Medical Center (2 videos)
6. **DM 101: Studies & Trials – Managing Expectations Q&A Session**, Nicholas Johnson, M.D., University of Rochester Medical Center (2 videos)
7. **Disease Mechanism Highlights**, Mani Mahadevan, M.D., FRCP, University of Virginia
8. **Clinical Science Highlights**, Tetsuo Ashizawa, M.D., University of Florida
9. **Therapy Highlights**, Andrew Berglund, Ph.D., University of Oregon
10. **Q&A with Families, Researchers and Clinicians Part 1 Part 2**, Moderator: Valerie Cwik, M.D., MDA (2 videos)
11. **The DM Patient Voice: Unmet Needs and Moving Therapies Forward**, Moderator: John Porter, Ph.D., NINDS (NIH)
12. **Congenital Myotonic Dystrophy**, Lisa M. Harvey, Executive Director, MDF, Family
13. **Juvenile Onset Myotonic Dystrophy**, Shannon Lord, Founding Chairman, Board of Directors, MDF, Family
14. **Adult Onset Myotonic Dystrophy**, John Brekka, Vice-Chairman, Board of Directors, MDF, Family
15. **Caregivers Perspective**, Diane Bade, MDAAASG, Family
16. **Bridging The Gap | Paradigm for Working Together: Dream Big**, Sarah Jordan, Cleveland Clinic Lerner School of Medicine, and Eric Wang, Ph.D., Harvard-MIT Health Sciences and Technology
17. **Becoming Your Own Health Advocate Q&A Session DM1 Health supervision checklist**, Jacinda Sampson, M.D., Ph.D., University of Utah School of Medicine (2 videos)
18. **Improving Respiratory Health Q&A Session**, Nicholas Johnson, M.D., University of Rochester Medical Center (2 videos)

19. **Managing Cardiac Care Q&A Session**, William Groh, M.D., Indiana University Health (2 videos)
20. **Promoting Gastrointestinal Health Q&A Session**, John W. Day, M.D., Ph.D., Stanford University School of Medicine (2 videos)
21. **Understanding the Brain in DM Q&A Session**, John W. Day, M.D., Ph.D., Stanford University School of Medicine (2 videos)
22. **Anesthesia and other Pharmacology Q&A Session**, Neal Campbell, M.D., University of Pittsburgh School of Medicine
23. **Congenital and Childhood Onset: Thriving Against All Odds Q&A Session**, Jacinda Sampson, M.D., Ph.D., University of Utah School of Medicine (2 videos)
24. **Exercise Recommendations for Health & Fitness | Assistive Devices to Maximize Mobility & Independence Q&A Session**, Shree Pandya, PT, DPT, MS and Katy Eichinger, PT, DPT, NCS, University of Rochester Medical Center (2 videos)
25. **Genetic Counseling**, Judith Ranells, M.D., University of South Florida
26. **Managing Myotonic Dystrophy Type 2 (DM2)**, John W. Day, M.D., Ph.D., Stanford University School of Medicine
27. **Planning for Your Future When Living with a Chronic Health Condition Part 1 Part 2**, Travis Finchum, ESQ, Beth W. Patterson, CPA and Lansing Roy, J.D. (2 videos)

GLOSSARY

Amniocentesis

A method of prenatal diagnosis at 15 weeks in which a fluid sample is removed from the womb and grown in tissue culture. It takes 2-3 weeks for results; a fetus can be tested for genetic diseases this way

Ankle Foot Orthosis (AFO)

Apparatus used to support, align, prevent, or correct deformities or to improve the function of the ankle and foot

Anticipation

Tendency in certain genetic disorders—like myotonic dystrophy—for individuals in successive generations to present with symptoms at an earlier age and/or with more severe manifestations; often observed in disorders resulting from the expression of a trinucleotide repeat mutation that tends to increase in size and have a more significant effect when passed from one generation to the next

Anticholinesterases

One of the drugs (such as neostigmine) that myotonic dystrophy patients should avoid; can adversely affect diameter of blood vessels, function of the intestines, and the part of the nervous system that controls smooth muscle, heart muscle and gland cells

Apnea

Periodic absence of breathing while sleeping

Armodafinil

A drug used to treat excessive daytime sleepiness (brand name is Nuvigil)

Arrhythmia

Irregular heart beat

Aspiration pneumonia

Serious form of pneumonia resulting from inhalation of foreign material, usually food particles or vomit, into the bronchi

Asymptomatic

Without symptoms; showing no evidence of disease

Atrial fibrillation

Abnormal heartbeat in which the normal rhythmical contractions of the upper chambers of the heart (cardiac atria) are replaced by rapid irregular twitchings of the muscular wall

Attention Deficit Hyperactivity Disorder

Behavior disorder originating in childhood in which the essential features are signs of developmentally inappropriate inattention, impulsivity and hyperactivity. Although most individuals have symptoms of both inattention and hyperactivity-impulsivity, one or the other pattern may be predominant. The disorder is more frequent in males than females. Symptoms often attenuate during late adolescence, although a minority experiences the full complement of symptoms into mid-adulthood.

Autosomal dominant

Pattern of inheritance in which if one parent has a mutated gene, each offspring has a 50% chance of inheriting it

Barium swallow test

Test in which a person swallows barium and the swallowing process is filmed to detect possible abnormalities

Blepharoplasty

Any operation for the correction of a defect in the eyelids that helps to improve the field of vision

Bradycardia

Any disturbance of the heart's rhythm resulting in a rate of less than 60 beats per minute

Bulbar weakness

Presence of weakness in the tongue, lips, palate, pharynx and larynx

Cataracts

A film that can form in the eye and cause complete or partial opacity of the ocular lens, or blurry vision; in myotonic dystrophy patients, often posterior subcapsular iridescent cataracts form; they are sometimes referred to as Christmas tree cataracts

Cardiac conduction

The electrical impulses that cause the heart to beat

Cardiomyopathy

Damage to the heart muscle that decreases its ability to pump blood effectively

Cardiotoxicity

Substance that is harmful to the heart

CCTG

The abbreviation for “cytosine, cytosine, thymidine, guanine”, the chemicals in the DNA that cause myotonic dystrophy type 2 (on chromosome 3) when they are created in repeats greater than the normal number

Chorionic villus sampling (CVS)

A method of prenatal diagnosis that is performed at around 10 weeks into the pregnancy; a biopsy in which a piece of membrane around the embryo is removed using a needle through the abdomen or vagina; results are usually available in 1-2 weeks

Chromosome

One of the bodies (normally 23 pairs) located in the nucleus of a cell that hosts the genes

Cisapride

Prokinetic drug (such as Propulsid) that should be avoided by individuals with myotonic dystrophy

Club foot

Inversion of the foot in which only the outer side of the sole touches the ground; also called talipes equinovarus

CNS

Abbreviation for central nervous system; brain

Cognitive problems

Difficulties with thinking, learning and memory

Conduction defects

Problems with the electrical impulses that regulate the heart beat

Congenital

Present at birth

Contractures

Permanent tightening of muscles causing abnormal joint rigidity

CPAP

Acronym for continuous positive airway pressure; a device that delivers air to the nose for easier breathing; often used at night for those with sleep apnea

Creatine Kinase (CK) levels

Important enzyme in muscle contraction

CTG

Abbreviation for “cytosine, thymidine, guanine”, the 3 chemicals in the DNA that cause myotonic dystrophy type 1 (on chromosome 19) when they expand beyond the normal 5-37 repeats found along the rung-like parts of the DNA's double helix that resemble a twisting ladder

Degenerative

Deteriorating, getting worse

Depolarizing neuromuscular blocking agents

Type of drugs (such as suxamethonium chloride) causing muscle relaxation and short-term muscle paralysis

Distal

Situated away from the trunk of the body, at the end of the limbs toward the feet and hands

DM1

Abbreviation for the Latin name for myotonic dystrophy (dystrophia myotonica) type 1, the more severe form of myotonic dystrophy with the mutation found on chromosome 19

DM2

Abbreviation for the Latin name for myotonic dystrophy (dystrophia myotonica) type 2, with the mutation found on chromosome 3

DMPK

The abbreviation for the myotonic dystrophy gene, Myotonic Dystrophy Protein Kinase, that causes DM1; it is located on chromosome 19

Double helix

Two strands of DNA held together by hydrogen bonds; when enlarged they resemble a tiny ladder (with many rungs) that has been uniformly twisted; it is along these rungs that the chemical repeats expand beyond their normal number and cause the mutation, or change, in the gene that causes myotonic dystrophy

Dominant inheritance

The expression of a gene where if one parent carries the mutated gene, the children have a 50% chance of getting it

Dysphagia

Difficulty swallowing

Dysphasia

Difficulty speaking

Dyspnea

Shortness of breath

Dystrophy

An inherited muscle disorder in which the muscles become weaker

Ectopic

Occurring in the wrong place in the body, such as the development of an impregnated egg outside the cavity of the uterus, or a cardiac beat originating elsewhere than at the sinoatrial node

EDS

Acronym for excessive daytime sleepiness

EKG or ECG

Electrocardiogram, a test that prints out a graphic record of a person's heart beat

Endocrine system

The body system that secretes hormones that enable the body to perform many of its functions

Epidemiology

The study of the distribution of health-related states (e.g. for a specific disease like myotonic dystrophy) or events in specified populations

Esophagus

The portion of the digestive canal between the pharynx and stomach

Expansion

Referring to enlargement of the myotonic dystrophy genetic mutation, or abnormality, as it passes to offspring; also refers to the enlargement of mutations within a given organ or system over the life of an affected individual (see somatic mosaicism); happens often in myotonic dystrophy

Foot drop

Partial or total inability to dorsiflex (lift upward) the foot

Gait

Manner of walking

Gastroenterologist

Doctor focusing on the function and disorders of the stomach, intestines and assorted organs that are often referred to as the GI tract

Gene

Functional unit of heredity (specifies eye and hair color, height and many other characteristics including inherited diseases) that occupies a specific place on a chromosome; it is capable of reproducing itself at each cell division and directs the formation of an enzyme or protein

Genetic

Pertaining to genes; inherited

Genetic counseling

Meeting with a medical professional, often a geneticist, to learn how a possible inherited disease can affect you, and how you can avoid passing it to your offspring

Genomic background

Referring to the complete set of genes inherited from one's parents

Genotypes

Sum total of the genetic material transmitted from a person's parents

GI tract

Bodily system referring to the stomach, intestines and related organs

Gonadal (or testicular) atrophy in men

Medical condition in which the male reproductive organs (the testes) diminish in size and fail to function

G-Tube

Implanted feeding tube supplying sustenance when person is unable to safely swallow on his own

Haplotype analysis

Molecular genetic testing to identify a set of closely linked segments of DNA

Heterotropia

Inability of one eye to attain binocular vision with the other because of imbalance of the muscles of the eyeball—also called strabismus or squint.

Hydramnios

Excessive amniotic fluid build-up in the amniotic sac during pregnancy

Hyperkalemia

Greater than normal concentration of potassium ions in the circulating blood

Hyperostosis

Excessive growth of bony tissue

Hypersomnia

Excessive daytime sleepiness

Hypertrophy

General increase in bulk or a part of an organ

Hypothermia

Body temperature significantly below 98.6

Hypotonia

Low muscle tone causing floppiness, as in a child with the congenital form of myotonic dystrophy

Implanted Cardioverter Defibrillator (ICD)

Cardiac device implanted in the chest; a combination pacemaker and defibrillator designed to regulate the heartbeat, to keep it from beating too fast or too slow

Impulse inhibition

Inability to control one's impulses

In vitro fertilization

Eggs are obtained from the female after her ovaries have been stimulated with infertility drugs. While under sedation and with the use of ultrasound guidance, a needle is inserted into the ovaries and eggs are aspirated. These eggs are then fertilized in the laboratory (in vitro) with the partner's sperm and the developing embryos are cultured from three to six days.

Incentive spirometry

Breathing device to help exercise breathing muscles and help maximize lung capacity

Induction drugs

Drugs given intravenously that quickly induce unconsciousness prior to surgery and certain other procedures

Insulin resistance

Diminished effectiveness of insulin in lowering blood sugar levels

Intercostal muscles

Muscles between the ribs

Intubation

Insertion of a tube into the lungs to provide pulmonary ventilation, or to assist with breathing

Mexiletine

A drug used to treat myotonia (delayed muscle relaxation after contraction) in muscle diseases such as myotonic dystrophy and myotonia congenital (brand name is Mexitil)

Modafinil

A drug is used to treat excessive daytime sleepiness (brand name is Provigil)

Motility

Power of spontaneous movement

Multisystemic disorder

Disease that can affect many different organs and systems in the body

Mutation

A change in the normal chemistry of a gene

Myotonia

Inability of contracted muscles to relax on command, or a special kind of muscle stiffness

Myopathy

Muscle weakness

NICU

Neonatal (new born) intensive care unit

Opiates

Any preparation or derivative of opium

Oro

Referring to the mouth

Oropharyngeal muscle weakness

Reduced strength in the upper expanded portion of the digestive tube between the soft palate and the epiglottis

PCR (polymerase chain reaction)

A procedure that produces millions of copies of a short segment of DNA; the amplified product, doubled each cycle for 30 more cycles, can then be subjected to further testing. It is a common procedure in molecular genetic testing designed to generate enough DNA to perform the test; in individuals suspected of having myotonic dystrophy, it can be used to determine the number of trinucleotide repeats in the *DMPK* gene on the 19th chromosome.

PGD

Abbreviation for Preimplantation Genetic Diagnosis, achieved through in vitro fertilization where analysis of embryos is done prior to being implanted by a doctor into the uterus of a woman

Pacemaker

Implanted heart device to correct a very slow or irregular heart beat

Perioperative

Before, during or immediately after the time of surgery

Pharynx

The passage that leads from the cavities of the nose and mouth to the larynx (voice box) and esophagus. Air passes through the pharynx on the way to the lungs, and food enters the esophagus from the pharynx.

Phenotype

The observable signs, symptoms and other aspects of a person's outward appearance and behavior

PICU

Pediatric intensive care unit

Pilomatixoma

Benign skin tumors under the skin; associated with hair follicles

Placenta

Organ formed inside the lining of the womb that provides nourishment for fetus and elimination of its waste products

Placenta accreta

Condition in pregnancy in which the placenta (see definition) has an abnormally deep attachment through the endometrium and into the myometrium (the middle layer of the uterine wall), causing full or partial placental retention. Condition typically requires surgery to prevent abnormal post-partum bleeding and fully remove the placenta. In severe cases can lead to a hysterectomy or can be fatal.

Placenta previa

Condition in pregnancy in which the placenta (see definition) is implanted in lower segment of womb close to the internal opening of the cervix, or sometimes completely covering that internal opening

Polyhydramnios

Excessive amniotic fluid build-up during pregnancy

Postoperative apnea

Absence of breathing after surgery

Postpartum hemorrhage

Heavy bleeding from the birth canal after vaginal delivery of a baby

Pre-mutation

Presence of slightly more than the normal number of nucleotide repeats in the genetic mutation (e.g. in DM1, somewhere between 38 and 50 CTG repeats); the person exhibits no symptoms but is at risk of having affected children

Prenatal diagnosis

Process of determining whether a child in the womb has a specific disorder

Prognosis

Forecast of the probable course and outcome of a disease or condition

PROMM (Proximal Myotonic Myopathy)

Another name for myotonic dystrophy type 2 (DM2)

Proximal

In medicine, referring to a part of the body that is nearest to the trunk of the body, such as thighs and upper arms

Ptosis

Droopy eyelids due to muscle atrophy

Pulse oximetry

Test to measure oxygen levels in the blood

Respiratory function test

Test that measures the amount of air a person can blow out

Smooth muscles

Muscles that are part of or surround internal organs, as along the gastrointestinal tract

Somatic

Physical

Somatic mosaicism

In DM1, the presence of different repeat numbers of CTG in DM1 and CCTG in DM2 (the abnormality) found in different organs and systems within the same person and very likely contributes to the tissue-specific and progressive nature of the symptoms seen in myotonic dystrophy

Sonogram

Image created by ultrasound obtained by a computerized instrument; it can reveal internal parts of the body, such as thyroid gland or fetus in utero

Steinert's disease

The first name given to myotonic dystrophy when it was identified as a disease by Dr. Hans Steinert of Germany in 1909

Strabismus

Inability of one eye to attain binocular vision with the other because of imbalance of the muscles of the eyeball—also called heterotropia or squint

Sudden heart block

Condition of the heart in which the passage of an electrical impulse is arrested, wholly or in part, temporarily or permanently

Tachyarrhythmia

Very rapid heart beats

Talipes equinovarus

Inversion of the foot in which only the outer side of the sole touches the ground; also called club foot

Testicular (or gonadal) atrophy

Condition in men in which the reproductive organs (testes) shrink and may lose function

Tetranucleotide repeats

As related to myotonic dystrophy, the series of 4 chemicals (abbreviated CCTG and found in the DNA of the *ZNF9* gene, on the 3rd chromosome) that repeats itself more times than normal and causes myotonic dystrophy type 2

Tracheostomy tube

Tube inserted into the windpipe to keep the opening free for breathing when a person has difficulty breathing independently

Tracheotomy

Implantation of a tube into the trachea to assist patient with breathing; inserted through neck just below the thyroid gland

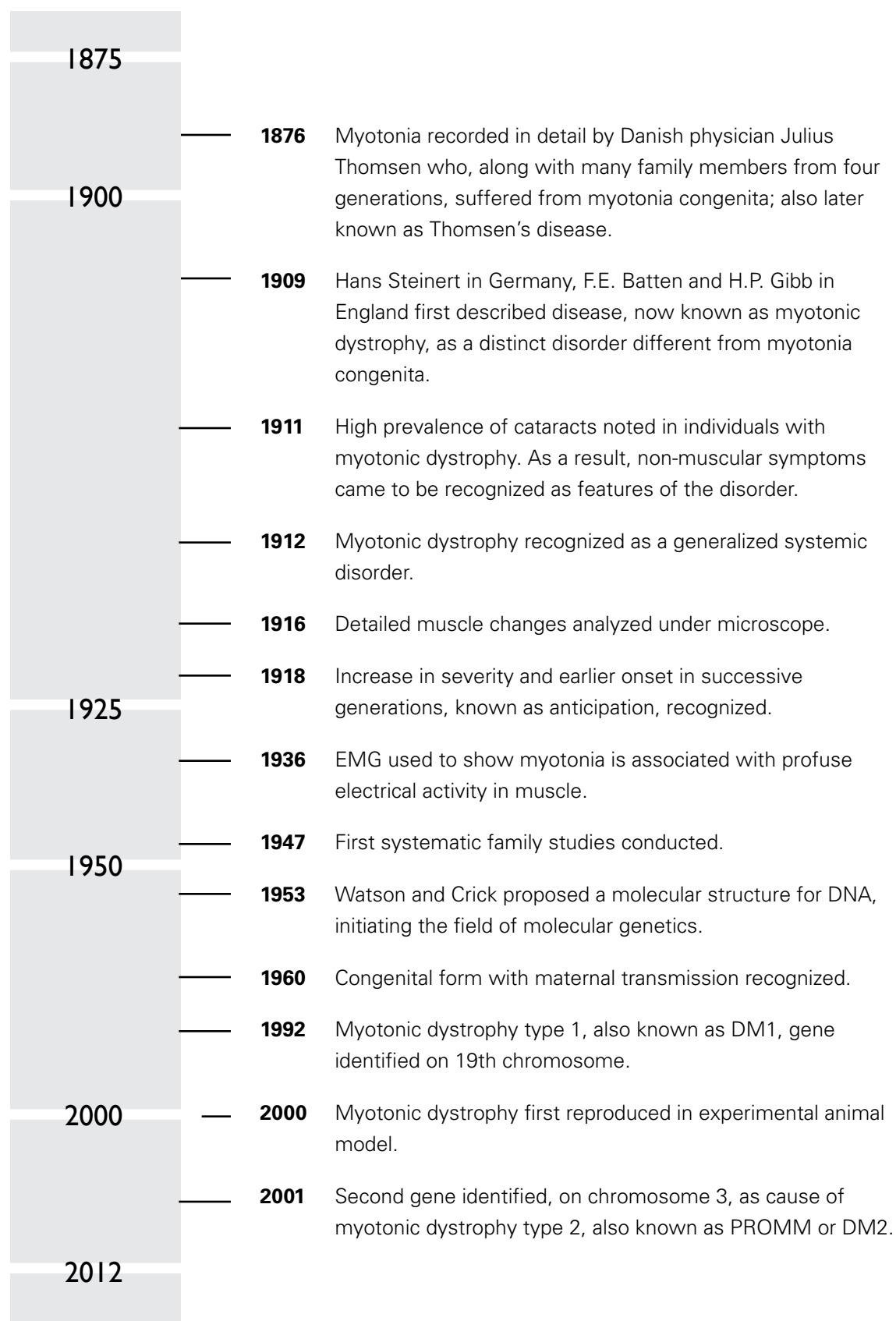
Trinucleotide repeats

As related to myotonic dystrophy, the series of 3 chemicals (abbreviated CTG and found in the DNA of the *DMPK* gene, on the 19th chromosome) that repeats itself more times than normal and causes myotonic dystrophy type 1

ZNF9

The mutated gene on chromosome 3 that causes DM2; sometimes called the zinc finger gene

KEY MILESTONES IN MYOTONIC DYSTROPHY



PART 3: INFORMATION FOR MEDICAL PROFESSIONALS

OVERVIEW

Myotonic dystrophy (DM) is a progressive, multisystemic disorder. It is one of the nine forms of muscular dystrophy and the most common form of adult-onset muscular dystrophy. Myotonic dystrophy is a triplet repeat disease caused by an autosomal dominant mutation. Other triplet diseases include Huntington's disease, spinal and bulbar muscular atrophy (SBMA), and fragile X syndrome.

Types of DM

Two well-defined, but overlapping types of myotonic dystrophy have been identified:

- **DM1.** The first type (also known as Steinert's disease) is the most prevalent form of the condition and generally the most severe. This form affects at least 1 in 8,000 people worldwide or 40,000 people in the United States alone, although prevalence may be significantly under-reported. DM1 has three subtypes that vary based on age at onset:

Congenital. Presents potentially life-threatening issues at birth

Childhood onset. Typically first presents with intellectual disability, and learning disabilities

Adult onset. Characterized by distal muscle weakness, atrophy, myotonia and many other multisystemic issues.

- **DM2.** Myotonic dystrophy type 2, also known as proximal myotonic myopathy (PROMM), is a milder form of myotonic dystrophy in which transient muscle pain is the most common complaint. Only adult-onset forms of DM2 have been recognized. To date, there have been few large scale or definitive studies to determine the prevalence of DM2.

Other possible types, caused by different genetic mutations, are currently being investigated.

Clinical presentation

Although the most pronounced characteristic of myotonic dystrophy is skeletal and smooth muscle dysfunction (weakness, stiffness, and pain), the condition can present with issues such as reduced cognitive function, vision impairment, gastrointestinal disturbances, endocrine deficiency, fertility issues, cardiovascular dysfunction, personality abnormalities, and respiratory insufficiency, in addition to muscle complaints.

The range of systems affected and the severity of symptoms seen can vary greatly between patients, even in the same family. However, an affected person does not typically exhibit all, or even most, of the possible symptoms. Often the disorder is mild and only minor muscle weakness or cataracts are seen late in life. At the opposite end of the spectrum, life-threatening neuromuscular, cardiac, and pulmonary complications can occur in the most severe cases when children are born with the congenital form of the disorder.

Diagnosis

Genetic tests

Genetic testing is available for myotonic dystrophy DM1 using standard DNA diagnostic protocols (PCR and southern blot) to determine definitively whether or not an individual has myotonic dystrophy.

Genetic testing is also available for DM2 using standard DNA diagnostic protocols, however, the repeat expansion may be too large for PCR testing in some cases. In those instances, southern blot techniques are used for diagnosis.

Systemic problems

A range of diagnostic tests are used to identify problems related to affected body systems. In the absence of genetic testing, electromyography (EMG) is a highly effective diagnostic tool for identifying myotonic dystrophy in a high proportion of people with DM1 or DM2. (See Neuromuscular Assessment, p. 50)

Management

Myotonic dystrophy is a progressive or degenerative disease. Symptoms tend to worsen gradually over several decades. While no treatment exists that slows the progression of myotonic dystrophy, management of its symptoms can greatly improve patient quality of life. Early intervention can reduce or avert complications that sometimes arise.

Childhood onset and congenital myotonic dystrophy present significantly differently from adult-onset forms of myotonic dystrophy, and require special management. Pregnancy in affected mothers poses serious complications for both the mother and the newborn, often requiring intensive intervention.

Because of the range of systems involved, affected individuals may see multiple specialists who are unaware of the full spectrum of issues experienced by their patient. This variability presents unique challenges in both the diagnosis and management of the disease. Multi-disciplinary teams are often required to provide comprehensive, coordinated clinical care.

Regardless of the form of DM or the severity of symptoms experienced by a patient, individuals with myotonic dystrophy can have severe and life-threatening reactions to anesthesia and should be monitored carefully whenever anesthesia is administered.

GENETIC CAUSES OF MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) was the first autosomal dominant disease found to be caused by a repeat expansion that is transcribed into RNA, but is not translated into protein. Transcriptions of the repeat expansion accumulate and, as toxic RNAs, disrupt the function of up to twenty other genes, causing the multiple symptoms of the disorder.

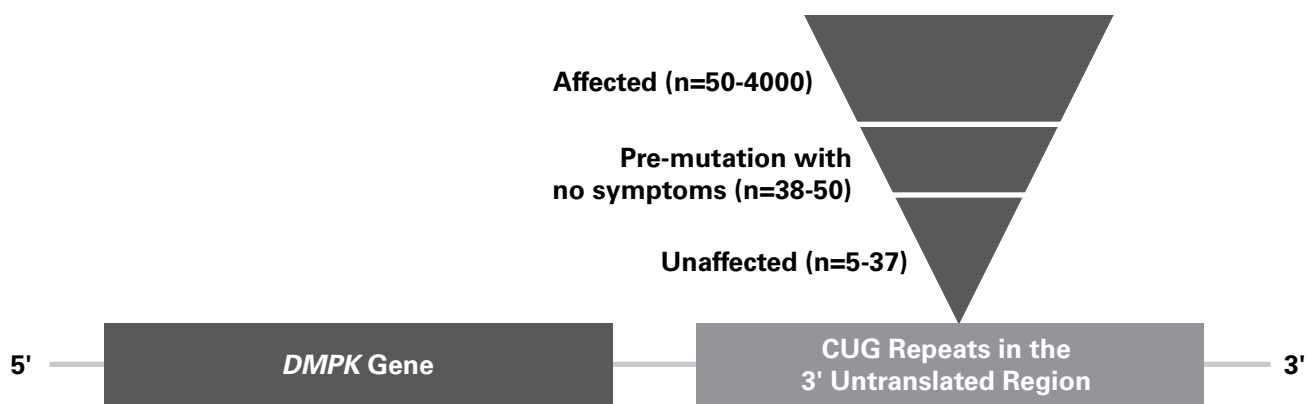
Although the two types of myotonic dystrophy present with similar symptoms, they have fundamentally different origins. The two forms (DM1 and DM2) are caused by distinct microsatellite expansions that occur in the non-coding regions of different genes. (The existence of other forms, caused by mutations at different sites, is currently being investigated.)

Causes of DM1

The genetic defect for this form of the disorder results in an expanded and unstable (CTG) trinucleotide repeat, localized to the 3' untranslated region of the dystrophin protein kinase (*DMPK*) gene on chromosome 19q13.3. Once there are more than 37 triplet repeats in the *DMPK* gene, the expanded sequence becomes unstable and slippage is more frequent. Disease symptoms are apparent in individuals once the CTG expansion exceeds 50 repeats. Disease severity roughly correlates with the number of repeats:

- Individuals with 5 to 37 repeats in the 3' UTR region are unaffected.
- Individuals with 38-50 repeats are said to carry the pre-mutation. These individuals are asymptomatic and are unlikely ever to show symptoms. However, these repeats are unstable and very likely to expand during meiosis. As a result, such individuals are at risk of having affected children.
- Individuals with >50 repeats to 4000 repeats have myotonic dystrophy. These individuals are symptomatic or likely to develop symptoms in later life. A looser correlation is seen between the form of the disease and repeat count in these individuals:
 - 50 to 150 repeats are consistent with the mild adult-onset form of myotonic dystrophy.
 - 100 to 1000 repeats are consistent with the classic adult or childhood onset form of myotonic dystrophy.
 - 750 repeats are consistent with the congenital form of myotonic dystrophy and often result in severe neonatal complications.

The figure below presents a visual explanation of the cause of DM1.

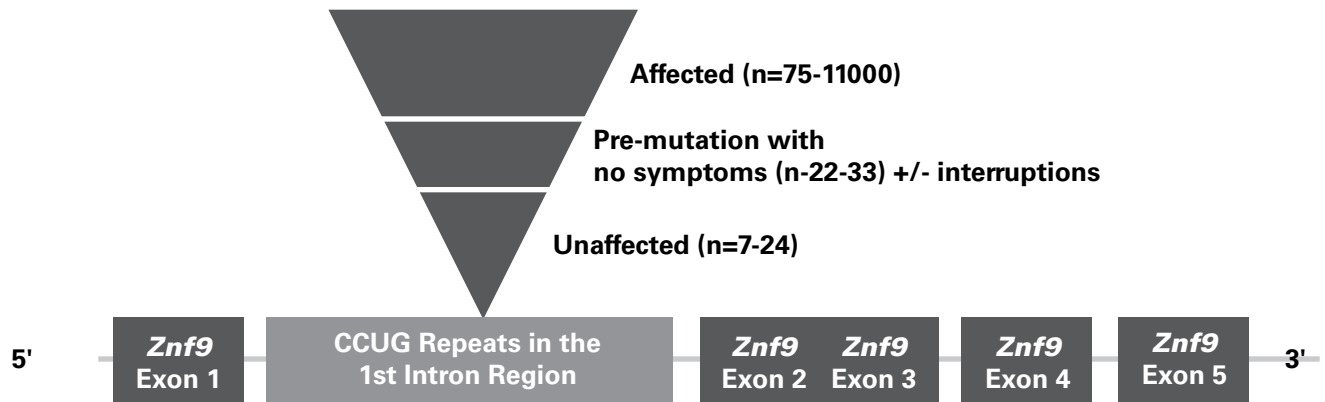


Causes of DM2

Also known as proximal myotonic myopathy (PROMM), this form is caused by an expanded and unstable (CCTG)_n tetranucleotide repeat in the first intron of the zinc finger 9 (*Znf9* also known as *Cnbp*) gene on chromosome 3. The repeat structure in DM2 is more complex than the triplet repeat seen in DM1.

- The normal repeat structure is approximately 10-20 repeats of a complex motif that is 104 to 176 nucleotides long ((TG)₁₂₋₂₆(TCTG)₇₋₁₂(CCTG)₃₋₉(g/tCTG)₀₋₄(CCTG)₄₋₁₅).
- Individuals with 22-33 uninterrupted CCTG repeats are said to carry a pre-mutation. These individuals are asymptomatic and are unlikely ever to show symptoms. However, these repeats are unstable and very likely to expand during meiosis. As a result, such individuals are at risk of having affected children.
- Unaffected individuals typically have less than 75 repeats. Once the repeat number exceeds 75, the expanded sequence becomes unstable and slippage is more frequent. Affected individuals can have between 75 and 11,000 copies of the repeat sequence.
- The minimum pathogenic length of the expanded region appears to be 75 uninterrupted CCTG repeats. Repeat counts can increase to over 11,000 in affected individuals, with a mean repeat length of ~5000 repeats. The expanded region has been shown to display an even greater instability than the DM1 mutation.
- Unlike DM1, the length of the DM2 repeated DNA expansion does not appear to correlate significantly with the age of onset or severity of disease symptoms.

The figure below presents a visual explanation of the cause of DM2.



Other forms

Additional forms (DM3, DM4) have been suggested, as a small number of individuals have been seen who have the characteristic symptoms of myotonic dystrophy, but who do not have the genetic mutations which cause these disorders. Considerable debate exists as to whether these individuals truly represent a new form of myotonic dystrophy or whether they simply present unique diagnostic challenges.

Origins of DM

The mutation involved in DM1 does not arise spontaneously. It appears that all affected individuals share a common ancestor. With the exception of one sub-Saharan family, the presence of DM1 has been associated with a single haplotype within and flanking the *DMPK* gene. This suggests predisposition for CTG instability has resulted from a single mutation event, which occurred after the migration from Africa to Europe.

A second alternative exists, where predisposition to CTG instability is due to elements within the haplotype. Individuals who do not possess this specific set of genetic alleles would have a stable number of repeats and not develop the disease.

Commonalities between DM1 and DM2

	DM1	DM2
Core Features		
Myotonia	++	(+) to +, on EMG
Muscle Weakness	++	(+) to ++
Cataracts	++	- to ++
Localization of Muscle Weakness		
Facial Weakness, Jaw Muscles	++	- to +
Distal Limb Muscle Weakness	++	- to +
Proximal Limb Muscle Weakness	(+)	+ to ++
Sternocleidomastoid Muscle	++	+ to ++
Muscle Symptoms		
Muscle/Joint Pain and Stiffness	-	- to ++
Muscle Strength Variations	-	- to +
Muscle atrophy	++, distal	- to +
Muscle Cramps	- to (+)	- to +
Calf Hypertrophy	-	- to ++
Muscle Biopsy		
Fiber Atrophy	- to +, type-1 fibers	+ to ++, type-2 fibers
Cardiac Arrhythmias	++	- to ++
Elevated Serum CK Levels	(+) to ++	(+) to ++
GGTase Elevation	+	- to +
Hypoimmunoglobulinemia IgG	+	- to +
Hyperhydrosis	-	- to +
Brain		
Tremors	-	- to ++
Late Change in Mental State	++	- to (+)
Hypersomnia	+	- to (+)
Mental Retardation	+, congenital form	-
Insulin Resistance/Glucose Intolerance/Diabetes	+	- to (+)
Male Hypogonadism	+	- to +
Frontal Baldness	++	- to (+)
Genetics		
Inheritance	AD	AD
Anticipation	++	- to (+)
Locus	<i>DMPK</i>	<i>ZNF9</i>
Chromosome	19q13.3	3q21.3
Expansion Mutation	(CTG) _n	(CCTG) _n
Congenital Form	+	-

*+, present; ++, pronounced; (+), variably present; -, absent. AD, autosomal dominant.

Differences in Clinical Manifestations between DM1 and DM2

	DM1	DM2
Genetics		
Inheritance	autosomal dominant	autosomal dominant
Anticipation	pronounced	exceptional
Congenital Form	yes	no
Chromosome	19q13.3	3q21.3
Locus	<i>DMPK</i>	<i>ZNF9</i>
Expansion Mutation	(CTG) _n	(CCTG) _n
Location of Expansion	3' UTR	Intron 1
Core Features		
Clinical Myotonia	evident in adult onset	present in <50%
EMG Myotonia	generally present	absent and variable in many
Muscle Weakness	disabling by age 50	onset as late as age 60-70
Cataracts	generally present	present in minority
Localization of Muscle Weakness		
Facial Weakness, Jaw Muscles	generally present	usually absent
Bulbar Weakness - Dysphagia	generally present later in life	not present
Respiratory Muscles	generally present later in life	exceptional cases
Distal Limb Muscle Weakness	generally prominent	flexor digitorum profundus on testing, but only in some
Proximal Limb Muscle Weakness	may be absent	main disability in most patients, late
Sternocleidomastoid Weakness	generally prominent	prominent in few
Muscle Symptoms		
Myalgic Pain	absent or mild	most disabling symptom in many
Muscle Strength Variations	no variations	can be considerable
Visible Muscle Atrophy	face, temporal, distal hands and legs	usually absent
Calf Hypertrophy	absent	present in ≥50%
Muscle Biopsy		
Fiber Atrophy	smallness of type-1 fibers	highly atrophic type-2 fibers
Nuclear clump fibers	in end-stage only	scattered early before weakness
Sarcoplasmic Masses	very frequent in distal muscles	extremely rare
Ring Fibers	frequent	may occur
Internal Nuclei	massive in distal muscle	variable and mainly in type-2 fibers
Cardiac Arrhythmias	generally present	highly variable: absent to severe
Brain		
Tremors	absent	prominent in many
Behavioral Changes	early in most	not apparent
Hypersomnia	prominent	infrequent
Cognitive Decline	prominent	not apparent
Manifest Diabetes	frequent	infrequent
Frontal Balding in Males	generally present	exceptionally
Other Features		
Childhood-onset CNS-problems	frequent	absent
Increased frequency of co-segregating heterozygous recessive <i>CLCN1</i> mutations	absent	present
Incapacity (Work and ADL)	always >30-35	rarely <60 unless severe pains
Life Expectancy	reduced	normal range

Bjarne Udd, MD, PhD, Professor, Neuromuscular Center, Tampere University Hospital, Tampere, Finland

Ralf Krahe, PhD, Associate Professor, Department of Genetics, University of Texas MD Anderson Cancer Center, Houston, TX

The prior tables are presented here by permission of the authors and represent a work in progress, as research continues to evolve on the understanding of the clinical manifestations of both diseases. Therefore, it is quite possible that a person will receive different opinions from different clinicians on certain aspects of these tables.

Bjarne Udd, M.D., Ph.D., Professor, Neuromuscular Center, Tampere University Hospital, Tampere, Finland

Ralf Krahe, Ph.D., Associate Professor, Department of Cancer Genetics, University of Texas MD Anderson Cancer Center, Houston, TX

Molecular basis of myotonic dystrophy

Myotonic dystrophy is one of the most complex disorders known. In addition to the incredible variability of clinical symptoms, the disease also has unique mechanistic features:

- **True autosomal inheritance.** The disease phenotype of patients who are homozygous for myotonic dystrophy is essentially the same as those who are heterozygous.
- **Variable penetrance.** Considerable variability is seen between affected individuals, even within the same family. Somatic mosaicism is common, where the genetic defect can be significantly different in various tissues in a single individual and can change over time.
- **Anticipation.** The disease symptoms tend to be more severe and occur earlier in successive generations.
- **Maternal transmission bias for the congenital form.** In the most severe form of myotonic dystrophy (congenital myotonic dystrophy: DM1), transmission is nearly always maternal and does not appear to be related to the severity of the disease in the mother. The mutated gene is only very rarely inherited from the father in newborns with myotonic dystrophy.

RNA toxicity

Studies have been done to understand how these non-coding mutations could have a trans-dominant effect (i.e. how they could affect other genes not associated with the mutation locus). This research suggests a gain-of-function RNA mechanism underlies the clinical features common to both diseases. In both forms of myotonic dystrophy, RNAs transcribed from the genes have unusually long repeats of either CUG (DM1) or CCUG (DM2). The nucleotide repeats cause the RNA strands to develop abnormal hairpin folds. These misshaped RNA structures then bind splice-regulating proteins, forming RNA-protein complexes that accumulate within nuclei. These nuclear foci can disrupt biological function by altering the available amounts of two classes of RNA-binding splice regulators:

- **Muscleblind-like (Mbnl) proteins (Mbnl1, Mbnl2 and Mbnl3).** Mbnl splice regulators are sequestered in the nuclear foci, resulting in nuclear depletion and a loss of function.
- **Cugbp and ETR-3 Like Factors (CELF).** The expression of Cugbp1 is increased through a signaling event that results in its phosphorylation and stabilization.

The disruption of these splice regulators interferes with the processing of transcripts in more than twenty other genes. In all cases, the aberrant splicing results in abnormal developmental processing where embryonic isoforms of the resulting proteins are expressed in adult myotonic dystrophy tissues. The immature proteins then appear to cause the clinical features common to both diseases. See examples of affected genes and the resulting clinical features in the chart below.

Clinical feature	Gene abnormalities
Brain dysfunction	Increased inclusion of NMDA NR1 receptor exon 5
	Decreased inclusion of Amyloid Precursor Protein exon 7
	Decreased inclusion of Tau exon 2, 3 and 10
Cardiac abnormalities	Increased inclusion of Cardiac Troponin T (cTNT or TNNT2) exon 5
Insulin resistance in muscle and liver	Decreased inclusion of Insulin Receptor (IR) exon 11
Muscle channelopathy, membrane hyperexcitability, and myotonia	3 defective splice isoforms of Muscle-Specific Chloride Channel CLCN1, each containing a premature termination codon
Muscle atrophy	Increased inclusion of fetal isoforms A and B of the Myotubularin-related 1 (MTMR1) gene
	Decreased inclusion of Dystrophin exon 71 or 78

Somatic mosaicism

Tissues in affected individuals can have unstable expanded regions. Once repeat counts reach an approximate threshold (>35 repeats for DM1 and >75 repeats in DM2), these sequences become highly unstable in both the soma and germ line. As a result, a single individual may have cells and tissues that differ in repeat count (referred to as somatic mosaicism). Somatic mosaicism is age and size-dependent, and a likely contributor to the tissue-specific and progressive nature of the myotonic dystrophy symptoms.

Several features of somatic mosaicism have been observed:

- Repeats show an expansion bias; i.e. the number of repeats tends to increase instead of decrease.
- Changes in repeat counts accumulate over time, so the expanded regions tend to grow through the life of individuals with myotonic dystrophy.
- Rate of change depends primarily on the inherited size of the mutation, with more repeats being more unstable and showing faster increases in the number of repeats.
- Level of mosaicism varies between tissues. In particular, the number of repeats in muscle cells is typically greater than those seen in circulating lymphocytes.
- Level of mosaicism can vary within a tissue (i.e. different cells within the same tissue have different number of repeats).

Although the mutational mechanism is not well understood, DNA replication and DNA repair are likely to be responsible for the changes in the number of repeat units in myotonic dystrophy patients. It is possible that individual specific factors (genetic and/or environmental) play an important role in the somatic dynamics of the repeat and that the process of somatic expansion may be very likely correlated with the clinical progression of the disease.

Anticipation

Because expansion of the CTG repeats commonly occurs during meiosis, the repeat count tends to increase over successive generations. As a result, children of affected individuals (including those with the pre-mutation) tend to experience more severe symptoms at an earlier age than their parent. This parent-to-child amplification of repeat count is termed anticipation.

The molecular cause of anticipation is based on the instability of long stretches of repeated nucleotide sequences. These repeats occur naturally, but are present in greater copy numbers in individuals with myotonic dystrophy. Once repeat counts reach a predictable threshold (>38 repeats for DM1 and >75 repeats in DM2), the sequences become highly unstable. The cellular machinery for DNA replication begins to slip across the expanded region, generating extra copies of the repeated sequence. The length changes caused by this slippage are relatively large, often with gains of 100 repeats or more.

These expansions occur in both somatic and germline tissues. Because the expanded repeats are particularly unstable in meiotic cells, slippage during gametogenesis is common. The resulting eggs or sperm have dramatically higher repeat counts than somatic parental cells. Repeat count tends to increase over successive generations as a result. Nearly all pedigrees show this progressive expansion, although decreases in copy number have been reported in rare cases.

The few reported decreases are due at least in part to the fact that the number of repeats changes, is different in different cells, and increases in number throughout the lifetime of the individual. Thus, the number of repeats reported in a diagnostic test will depend on how old the individual was when sampled, which tissue was tested and then will only measure the average number of repeats.

Symptomatic Consequences of Anticipation

- **DM1.** The repeat length shows a positive correlation with the severity of the disease. In addition, the number of repeats shows a negative correlation with the age of onset. As repeat counts increase over successive generations, the progeny tend to experience more severe symptoms at an earlier age. However, these correlations are not very precise, and it is not possible to accurately predict how severely and when an individual will be affected.

Therefore, the use of pre-symptomatic testing in this disorder should be carefully considered. The size of repeat expansions (measured by the standard method) in white blood cells should not be considered predictive of the age of onset and severity of symptoms. New assays that can measure age-independent repeat expansions are required and are being developed.

- **DM2.** Repeat expansions tend to be more extensive than those seen in DM1. However, anticipation is less pronounced as repeat length does not correlate strongly with increased severity or earlier onset of disease symptoms. The degree of anticipation may be underestimated, however, as the extensive somatic mosaicism seen in DM2 patients confounds assessment of the phenomenon.

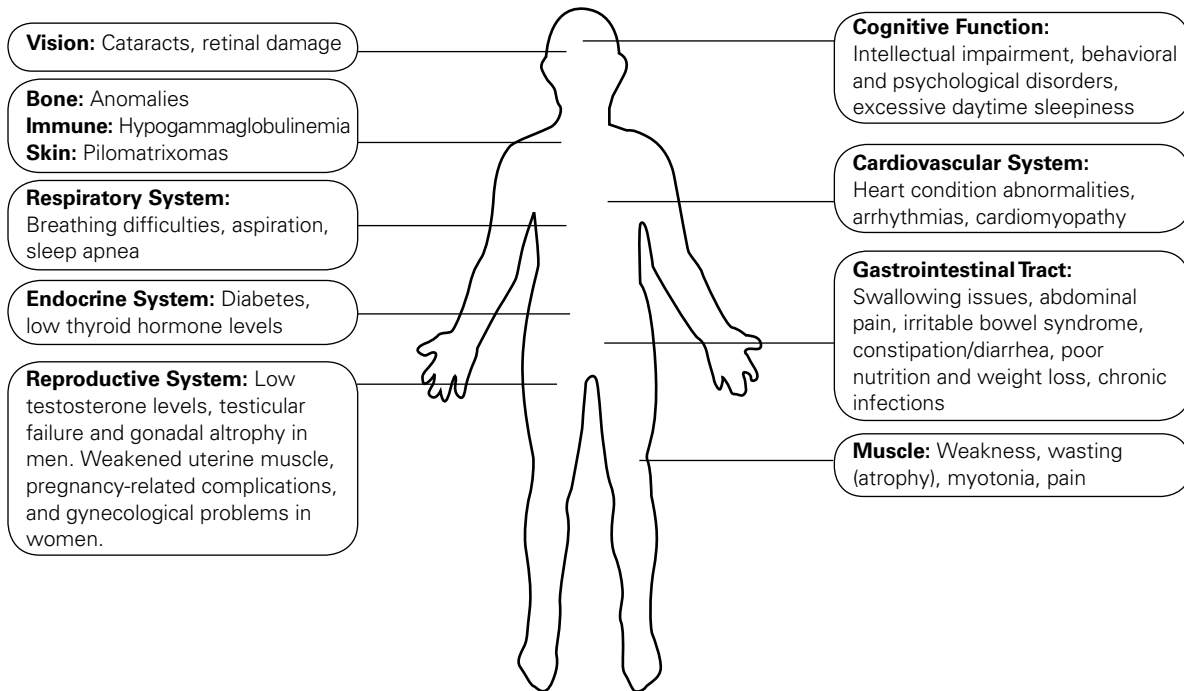
Maternal transmission of congenital DM1

Anticipation occurs differently in males and females. Extreme amplifications are seen during gametogenesis in females with DM1, elevating their risk of having a child with congenital DM1. These large increases in repeat count are only rarely seen in males. It is hypothesized that maternal imprinting plays a role in the difference seen, although minimal methylation evidence exists to support this conclusion.

As a result of this anticipation bias, newborns with the severe congenital form of myotonic dystrophy are almost always the offspring of affected mothers. Because the increase in repeat count can be dramatic, the mothers may be asymptomatic or have symptoms so mild that they are unaware they have the disease. In such cases, the child is often the index case in the extended family and other relatives may be subsequently identified as having the disease.

MULTISYSTEMIC FEATURES OF MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) is a multisystemic disorder that can affect all age groups. Because of the range of systems affected, management requires a more expansive approach than most disorders and care is best provided by a coordinated, multidisciplinary team.



Skeletal muscles

Symptoms

Myotonia

Sustained muscle contraction (myotonia) is a distinctive aspect of myotonic dystrophy. The presence of myotonia is not the most disabling aspect of DM, but it is the recognized hallmark of the condition, and the aspect of the disease that distinguishes it from other forms of muscular dystrophy.

Myotonia stems from an abnormality of the muscle fiber membrane (sarcolemma) that results in an extended delay before muscles can relax after a contraction. A muscle starts its contraction on cue, but the electrical activity continues after the nerve signal has ended, causing a stiffness or “locking up” of the muscle.

Myotonia can be observed by having a patient grip tightly with the fingers. It may take the hand muscles 20 seconds or more to fully relax after a sustained grip (grip myotonia). Myotonia can also be demonstrated by tapping a muscle with a reflex hammer (percussion myotonia). Current research indicates that myotonia may be related to decreased chloride ion conduction across the sarcolemma.

Myotonia in DM1
<ul style="list-style-type: none"> • Most prominent in the forearm and finger muscles, causing grip lock • Sometimes affects tongue and jaw muscles, leading to difficulty with speech and chewing • Commonly worse in cold weather
Myotonia in DM2
<ul style="list-style-type: none"> • Affects finger grip muscles • Also noticeable in leg muscles, especially in thighs, and in the back and shoulders • Quick movements may trigger muscle stiffness (e.g. hitting a baseball and running to base; sprinting up stairs)

Muscle weakness and atrophy

Muscle weakness is the main cause of disability in myotonic dystrophy. The problem tends to affect some muscles more than others; it is common for certain muscles to be severely weak while others have normal strength. Muscle weakness often affects mobility, hand dexterity, and lifting. Serious problems in DM1, such as difficulty with breathing or swallowing, are caused by weakness of the muscles in the throat and chest.

Muscle weakness generally worsens over time, but the rate of deterioration is slow. The severity of muscle atrophy and weakness varies considerably among individuals with myotonic dystrophy, even among members of the same family. (See Patterns of Muscle Weakness in DM1, p.48) For some people the weakness is obvious in childhood, but for others it remains mild even into the 6th decade. Most people experience weakness on a spectrum between these two extremes.

For most people, noticeable increases in weakness occur year-to-year, or season-to-season. Weakness that accelerates more rapidly (i.e. week-by-week or month-by-month) is not typical in myotonic dystrophy. In these cases other explanations should be considered, such as medication side effects, or an illness unrelated to myotonic dystrophy. Many people will experience extended periods when the condition seems to remain relatively stable.

Researchers still do not have a clear understanding of what causes muscles to become weak and atrophic in myotonic dystrophy. Although this is an area of active research, so far there are no treatments to prevent or slow muscle weakness. Assistive devices such as braces, canes, walkers, and wheelchairs can help individuals maintain independence and mobility.

Muscle pain

Myotonic dystrophy can be associated with pain. In some cases the pain originates inside the muscles. In other cases, the pain originates in the joints, ligaments, or spine. Muscle weakness may predispose individuals to arthritic changes or strain in these areas.

Patterns of Muscle Weakness in DM1

Congenital DM1
<p><i>Prenatal</i></p> <ul style="list-style-type: none"> • Lower than normal fetal movement • Buildup of fluid (edema) in fetus organs and tissues (hydrops fetalis) • Increased amniotic fluid in mother (polyhydramnios). Breech presentation, placental abruption, and umbilical cord prolapse may result.
<p><i>Newborn</i></p> <ul style="list-style-type: none"> • Severe muscle weakness in newborns • Substantial improvement in children who survive the first six months, often with delayed motor development in infancy and childhood • Development of symptoms that mimic adult onset DM1 in the later years
<p><i>Childhood/Adolescence</i></p> <ul style="list-style-type: none"> • Gradual improvement of newborn hypotonia and feeding issues (only rarely present at age 3-4 years) • Delayed gross motor skill development. Nearly all children learn to walk independently, although great variability exists as to when they achieve this milestone. • Delayed fine motor skill development: grasping a toy or finger; transferring a small object from hand to hand; pointing out objects; following movement with the eyes; self feeding • Myotonia is typically not present at birth, but typically begins in adolescence or early twenties. • Weakness in muscles (including the hands, feet, and face) that may interfere with mobility and necessitate the use of assistive devices (such as ankle braces or canes) • Lack of facial expression due to weakness of facial muscles • Muscle impairment in the mouth, palate and jaw that can delay speech development and inhibit proper pronunciation (may be exacerbated by hearing loss)
<p><i>Adulthood</i></p> <ul style="list-style-type: none"> • Gradual worsening of symptoms; symptomatic progression similar to that seen in adult onset DM1
Childhood Onset DM1
<p><i>Childhood/Adolescence</i></p> <ul style="list-style-type: none"> • Normal or slightly delayed early motor development • Facial and neck muscle problems, typically without the facial appearance that is associated with the congenital form • Foot drop (lower leg, foot and ankle dorsiflexor weakness) leading to a characteristic high-stepping, toe-dragging, or shuffling gait that may result in an increased number of falls • Weakness in distal muscle (including hands, feet, and face) that may interfere with mobility and necessitate the use of assistive devices (such as ankle braces and canes) • Myotonia, particularly in hand intrinsic muscles (leading to difficulty relaxing grasp, especially in the cold) and the tongue (leading to slurred and slow speech, exacerbated by weakness of the facial muscles) • Additional symptoms of adult onset myotonic dystrophy DM1 will appear in later years.
<p><i>Adulthood</i></p> <ul style="list-style-type: none"> • Gradual worsening of symptoms; symptomatic progression similar to that seen in adult onset myotonic dystrophy DM1

Adult Onset DM1

Classic form

- Commonly starts in the teens, twenties, or thirties with myotonia of the hand grip.
- Symptoms progress to weakness of gripping or pinching with the fingers, or moving the ankles.
- Examination at this point usually shows weakness and wasting in the long finger flexors and weakness of the facial and neck flexor muscles.
- Typical effects of adult-onset DM1 include:
 - Weakness and atrophy of the jaw (masseter and temporalis) and facial muscles, leading to thinning of the facial contour and reduced facial expression
 - Indistinct speech and problems with articulation due to weakness of facial, tongue, and palatal muscles, and myotonia of the tongue
 - Drooping of the eyelids (ptosis) due to weakness of muscles levator palpebrae and Mueller muscle
 - Limitation of lateral and vertical eye movements due to weakness of the other ocular muscles
 - Weakness in distal muscles that interferes with dexterity, handwriting and mobility. The combination of finger weakness and myotonia is particularly challenging for jobs that require rapid, repeated, or forceful finger movements.
 - Characteristic high-stepping, toe-dragging, or shuffling gait due to difficulty lifting the toes and foot (“foot drop”)
 - Difficulty jumping or rising up on the toes due to weakness of the calf muscles. When combined with foot drop, this can lead to instability of the ankles, difficulty standing still, and frequent falls.
 - Weakness of neck flexor muscles, causing difficulty raising head from pillow
 - Dropped head posture and difficulty holding head upright due to weakness in the neck extensor muscle
 - Shortness of breath due to weakness of the diaphragm and other breathing muscles. Breathing problems may occur during exercise but are most prevalent during sleep. It is important to identify weakness of the breathing muscles before attempting surgery.
 - Reduced muscle stretch reflexes
 - Decline in myotonia as muscle weakness increases

Mild form

- Minor weakness and very mild myotonia that begins in a person’s fifties, sixties, or seventies. This form of the condition can be so mild that a person never seeks medical attention, explaining how the disease may be inherited even if neither parent was known to be affected.

DM2

- Muscle symptoms in DM2 may begin in the teenage years, but more commonly symptoms develop in the twenties, thirties, forties, or fifties. The congenital and childhood-onset forms of the disease probably do not occur in DM2.
- Initial symptoms may relate to grip myotonia. Alternatively, myotonia may be inconspicuous, and the initial symptoms may involve weakness of muscles around the hips or shoulders.
- Common symptoms are difficulty standing up from a low chair, rising from the ground or a squatting position, or climbing stairs. Reaching up or working with the arms overhead also may be difficult. People with DM2 often experience unusual fatigue with exercise.
- Muscle atrophy is present but less noticeable than in DM1 and occurs later in life.
- Muscle pain in the neck, back, shoulders, hip flexors, and upper legs may be a prominent symptom.
- Severity of pain can fluctuate from day to day.

Diagnosis

Neuromuscular assessment

Careful neurological and sometimes ophthalmological examination is the most important element in making a diagnosis of DM1. When the characteristic changes of myotonia and muscle weakness have occurred, the examination can provide strong evidence for DM1, and the physician can be reasonably confident of the diagnosis.

Checking for myotonia is not routine for most general physicians. Neuromuscular specialists generally check for this symptom either by having a person make a tight grip or using a percussion hammer to tap the muscles in the hand or forearm.

Delay in reaching a diagnosis is common because people with DM1 may not recognize the exact nature of their symptoms. Physicians in several specialties are often consulted before the diagnosis of DM1 is even considered. Congenital DM1 is more difficult to recognize because there can be multiple causes of weakness and hypotonia in newborns. DM2 can be difficult to differentiate from other types of late-onset muscular dystrophy, especially when the myotonia is not readily apparent and cataracts are not recognized. Other diagnostic procedures can be helpful in establishing a definitive diagnosis:

Electromyography (EMG)

A needle electrode placed in the muscle can record myotonic discharges. Extended bursts of electrical discharges in a saw tooth-like pattern are indicative of the abnormal electrical signals associated with slowing of muscle relaxation. This procedure shows myotonia in a high proportion of people with DM1 or DM2.

Muscle biopsy

Pathological features observed on muscle biopsy can strongly indicate the presence of DM but are not definitive in making the diagnosis. However, research techniques which can provide a highly accurate analysis are becoming more widely used in non-research pathology laboratories. Muscle biopsies are performed less frequently in the diagnosis of DM1 because of increased availability of genetic testing.

Identifying DM2 can present a greater diagnostic challenge. Abnormal muscle biopsy results may be the initial indicator of the presence of DM2.

Serum CK concentration

The enzyme creatine kinase (CK) leaks into blood when muscle tissue is damaged. Serum CK concentration may be mildly elevated in individuals with DM1 with weakness, but is normal in asymptomatic individuals.

Other blood tests

Enzymes such as ALT or AST can leak into the blood when there is muscle damage. Tests for these substances are a routine part of a general physical to screen for liver health. If a muscle condition is not suspected, the presence of ALT or AST is attributed to liver damage rather than muscle abnormalities. This assumption can create confusion when DM2 is present.

Genetic testing

Confirmation of a DM1 or DM2 diagnosis can be achieved through molecular genetic testing. The presence of the characteristic genes indicates that the person has DM or is at risk for developing it; the absence of the mutations means the disease is not present.

Treatment

Weakness

There are currently no medications available that address myotonic dystrophy weakness. Symptomatic treatments include:

- Occupational therapy and physiotherapy
- Molded ankle supports and leg braces to reduce foot-drop and enhance gait stability
- Fitted collar to reduce the effects of neck muscle weakness
- Low-intensity exercise strength training, to the extent that individuals are capable and without undue physical or cardiac stress (see *Patterns Of Cardiovascular System Problems*, p. 52)

Pain

Conventional pain medications may be useful in treating the painful aspects of myotonic dystrophy.

Myotonia

Drugs affecting ion channels, such as mexiletine, can improve myotonia. Although additional testing of these medications is needed, it may be reasonable for people with moderate to severe DM or symptoms to consider use of these medications if the condition sufficiently interferes with the individual's daily activities. Potential side effects need to be carefully considered, however. Symptomatic relief may be achieved by using regular or heated gloves to keep hands warm in cold temperatures.

Future directions in treatment

A major focus of current research, including research supported by the Myotonic Dystrophy Foundation, is to clarify why muscles become weak, and find treatments that can prevent the onset of weakness or restore strength to weakened muscles.

The pace of research progress has accelerated rapidly in the last decade. Researchers are focusing for the first time on correcting the chemical irregularities that exist in muscle cells of people with myotonic dystrophy. Although initial studies in this area are encouraging, it is difficult to predict when therapies may become available to patients. The Myotonic Dystrophy Foundation will make every effort to encourage these efforts and track their progress.

Cardiovascular System

Symptoms

Sudden death

Preventing sudden death is the highest priority in care of people with DM1. Sudden cardiac deaths in DM1 are mostly attributable to complete cardiac conduction block and ventricular fibrillation/tachycardia caused by cardiomyopathy.

Syncope and presyncope

Cardiogenic syncope should be first considered in management of patients with DM1. Cardiogenic syncope and presyncope may precede a sudden cardiac death. Milder complaints, such as non-vertiginous dizziness and lightheadedness, should also be considered as potential cardiogenic events.

Cardiac conduction defects

While patients with severe cardiac conduction block may present with the above-mentioned symptoms, patients with milder conduction blocks may be asymptomatic, especially when the conduction block does not cause significant hemodynamic changes. However, conduction delays at the AV node, the His bundle, and within the ventricle should be carefully assessed for indications of potential interventions.

Cardiac arrhythmias

The most common type of arrhythmia in patients with DM1 is atrial fibrillation/flutter, which poses risks for cardiogenic embolism. Various tachyarrhythmias and bradyarrhythmias are often symptomatic and may cause palpitations, fatigue, chest pressure or pain, dyspnea, syncope, presyncope, lightheadedness and dizziness. A high-degree AV block should be first considered as a possible cause of bradycardia in DM1 patients. Episodes of ventricular and supraventricular tachyarrhythmias may cause syncope or presyncope.

Hypotension

Hypotension is often found in patients with DM1 or DM2. Although hypotension has been attributed to autonomic dysfunction, the exact mechanism remains unknown.

Congestive heart failure

Dilated cardiomyopathy may lead to congestive heart failure in advanced stages of the disease. Pulmonary hypertension often leads to cor pulmonale in neonates born with congenital myotonic dystrophy DM1.

Adult myotonic dystrophy DM1 patients usually (but not always) develop cardiac manifestations after developing neuromuscular symptoms. Some asymptomatic children with DM may be at risk for sudden cardiac death.

Patterns Of Cardiovascular System Problems

Congenital DM1
<i>Newborn</i> <ul style="list-style-type: none">• Pulmonary hypertension and cor pulmonale• Cardiomyopathy in rare cases
<i>Childhood/Adolescence</i> <ul style="list-style-type: none">• Possible early cardiomyopathy and cardiac conduction problems
<i>Adulthood</i> <ul style="list-style-type: none">• Dilated cardiomyopathy and cardiac conduction defects beginning in early adulthood. These heart problems are one of the main causes of early mortality seen in adult patients with congenital myotonic dystrophy DM1.

Childhood Onset DM1
<p><i>Childhood/Adolescence</i></p> <ul style="list-style-type: none"> • Possible cardiomyopathy and cardiac conduction problems beginning in the second decade
<p><i>Adulthood</i></p> <ul style="list-style-type: none"> • Dilated cardiomyopathy and cardiac conduction defects sometimes present beginning in early adulthood • Complications in severe cases can lead to heart failure and sudden death, even in asymptomatic individuals. • Hypotension
Adult Onset DM1
<p><i>Hypotension</i></p> <ul style="list-style-type: none"> • Dilated cardiomyopathy and cardiac conduction defects possible. Complications in severe cases can lead to heart failure and sudden death, even in asymptomatic individuals.
DM2
<p><i>Hypotension</i></p> <ul style="list-style-type: none"> • Mild arrhythmia and other conduction issues occasionally present • Dilated cardiomyopathy and cardiac conduction defects possible, but less common than DM1. Complications in severe cases can lead to heart failure and sudden death, even in asymptomatic individuals.

Diagnosis

- Annual cardiological history and physical examination
- Annual 12-lead electrocardiogram (EKG)
- 24h portable Holter monitor if symptoms suggest cardiac arrhythmias or cardiogenic syncope, or if EKG shows cardiac arrhythmias or conduction abnormalities
- 2D / M-Mode Echocardiography every 2-5 years
- Invasive electrophysiology (EP) testing when potential for serious conduction blocks or arrhythmias are suspected. Because of the possibility of sudden death, the EP testing should be performed with relatively liberal indications.

Treatment

Cardiac Devices

The use of implantable cardiac pacemakers and cardioverter defibrillator devices may be warranted, depending on EP results. Due to the potential for sudden, rapid symptomatic progression and recurrent cardiac events, patients with DM are considered to have a class I indication for cardiac pacing with second and third degree AV block, and a class IIb indication for cardiac pacing even with first degree AV block, regardless of symptoms. (See Europace 2007 9(10):959-998 for guidelines on cardiac pacing and cardiac resynchronization therapy). However, some debate exists regarding the use of these devices, as their utility has not been established for all patients.

Medications

Anti-arrhythmic drugs are available for individuals with milder symptoms. However, Class I anti-arrhythmic drugs are contraindicated as they may have pro-arrhythmic effects. Sudden vigorous exertions should be avoided since sudden death has been associated with rapidly elevated heartbeat. Congestive heart failure should be managed with conventional treatments.

The cautious use of anti-myotonic medications and general anesthetics is also warranted, as they can elevate the risk of cardiorespiratory complications.

Respiratory System

Symptoms

Respiratory muscle weakness

People with myotonic dystrophy commonly have significant breathing problems that can lead to respiratory failure or require mechanical ventilation in severe cases. These issues may result from muscle weakness (diaphragm, abdominal, and intercostals muscles) and myotonia of respiratory muscles, which lead to poor breathing force and results in low blood oxygen/elevated carbon dioxide levels.

Aspiration

Breathing of foreign material, including food and drink, saliva, nasal secretions, and stomach fluids, into the lungs (aspiration) can result from abnormal swallowing. Without adequate diaphragm, abdomen and chest wall coughing strength to remove the foreign material, the inhaled acidic material can cause chemical injury and inflammation in the lungs and bronchial tubes. The injured lungs are then susceptible to infections that can lead to respiratory distress.

Sleep apnea

Insufficient airflow due to sleep apnea (periods of absent airflow due to narrow airways and interrupted breathing) can result in dangerously low levels of oxygen and high levels of carbon dioxide in the blood. In mild cases, apnea can cause disrupted sleep, excessive fatigue, and morning headaches. In severe cases, apnea can cause high blood pressure, cardiac arrhythmias, and heart attack.

The respiratory issues seen with myotonic dystrophy vary depending on the form of the disease.

Patterns of Respiratory System Problems

Congenital DM1
<i>Prenatal</i> <ul style="list-style-type: none">• Failure of cerebral respiratory control, which may result in fetal distress• Pulmonary immaturity, which may be further complicated by premature birth
<i>Newborn</i> <ul style="list-style-type: none">• Respiratory insufficiency due to a combination of weak diaphragm and intercostals muscles, pulmonary immaturity, and failure of cerebral respiratory control. Severe cases may require mechanical ventilation for extended periods. Respiratory issues are the principal cause of death in newborns with congenital myotonic dystrophy DM1.• Weak facial and esophagus muscles that may lead to sucking and swallowing problems, which can allow fluids to enter the lungs and result in chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia.

Childhood/Adolescence

- Weakness of the diaphragm, abdomen and chest wall muscles affecting the ability to cough, resulting in chronic lung infections, chronic bronchitis and bronchiectasis (abnormal stretching and enlarging of the bronchial tubes, which remain chronically infected)
- Chronic upper airway infections, which potentially can lead to hearing loss at a young age
- Weak facial and esophagus muscles that may lead to swallowing problems, which can allow fluids to enter the lungs and result in chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia

Adulthood

- Weakness of the diaphragm, abdomen and chest wall muscles affecting the ability to cough, resulting in chronic lung infections, chronic bronchitis and bronchiectasis (abnormal stretching and enlarging of the bronchial tubes, which remain chronically infected)
- Weak facial and esophagus muscles that may lead to sucking and swallowing problems, which can allow fluids to enter the lungs and result in chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia
- Weakness and myotonia of the diaphragm and other respiratory muscles, leading to insufficient exchange of oxygen and carbon dioxide in the lungs (hypoventilation)
- Sleep apnea, which can result in dangerously low levels of oxygen and high levels of carbon dioxide in the blood. In mild cases, apnea can cause disrupted sleep, excessive fatigue, and morning headaches. In severe cases, apnea can cause high blood pressure, cardiac arrhythmias, and heart attack.
- Severe respiratory failure is also seen in some individuals with myotonic dystrophy, particularly late in life. These pulmonary problems are one of the main causes of mortality in adults with the congenital form of myotonic dystrophy DM1.

Childhood Onset DM1

Childhood/Adolescence

- Weakness of the diaphragm, abdomen, and chest wall muscles affecting the ability to cough, resulting in chronic lung infections, chronic bronchitis and bronchiectasis
- Chronic upper airway infections, which potentially can lead to hearing loss at a young age
- Weak facial and esophagus muscles leading to swallowing problems, which can result in fluids entering the lungs that cause chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia

Adulthood

- Weakness of the diaphragm, abdomen and chest wall muscles affecting the ability to cough, resulting in chronic lung infections, chronic bronchitis, and bronchiectasis
- Weak esophagus muscles and swallowing problems, which can allow fluids to enter the lungs and result in chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia
- Weakness and myotonia of the diaphragm and other respiratory muscles, leading to insufficient exchange of oxygen and carbon dioxide in the lungs (hypoventilation)
- Sleep apnea which can result in dangerously low levels of oxygen and high levels of carbon dioxide in the blood. In mild cases, apnea can cause disrupted sleep, excessive fatigue, and morning headaches. In severe cases, apnea can cause high blood pressure, cardiac arrhythmias, and heart attack.
- Severe respiratory failure, particularly late in life. Pulmonary problems are one of the main causes of mortality for individuals with childhood onset myotonic dystrophy DM1

Adult Onset DM1

- Weakness of the diaphragm, abdomen and chest wall muscles affecting the ability to cough, resulting in chronic lung infections
- Weak esophagus muscles and swallowing problems, which can allow fluids to enter the lungs and result in chemical injury to the respiratory passages, chronic lung inflammation, and aspiration pneumonia
- Weakness and myotonia of the diaphragm and other respiratory muscles, leading to insufficient exchange of oxygen and carbon dioxide in the lungs (hypoventilation)
- Sleep apnea, which can result in dangerously low levels of oxygen and high levels of carbon dioxide in the blood. In mild cases, apnea can cause disrupted sleep, excessive fatigue, and morning headaches. In severe cases, apnea can cause high blood pressure, cardiac arrhythmias, and heart attack.
- Severe respiratory failure, particularly late in life. Pulmonary problems are one of the main causes of mortality for individuals with adult onset myotonic dystrophy DM1.

DM2

- Respiratory complications are uncommon.

Diagnosis

Clinical observation of gas exchange

- Measurement of respiration rate and work of breathing; comfort level; tachypnea
- Assessment of chest wall motion; abdominal muscle recruitment
- Observation for evidence of diaphragmatic paralysis
- Monitoring of breath sounds using a stethoscope (auscultation) to evaluate air entry into the lung base

Observation for pneumonia

Weakened breathing muscles put patients at risk for lung infections so careful monitoring for signs of pneumonia is important.

Inquiry about sleep disturbances

Symptoms such as nocturnal restlessness, unexplained awakenings, loud snoring punctuated by occasional awakening and gasping for breath may suggest the presence of a sleep-related respiratory disorder. Further study with a polysomnographic evaluation is recommended when symptoms are present.

Pulmonary function tests

These measures are used as a predictive measure of respiratory failure susceptibility and likely need for mechanical ventilation, and include:

- FVC (forced vital capacity). The total amount of air that can be forcibly blown out after full inspiration, measured in liters
- FEV1 (Forced Expiratory Volume in 1 Second). The amount of air that can be forcibly blown out in one second, measured in liters
- Maximal inspiration force. Ability to force air into the lungs
- Gas diffusion studies
- Arterial blood gases
- Carbon monoxide diffusing capacity (also called transfer factor, or TF)

Imaging studies

- Chest radiography to detect recurrent or chronic infections
- High-resolution computed tomography (HRCT) scans to look for lung abnormalities (e.g. pulmonary fibrosis, bronchiectasis, parenchymal scarring, pleural thickening) in patients with respiratory weakness with or without hypogammaglobulinemia. HRCT scans are considered to be more sensitive than chest radiography for helping detect the silent or asymptomatic structural changes of airways and lung parenchyma that sometimes occur.

Treatment

Nocturnal mechanical ventilation

Noninvasive positive pressure ventilation or bilevel positive airway pressure ventilation may relieve chronic hypoventilation-related symptoms and sleep apnea-hypopnea. In later stages, patients may become symptomatic from alveolar hypoventilation even with the use of nocturnal support as muscle weakness progresses; full-time ventilation may be required.

Manual and assisted coughing and/or cough assist device

In patients demonstrated to have difficulty clearing airway secretions, regular use of manual assisted coughing and/or a cough assist device may help to reduce the risk of pneumonia.

Incentive spirometry

Use of breathing exercise such as incentive spirometry may also help to clear mucus from the lungs and increase the amount of oxygen that gets deep into the lungs. Treatment for pneumonia follows standard clinical practice.

Continuous endotracheal mechanical ventilatory support

Infants with congenital myotonic dystrophy DM1 often require this level of support.

Nasal continuous positive airway pressure (N-CPAP)

This can facilitate weaning infants from ventilation and minimize morbidity and mortality associated with prolonged (>4 weeks) intubation.

Gastrostomy tube

Because feeding difficulties are common for children with congenital myotonic dystrophy DM1 with an increased risk for aspiration, individuals may benefit from feeding evaluation and gastrostomy tube insertion for airway protection and enteral feeding in early life.

Gastrointestinal Tract

Symptoms

Gastrointestinal (GI) symptoms that result from dysfunction of alimentary tract skeletal or smooth muscles are common. They can be a disabling and potentially serious feature of myotonic dystrophy (DM). Common GI symptoms include:

- Chewing and swallowing difficulties due to mouth, tongue or throat weakness or myotonia
- Gastroesophageal reflux caused by esophageal sphincter laxity
- Abdominal or chest pain (dyspepsia), nausea, vomiting, bloating or bowel pseudo-obstruction due to ineffective peristalsis
- Cholestasis (gallstones) due to ineffective gallbladder or bile duct musculature
- Constipation, diarrhea or malabsorption caused by bowel dysmotility (with secondary bacterial overgrowth), creating risk for fecal impaction, megacolon, bowel perforation and sepsis

- Impaired or painful bowel movements (dyschezia)
- Fecal incontinence due to anal sphincter and pelvic floor muscle weakness

Patterns of Gastrointestinal System Problems

Congenital DM1
<p><i>Prenatal</i></p> <ul style="list-style-type: none"> • Accumulation of amniotic fluid in the mother caused by reduced ingestion of amniotic fluid by the fetus (polyhydramnios)
<p><i>Newborn</i></p> <ul style="list-style-type: none"> • Ineffective nursing and failure to thrive due to weak suck • Ineffective swallow caused by craniofacial skeletal abnormalities and weakness of face, tongue, and jaw muscles • Inhalation of ingested liquid or secretions due to pharyngeal weakness and incoordination, potentially causing aspiration pneumonia (aspiration)
<p><i>Childhood/Adolescence/Adulthood</i></p> <ul style="list-style-type: none"> • Ineffective swallow (dysphagia) caused by craniofacial skeletal anomalies, or weakness, incoordination and myotonia of face, tongue, jaw, esophagus, and throat muscles • Aspiration due to pharyngeal weakness, potentially causing pneumonia • Recurrent post-prandial abdominal pain and bloating due to ineffective peristalsis or bowel pseudo-obstruction • Constipation, diarrhea, irritable bowel syndrome, caused by ineffective peristalsis or secondary intestinal bacterial overgrowth • Gallstones, due to abnormal gallbladder, bile duct, or sphincter musculature • Dilated colon, potentially leading to stool impaction, bowel perforation or megacolon
Childhood Onset DM1 and Adult Onset DM1
<ul style="list-style-type: none"> • Difficulty swallowing (dysphagia) caused by weakness or myotonia of the face, tongue, jaw, esophagus, and throat muscles • Aspiration due to pharyngeal weakness, potentially causing pneumonia • Recurrent abdominal pain and bloating, especially post-prandially • Constipation, diarrhea and irritable bowel symptoms • Gallstones due to abnormal muscle function of the gallbladder, bile duct and sphincter • Dilated colon, which can result in fecal impaction, possibly associated with megacolon or bowel perforation and sepsis
DM2
<ul style="list-style-type: none"> • Common symptoms include constipation, diarrhea, irritable bowel complaints, post-prandial bloating and abdominal pain, or gastroesophageal reflux • Additional investigations are required to determine whether these features and their molecular and cellular causes are similar.

Diagnosis

Careful assessment of the digestive tract is essential to relieve symptoms and to avoid secondary effects and complications. Gastrointestinal symptoms often develop gradually so that patients adopt compensatory mechanisms and consequently avoid necessary examinations. Patients and physicians can thus be unaware of gastrointestinal dysfunction until it comes to clinical attention due to acute exacerbation. For example, mild bowel dysmotility can be overlooked until a patient presents with symptoms of advanced pseudo-obstruction, at which time misdiagnosis of the severe abdominal pain and bloating as a complete mechanical bowel obstruction can lead to the potentially disastrous consequences of inappropriate abdominal surgery. This situation can be avoided only by conscientious and detailed inquiry about gastrointestinal problems at the time of routine clinical care, investigating, treating and educating patients at an early stage rather than when symptoms climax in an acute abdomen.

Routine gastrointestinal assessment

History and review of symptoms should cover chewing problems (myotonia or fatigue); difficulty swallowing (dysphagia for solids; aspiration of liquids, or frequent dry cough suggesting aspiration of secretions) gastroesophageal reflux; eating patterns; post-prandial bloating or pain and characteristics of any abdominal pain; frequency and character of bowel movements; fecal or urinary incontinence.

Routine physical examination

Special attention should be paid to evidence of involuntary weight loss, dysphonia indicative of pharyngeal weakness, frequent cough indicative of aspiration, abdominal pain on palpation, either generally or at gallbladder, and abdominal bloating.

Evaluation of asymptomatic individuals

Additional evaluation may include:

- Abdominal X-ray to evaluate abnormal bowel gas or stool, or free abdominal air
- A swallow study to characterize dysynergic movements, pharyngeal weakness, pharyngeal or esophageal constriction, or aspiration
- Abdominal ultrasound or MRI scans can detail stomach, small bowel, large bowel or gallbladder anatomy
- Barium upper GI radiographic evaluation to assess lower esophageal function and reflux, gastric emptying, and small bowel anatomy and function. If acute bowel obstruction is considered, a barium radiographic investigation with small-bowel follow-through distinguish pseudo-obstruction from the surgical emergency of true bowel obstruction.
- Manometry to demonstrate weakness or disordered contraction of esophagus, gastroesophageal sphincter, stomach, small bowel, rectum and anal sphincter
- Endoscopy to define abnormal structure or function of pharynx, esophagus, stomach, small intestine, or large intestines
- Blood tests to investigate cholestasis or hepatic involvement. Results should be interpreted cautiously since elevated AST and ALT in myotonic dystrophy can be evidence of muscle damage rather than liver dysfunction. Similarly, gamma-glutamyltransferase (GGT) blood level does not correlate with liver damage in myotonic dystrophy because it too is often elevated in all DM1 and DM2 subjects. Alternatively, serum alkaline phosphatase and bilirubin elevation do correlate with cholestasis in myotonic dystrophy.

Treatment

Accurate diagnosis is critical when treating GI symptoms in people with myotonic dystrophy. For example, painful bowel dilatation caused by myotonic dystrophy pseudo-obstruction may be mistakenly diagnosed as an acute bowel obstruction, which could expose the patient needlessly to the risks of anesthesia and surgery and post-surgical complications. Alternatively, clinical or radiographic verification of pseudo-obstruction allows conservative management with medication and other measures.

Pharmacologic approaches to GI symptoms

- Mexiletine to reduce myotonia in muscles of mastication that interfere with chewing, or in pharyngeal and proximal esophageal muscles responsible for dysphagia
- Prokinetic drugs (such as metoclopramide, and erythromycin) used intermittently to reduce symptoms of bowel hypomotility (bloating, abdominal pain, constipation), although diminished response prevents the utility of chronic treatment with these medications (Prokinetic agents can sometimes help control diarrhea that results from the bacterial overgrowth that is caused by hypomotility and malabsorption.)
- Cholestyramine to treat diarrhea, incontinence, and pain

Treatments for dysphagia

- Dietary modification (mechanically soft foods are easiest to swallow)
- Involvement of a speech therapist to teach behavioral and postural modification (e.g., neck flexed when swallowing, reduction of mouthful volume, alternation of solids and liquids, use of a particular implement, such as a cup, straw or spoon that improves swallowing)
- Gastrostomy feeding to maintain nutrition and protect the airway. Nasogastric tubes are typically contraindicated in myotonic dystrophy patients because they increase risk of aspiration.

Central Nervous System

Symptoms

Cognitive impairment

Intellectual disability is expected in individuals with clinically evident myotonic dystrophy at birth. In less severe forms of the disease, cognitive and behavioral abnormalities can involve IQ, executive function, visual-spatial construction, arithmetic ability, attention, and personality to variable degrees. Intellectual disability is a static abnormality associated with brain maldevelopment, but whether DM can also cause a progressive, degenerative, or even dementing disorder remains controversial. In addition to the primary alteration in brain function caused directly by the myotonic dystrophy mutation, hormonal or other systemic abnormalities in myotonic dystrophy might cause or exacerbate intellectual dysfunction by secondarily affecting the central nervous system (CNS).

Excessive daytime sleepiness

Excessive daytime sleepiness (hypersomnia) is common in myotonic dystrophy and can develop at any age. As opposed to generalized fatigue, which is also common in myotonic dystrophy, hypersomnia causes patients to sleep frequently, and often unpredictably, throughout the day despite having normal or greater than normal duration of sleep at night. Hypersomnia in myotonic dystrophy can result from several distinct mechanisms, including:

- Behavioral abnormalities with an erratic sleep schedule and poor sleep hygiene
- Ventilatory muscle weakness with sleep-related hypoventilation and non-restorative sleep
- Airway obstruction due to pharyngeal weakness and obstructive sleep apnea
- CNS causes of central alveolar hypoventilation
- CNS causes of central hypersomnia due to disordered arousal

Behavioral, emotional, and socialization difficulties

- Behavioral phenotypes such as avoidant personality are more common in patients with low cognitive ability and advanced physical handicap, but have also been described in DM1 and DM2 patients with normal IQ.
- Physical disabilities in severely affected individuals (such as craniofacial abnormalities, dysarthria and abnormal facial appearance) also influence behavior, emotional state, and socialization.
- Substance abuse is common in a subset of myotonic dystrophy subjects, but requires additional investigation to determine its cause.
- Frequency and severity of depression in myotonic dystrophy is often difficult to assess due to the concurrence of apparently unrelated apathetic or avoidant personality, sleep and eating dysfunction, and inexpressive facial appearance due to facial muscle involvement.

Peripheral Neuropathy

Minimal abnormalities in peripheral nerve function have been confirmed by nerve conduction studies, but significant peripheral nerve abnormalities, previously suggested by muscle biopsy features, have not been confirmed. Symptoms attributable to peripheral nerve involvement are uncommon and rarely clinically significant.

Patterns of CNS Problems

Congenital DM1
<p><i>Childhood/Adolescence</i></p> <ul style="list-style-type: none">• Intellectual impairment due to potentially severe intellectual disability. Speech abnormalities, dysmorphic facial appearance, and lack of facial expression can make mild or normal cognitive impairment appear more marked.• Developmental delays and learning disabilities related to the cognitive impairment and exacerbated by craniofacial abnormalities (dysarthria, lack of facial expression), and distal weakness (lack of dexterity, generalized fatigue)• Apparent apathy and inertia can be exacerbated by multiple causes, including cognitive impairment, avoidant personality, daytime hypersomnia, neuromuscular fatigue, and inexpressive facial appearance due to facial muscle weakness• Psychiatric disorders (including attention deficit, socialization difficulties, anxiety, substance abuse, and depression)• Visual-spatial and constructional difficulties due to cognitive deficits are exacerbated by motor impairment
<p><i>Adulthood</i></p> <ul style="list-style-type: none">• Executive function abnormalities, daytime sleepiness and psychiatric disorders frequently become more evident with age
Childhood Onset DM1
<p><i>Childhood/Adolescence</i></p> <ul style="list-style-type: none">• Variable cognitive impairment. Patients who come to medical attention during childhood but after the neonatal period may have congenital defects including intellectual disability, which is mild compared to those with overt congenital disabilities. Dysarthria, dysmorphic facial appearance, and lack of facial expression can result in subjects with mild cognitive impairment appearing more markedly affected than is accurate. These mistaken impressions can occur both during casual interactions and on formal neuropsychological testing unless the evaluator appropriately corrects for the patient's physical disabilities.• Apparent apathy and inertia resulting from and exacerbated by multiple causes, including cognitive impairment, avoidant personality, daytime hypersomnia, neuromuscular fatigue, and inexpressive facial appearance due to muscle weakness• Developmental delay and learning disabilities• Psychiatric disorders including attention deficit, socialization difficulties, anxiety, substance abuse and depression• Visual-spatial and constructional difficulties due to cognitive deficits which are exacerbated by motor impairment
<p><i>Adulthood</i></p> <ul style="list-style-type: none">• Increasing age is associated with more evident executive function abnormalities, daytime sleepiness and psychiatric disorders.
Adult Onset DM1
<p><i>Classic form</i></p> <ul style="list-style-type: none">• Intellectual impairment or static cognitive impairment is NOT expected in patients without clinical features of myotonic dystrophy until adulthood (as opposed to those with early onset symptoms who are not correctly diagnosed until adulthood).• Progressive cognitive loss can occur in true adult onset DM1, typically in association with multisystemic deterioration, though the relationship of this apparent dementing process with executive function loss and psychiatric disorders that both increase with age requires further investigation.• Psychiatric disorders including attention deficit, avoidant personality, socialization difficulties, anxiety, and depression increase with age, and are exacerbated by hypersomnia and multisystemic disease.• Excessive daytime sleepiness can be the primary and presenting symptom in some individuals with adult onset disease.• Visual-spatial constructional difficulties may be present in true adult onset DM1 but have not yet been thoroughly investigated.• Executive function deteriorates with age in adult onset DM1 subjects, leading to greater difficulty in organizing and responsibly performing routine lifetime activities (paying bills, keeping appointments, arranging schedules, etc.)

DM2

- Overall less is known about CNS effects of DM2, and additional research is needed.
- As in true adult-onset DM1 patients, intellectual impairment or static cognitive impairment is NOT expected in DM2.
- As in true adult-onset DM1 patients, progressive cognitive loss can occur in DM2, typically in association with multisystemic deterioration, executive function loss and psychiatric disorders.
- Psychiatric disorders including attention deficit, avoidant personality, and depression become more common with age, and are exacerbated by hypersomnia and multisystemic disease.
- Executive function deteriorates with age in adult onset DM2 subjects, leading to greater difficulty in organizing and responsibly performing routine lifetime activities (paying bills, keeping appointments, arranging schedules, etc.).

Diagnosis

Evaluation of excessive daytime sleepiness (EDS)

Excessive daytime sleepiness results in significant morbidity and mortality due to accidents while driving, at work or at home, therefore it is important to recognize the problem and determine the underlying cause. In situations requiring quantification, the degree of excessive sleepiness can be formally evaluated by sleepiness scales. (A subset of the Stanford Sleepiness Scale has been validated in DM1.) The following set of questions can be used for simple identification of hypersomnia in clinic patients:

- When do you go to sleep each night and how many hours do you sleep?
- Do you take one or more naps during the day?
- Do you at times experience a sudden need to sleep during the day?
- Do you often fall asleep while watching TV or at the movies or a show?
- Do you have difficulty being inactive for prolonged periods?
- Are you generally in great shape and alert during the day?

The following screening measures can be used to help determine whether intervention or referral to a sleep laboratory is indicated:

- Sleep diaries: Help patients and physicians objectify a sense of sleepiness
- Actigraphy: Provides a quantitative measure of sleep habits, recording movements and documenting hours of inactivity and sleep over periods of days
- Nocturnal oxymetry: Performed at home to measure nocturnal hypoventilation and help determine if ventilatory failure, sleep apnea or central hypoventilation are responsible for impaired sleep and excessive daytime sleepiness

Evaluation methods available at comprehensive sleep centers include:

- Polysomnogram: Test that monitors electroencephalographic activity to determine sleep stage and duration, and compare it to ventilatory effort and oxygenation. This information can help define causes of hypoxia during sleep. Due to the multiple potential causes of daytime sleepiness in myotonic dystrophy, qualified comprehensive sleep laboratory evaluation is required to determine presence of any parasomnias, sleep apnea, central or neuromuscular hypoventilation or central hypersomnia, each of which has specific significance and treatment. Unfortunately, many sleep laboratories focus only on sleep apnea, being unaware of the complexities of sleep disturbance in myotonic dystrophy. Standard treatment of sleep apnea in non-myotonic dystrophy patients (CPAP) is often contra-indicated in DM patients, so knowledge of the multiple causes of sleep disturbance in myotonic dystrophy is essential.
- Multiple Sleep Latency Test [MSLT]: Measures the time it takes to repeatedly fall asleep. To assure comparable sleep history, this test is best performed after a standard night's sleep monitored with polysomnography. MSLT is often essential for the diagnosis of central hypersomnia in myotonic dystrophy.
- Structural assessment. Magnetic resonance imaging (MRI) can be used to identify the high-T2 signal abnormalities that are common in DM1 and DM2 cerebral white matter. The pathophysiological significance of these abnormalities is controversial, so at present the primary importance is to recognize that they are common in myotonic dystrophy in order to avoid misdiagnosis. Congenital and childhood forms of DM1 are associated with generalized atrophy on MRI studies, and initial studies have shown cerebral volume loss in adults with DM1 and DM2 compared to age-matched controls. In patients with DM1 and DM2, positron emission tomography (PET) studies can identify reduced frontal and temporal lobe blood flow, though the causal relationship of this finding to cognitive or executive dysfunction is yet to be determined.
- Neuropsychological assessment: Evaluation performed to assess cognitive strengths and weaknesses. In particular, testing in DM1 children should be considered routinely when early signs of cognitive or developmental issues are present. Any evaluation should accommodate the physical impairments that may be present (such as hearing loss or speech deficits) and differentiate between physical and mental issues that may be perceived as cognitive dysfunction. Tests include:

Cognitive skills tests

- Age appropriate IQ (eg. WPPSI and WISC)
- Executive function and higher cognition skills
- Visual-spatial ordering skills
- Visual perception/construction/memory skills
- Attention skills
- Verbal abstract reasoning skills
- Temporal-sequential ordering skills

Tests for other neuropsychological functions

- Attention-deficit/hyperactivity disorder (ADHD)
- Energy levels
- Social skills and general behavior
- Emotional facility (such as evaluation of anxiety, withdrawal, depression, conduct disorders)

Treatment

Excessive Daytime Sleepiness (EDS)

Wakefulness-promoting agents for narcolepsy, such as modafinil, are sometimes prescribed off-label for attention-deficit hyperactivity disorder (ADHD) and excessive daytime sleepiness. These agents have shown modest benefit as assessed by the Epworth sleepiness scale.

Cognitive Dysfunction

Identification of cognitive dysfunction is crucial to providing appropriate individualized interventions and behavioral therapy. Early intervention for cognitive weaknesses, academic achievement problems, and behavior, attention, or social issues can have significant impact on a child's success in later life. The knowledge of specific deficits may also inform staff as to how medical problems may affect schoolwork, and therefore aid in behavior management.

Reproductive System

Symptoms

Testicular Atrophy

Primary hypogonadism in males (testicular atrophy) is usually not recognized until adulthood. Symptoms can include:

- Small testes, associated with decreased or absent sperm production. Infertility issues are more common in patients with DM1.
- Weak secondary sex characteristics, including decreased energy, libido, sexual hair, muscle mass, and bone mineral density
- Low serum testosterone (low or low-normal urinary 17-ketosteroid (17-KS) excretion, prohormone precursors of testosterone and estrone/estradiol)
- Elevated serum FSH and LH concentration
- Elevated FSH levels can result in high estradiol:testosterone ratios, leading to gynecomastia

Female Infertility

- Reduced fertility is seen in females with myotonic dystrophy, however there is little evidence of gonadal dysfunction or hypogonadism. Infertility symptoms include:
 - Increased spontaneous abortion and stillbirth rate
 - Early menopause in rare cases

Pregnancy Complications

Maternal complications during pregnancy may include:

- Prolonged labor and delivery related to uterine dysfunction, maternal weakness, and lack of voluntary assistance
- Uterine overdistention, related to polyhydramnios, which can cause preterm labor, inadequate uterine contractions (atonic uterus), or premature spontaneous rupture of membranes
- Myotonic spasms following the administration of depolarizing agents; respiratory depression following the administration of barbiturates
- Post-partum hemorrhage due to inadequate uterine contractions (atonic uterus) or retained placenta

Neonatal Complications

Fetal and neonatal complications in newborns with congenital myotonic dystrophy type 1 (DM1) may include:

- Polyhydramnios, which is associated with increased risks of adverse pregnancy outcome
- Umbilical cord prolapse or placental abruption
- Fetal malposition due to reduced fetal mobility
- Pre-term labor
- Hydrops fetalis
- Fetal akinesia

Diagnosis

Reproductive issues

Diagnosis of fertility issues of individuals (males and females) with myotonic dystrophy may include:

- Blood tests to measure circulating hormone levels (including testosterone, estradiol, FSH, LH, and thyroid hormones)
- Semen analysis (where possible)

Pregnancy Complications

Polyhydramnios is typically diagnosed by ultrasound examination. An increase in amniotic fluid volume may be qualitative or quantitative. Serial examinations can identify potential issues, even if sensitivity and positive predictive values are low in any one test.

Fetal hydrops

Fetal hydrops is typically diagnosed by ultrasound examination.

Treatment

Reproductive Issues

Although there is often no effective treatment to restore fertility, assisted reproductive technology with or without oocyte/sperm donation may be helpful. Prenatal genetic diagnosis may also be performed to identify whether an expanded myotonic dystrophy allele has been passed along to the embryo.

Pregnancy Complications

Due to the increased incidence of complications during pregnancy with a child with congenital myotonic dystrophy DM1, intensive obstetric and perinatal care is recommended.

Neonatal complications

- Polyhydramnios: Amniotic fluid volume reduction may be considered only if there is preterm labor or significant maternal discomfort. Methods for reducing excessive amniotic fluid volume include:
 - Amnioreduction: Amniotic fluid is suctioned to reduce the edema seen. While amnioreduction can be repeated if severe polyhydramnios recurs, this exposes the fetus to the risks of serial invasive procedures and should be done only where symptoms warrant.
 - Maternal administration of prostaglandin synthetase inhibitors. These agents stimulate fetal secretion of arginine vasopressin, which reduces renal blood flow and fetal urine flow. This has been seen to impair production and/or enhance reabsorption of lung liquid. Fetal and maternal side effects of these drugs include constriction of the ductus arteriosus, esophageal reflux, gastritis, and emesis, which must be monitored.
- Fetal hydrops: During pregnancy, treatment of hydrops is limited. Management of hydrops in newborn babies may include:
 - Support for respiratory distress using supplemental oxygen or mechanical ventilation
 - Removal of excessive fluid from spaces around the lungs and abdomen
 - Medications to help the kidneys remove excess fluid

Endocrine System

Symptoms

Insulin Resistance

In myotonic dystrophy patients, insulin-stimulated uptake of glucose is reduced due to insulin receptor deficiencies. To compensate for suppressed responsiveness (insulin resistance), insulin secretion may be increased. Elevated levels of circulating insulin, increased serum glucose, and dyslipidaemia may be present. Although diabetic symptoms may be seen, the insulin resistance issues tend to be mild and rarely result in full diabetes in DM1. The prevalence of diabetes is greater in DM2.

Frontal Balding

Premature male-pattern frontal balding is seen in both DM1 and DM2.

Diagnosis

Insulin Resistance

Diagnosis of insulin resistance in individuals with myotonic dystrophy typically involves blood tests that measure:

- Fasting serum insulin levels
- Fasting serum glucose concentration
- Fasting serum glycosylated hemoglobin concentration

Treatment

Insulin Resistance

Insulin resistance can be managed in the following ways:

- Lifestyle changes: The need for insulin can be reduced by modifying lifestyle (eg. exercise, balanced diet, removal of majority of sugar from the diet).
- Medications: Blood glucose and insulin levels can be normalized by drugs that either prevent the liver from releasing glucose into the blood or increase the sensitivity of muscle and fat cells to insulin.

Immune System

Myotonic dystrophy is associated with a modest reduction in the amount of immunoglobulin in the blood (hypogammaglobulinemia). The production of antibodies is normal, however the antibodies do not last as long in the circulation, hence the amount in the blood at any time is somewhat reduced. The myotonic dystrophy-associated reduction of immunoglobulin appears to be well tolerated. So far there is no clear evidence that alteration is associated with an increased frequency of infection.

Tumors

People with myotonic dystrophy DM1 have an increased frequency of pilomatrixoma, a type of benign skin tumor. This type of tumor is rare in the general population but fairly common in people with myotonic dystrophy DM1. (No association between pilomatrixomas and DM2 has been reported).

Pilomatrixomas often occur around the head or neck and feel like firm lumps just beneath the surface of the skin. These tumors are benign and can be cured by surgical removal. Some researchers have suggested that DM1 may also be associated with an increased frequency of other types of tumors, such as tumors of the parathyroid, pituitary, or thymus glands. However, at this point there is no clear evidence to support this idea.

Vision

Signs and Symptoms

Blurred Vision

Visual impairments in patients with DM1 and DM2 are most often caused by cataracts. Posterior subcapsular iridescent lens opacities represent an initial phase of cataract formation in myotonic dystrophy and are detectable only with slit lamp biomicroscopy. These opacities are usually found in patients who have not developed any visual symptoms. The presence of these types of lens opacities and more mature cataracts may be the only sign of the disease. Posterior subcapsular iridescent lens opacities are highly diagnostic of DM1 and DM2 although not pathognomonic. Glare and blurriness of the vision develop as the progression of the lens opacities into stellate cataracts and eventually mature cataracts, which are indistinguishable from usual cataracts. Cataracts in DM1 and DM2 may progress faster than usual cataracts, and thus patients with DM1 and DM2 may be presented with early-onset cataracts.

Retinopathy

Retinopathy is often detected by electroretinogram (ERG), but seldom causes clinically significant visual impairments. In rare cases, gradual progressive changes in the pigment epithelium of the retina can be detected with indirect ophthalmoscopic examination.

Bilateral Blepharoptosis (Ptosis)

Bilateral ptosis is a frequent feature of DM1 but seldom seen in patients with DM2. It is often found in DM1 patients with characteristic hatchet facies. In severe cases, ptosis can obstruct vision and require intervention.

Ocular Hypotension

Reduced ocular pressure is detected by ocular tonometry as an incidental finding during a routine eye examination.

Ocular Myotonia

Unlike other myotonic disorders caused by muscle chloride (Thomsen's and Becker's myotonia congenita) and sodium (paramyotonia) channel gene mutations, DM1 and DM2 do not cause overt ocular myotonia (often detected as delayed eye opening after forceful eye closure). Lid lag is also usually absent in patients with DM1 and DM2. Although saccadic eye movements may be affected by myotonia, they are generally of no clinical significance.

Diagnosis

Annual ophthalmological examination

Annual eye examinations should be done on every myotonic dystrophy DM1 and DM2 patient to assess above-described eye problems.

Slit-lamp biomicroscopic examination

Slit-lamp biomicroscopic examination must be performed to diagnose these early lens opacities. A general assessment for lens opacities and cataracts may be done during a regular eye exam, but ophthalmologists and optometrists often do not recognize the iridescent lens opacities unless prompted.

Electroretinogram (ERG)

A moderate-to-advanced cataract can interfere with the diagnosis of retinopathy. ERG is not routinely performed unless retinopathy is suspected by routine eye examinations.

Treatment

Prevention of lens opacities

There is no proven therapy to slow or prevent the progression of lens opacity once it develops. Reducing UV ray exposures by wearing sunglasses is generally recommended.

Cataract surgery

Surgical removal of the opaque lens with intraocular lens implantation is indicated when cataracts interfere with the patient's ability to meet the needs of daily living. It is no longer necessary to wait for "ripeness" (vision impairment severe enough to absolutely require surgery). Similarly, there is no technical or medical advantage to taking out a cataract sooner; later treatment does not cause adverse outcomes, since pre-operative visual acuity has no bearing on the outcome of cataract surgery.

Modern microsurgical techniques

Techniques such as standard extracapsular cataract extraction and phacoemulsification (also called small incision surgery) allow cataract surgery to be performed under local anesthetic on an outpatient basis. The surgery is a low risk procedure, but careful pre- and post-operative evaluation is nevertheless important, particularly since myotonic dystrophy patients have elevated risks associated with anesthesia and often have other chronic medical conditions. General anesthesia is necessary only for patients who cannot be counted on to cooperate under local anesthesia, such as those who are significantly cognitively impaired or very young.

Blepharoplasty

The following interventions may be warranted when ptosis is severe and obstructs vision. (Surgery is often delayed as long as possible in patients with muscle disease because repeated procedures will likely be required due to the progressive nature of the disease.)

- **Crutches.** Eyelid crutches inserted into eyeglasses should be tried before blepharoplasty is considered.
- **Frontalis suspension of eyelids.** When severe bilateral ptosis and poor levator function are present, frontalis suspension surgery may be performed. A sling is formed which lies below the skin surface and connects the upper eyelid to the frontalis muscle.
- **Cosmetic surgery.** Surgery may also be considered for cosmetic reasons, but patients should be aware of the potential complications. The most common troubling complication of ptosis surgery is lagophthalmos or failure of the eye to close completely. This in turn may lead to dry eye and exposure keratopathy.

PART 4: RESOURCES FOR MEDICAL PROFESSIONALS

MEDICAL GUIDELINES

Role of Physical Therapy in the Assessment and Management Of Individuals with Myotonic Dystrophy

Shree Pandya, PT, DPT, MS, Katy Eichinger, PT, DPT, NCS

Department of Neurology, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Occupational Therapy Suggestions for the Management of a Myotonic Dystrophy Patient

Cynthia Gagnon, erg, Ph.D. Professeur adjoint,, École de réadaptation, Faculté de médecine et des sciences de la santé Université de Sherbrooke, Groupe de recherche interdisciplinaire sur les maladies neuromusculaires

Practical Suggestions for the Anesthetic Management of a Myotonic Dystrophy Patient

Neal Campbell, M.D.1, Barbara Brandom, M.D. 2, John W. Day, M.D., Ph.D. 3, Richard Moxley, M.D. 4

1 - Fellow, Pediatric Anesthesiology, Department of Anesthesiology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, UPMC, Pittsburgh, PA

2 - Professor, Department of Anesthesiology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, UPMC, Pittsburgh, PA

3 - Professor, Department of Neurology, University of Minnesota School of Medicine, University of Minnesota Medical Center, Fairview, Minneapolis, MN

4 - Professor, Department of Neurology, University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY

DMI HEALTH SUPERVISION CHECKLIST

Reprinted from Neuromuscular Disorders, Health supervision and anticipatory guidance in adult myotonic dystrophy type 1, 20(12), Gagnon, C, Chouinard, M.C., Laberge, L., Veillette, S., Bégin, P., Breton, R., Jean, S., Brisson, D., Gaudet, D., Mathieu, J. Appendix 1. Copyright (2011), with permission from Elsevier.

CONCERNS		INTERVENTIONS
Central nervous system concerns		
Cognitive impairments	<input type="checkbox"/> Normal IQ <input type="checkbox"/> Low IQ <input type="checkbox"/> Intellectual Disability <input type="checkbox"/> Evaluation required	_____
Depression	<input type="checkbox"/> Absent <input type="checkbox"/> Evaluation/treatment required	_____
Excessive daytime sleepiness	<input type="checkbox"/> Absent <input type="checkbox"/> Mild symptoms <input type="checkbox"/> Evaluation/treatment required	_____
Fatigue	<input type="checkbox"/> Absent <input type="checkbox"/> Mild symptoms <input type="checkbox"/> Evaluation/treatment required	_____
Visual concerns		
Ptosis	<input type="checkbox"/> Absent <input type="checkbox"/> Mild, reassess at follow-up <input type="checkbox"/> Moderate <input type="checkbox"/> Evaluation required	_____
Cataracts	<input type="checkbox"/> Absent or aphakia <input type="checkbox"/> Present <input type="checkbox"/> Evaluation required	_____
Respiratory concerns		
Pneumonia	<input type="checkbox"/> Absent <input type="checkbox"/> One or more in the last 6 months	_____
Chronic respiratory failure	<input type="checkbox"/> Absent <input type="checkbox"/> Arterial blood gas and spirometry required	_____
Sleep disturbances	<input type="checkbox"/> Absent <input type="checkbox"/> Insomnia <input type="checkbox"/> Sleep apnea symptoms <input type="checkbox"/> Oxymetry/PSG required	_____
Vaccination	<input type="checkbox"/> Annual influenza vaccine <input type="checkbox"/> Pneumovax vaccine <input type="checkbox"/> year	_____
Anesthetic risks	<input type="checkbox"/> Information provided	_____
Cardiovascular concerns		
Conduction defects	<input type="checkbox"/> Absent <input type="checkbox"/> Asympto. ECG abnormalities <input type="checkbox"/> Evaluation in cardiology needed	_____
	<input type="checkbox"/> Pacemaker <input type="checkbox"/> year <input type="checkbox"/> Pacemaker/defibrillator <input type="checkbox"/> year	_____
Arterial hypotension	<input type="checkbox"/> Absent <input type="checkbox"/> Asymptomatic <input type="checkbox"/> Symptomatic AT /	_____
Muscular concerns		
Myotonia	<input type="checkbox"/> Absent <input type="checkbox"/> Mild, no disturbance <input type="checkbox"/> Intervention required	_____
Muscular weakness	MIRS grade	_____
Walking limitations	<input type="checkbox"/> No risk of falls <input type="checkbox"/> Physiotherapist evaluation/equipment required	_____
Transfer difficulties	<input type="checkbox"/> No difficulties <input type="checkbox"/> Occupational therapist evaluation/technical aids required	_____
Wheelchair dependence	<input type="checkbox"/> Not required <input type="checkbox"/> Already provided <input type="checkbox"/> Intervention required	_____
Gastrointestinal concerns		
Dysphagia	<input type="checkbox"/> Absent <input type="checkbox"/> Present but no intervention needed <input type="checkbox"/> Intervention required	_____
Gastroparesis	<input type="checkbox"/> Absent <input type="checkbox"/> Mild/occasional N/V <input type="checkbox"/> Intervention required	_____
Gall-bladder problems	<input type="checkbox"/> Absent/cholecystectomy <input type="checkbox"/> Evaluation required <input type="checkbox"/> Intervention required	_____
Abdominal pain	<input type="checkbox"/> Absent <input type="checkbox"/> Mild/occasional pain <input type="checkbox"/> Intervention required	_____
Constipation/diarrhea	<input type="checkbox"/> Absent <input type="checkbox"/> Mild/occasional constipation or diarrhea <input type="checkbox"/> Intervention required	_____
Anal incontinence	<input type="checkbox"/> Absent <input type="checkbox"/> Mild/occasional incontinence <input type="checkbox"/> Intervention required	_____
Malnutrition	<input type="checkbox"/> Absent <input type="checkbox"/> Mild loss of weight <input type="checkbox"/> Intervention required	_____
Genitourinary and sexual concerns		
Urinary incontinence	<input type="checkbox"/> Absent <input type="checkbox"/> Incontinence ≤ once/month <input type="checkbox"/> Intervention required	_____
Erectil dysfunction	<input type="checkbox"/> Absent/NA <input type="checkbox"/> Presence but no disturbance <input type="checkbox"/> Intervention required	_____
Male infertility	<input type="checkbox"/> Absent/NA <input type="checkbox"/> Intervention required	_____
Gynecologic problems	<input type="checkbox"/> Absent/NA <input type="checkbox"/> Mild menstrual pain/dysmenorrhea <input type="checkbox"/> Intervention required	_____
Metabolic and endocrine concerns		
Obesity	<input type="checkbox"/> Absent <input type="checkbox"/> BMI ≥30 <input type="checkbox"/> BMI >45 <input type="checkbox"/> Weight (kg) <input type="checkbox"/> WC(cm)	_____
Diabetes	<input type="checkbox"/> Absent <input type="checkbox"/> Present <input type="checkbox"/> Last check/year	_____
Hypothyroidism	<input type="checkbox"/> Absent <input type="checkbox"/> Present <input type="checkbox"/> Last check/year	_____
Hypogonadism	<input type="checkbox"/> Absent <input type="checkbox"/> Present <input type="checkbox"/> Last check/year	_____
Dyslipidemia	<input type="checkbox"/> Absent <input type="checkbox"/> Present <input type="checkbox"/> Last check/year	_____
Chronic hepatic dysfunction	<input type="checkbox"/> Absent <input type="checkbox"/> Present	_____
Genetic concerns		
Genetic counselling	<input type="checkbox"/> Information provided <input type="checkbox"/> Family tree completed	_____
Family planning	<input type="checkbox"/> NA <input type="checkbox"/> Appropriate contraception <input type="checkbox"/> Genetic counselling required	_____
Risk for family members	<input type="checkbox"/> NA <input type="checkbox"/> Genetic counselling required	_____
Other health concerns		
Inappropriate use of medication	<input type="checkbox"/> Absent <input type="checkbox"/> Doubt <input type="checkbox"/> Supervision needed	_____
Drug abuse	<input type="checkbox"/> Absent <input type="checkbox"/> Occasional user <input type="checkbox"/> Drug abuse interfering with ADL	_____
Smoking	<input type="checkbox"/> No smoking <input type="checkbox"/> ≤ 40 packs/years <input type="checkbox"/> > 40 packs year	_____
Personal care deficiency	<input type="checkbox"/> No difficulty <input type="checkbox"/> With difficulty but no assistance <input type="checkbox"/> Evaluation required	_____
Pain	<input type="checkbox"/> Absent <input type="checkbox"/> Investigation and treatment required	_____
End of life issues	<input type="checkbox"/> Not appropriate <input type="checkbox"/> Discussion done on advance directives	_____
Information needs	<input type="checkbox"/> Information provided about the disease, researchs and support groups	_____
Social concerns		
Education	Education grade	_____
Employment	<input type="checkbox"/> Never worked <input type="checkbox"/> Currently working <input type="checkbox"/> Used to work/assistance required	_____
Income and financial assistance	<input type="checkbox"/> No problem <input type="checkbox"/> Assistance needed	_____
Home maintenance	<input type="checkbox"/> No difficulty /NA <input type="checkbox"/> Badly kept but acceptable <input type="checkbox"/> Intervention required	_____
Familial and social network	<input type="checkbox"/> Normal social environment <input type="checkbox"/> Unsatisfied by social life <input type="checkbox"/> Social deprivation	_____
Parental care deficiency	<input type="checkbox"/> Absent/NA <input type="checkbox"/> Doubt <input type="checkbox"/> Evaluation required	_____
Car driving	<input type="checkbox"/> NA <input type="checkbox"/> No difficulties <input type="checkbox"/> Evaluation required	_____
Leisure activities	<input type="checkbox"/> Normal hobbies <input type="checkbox"/> Unsatisfied <input type="checkbox"/> Appropriate services required	_____

PRACTICAL SUGGESTIONS FOR THE ANESTHETIC MANAGEMENT OF A MYOTONIC DYSTROPHY PATIENT

Neal Campbell, M.D.¹, Barbara Brandom, M.D.², John W. Day, M.D., Ph.D.³, Richard Moxley, M.D.⁴

¹Fellow, Pediatric Anesthesiology, Department of Anesthesiology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, UPMC, Pittsburgh, PA

²Professor, Department of Anesthesiology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, UPMC, Pittsburgh, PA

³Professor, Departments of Neurology and Pediatrics, Stanford University School of Medicine, Stanford Hospitals and Clinic and Lucile Packard Children's Hospital, Stanford, CA

⁴Professor, Department of Neurology, University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY

FOREWORD:

The anesthetic management of patients with myotonic dystrophy (dystrophia myotonica, DM) can be challenging. "Complications are not proportional to the severity of the disease; they often arise in mildly affected patients" (15). Indeed, there are multiple reports within the medical literature that detail poor outcomes related to the following complications: loss of airway secondary to medication-induced respiratory depression; aspiration of stomach contents; sudden death that is usually secondary to cardiac conduction delays and dysrhythmias. One must consider if, in light of these complications, "regional anesthesia is a viable alternative or if the surgical procedure is really necessary" (15).

The following points about myotonic dystrophy in this foreword can help a vigilant anesthesiologist avoid complications and provide safe anesthesia care to DM patients presenting for surgery:

- 1. General:** "Myotonia" is described as muscle contraction (voluntary or otherwise) with abnormal, prolonged relaxation (3). Triggers for myotonia include certain medications, potassium, hypothermia, shivering, or any mechanical or electrical stimulus (2, 3, 4). Patients also exhibit profound skeletal muscle weakness secondary to muscle degeneration.
- 2. Medications:** DM patients are exquisitely sensitive to the respiratory depressant effects of anesthetic medications (3). Be sure to have appropriate airway and monitoring equipment available when using these medications, and prepare for the likelihood of postoperative mechanical ventilation until strict extubation criteria are met. In addition, postoperative pain control should be managed with NSAIDs, regional techniques using local anesthetics, and acetaminophen when possible. If opioids are employed (systemic or neuraxial), then ICU care and continuous pulse oximetry must be considered given the high risk for respiratory depression and aspiration.

3. **Airway:** Rapid sequence induction with cricoid pressure is recommended. Weakness of the pharyngeal muscles and a delayed gastric emptying time predispose DM patients to aspiration (3, 21). Also, succinylcholine effects are unpredictable in DM patients: one case report describes jaw rigidity and impossible intubation after succinylcholine administration (19); prolonged laryngospasm and cyanosis has been reported in myotonia congenita, but could theoretically also occur in DM (20). Avoid succinylcholine when possible.
 4. **Respiratory System:** The effects of myotonic dystrophy on the respiratory system are profound and common (1, 24). Respiratory muscle weakness predisposes DM patients to restrictive lung disease with concurrent dyspnea and ineffective cough (3). Moreover, arterial hypoxemia and a diminished ventilatory response to hypoxia and hypercapnia are frequent associations (3). Accordingly, these factors place DM patients at an increased risk for pneumonia and other perioperative pulmonary complications (1). Ventilatory weakness contributes to the complex sleep disorders of DM, which frequently results in profound pre-operative sleep deprivation that further complicates post-anesthetic care.
 5. **Cardiac System:** DM patients can have cardiac abnormalities that may lead to sudden death secondary to various cardiac conduction delays or other dysrhythmias (3, 6). Thoroughly evaluate the cardiac system – including echocardiogram, 12-lead EKG, and interrogation of the internal cardiac rhythm device (if present) – before any anesthetic care is given.
 6. **Central Nervous System:** The many CNS effects of DM further complicate perioperative care. For example, behavioral and cognitive problems in the patient and other family members can complicate pre-operative preparation. Hypersomnia is a common and sometimes the primary manifestation of DM that can result from a narcolepsy-like central hypersomnia as well as sleep-related ventilatory insufficiency or obstructive sleep apnea, any of which can lead to profound sleep deprivation in the pre-operative period as well as multiple management difficulties post-anesthesia. Also, DM subjects have heightened CNS sensitivity to sedatives, anxiolytics and analgesics, further impeding ventilatory drive and airway protection. Perioperative casualties often develop several days post-operatively due to aspiration or inadequate monitoring of hypoxia, during the period in which DM patients become increasingly encephalopathic due to sleep deprivation or the unintended effects of medication.
-

PRE-OPERATIVELY:

1. **Multi-disciplinary medical team:** It is well documented that the medical and surgical management of patients with myotonic dystrophy (DM) can be challenging and fraught with complications (1, 3, 4, 6, 21). For these reasons, coordination of the pre- and post-operative plans for care should be made at least 1-4 weeks in advance using a multi-disciplinary medical team. This team would ideally consist of the surgeon, anesthesiologist, primary care physician, intensivist, and, if indicated, the pulmonologist and cardiologist (see 'consultations' below). Furthermore, the addition of a neuromuscular specialist (i.e. neurologist) with expertise in the pathophysiology and natural course of DM would be highly beneficial.

- 2. Pre-anesthetic evaluation:** In addition to a comprehensive preoperative evaluation completed by the DM patient's primary care physician (PCP), an anesthesiologist should perform a careful and detailed pre-anesthetic assessment 1-4 weeks prior to surgery. Such an evaluation may prevent serious complications and fatalities in DM patients. Their abnormal and often unpredictable responses to common anesthetic medications are well described in the medical literature and were summarized in the foreword (2, 3, 5, 7, 8, 11, 18, 19, 20). Indeed, a thoughtful and comprehensive anesthetic plan is warranted in advance of the day of surgery. The absence of such a preoperative evaluation by the PCP (at minimum) and the anesthesiologist could be considered cause for case cancellation.

The anesthesiologist should devote particular attention to the cardiopulmonary systems during their pre-anesthetic evaluation. It is not uncommon for DM patients to have a history of hypoxia, dyspnea, sleep apnea requiring CPAP, or marked ventilatory muscle weakness necessitating BIPAP. Given the anesthetic implications of these disorders, a measure of their severity is warranted. In addition, further questioning should involve whether or not the DM patient has a history of arrhythmia, heart failure, and/or an internal cardiac rhythm management device. All internal cardiac rhythm devices require interrogation by a cardiac electrophysiologist. A baseline echocardiogram, 12-lead EKG, and a chest radiograph should also be completed preoperatively (see 'consultations' below).

- 3. Consultations:** Based on the PCP's and anesthesiologist's preoperative evaluations and assessments, a thorough cardiopulmonary evaluation by a cardiologist and pulmonologist completed at least 3 weeks prior to elective surgery may be necessary because of the high incidence of morbidity and mortality related to these systems (1, 6). Indeed, all DM patients presenting for surgery should have a preoperative baseline echocardiogram, a 12-lead EKG, and a chest radiograph, each with expert interpretation. Moreover, all internal cardiac rhythm management devices must be interrogated by a cardiac electrophysiologist prior to entering the operating room. Pulmonary function tests (including supine and sitting vital capacities) and preoperative arterial blood gases may also be useful and should be requested at the discretion of the primary or consulting physician(s) before elective surgery.
- 4. Premedications:** DM patients can be exquisitely sensitive to the respiratory depressant effects of commonly used premedications (e.g. opioids and benzodiazepines). Therefore, make sure that appropriate equipment for monitoring and performing urgent intubation are available prior to the administration of premedication, or any other sedative. DM patients also frequently suffer from gastroparesis, predisposing them to episodes of acute pseudo-obstruction, which can be further exacerbated by opioids, further complicating ventilatory function and airway protection.
- 5. Regional anesthesia:** Regional anesthesia including neuraxial techniques have been described in the literature as successful primary anesthetics for DM patients (3, 22). They can help avoid some of the frequent complications associated with general anesthesia in the DM patient. However, there are case reports that describe an "incomplete motor block and shivering sufficient to stimulate myotonic contractures with epidural anesthesia" ([direct quote from 12], 13, 14) in DM patients. After the risks and benefits of regional anesthesia are assessed, techniques should ultimately be employed when applicable.

INTRA-OPERATIVELY:

1. Environment:

- a. Hypothermia and shivering can induce a myotonic contracture (2). Therefore, keep the operating room and table warm so that the patient will be better able to maintain a normal body temperature.
- b. Use warmed IV fluids as well as forced-air blankets during surgery.

2. Monitoring:

- a. Employ standard American Society of Anesthesiologists (ASA) monitors including thermometer (3).
- b. Strongly consider attaching an external pacer/defibrillator to the patient. DM patients are at high risk for arrhythmias and sudden death (6).
- c. Consider placing an arterial line in order to verify the adequacy of oxygenation and ventilation via blood gas interpretation, and for continuous blood pressure monitoring.
- d. Monitor neuromuscular blockade with a peripheral nerve stimulator, but do so with caution: the electrical stimulus could induce a myotonia and be misinterpreted as sustained tetany indicative of full reversal of neuromuscular blockade (2).
- e. Invasive cardiac monitoring (TEE, PA catheters, CVP lines) should be reserved for DM patients that have significant cardiopulmonary dysfunction. The cardiologist's pre-operative consultation and assessment may help guide the decision of whether to employ these monitors.

3. Induction:

The superiority of one specific induction agent over another has not been established for elective surgeries. Etomidate, thiopental, and propofol have all been used safely for induction. However, using agents with a short beta half-life seems logical to minimize the possibility of prolonged postoperative mechanical ventilation.

- a. Ensure adequate pre-oxygenation.
- b. DM patients are at risk for aspiration secondary to their dysphagia and altered gastric motility (21). Therefore, consider administering sodium citrate, an H₂-antagonist, and/or metoclopramide prior to induction. Lastly, a rapid sequence induction with cricoid pressure is warranted.
- c. Rapid Sequence Induction:
 - i. Maintain cricoid pressure
 - ii. A hypnotic agent with a short beta half-life (e.g. propofol) is recommended in light of the exaggerated apneic response characteristic of DM patients. Titrate the hypnotic to effect—a lower dose is likely to be sufficient in a DM patient.

- iii. Avoid succinylcholine. The DM patient's response to succinylcholine is unpredictable and may lead to a difficult or impossible intubation secondary to exaggerated contracture, masseter spasm, and laryngospasm (2, 19, 20). In addition, "because of dystrophic muscle changes, it is possible that in advanced cases succinylcholine might result in an exaggerated hyperkalemic response" (9).
 - iv. Tracheal intubation can be successful in DM patients without a muscle relaxant (9). If a muscle relaxant is needed, then a non-depolarizing agent with a short recovery index should be chosen (e.g. Rocuronium, Cis-atracurium) (7).
 - v. The temporomandibular joint may have a tendency to dislocate in DM patients. Laryngoscopy and jaw manipulation should be done with care (15).
- d. Difficult Airway: Follow the *ASA Difficult Airway Algorithm* (23).

4. Maintenance:

- a. **Volatile agents:** DM patients are no more susceptible to the development of malignant hyperthermia than the rest of the general population (16, 17). Volatile anesthetics are effective for maintenance of anesthesia, but they may exacerbate a patient's cardiomyopathy secondary to their myocardial depressive effects. In addition, desflurane, for example, may be the agent of choice considering its theoretical advantage of faster emergence upon completion of surgery (3).
- b. **Muscle relaxation:** If possible, avoid muscle relaxants altogether and maintain akinesia with deep inhalational/intravenous anesthesia, or have the surgeon infiltrate the skeletal muscle tissue within the surgical field with local anesthetic. When further muscle relaxation is required, use a non-depolarizing agent remembering that DM patients will exhibit an exaggerated response to it. Therefore, initial doses should be reduced while subsequent doses titrated to effect via the peripheral nerve stimulator (2).
- c. **Intravenous agents:** Safe and effective anesthesia using propofol and remifentanyl for total intravenous anesthesia has been described in the medical literature (4, 5).
- d. **Intravenous Fluids:** Consider using crystalloid fluids that do not have any added potassium. DM patients have reduced Na⁺-K⁺ pump capacity and may be prone to the development of hyperkalemia (10). There is no apparent contraindication to the use of colloids.

5. Emergence:

- a. **Reversal agents:** Neostigmine has been purported to induce myotonia (18). Therefore, avoid its use and plan for the non-depolarizing muscle relaxant effect to simply wear off.
- b. **Extubation:** Considering the multi-systemic effects of DM (cardiopulmonary pathology, profound peripheral weakness, altered gastric motility, pharyngeal weakness with poor airway protection, increased sensitivity to all anesthetic medications) adhere to strict extubation criteria. These patients may need supportive mechanical ventilation in the PACU and perhaps in the ICU until extubation criteria are met. Additionally, be aware that there is an increased risk of delayed-onset apnea after extubation during the immediate 24 hours after surgery, and even

longer if post-operative opioid analgesics are administered. Close and continuous monitoring of cardiopulmonary function (SpO2 and EKG) is needed during this time period.

- c. **Disposition:** Consider ICU admission if there is an anticipated need for mechanical ventilation, significant opioid analgesia, or other necessary critical care management.

POST-OPERATIVELY:

Admission to the intensive care unit (ICU) for postoperative management should always be considered given the significant complications that may occur as a result DM. At the very least, patients should be monitored postoperatively with continuous pulse oximetry and EKG for a period of 24 hours. Below are specific points that support these recommendations:

1. Pain Control:

- a. First and foremost, consider the use of regional anesthesia, NSAIDS, and acetaminophen (rectal or oral) for control of postoperative pain. If these medications/modalities are contraindicated, then the use of opioids must be administered with caution and vigilant monitoring (see below).
- b. The exquisite sensitivity of DM patients to the respiratory depressant effects of opioids (systemic or neuraxial) can equate to fatal outcomes in the postoperative period. The most common route of opioid administration that places DM patients at high risk for respiratory depression is intravenous, yet there is a case report that details respiratory depression following a small dose of epidural morphine as well (8). Another case report demonstrated adequate analgesia with epidural opioid administration without respiratory depression (11). Ultimately, these patients need to be closely monitored. An ICU is therefore the safest environment in which to administer postoperative opioids, titrating them to effect. Lastly, be aware that opioids can exacerbate one of the common features of DM, gastrointestinal paresis. Depending on the severity, gastroparesis could increase the risk of reflux and aspiration.

2. Pulmonary Considerations:

In a retrospective analysis of 219 DM patients who underwent surgery under general anesthesia, Matheiu et al found that most perioperative complications were related to the pulmonary system (1). In particular, DM patients who were symptomatic, who underwent upper abdominal surgery, or who had severe muscular disability were especially at risk. Therefore, "careful monitoring during the early postoperative period, protection of the upper airways, chest physiotherapy, and incentive spirometry are mandatory" (1).

It can not overstated just how important continuous monitoring is in a DM patient during the postoperative period, especially if ventilatory function is compromised secondary chest or abdominal surgery, pain, or muscle weakness inherent of the disease. Delayed-onset apnea is most likely to develop in the first 24 hours postoperatively, and an exaggeration of any baseline hypersomnia could become apparent with morbid results. An ICU would be most appropriate for the detection and treatment of these complications should they arise.

SUMMARY:

1. Perform an extensive preoperative evaluation. Organize a multi-disciplinary medical team.
2. Use regional anesthesia when appropriate.
3. Be cautious with premedications (benzodiazepines and opioids).
4. Keep the patient warm.
5. Consider applying defibrillator/pacer pads.
6. On induction, be aware of the high likelihood of aspiration and other airway complications. Avoid succinylcholine when possible.
7. Adhere to strict extubation criteria. Given the effects DM has on the pulmonary system, anticipate the need for supportive mechanical ventilation until extubation criteria are met.
8. Plan for the continuous SpO₂ and EKG monitoring postoperatively.
9. Manage postoperative pain with NSAIDs, regional techniques, and acetaminophen when appropriate. Use opioids with extreme caution.
10. Encourage aggressive pulmonary toileting postoperatively.

REFERENCES:

1. Mathieu J, Allard P, et al: **Anesthetic and surgical complications in 219 cases of myotonic dystrophy.** *Neurology* 1997; 49:1646-1650.
2. Azar I: **The Response of Patients with Neuromuscular Disorders to Muscle Relaxants: A Review.** *Anesthesiology* 1984; 61:173-187.
3. Barash PG, et al. **Clinical Anesthesia.** 4th edition. pgs. 32-34, 493-494, 1997.
4. Catena V, et al. **Anesthesia and myotonic dystrophy (Steinert's syndrome). The role of intravenous anesthesia with propofol, cis-atracurium, and remifentanyl. A case report.** *Minerva Anesthesiol.* 2007 Sept; 73(9) 475-9.
5. Bennum M, Goldstein B, et al. **Continuous propofol anaesthesia for patients with myotonic dystrophy.** *Br J of Anaesth* 2007; 85(3):407-9.
6. Groh WJ, Groh MR, et al. **Electrocardiographic abnormalities and sudden death in myotonic dystrophy type I.** *N Engl J Med* 2008; 358:2688-97.
7. Diefenbach C, Lynch J, et al. **Vecuronium for muscle relaxation in patients with dystrophica myotonica.** *Anesth Analg* 1993; 76:872-4.

8. Ogawa K, Iranami H, et al. **Severe respiratory depression after epidural morphine in a patient with myotonic dystrophy.** *Can J Anaesth* 1993; 40:968-970.
9. Baum VC, O'Flaherty J. **Anesthesia for Genetic, Metabolic, and Dysmorphic Syndromes of Childhood.** Lippencott Williams and Wilkens. 2006: 212-214.
10. Torben C. **Na⁺-K⁺ pump regulation and skeletal muscle contractility.** *Physiol Rev* 2003; 83:1269-1324.
11. Takeda T, Tohmatsu T, et al. **Postoperative continuous epidural infusion of morphine in a patient with myotonic dystrophy.** *Masui – Japanese J of Anesth* 1996; 45(11):1384-7.
12. Cope DK, Miller JN. **Local and spinal anesthesia for cesarean section in a patient with myotonic dystrophy.** *Anesth Analg* 1986; 65:687-90.
13. Harris MN. **Extradural analgesia and dystrophia myotonica.** *Anaesthesia* 1984; 39:1032-3.
14. Paterson RA, Tousignant M, et al. **Caesarian section for twins in a patient with myotonic dystrophia.** *Can Anaesth Soc J* 1985; 32:418-421.
15. Payne B, Ashizawa T. **Practical recommendation for surgery and anesthesia in myotonic dystrophy and Recommendations for surgery and anesthesia (previous version).** Myotonic Dystrophy Foundation. Aug 2006. 7 Jan 2009. <<http://www.myotonic.com/go/mdf/disease-information/medical-resources/anesthesia-guidelines>>
16. Moulds RFW, Denborough MA: **Myopathies and malignant hyperpyrexia (Correspondence)** *Br Med J* 1974; 3:520.
17. Britt BA, Kalow W: **Malignant hyperthermia: A statistical review.** *Can Soc Anaesth Soc J* 1970; 17: 293-315.
18. Kennedy F, Wolf A. **Experiments with quinine and prostigmine in treatment of myotonia and myasthenia.** *Arch Neurol Psychiatry* 1937; 37:68-74.
19. Thiel RE. **The myotonic response to suxamethonium.** *Br J Anaesth* 1967; 39:815-820.
20. Paterson IS. **Generalized myotonia following suxamethonium.** *Br J Anaesth* 1962; 34:340-342.
21. Ishizawa Y, et al. **A serious complication due to gastrointestinal malfunction in a patient with myotonic dystrophy.** *Anesth Analg* 1986; 65:1066-1068.
22. Aquilina A, Groves J. **A combined technique utilizing regional anesthesia and target-controlled sedation in a patient with myotonic dystrophy.** *Anaesthesia* 2002; 57:385.
23. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practical.
24. Harper PS. **Myotonic dystrophy.** 2nd ed. London: WB Saunders, 1989.

OCCUPATIONAL THERAPY SUGGESTIONS FOR THE MANAGEMENT OF A MYOTONIC DYSTROPHY PATIENT

Cynthia Gagnon, erg, Ph.D.

*Professeur adjoint,, École de réadaptation, Faculté de médecine et des sciences de la santé
Université de Sherbrooke, Groupe de recherche interdisciplinaire sur les maladies neuromusculaires*

GOAL OF OCCUPATIONAL THERAPY (OT)

Occupational therapy is a health profession concerned with promoting health and well-being through occupation. Occupation refers to everything that people do during the course of everyday life (CAOT Position Statement on Everyday Occupations and Health, 2003) and can relate to participation. The primary goal of occupational therapy is to enable people to participate in the occupations which give meaning and purpose to their lives ¹. Occupational therapists have a broad education that provides them with the skills and knowledge to work collaboratively with people of all ages and abilities that experience obstacles to participation. These obstacles may result from a change in function (thinking, doing, feeling) because of illness or disability, and/or barriers in the social, institutional or and physical environment (Adapted from the World Federation of Occupational Therapists, 2004).

MYOTONIC DYSTROPHY TYPE 1: CLINICAL FEATURES RELATED TO OT INTERVENTIONS

In that DM1 is a complex multisystemic disorder, only a brief description of clinical features related to OT interventions will be done as a general portrait is available elsewhere ². This portrait is related to the adult phenotype only although general recommendations could apply to all phenotypes.

DAILY ACTIVITIES

Category	Social Participation
----------	----------------------

	Meal preparation: 27.5 % reported needing human help or not carrying it out ³ .
Nutrition	Taking a meal: Taking a meal is usually adequate although dysphagia may be present. In 40 patients, 45% reported having symptoms of dysphagia. ⁴ In a radiological study, 20% had aspirations (3/15) with or without symptoms of dysphagia. ⁵ The nature of the swallowing defect in DM1 is complex, and investigations revealed abnormalities in smooth as well as in striated muscles ⁵ .

Bathing: 17% - 42% experienced problems (having difficulty, needing human help and/or using technical aids) ⁶.

Personal Care

Using toilets: 22% experienced problems (having difficulty, needing human help and/or using technical aids){Mathieu, Submitted #3826}.

Dressing: 15% experienced problems (having difficulty, needing human help and/or using technical aids) {Mathieu, Submitted #3826}.

General mobility is among the most affected area of daily activities.

Mobility

Wheelchair: One study reported that among 51 patients, 6% reported using a wheelchair.^{#5117} From a large sample (n = 200), 17.5% were using a wheelchair{Mathieu, Submitted #3826} .

Driving: More than 50% are still driving but vigilance should be kept for factors which could influence driving such as myotonia, hypersomnolence, cognitive functions and grip strength{Mathieu, Submitted #3826}.

Lower extremity strength, education, technology, support and attitude from family and friends, government and public services, fatigue and gender could partly predict disruption of participation in the mobility-related area ⁸.

Social deterioration secondary to muscular dystrophy, intelligence deterioration and reduction of initiative were first described by Thomasen in 1948. ⁹ Caughey and Myriantopoulos introduced the term "myotonic's home" because "it was possible to identify a residence by its neglected appearance, the obvious need of repairs, the unkempt yard and garden choked with overgrown grass and weeds, which provided a vivid contrast to the surrounding well-kept homes". ¹⁰

Housing

Doing major household tasks: 68% experienced problems (having difficulty, needing human help and/or using technical aids)³. Natterlund reported that 32.6% of the DM1 patients are not doing activities related to home maintenance and 25.8% do it with problems ¹¹

Maintaining the house: 50% experienced problems (having difficulty, needing human help and/or using technical aids)³

Lower extremity strength, fatigue, support and attitude of family and friends, education and income could predict disruption of participation with housing related tasks ⁸.

SOCIAL ROLES

Category

Social participation

Community Life

Getting to public buildings or commercial establishments : 24.7% experienced problems (having difficulty, needing human help and/or using technical aids)³

Work

Different studies ^{12; 13} showed that 12% to 31% of DM1 patients held a job and that 52% to 66% used to work. In 2007, a reappraisal of the DM1 population from the Saguenay-Lac-Saint-Jean region has shown that 20% are currently working, 66% used to work and 14% never worked. ¹⁴ In the same population, 44.5 % reported employment as severely restricted and caused then the highest level of dissatisfaction. ³. Many aspects of DM1 such as muscular impairment, low education, excessive daytime sleepiness, and apathy, problems with access, equipment and transportation may restrict opportunities to employment as well as leisure.

Technology, lower extremity strength, fatigue and pain could partly predict disruption of participation in the work-related area (paid and unpaid work) ⁸.

Leisure activities (sports, craft, outdoor or tourist activities) are severely restricted in 22 to 26% of DM1 patients and 24% of this population reported a high level of dissatisfaction about it³. From another study, restricted participation in leisure activities was found to be around 63%⁶.

Recreation

The following problems to pursue leisure activities were expressed by the patients: physical limitations (29% of the patients); lack of money (28%); fatigue (25%); distance (18%); activities not adapted to their condition (14%); help needed (13%); no transportation available (11%).

Technology, lower extremity strength, fatigue and pain could partly predict (R² 42%) disruption of participation in the work-related area (paid and unpaid work)⁸.

REHABILITATION CONCEPTUAL FRAMEWORK

Rehabilitation professionals are becoming increasingly aware of the importance of evaluating not only the reduction in mental and physical capabilities but also the restriction of participation that may occur in neuromuscular disorders and especially DM1. According to the International Classification of Functioning, Disability and Health (ICF) model, participation (previously called handicap) is defined as involvement in a life situation, and participation restriction is defined as problems an individual may experience in involvement in life situations¹⁵. The nature, quality and/or duration of participation may be restricted and the comparison is based on an individual without a similar health condition¹⁵. This refers to the concept of society-perceived participation as opposed to person-perceived participation¹⁶. This approach, although sometimes useful when comparing populations, can have limited utility in rehabilitation, as it tends to overlook the ability of individuals to make autonomous choices about the way they conduct their lives since the scores are based on a societal and normative perspective of what constitutes optimal social participation. On the other hand, the Disability Creation Process model had operationalized social participation via the concept of life habit, which is defined as “a daily activity or social role valued by the person or his/her sociocultural context according to his/her characteristics (age, sex, sociocultural identity, etc.) and which ensures his/her survival and well-being in society throughout his/her life”¹⁷. This definition is closer to person-perceived participation, the importance of which has been recognized, especially in chronic conditions where readjustment of life goals and expectations is part of the rehabilitation process¹⁸. Among several issues, the various clinical phenotypes present in DM1 should also be taking into consideration upon establishing a portrait of participation. Clinically, patients with the mild and adult phenotypes exhibit clearly different pictures and require distinct types of rehabilitation and community follow-ups. Satisfaction related to participation is increasingly gaining attention from literature as it has been associated more strongly with subjective quality of life than the performance component¹⁹. The individual’s feelings about or appraisals of his/her participation has thus been suggested as a promising approach in quality of life assessment as well as in healthcare and community services planning and delivery²⁰. Tailoring our intervention towards the areas demonstrating less satisfaction may improve quality of life more than solely focussing on traditional rehabilitation areas such as activities of daily living, which only predict a small proportion of quality of life among a neuromuscular population¹¹.

OT EVALUATION FRAMEWORK

Occupational therapists evaluate client's occupational performance (social participation), performance components (personal factors), and performance contexts (environmental factors) ²¹. OT evaluation should define occupational problems of concern to the client ²¹.

A) Evaluation Of Occupational Performance (Social Participation)

Several interview procedures are available for the assessment of social participation. A few instruments were recently designed to assess participation from the individual's perspective, such as the Impact on Participation and Autonomy Questionnaire (IPA)²², the Late Life Function and Disability Instrument (Late-Life FDI)²³ and the Assessment of Life Habits (LIFE-H) ²⁴. The Canadian Occupational Performance Measure is also often used in clinical practice. Only the LIFE-H has defined metrological properties with a DM1 population (reliability between evaluation and between assessors). The LIFE-H documents the manner in which people carry out activities of daily living and social roles. It is a generic tool that takes into consideration the individual's subjective perception regarding the disruption in the accomplishment of a specific life habit such as preparing a meal or doing volunteer work ²⁵. Although based on a different conceptual model, the LIFE-H ²⁴ is among the instruments that capture most of the items of the ICF participation dimension when compared with several participation measures ²⁶. The LIFE-H demonstrated adequate validity ²⁷. The LIFE-H demonstrates high to moderate test-retest and inter-rater reliability when used with a DM1 population ²⁸.

B) Evaluation of Performance Components (personal factors)

DM1 being a progressive disorder, evaluation of performance components should be evaluated within a functional state of mind and strongly related to occupational performance priority area identified by the person with DM1.

Evaluation of sensory and neuromuscular performance components

Decreased muscle strength is the hallmark feature of all neuromuscular disorders. However, in DM1, other symptoms often precede the decrease of muscle strength. In DM1, slowly progressive muscle weakness is present with a pattern of distal to proximal involvement. In addition, facial weakness, atrophy, ptosis, and weakness of the sterno-mastoid and neck flexor muscles, long finger flexors and foot dorsiflexor muscles are the earlier muscular features of DM1 ²⁹. Myotonia is a frequent presenting symptom (36 -75.9%) ^{29,30}. Upper extremity range of motion will often be affected in relation to decreased muscle strength but no treatment has been shown to be effective. Again, endurance, gross coordination, postural control, fine coordination and dexterity are affected but no treatment has been shown effective. Reflexes are also preserved in DM1. Sensory testing is rarely necessary as myotonic dystrophy has not been associated with any sensory involvement apart from cold sensitivity where counselling can be given ²⁹. Soft tissue evaluation is rarely of concern.

Evaluation of perception and cognition

Evaluation of perception and cognition is usually done by a neuropsychologist. The OT can provide a unique contribution in evaluating the effect of cognitive-perceptual impairments on participation in daily activities and social roles ²¹. In DM1, special attention should be devoted to fatigue, hypersomnolence, executive function and apathy.

Evaluation of psychosocial skills and psychological components

Evaluation of psychosocial skills and psychological components includes the ability to interact in society and to process emotions ²¹. It is necessary to gain knowledge about these components in order to help clients maximize function. It includes psychological skills (values, interests and self-concept), social skills (role performance, social conduct, interpersonal skills, and self-expression), and self-management (coping skills, time management and self-control). In the context of DM1, knowledge about these concepts should be gained in order to interpret social participation in relation to well-known features of DM1 which could be present such as avoidant personality traits ³¹, diminished affect and few interests.

C) Evaluation of Performance Contexts (environmental factors)

DM1 being a progressive disorder, the role of environmental factors and especially the implementation of community services (home services, meal preparation, nursing at home, budget management, etc.) should not be underscored as these are most probably effective measures for alleviating some of the consequences and burden imposed by the disease ³. As a group, DM1 patients show poor academic achievement, high unemployment, low family income, and high reliance on social assistance compared with the general reference population thus confirming a socioeconomic disadvantage ^{13; 14}. Using socio-spatial modelling of a Saguenay-Lac-Saint-Jean urban area, DM1 was found to be six times more prevalent in disadvantaged neighbourhoods compared with advantaged ones ³². Such patterns of residential segregation impose a double burden on deprived people: they not only have to struggle with many problems arising from their own lack of income but also they have to live with the social effects of residing in a neighborhood where the majority of their neighbours are also poor ³³. Such a phenomenon can play a role in the perpetuation of poverty in DM1 and can contribute to social exclusion and isolation ³³. Residents of extremely poor neighborhoods often report the absence of regular sources of social support, including a marital partner and close friends. Also, people who receive less social and emotional support from others are more likely to experience less well-being, more depression, and higher levels of disability from chronic diseases ³⁴. The perception of negative support and attitude of family and friends was an explanatory factor for level of participation in work, leisure and mobility. The perception of obstacles related to access and use of technology and government services is also related to level of participation ⁸.

OT INTERVENTION AREA

Recommendations are usually based on clinical practice because there are very few studies in occupational therapy. Based on the findings from qualitative studies, a recent review of the literature ¹ recommended a client-centered approach that includes the following aspects: educating the patient about the disease because education plays an important role in his or her understanding of the need to implement adaptive strategies (Jönsson et al., 1999; Nätterlund & Ahlström, 1999; Young, 1989); evaluating the patient's perception of his or her life history, personal values, goals, and problems (Jönsson et al., 1999); informing the patient about the adaptive strategies available; and identifying the patient's adaptive strategies, which can be used in occupational therapy to empower the patient to make changes in his or her occupational performance (Jönsson et al., 1999). Occupational therapy interventions had to include training of activities of daily living, skills training (fine motor skills), advice and instruction in the use of assistive devices, provision of splints and slings, counselling on energy conservation strategies, educating patients, families, and caregivers or a combination of the above.

A) Occupational performance treatment

The purpose of OT treatment is to help clients learn or relearn occupational performance that they need to live as independently as possible ²¹. Treatment strategy will be mostly geared toward compensation and education. For the compensation approach, three options can be explored with the client: 1) Alter the task method; 2) Prescribe assistive devices or; 3) Adapt the task environment ²¹. Education can be a real challenge with DM1 in relation to cognitive functions. From a large study, the highest level of dissatisfaction is related to participation in work and leisure as long as engaging in physical fitness activities (40 – 25 % are highly dissatisfied).

Personal Care: Specific problems that are often encountered may relate to upper limb function (such as picking up a cup, washing hair, wiping oneself after going to the toilet, doing up buttons), to lower limb function (such as walking to the toilet, standing in the shower) or both (such as putting on trousers, getting into or out of a bath). Multisystemic complications such as diarrhea, anal incontinence and dysphagia, may add to these - so considering ameliorating them can assist in personal care. These aspects are usually approached in a problem-oriented way by suggesting adaptive techniques, specialized equipment and/or community services ³⁵.

Mobility: Some patients have an early and severe involvement of the knee extensors, complain of multiple falls and are rapidly wheelchair dependent. Patients who require wheelchairs will often have moderate to severe proximal and truncal weakness. Therefore, when the wheelchair is prescribed, attention must be paid to stability and posture while seated, the ability to stand from the chair and the ability to transfer ³⁵. The need of an electric wheelchair or a four-wheel scooter can also be explored, although their use is less frequent.

Work: No specific treatment option has been explored.

Leisure: No specific treatment option has been explored.

B) Performance components treatment

Muscle strength: Only strengthening of the hand muscle has been tried in OT in one study with five subjects that is insufficient on which to base clinical guidelines ³⁶. A recent Cochrane Collaboration review came to the conclusion that in myotonic dystrophy moderate-intensity strength training appears not to do harm but there is insufficient evidence to establish that it offers benefit ³⁷.

Myotonia : A recent Cochrane Collaboration review concluded that due to insufficient good quality data and lack of randomised studies, it is impossible to determine whether drug treatment is safe and effective in the treatment of myotonia ³⁸.

Dysphagia: Conclusion of a Cochrane Review reported that no trial has adequately evaluated treatments in the management of dysphagia for chronic muscle diseases.³⁹ They reported that the main treatment options are mostly based on stroke population and include dietary manipulation, adoption of safe swallowing techniques, surgical intervention and enteral feeding. No single universally effective treatment for dysphagia in DM1 has been described. This probably reflects the many different mechanisms underlying dysphagia in DM1 ⁴⁰. Strategies to facilitate pharyngeal functions in DM1 patients include: 1) strict adherence to reflux precautions; 2) education of friends and family members in the performance of the Heimlich manoeuvre; 3) dietary counselling emphasizing maximum nutritional density within a restricted range of consistencies

(identified as safest, most effective); 4) strategies to facilitate pharyngeal clearing, i.e., careful chewing and bolus preparation to a liquid consistency, repeat swallows, alternating thin with thick consistencies (if possible without aspiration); and 5) airway protection strategies when aspiration risk is elevated ⁴¹.

C) Performance context environment

Provision of education and information has been stressed as a mean of assisting patients and families to cope with neuromuscular diseases ⁴². Supportive relationships, whether in the form of practical help, emotional support, or provision of information, may facilitate health-promoting behaviours in patients with DM1 and should be encouraged as such ¹⁴. At the community level, designing facilities to promote social interaction may reduce social isolation in patients with DM1. In this respect, belonging to a lay association has improved the level of well-being in patients with DM1 ⁴³.

OT INTERVENTION EFFICACY

Cup & al, (2008)¹ performed an extensive review of the literature to assess whether there is evidence for occupational therapy for patients with neuromuscular diseases. The initial search strategy resulted in a total of 3,534 citations but after screening the majority of the studies (3,528) they did not meet the predefined criteria. Six full-text articles were retrieved and from them, only one was concerned with myotonic dystrophy type 1 ¹. The objective was to evaluate an individualized hand training program with silicone-based putty in five patients with DM1. There was improvement in self-rated performance and satisfaction with performance using the Canadian Occupational Performance Measure ³⁶, as well as muscle strength increase and fine motor control but not grip force and pinch strength. This study provides some indications for the efficacy of a hand-training program in muscle disease with at least 3 of 5 manual muscle tests in the wrist and hand. The intervention was a 12-week, 3 times a week, 45-minute regimen with silicone-based putty and a stretching program.

EVALUATION OF THE NEED FOR REFERRAL TO OCCUPATIONAL THERAPY

Perceived Limitations in Activities and Needs Questionnaire (PLAN-Q) ^{44, 45}. It is a screening tool to select those patients with NMD that need referral for a one-time consultation by OT, PT and ST. The PLAN-Q only screens patient-opinions and the results demonstrated that the results were not reliable from one time to another. Indeed, patients change their need for referral within a two weeks period.

REFERENCES:

1. Cup EHC, Sturkenboom IHW, Pieterse AJ, et al. **The evidence for occupational therapy for adults with neuromuscular diseases: a systematic review.** *OTJR: Occupation, Participation & Health* 2008;28:12-8.
2. Gagnon C, Noreau L, Moxley RT, et al. **Towards an integrative approach to the management of myotonic dystrophy type 1.** *J Neurol Neurosurg Psychiatry* 2007;78:800-6.
3. Gagnon C, Mathieu J, Noreau L. **Life habits in myotonic dystrophy type 1.** *J Rehabil Med* 2007;39:560-6.
4. Ronnblom A, Forsberg H, Danielsson A. **Gastrointestinal symptoms in myotonic dystrophy.** *Scand J Gastroenterol* 1996;31:654-7.
5. Marcon M, Briani C, Ermani M, et al. **Positive correlation of CTG expansion and pharyngoesophageal alterations in myotonic dystrophy patients.** *Ital J Neurol Sci* 1998;19:75-80.
6. Natterlund B, Ahlstrom G. **Problem-focused coping and satisfaction with activities of daily living in individuals with muscular dystrophy and postpolio syndrome.** *Scand J Caring Sci* 1999;13:26-32.
7. Nitz JC, Burns YR, Jackson RV. **Sit-to-stand and walking ability in patients with neuromuscular conditions.** *Physiotherapy* 1997;83:223-7.
8. Gagnon C, Mathieu J, Jean S, et al. **Predictors of disrupted social participation in myotonic dystrophy type 1.** *Arch Phys Med Rehabil* 2008;89:1246-55.
9. Thomasen E. **Myotonia:** Aarhus: Universitetsforlaget; 1948.
10. Caughey JE, Myriantopoulos NC. **Dystrophia Myotonica and Related Disorders:** Springfield. Ill: Charles C Thomas; 1963.
11. Natterlund B, Ahlstrom G. **Activities of daily living and quality of life in persons with muscular dystrophy.** *J Rehabil Med* 2001;33:206-11.
12. Andries F, Wevers CWJ, Wintzen AR, et al. **Vocational perspectives and neuromuscular disorders.** *International Journal of Rehabilitation Research* 1997;20:255-73.
13. Perron M, Veillette S, Mathieu J. **La dystrophie myotonique: I. Caracteristiques socio-economiques et residentiellles des malades.** *Can J Neurol Sci* 1989;16:109-13.
14. Laberge L, Veillette S, Mathieu J, Auclair J, Perron M. **The correlation of CTG repeat length with material and social deprivation in myotonic dystrophy.** *Clin Genet* 2007;71:59-66.
15. WHO. **International Classification of Functioning, Disability and Health** : ICF. Geneva: WHO; 2001.
16. Cardol M, Brandsma JW, de Groot IJ, van den Bos GA, de Haan RJ, de Jong BA. **Handicap questionnaires: what do they assess?** *Disabil Rehabil* 1999;21:97-105.

17. Fougeyrollas P, Cloutier R, Bergeron H, Côté J, St-Michel G. **The Quebec classification: Disability Creation Process. Lac-St-Charles, Quebec:** International Network on the Disability Creation Process; 1999.
18. Sivaraman Nair KP. **Life goals: the concept and its relevance to rehabilitation.** *Clin Rehabil* 2003;17:192-202.
19. Levasseur M, Desrosiers J, Noreau L. **Is social participation associated with quality of life of older adults with physical disabilities?** *Disabil Rehabil* 2004;26:1206-13.
20. Johnston M, Nissim EN, Wood K, Hwang K, Tulsy D. **Objective and subjective handicap following spinal cord injury: interrelationships and predictors.** *J Spinal Cord Med* 2002;25:11-22.
21. Neistadt ME, Crepeau Blesedell E. **Occupational Therapy.** 9th ed. Philadelphia: Lippincott; 1998.
22. Cardol M, de Haan RJ, de Jong BA, van den Bos GA, de Groot IJ. **Psychometric properties of the Impact on Participation and Autonomy Questionnaire The development of a handicap assessment questionnaire: the Impact on Participation and Autonomy (IPA).** *Arch Phys Med Rehabil* 2001;82:210-6.
23. Jette AM, Haley SM, Coster WJ, et al. **Late life function and disability instrument: I. Development and evaluation of the disability component.** *J Gerontol A Biol Sci Med Sci* 2002;57:M209-16.
24. Fougeyrollas P, Noreau L. **Life Habits Measure - General Short Form LIFE-H 3.1).** Lac St-Charles, Québec, Canada: INDCP; 2003.
25. Noreau L, Fougeyrollas P, Vincent C. **The LIFE-H : Assessment of the quality of social participation.** *Technology and Disability* 2002;14:113-8.
26. Dijkers MP, Whiteneck G, El-Jaroudi R. **Measures of social outcomes in disability research.** *Arch Phys Med Rehabil* 2000;81:S63-80.
27. Fougeyrollas P, Noreau L, Bergeron H, Cloutier R, Dion SA, St-Michel G. **Social consequences of long term impairments and disabilities: conceptual approach and assessment of handicap.** *Int J Rehabil Res* 1998;21:127-41.
28. Gagnon C, Mathieu J, Noreau L. **Measurement of participation in myotonic dystrophy: reliability of the LIFE-H.** *Neuromuscul Disord* 2006;16:262-8.
29. Harper P. **Myotonic dystrophy.** 3rd ed. London: WB Saunders; 2001.
30. Mathieu J, De Braekeleer M, Prévost C, Boily C. **Myotonic dystrophy: clinical assessment of muscular disability in an isolated population with presumed homogeneous mutation.** *Neurology* 1992;42:203-8.
31. Meola G, Sansone V, Perani D, et al. **Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2).** *Neuromuscul Disord* 2003;13:813-21.

32. Veillette S, Perron M, Mathieu J, Prévost C, Hébert G. **Socio-cultural factors influencing the spread of myotonic dystrophy in the Saguenay-Lac-Saint-Jean region of the province of Quebec (Canada).** In: Genetics, Demography and Health, Minority Populations. London: The Macmillan Press Ltd; 1992:83-101.
33. Wilson WJ. **The truly disadvantaged.** Chicago: University of Chicago Press; 1987.
34. Wilkinson R, Marmot M. **Social determinants of health: the solid facts.** Geneva: World Health Organization; 1998.
35. Phillips MF, Mathieu J. **Physical disability in myotonic dystrophy.** In: Harper P, van Engelen B, Eymard B, Wilcox DE, eds. Myotonic Dystrophy: Present Management, Future Therapy. New York: Oxford University Press; 2004.
36. Aldehag AS, Jonsson H, Ansved T. **Effects of a hand training programme in five patients with myotonic dystrophy type 1.** *Occup Ther Int* 2005;12:14-27.
37. van der Kooi EL, Lindeman E, Riphagen I. **Strength training and aerobic exercise training for muscle disease.** *Cochrane Database Syst Rev* 2005:CD003907.
38. Trip J, Drost G, van Engelen BGM, Faber CG. **Drug treatment for myotonia.** *Cochrane Database of Systematic Reviews* 2006.
39. Hill M, Hughes T, Milford C. **Treatment for swallowing difficulties (dysphagia) in chronic muscle disease.** *Cochrane Database Syst Rev* 2004:CD004303.
40. van Engelen BGM, Brunner HG. **Gastrointestinal dysfunction in myotonic dystrophy.** In: **Myotonic Dystrophy: Present Management, Future Therapy.** New York: Oxford University Press; 2004.
41. Leonard RJ, Kendall KA, Johnson R, McKenzie S. **Swallowing in myotonic muscular dystrophy: a videofluoroscopic study.** *Arch Phys Med Rehabil* 2001;82:979-85.
42. Sigford BJ, Lanham RA, Jr. **Cognitive, psychosocial, and educational issues in neuromuscular disease.** *Physical Medicine and Rehabilitation Clinics of North America* 1998;9:249-70.
43. van Haastregt JC, de Witte LP, Terpstra SJ, Diederiks JP, van der Horst FG, de Geus CA. **Membership of a patients' association and well-being. A study into the relationship between membership of a patients' association, fellow-patient contact, information received, and psychosocial well-being of people with a neuromuscular disease.** *Patient Educ Couns* 1994;24:135-48.
44. Pieterse AJ, Cup EH, Knuijt S, et al. **Development of a tool to guide referral of patients with neuromuscular disorders to allied health services. Part one.** *Disabil Rehabil* 2008;30:855-62.
45. Pieterse AJ, Cup EH, Knuijt S, et al. **Development of a tool to guide referral of patients with neuromuscular disorders to allied health services. Part two.** *Disabil Rehabil* 2008;30:863-70.

ROLE OF PHYSICAL THERAPY IN THE ASSESSMENT AND MANAGEMENT OF INDIVIDUALS WITH MYOTONIC DYSTROPHY

Shree Pandya, PT, DPT, MS, Katy Eichinger, PT, DPT, NCS

Department of Neurology, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Physical therapists are healthcare professionals who hold a post-baccalaureate graduate degree (MPT, DPT) from a college or university. They also may be certified specialists in an area of expertise, such as pediatrics (PCS), geriatrics (GCS), neurologic (NCS), cardiopulmonary (CCS) or orthopedic physical therapy (OCS). Physical therapists practice in a variety of settings including hospitals and nursing homes, outpatient clinics, home health care, and schools.¹ Most individuals with myotonic dystrophy (DM) will probably first encounter a physical therapist in the multidisciplinary clinic where they receive care for their muscular dystrophy related problems. In this setting, the physical therapist plays a consultative role providing evaluation, education, instructions and recommendations based on individual patient needs. They may also act as a liaison and help coordinate care with school or community based therapists who may be providing direct care as necessary. Some common areas that will be addressed by physical therapists are related to exercise/activities, pain and/or fatigue management, orthotics/braces and assistive/adaptive equipment. The goals of physical therapy management are to maximize functional ability, delay secondary complications and improve quality of life for individuals with DM.

Myotonic dystrophy is the most common form of muscular dystrophy in adults. It is an autosomal dominant disorder, which means that a person carrying the gene has a 50-50 chance of passing it on to a child. It is a multi systemic progressive disorder that affects the muscular, respiratory, cardiac, nervous and endocrine systems. Currently 2 variants of DM are recognized – DM1 which arises from a defect on chromosome 19 and DM2 which results from a defect on chromosome 3.² DM1 was first described in the early 1900's and hence is a much better studied entity while DM2 was only described in the past decade and hence there is a lot to learn regarding this phenotype.³ DM1 and DM2 share many common features, but there are also significant differences. Individuals with DM1 can present with symptoms at different ages; at birth (congenital), during childhood (pediatric), during adulthood, or later in life and thus four clinical phenotypes are described in the literature. Congenital phenotypes have not been described in DM2 yet and most patients present in adulthood. Weakness and wasting (atrophy) are prominent features in DM1 whereas muscle pain and myotonia are prominent in DM2. Individuals with DM1 primarily exhibit facial and distal limb weakness whereas individuals with DM2 exhibit proximal weakness. Muscle related problems - weakness, wasting and functional problems - are very often the concerns that lead individuals to seek attention and help from physical therapists. However, DM is a multi systemic disorder and hence it is essential to understand all the systemic complaints and help manage the muscle related symptoms in the overall context of concerns for an individual.^{2,3,4} Congenital and childhood onset DM1 have unique features, and therefore, we have chosen to address the physical therapy management of these conditions separately later in this section.

PHYSICAL THERAPY ASSESSMENT

During an initial evaluation a physical therapist will obtain a detailed history of the symptoms and/or problems, how they have changed over time, factors that make them better or worse and how they affect the daily activities and lives of the affected individual. Information regarding the person's occupation, lifestyle, leisure activities, and their role in the family unit is essential to the evaluation process.

As stated before, myotonic dystrophy is a systemic condition. It is therefore important for the physical therapist to perform a systems review according to the Guide to Physical Therapy⁵ including review of cognition/communication, musculoskeletal system, neuromuscular system, cardiovascular/pulmonary system, and integumentary/skin system.

Individuals with DM can have difficulties in both, cognition and communication.^{2,3,4} Symptoms include, somnolence, apathy, specific personality traits, deficit in executive functions, depression and fatigue. These cognitive deficits may impact a person's ability to comply with recommendations and are important to take into consideration when establishing a plan of care or management program. Communication difficulties can arise as a result of weakness of the facial muscles as well as the presence of myotonia in the jaw and tongue. This not only impacts proper communication between patients and care providers, but also has an effect on social communication leading to some of the psychosocial issues mentioned previously.

The neuromuscular and musculoskeletal systems are often the focus of the examination, as weakness and resulting functional difficulties are often the most disabling features of the disorder. The most common pattern of muscle involvement in DM1 includes the facial (masseter and temporalis) muscles, neck muscles (sternocleidomastoids), long finger flexors of the hand and ankle dorsiflexors and/or plantarflexors⁴. Muscle involvement usually begins in the teens, twenties or thirties and is slowly progressive. The weakness progresses from the distal to proximal muscles. Muscular weakness in congenital myotonic dystrophy presents during the neonatal period with generalized hypotonia. In DM2 the muscular involvement is predominantly proximal and also slowly progressive, beginning in the 'mid-adult' life². It is critical that physical therapists are knowledgeable in manual muscle testing for all muscles, as the pattern of weakness can be predictive of both the disease itself as well as mobility concerns that may arise. Strength can also be measured more objectively by hand-held dynamometers as well as expensive systems such as a Quantitative Muscle Assessment (QMA) system. QMA systems are often utilized in the research setting. Normative data for both of these methods have been established in the pediatric as well as adult populations.⁶⁻¹⁰

Myotonia is the other musculoskeletal manifestation of myotonic dystrophy. Myotonia is the inability to relax a muscle after a forceful contraction. Individuals with myotonia affecting the hand musculature often report difficulty releasing their grip after a vigorous handshake which creates an embarrassing social situation. Complaints of myotonia are also reported in the jaw and tongue leading to difficulties with speech, swallowing and chewing^{2,3,4}. Myotonia in the leg muscles may lead to difficulty with movements like climbing stairs, running etc. Symptoms of myotonia may also be present in other parts of the body. Often patients will report that their myotonia symptoms are worse in cooler temperatures. Myotonia has been managed with medications such as Mexilitene.¹¹

DM1 is a slowly progressive disease and as strength decreases, individuals may become adept in substituting less affected muscles to perform movement. Hence it is important to assess simple functional activities, including the ability to get up from a chair, ambulate and climb stairs. These functional tasks can also be timed and used as outcome measures to document benefits of interventions or to monitor the progression of the disease. Assessment of hand function, including grip and pinch strength, is also important in this population. Detailed information related to hand function testing and treatment is provided in the section on occupational therapy.

The cardiovascular system can be compromised by the presence of cardiac arrhythmias and conduction defects as well as involvement of the cardiac muscle itself². Insufficiency of the respiratory system may be a result of both myotonia and weakness in the muscles that control respiration.² Respiratory muscle involvement often leads to a reduced vital capacity later in the disease. Individuals with DM1 who have reduced respiratory function are often at more risk for pulmonary complications such as pneumonia⁴. When making exercise recommendations for a home program, it is essential to educate individuals about how to monitor their cardio respiratory responses with simple tools like pulse monitors, Borg scale, etc. It is essential that individuals report their responses to exercise to the person overseeing and/or monitoring the home program. Depending on the progression of their disease, individuals with myotonic dystrophy may have limited exercise tolerance and will need to be monitored carefully.

The integumentary system is not usually involved as the sensory system is spared in myotonic dystrophy. However, if poor mobility is demonstrated and bony prominences are exposed secondary to muscle wasting, the integumentary system may require attention.

Pain and Fatigue are common complaints among individuals with DM1 and DM2¹²⁻¹⁶. In a study by Jensen et al.¹⁴, complaints of pain were reported most commonly in the low back and legs. More than 60% of patients with neuromuscular disorders complain of fatigue. Fatigue can have a major impact on the employment status of patients with DM. Therefore, pain and fatigue should be assessed and addressed in the treatment plan as necessary.

Lastly, it should also be mentioned that many of these individuals have gastrointestinal manifestations that may be present anywhere along the digestive tract. Symptoms reported span the spectrum of dysphasia and heartburn to abdominal pain and changes in bowel function.^{17, 18} Involvement of the GI system may be very disabling to the individual and again, may impact the person's ability to participate in exercise programs.

PHYSICAL THERAPY MANAGEMENT

Exercise

Individuals with myotonic dystrophy often have questions about exercise. Exercise, including range of motion, strengthening and cardiovascular (aerobic) exercise, is important for the management of the musculoskeletal and cardiorespiratory manifestations of myotonic dystrophy. Range of motion exercises are important in maintaining joint function and muscular balance and may play a role in reducing pain that is caused by muscular imbalance or tightness. As muscles atrophy resulting in weakness, gravitational pull may limit a person's ability to move a body part through its entire range of motion and therefore it may be important to change the position of the body part to minimize the pull of gravity. For example, people may have difficulty raising their arms up in sitting or standing position, i.e. performing shoulder abduction in an antigravity position, but may have the ability to perform this movement when lying down in a supine position where gravity is eliminated. Individuals may also participate in range of motion exercises that are more dynamic in nature. This includes Yoga and Pilates based activities that can either be done individually or in a class setting. Education regarding range of motion exercise is essential to the management of the symptoms related to the musculoskeletal system.

Weakness occurs as part of the disease process; however, weakness may also develop secondary to disuse. Strengthening exercises may help to minimize the disuse weakness; but there is also a concern that too much exercise or inappropriate exercise may hasten disease progression, and hence finding the right balance for each individual is important. The evidence available regarding the role of exercise in myotonic dystrophy is limited. In a Cochrane review published in 2010.¹⁹, the authors examined the safety and efficacy of strength and aerobic training in neuromuscular diseases. They identified a total of 36 studies; however, there were only three randomized controlled trials that fulfilled their inclusion criteria. Based on these studies the authors concluded that strengthening exercises at a moderate intensity did not worsen the disease progression in persons with myotonic dystrophy.^{19, 20} Many of the studies involving individuals with myotonic dystrophy were excluded from the review because they lacked randomization. Many of these studies also grouped different neuromuscular diseases together, making it difficult to draw conclusions about the individual's response to exercise in a specific disease like DM. Disorders like DM are difficult to study as they are rare diseases and it is difficult to enroll enough patients to carry out a well powered randomized control trial. Other problems cited with the reviewed studies included lack of detailed descriptions of the exact exercise protocols used and short durations of the exercise trials. Orngreen and colleagues studied the benefits of aerobic exercise using bicycle ergo meters in patients with DM1 and concluded that aerobic exercise is safe and improves fitness in patients with DM1.²¹ Cup et al²² chose to look at the evidence related to exercise in individuals with neuromuscular diseases with expanded criteria than those in the Cochrane reviews. Based on their analysis of the studies they concluded that the evidence suggests that strengthening exercises in combination with aerobic exercises are "likely to be effective". Given the evidence from the 2 major reviews that exercise may be effective and that moderate exercise does not worsen disease progression, some general recommendations regarding exercise can be made to guide clinicians and individuals with myotonic dystrophy.

Depending on the activity level of the individuals, they may benefit from a strengthening program. Individuals who lead an active lifestyle may not have much disuse weakness, and further activity may be fatiguing to them. However, others who lead a more sedentary lifestyle may benefit from a

strengthening program. Strengthening exercise can be accomplished in several ways with resistance provided by gravity, water – in a pool - or equipment such as elastic bands, free weights and machines. Yoga and Pilates types of exercises may also be recommended as part of a strengthening program, but there are no studies reported that have examined the effects of these specific interventions in patients with DM. It is essential that individuals with myotonic dystrophy work with providers knowledgeable about their condition; have proper baseline evaluation and appropriate follow-up to monitor and modify the program as necessary.

Cardiovascular exercise performed at a low to moderate intensity has been found to be safe in people with myotonic dystrophy. Cup et al.²² also concluded that there was “indication of effectiveness” for aerobic exercises in individuals with muscle disorders. However, because of the cardiac involvement that can occur in persons with myotonic dystrophy, it is essential that individuals have a physical, appropriate cardiac evaluations and clearance from their primary care physicians prior to initiating an aerobic exercise program.

Current recommendations from the U.S Department of Health and Human Services (HHS) suggest that for all individuals, some activity is better than none and that the health benefits of physical activity far outweigh the risks.²³ They recommend that children, adolescents, adults (ages 18-64) and older adults follow the appropriate guidelines to the best of their ability. Individuals with chronic conditions perform as much activity and/or exercise as their condition allows. These include about 2 hours and 30 minutes a week of moderate intensity exercise. Aerobic exercise should be performed in episodes of at least 10 minutes preferably spread throughout the week. Muscle strengthening activities that involve all major muscle groups should be performed at least 2-3 days a week.

Examples of moderate intensity activities include – walking briskly, biking on level ground or on a stationary bicycle, ballroom and line dancing, general gardening, household activities, canoeing, using hand cycles, using a manual wheelchair and water aerobics. Moderate exercises are activities that you can perform while still continuing a conversation –without having to stop to catch your breath.

Pain

A wide variety of methods have been used in the treatment of pain in individuals with myotonic dystrophy. The use of non-steroidal anti-inflammatory medications or acetaminophen, exercise (strengthening and ROM), and heat are the most common therapies used to manage pain.¹⁶ Individuals should consult their physician for recommendations regarding the use of medication for pain relief.

Fatigue

Currently there are no reports of specific interventions and their impact on management of fatigue in patients with DM. Interventions may need to be individualized based on specific factors contributing to the complaint of fatigue.

Orthotics

Lower extremity weakness can affect a person's ability to walk safely, especially on uneven surfaces. Ankle dorsiflexion weakness often leads to a foot drop and decreased foot clearance during the swing phase of gait. Some individuals may compensate for the ankle dorsiflexion weakness by using a steppage gait pattern, i.e. lifting their knees higher to help the foot clear the ground. The use of ankle-foot-orthotics can help to correct the foot drop; however, care must be taken in prescribing an AFO. Several factors may play a role in the effectiveness of orthotic use in the lower extremities. The additional weight that may be added to the lower extremity by a brace can significantly alter the person's ability to ambulate, and hence it is important that the orthotics are made of the lightest materials available. It is also important to consider the person's ability to don and doff the orthotic devices, especially in the presence of hand weakness and decreased hand function. Orthotic fit is often difficult because people with myotonic dystrophy have muscular wasting, and bony landmarks often become more prominent and susceptible to skin irritation and breakdown. Comfort and satisfaction are important in promoting the use of the prescribed device. Compliance suffers if the prescribed orthotic device is uncomfortable or too difficult for the client to get on and off independently. Furthermore, there has been very limited research on the effect of orthotic use on energy expenditure during walking and is definitely an area that needs further investigation to prescribe appropriate orthotics to this patient population.²⁴ In cases where the neck muscles are also affected, neck braces may also be beneficial. Many of these braces are off the shelf and can be fit by an orthotist.

Assistive Devices/Adaptive Equipment

Individuals with myotonic dystrophy are at a higher risk for falls. Decreased visual acuity, lower extremity weakness and depression can play a role in increasing the risk for stumbles and falls.²⁵ The use of canes, walkers, wheelchairs, and powered mobility devices can be used to allow a person to continue to be safe and independent in mobility. Adaptive equipment, such as long handled sponges, foam buildups on silverware and pens, and button hooks can make performing bathing and dressing easier and allow individuals to be more independent in caring for themselves. When assessing for adaptive equipment, a referral to an occupational therapist may also be beneficial.

Children with Myotonic Dystrophy

Even though DM1 is considered the most common of the adult muscular dystrophies, congenital (present at birth) and childhood presentations are recognized. Congenital myotonic dystrophy tends to be more severe than the childhood form and is often associated with hypotonia, respiratory insufficiency and feeding problems.^{4, 26} When symptoms arise during the childhood years, the progression is similar to that in adult onset myotonic dystrophy, however since the symptoms start earlier, they may be more severe later in life.² Cognitive impairment is also present in these phenotypes, with the involvement being more severe in the congenital form.^{27, 28} The need for physical therapy services can be highly variable and individualized based on the type and severity of the symptoms. The areas addressed by physical therapists will be the same as in the adult population, including recommendations regarding exercise, orthotics, and adaptive equipment. Additionally, the child will be developing motor skills, and there may be a need for short episodes of intensive hands on therapy to facilitate motor development and attainment of motor milestones. Hands on physical therapy services can be provided in several different settings including home, daycare, school, playground and clinic depending on the goals of the therapy session. In addition to typical interventions such as range of motion and strengthening exercises,

practice of activities of daily living, motor skill development, therapy may include aquatic therapy or hippotherapy - the utilization of equine movement.

Aquatic therapy uses the physical properties of water to perform exercise. The buoyancy provides support and facilitates movements. The viscosity or resistive properties of the water allow for strengthening of the postural and limb muscles. These qualities of the aquatic environment have been shown to be beneficial in improving functional mobility of children with mobility limitations.²⁹

³⁰ Hippotherapy is another treatment strategy in which the movement of a horse is used to address impairments and functional limitations in people with neuromuscular dysfunction. Hippotherapy has been shown to improve upright posture, and balance therefore positively impacting gross motor function and walking ability in children with developmental delay.^{31, 32}

There are no reports of any studies that have looked specifically at using aquatherapy or hippotherapy in children with myotonic dystrophy. It is difficult to document the specific impact of these interventions versus the natural gains that occur with development since there are very few appropriately controlled longitudinal case studies reported in the literature. Hence further research is needed to determine the appropriate type, frequency, intensity, and duration of physical therapy services in children with myotonic dystrophy.

Currently, the frequency and intensity of the hands on services vary depending on the individual child's needs. These may be followed by more limited episodes where the physical therapist will play a more consultative role, monitoring the child's development and working with the family to set up a home based program of daily activities and exercises to maximize the child's functional abilities. Within the school system, the physical therapist will work with the school team – classroom teachers, gym teachers, school nurse, and counselors etc educating them regarding the condition and the appropriate activities and supports within the school environment to assure safety, mobility and maximize the learning opportunities.

In this section we have attempted to meet the needs of therapists who may rarely encounter patients with DM and hence may not have much knowledge of the condition. We hope that the information and the references we have provided will help them get started in meeting the needs of their patients. For individuals with myotonic dystrophy who may be reading this section – we hope we have given you enough information about the role of physical therapists in your care, so that you are better prepared to partner with them in meeting your needs. We would appreciate any feedback from all readers about how we might make this section more responsive to their needs. We appreciate the opportunity and support provided by the Myotonic Dystrophy Foundation to share this information with you.

REFERENCES

1. American Physical Therapy Association. http://www.apta.org/AM/Template.cfm?Section=About_Physical_Therapy&TEMPLATE=/CM/HTMLDisplay.cfm&CONTENTID=33205. Available at: 2nd2009.
2. Turner C, Hilton-Jones D. **The myotonic dystrophies: diagnosis and management.** *J Neurol Neurosurg Psychiatry* 2010;81:358-367.
3. Udd B, Meola G, Krahe R et al. **Myotonic dystrophy type 2 (DM2) and related disorders. Report of the 180th ENMC workshop including guidelines on diagnostics and management.** *Neuromusc disorders* 21 (2011) 443-450.
4. Peter S. Harper, Baziél van Engelen, Bruno Eymard, Douglas E. Wilcox. Editors. **Myotonic Dystrophy. Present management, future therapy.** Oxford University Press 2004.
5. American Physical Therapy Association. **Guide to Physical Therapist Practice.** 2nd ed.; 2003.
6. **Muscular weakness assessment: Use of normal isometric strength data. The National Isometric Muscle Strength (NIMS) Database Consortium.** *Archives of Physical Medicine & Rehabilitation.* 1996; 77:1251-1255.
7. Hogrel JY, Payan CA, Ollivier G, et al. **Development of a French isometric strength normative database for adults using quantitative muscle testing.** *Archives of Physical Medicine & Rehabilitation.* 2007; 88:1289-1297.
8. Andrews AW, Thomas MW, Bohannon RW. **Normative values for isometric muscle force measurements obtained with hand-held dynamometers.** *Phys Ther.* 1996;76:248-259.
9. Beenakker EA, van der Hoeven JH, Fock JM, Maurits NM. **Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry.** *Neuromuscular Disorders.* 2001; 11:441-446.
10. Moxley 3rd RT, Logigan EL, Martens WB et al. **Computerized hand grip myometry reliably measures myotonia and muscle strength in myotonic dystrophy (DM1).** *Muscle and Nerve* 2007;36 (3) :320-8.
11. Trip J, Drost Gv, B.G.M., Faber CG. **Drug treatment for myotonia.** *Cochrane Database of Systematic Reviews.* 2006.
12. George A, Schneider-Gold C, Zier S, Reiners K, Sommer C. **Musculoskeletal pain in patients with myotonic dystrophy type 2.** *Arch Neurol.* 2004; 61:1938-1942.
13. Guy-Coichard C, Nguyen DT, Delorme T, Boureau F. **Pain in hereditary neuromuscular disorders and myasthenia gravis: A national survey of frequency, characteristics, and impact.** *J Pain Symptom Manage.* 2008; 35:40-50.
14. Jensen MP, Hoffman AJ, Stoelb BL, Abresch RT, Carter GT, McDonald CM. **Chronic pain in persons with myotonic dystrophy and facioscapulohumeral dystrophy.** *Am J Phys Med Rehabil.* 2008; 89:320-328.
15. Kalkman JS, Zwarts MJ, Schillings ML et al. **Different types of Fatigue in patients with Facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-1. Experienced fatigue and physiological fatigue.** *Neurol Sci* 2008 Sep; 29 Suppl 2: S238-240.
16. Minis MA, Kalkman JS, Akkermans RP et al **Employment status of patients with neuromuscular diseases in relation to personal factors, fatigue and health status; a secondary analysis.**
17. Bellini M, Biagi S, Stasi C, et al. **Gastrointestinal manifestations in myotonic muscular dystrophy.** *World J Gastroenterol.* 2006;12:1821-1828.

18. Tieleman AA, van Vliet J, Jansen JB, van der Kooi AJ, Borm GF, van Engelen BG. **Gastrointestinal involvement is frequent in myotonic dystrophy type 2.** *Neuromuscul Disord.* 2008; 18:646-649.
19. van der Kooi AJ, Lindeman E, Riphagen I. **Strength training and aerobic exercise training for muscle disease.** *The Cochrane Library.* 2010; 2.
20. Lindeman E, Leffers P, Spaans F et al. **Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy:a randomized clinical trial.** *Arch Phys Med and Rehab* 1995; 76 (7): 612-20.
21. Orngreen MC, Olsen DB, Vissing J. **Aerobic training in patients with myotonic dystrophy type 1.** *Ann Neurol.* 2005; 57:754-757.
22. Cup EH, Pieterse AJ, ten Broek-Pastoor J, et al. **Exercise therapy and other types of physical therapy for patients with neuromuscular diseases; a systematic review.** *Arch Phys Med Rehabil.* 2007; 88:1452-1464.
23. **Physical Activity Guidelines for Americans.** U.S. Department of Health and Human Services. <http://www.health.gov/paguidelines>.
24. Sackley C, Disler PB, Turner-Stokes L, Wade DT. **Rehabilitation interventions for foot drop in neuromuscular disease.** *The Cochrane Library.* 2007; 4.
25. Wiles CM, Busse ME, Sampson CM, Rogers MT, Fenton-May, J. van Deursen, R. **Falls and stumbles in myotonic dystrophy.** *J Neurol Neurosurg Psychiatry.* 2006:393-396.
26. Echenne B, Rideau A, Roubertie A, Sebire G, Rivier F, Lemieux B. **Myotonic dystrophy type I in childhood long-term evolution in patients surviving the neonatal period.** *European Journal of Paediatric Neurology.* 2008; 12: 210-223.
27. Ekstrom AB, Hakenas-Plate L, Tulinius M, Wentz E. **Cognition and adaptive skills in myotonic dystrophy type 1: A study of 55 individuals with congenital and childhood forms.** *Dev Med Child Neurol.* 2009.
28. Angeard N, Gargiulo M, Jacquette A, Radvanyi H, Eymard B, Heron D. **Cognitive profile in childhood myotonic dystrophy type 1: Is there a global impairment?** *Neuromuscular Disorders.* 2007; 17: 451-458.
29. Fragala-Pinkham MA, Dumas HM, Barlow CA, Pasternak A. **An aquatic physical therapy program at a pediatric rehabilitation hospital: A case series.** *Pediatric Physical Therapy.* 2009; 21: 68-78.
30. McManus BM, Kotelchuck M. **The effect of aquatic therapy on functional mobility of infants and toddlers in early intervention.** *Pediatric Physical Therapy.* 2007; 19: 275-282.
31. McGibbon NH, Andrade CK, Widener G, Cintas HL. **Effect of an equine-movement therapy program on gait, energy expenditure, and motor function in children with spastic cerebral palsy: A pilot study.** *Developmental Medicine & Child Neurology.* 1998; 40: 754-762.
32. Winchester P, Kendall K, Peters H, Sears N, Winkley T. **The effect of therapeutic horseback riding on gross motor function and gait speed in children who are developmentally delayed.** *Phys Occup Ther Pediatr.* 2002; 22:37-50.

MEDICAL REFERENCES

DISEASE MECHANISM

Causes of DM

Cho, D.H.; Tapscott, S.J. **Myotonic dystrophy: emerging mechanisms for DM1 and DM2.**

Biochim Biophys Acta Feb 1772:195-204, 2007.

Ranum L.P.; Cooper T.A. **RNA-mediated neuromuscular disorders.** *Annu Rev Neurosci* 29:259-77, 2006.

Machuca-Tzili L.; Brook J.D.; Hilton-Jones D. **Clinical and molecular aspects of the myotonic dystrophies: a review.** *Muscle Nerve* Jul 32:1-18, 2005.

Harper P.S.; van Engelen B.G.; Eymard B.; Rogers M.; Wilcox D. **(2004) 99th ENMC international workshop: myotonic dystrophy: present management, future therapy.** 9-11 November 2001, Naarden, The Netherlands. Oxford University Press, Oxford UK.

Day J.W.; Ranum L.P. **RNA pathogenesis of the myotonic dystrophies.** *Neuromuscul Disord* Jan 15:5-16, 2005.

Ranum L.P.W.; Day J.W. **Myotonic Dystrophy: RNA Pathogenesis Comes into Focus.** *American Journal of Human Genetics* 74: 793-804, 2004.

Harper P.S. (2001) **Myotonic Dystrophy, 3rd ed.** W.B. Saunders, London.

Korade-Mirnic Z.; Babitzke P.; Hoffman E. **Myotonic dystrophy: molecular windows on a complex etiology.** *Nucleic Acids Res* Mar 15 26:1363-8, 1998.

Roses AD (1997) **Myotonic dystrophy.** In: Rosenberg RN, Prusiner SB, Dimauro S, Barchi RL (eds) **The Molecular and Genetic Basis of Neurological Disease**, 2 ed. Butterworth-Heinemann, Stoneham, MA.

Harris S.; Moncrieff C.; Johnson K. **Myotonic dystrophy: will the real gene please step forward!** *Hum Mol Genet* 5 Spec 1417-23, 1996.

Pizzuti A.; Friedman D.L.; Caskey C.T. **The myotonic dystrophy gene.** *Arch. Neurol* 50: 1173-9, 1993.

Brook J.D.; McCurrach M.E.; Harley H.G.; Buckler A.J.; Church D.; Aburatani H.; Hunter K.; Stanton V.P.; Thirion J.-P.; Hudson T.; Sohn R.; Zemelmann B.; Snell R.G.; Rundle S.A.; Crow S.; Davies J.; Shelbourne P.; Buxton J.; Jones C.; Juvonen V.; Johnson K.; Harper P.S.; Shaw D.J.; Housman D.E. **Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3-prime end of a transcript encoding a protein kinase family member.** *Cell* 68: 799-808, 1992.

Buxton J.; Shelbourne P.; Davies J.; Jones C.; Van Tongeren T.; Aslanidis C.; de Jong P.; Jansen G.; Anvret M.; Riley B.; Williamson R.; Johnson K. **Detection of an unstable fragment of DNA specific to individuals with myotonic dystrophy.** *Nature* 355: 547-8, 1992.

Fu Y.-H.; Pizzuti A.; Fenwick R.G., Jr.; King J.; Rajnarayan S.; Dunne P.W.; Dubel J.; Nasser G.A.; Ashizawa T.; de Jong P.; Wieringa B.; Korneluk R.; Perryman M.B.; Epstein H.F.; Caskey C.T. **An unstable triplet repeat in a gene related to myotonic muscular dystrophy.** *Science* 255: 1256-8, 1992.

Mahadevan M.; Tsilfidis C.; Sabourin L.; Shutler G.; Amemiya C.; Jansen G.; Neville C.; Narang M.; Barcelo J.; O'Hoy K.; Leblond S.; Earle-Macdonald J.; de Jong P.J.; Wieringa B.; Korneluk R.G. **Myotonic dystrophy mutation: an unstable CTG repeat in the 3-prime untranslated region of the gene.** *Science* 255: 1253-5, 1992.

Causes of DM2

Ranum L.P.; Cooper T.A. **RNA-mediated neuromuscular disorders.** *Annu Rev Neurosci* 29:259-77, 2006.

Udd B.; Meola G.; Krahe R.; Thornton C.; Ranum L.P.; Bassez G.; Kress W.; Schoser B.; Moxley R. **140th ENMC International Workshop: Myotonic Dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management.** *Neuromuscul Disord* Jun 16:403-13, 2006.

Day J.W.; Ranum L.P. **RNA pathogenesis of the myotonic dystrophies.** *Neuromuscul Disord* Jan 15:5-16, 2005.

Machuca-Tzili L.; Brook J.D.; Hilton-Jones D. **Clinical and molecular aspects of the myotonic dystrophies: a review.** *Muscle Nerve* Jul 32:1-18, 2005.

Meola G.; Moxley R.T. 3rd. **Myotonic dystrophy type 2 and related myotonic disorders.** *J Neurol* Oct 251:1173-82, 2004.

Ranum L.P.W., and Day J.W. **Myotonic Dystrophy: RNA Pathogenesis Comes into Focus.** *American Journal of Human Genetics* 74: 793-804, 2004.

Day J.W.; Ricker K.; Jacobsen J.F.; Rasmussen L.J.; Dick K.A.; Kress W.; Schneider C.; Koch M.C.; Beilman G.J.; Harrison A.R.; Dalton J.C.; Ranum L.P.; **Myotonic dystrophy type 2: molecular, diagnostic and clinical spectrum.** *Neurology* Feb 25 60:657-64, 2003.

Finsterer J. **Myotonic dystrophy type 2.** *Eur J Neurol* Sep 9:441-7, 2002.

Harper P.S. (2001) **Myotonic Dystrophy**, 3rd ed. W.B. Saunders, London.

Liquori C.L.; Ricker K.; Moseley M.L.; Jacobsen J.F.; Kress W.; Naylor S.L.; Day J.W.; Ranum L.P. **Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9.** *Science* 293:864-7, 2001.

Larkin K, Fardaei M. **Myotonic dystrophy--a multigene disorder.** *Brain Res Bull* Oct-Nov 1 56:389-95, 2001.

Day J.W.; Roelofs R.; Leroy B.; Pech I.; Benzow K.; Ranum L.P. **Clinical and genetic characteristics of a five-generation family with a novel form of myotonic dystrophy (DM2).** *Neuromuscul Disord* 9:19-27, 1999.

Udd B.; Krahe R.; Wallgren-Pettersson C.; Falck B.; Kalimo H. **Proximal myotonic dystrophy--a family with autosomal dominant muscular dystrophy, cataracts, hearing loss and hypogonadism: heterogeneity of proximal myotonic syndromes?** *Neuromuscul Disord* 7:217-28, 1997.

Meola G.; Sansone V.; Radice S.; Skradski S.; Ptacek L. **A family with an unusual myotonic and myopathic phenotype and no CTG expansion (proximal myotonic myopathy syndrome): a challenge for future molecular studies.** *Neuromuscul Disord* 6:143-50, 1996.

Thornton, C.A.; Griggs, R.C.; Moxley, R.T.III. **Myotonic dystrophy with no trinucleotide repeat expansion.** *Ann. Neurol* 35: 269-72, 1994.

RNA Pathogenesis

Wang G.-S.; Kearney D.L.; De Biasi M.; Taffet G.; Cooper T.A. **Elevation of RNA-binding protein CUGBP1 is an early event in an inducible heart-specific mouse model of myotonic dystrophy.** *J. Clin. Invest* 117: 2802-11, 2007.

Wheeler T.M.; Lueck J.D.; Swanson M.S.; Dirksen R.T.; Thornton C.A. **Correction of CIC-1 splicing eliminates chloride channelopathy and myotonia in mouse models of myotonic dystrophy.** *J Clin Invest* 117:3952-7, 2007.

Smith K.P.; Byron M.; Johnson C.; Xing Y.; Lawrence J.B. **Defining early steps in mRNA transport: mutant mRNA in myotonic dystrophy type I is blocked at entry into SC-35 domains.** *J Cell Biol Sep* 10 178:951-64, 2007.

Yuan Y.; Compton S.A.; Sobczak K.; Stenberg M.G.; Thornton C.A.; Griffith J.D.; Swanson M.S. **Muscleblind-like 1 interacts with RNA hairpins in splicing target and pathogenic RNAs.** *Nucleic Acids Res* 35:5474-86, 2007.

Paul S.; Dansithong W.; Kim D.; Rossi J.; Webster N.J.; Comai L.; Reddy S. **Interaction of muscleblind, CUG-BP1 and hnRNP H proteins in DM1-associated aberrant IR splicing.** *EMBO J Sep* 20 25:4271-83, 2006.

Timchenko, L. **Reversal of fortune.** *Nature Genet* 38: 976-7, 2006 Kanadia R.N.; Shin J.; Yuan Y.; Beattie S.G.; Wheeler T.M.; Thornton C.A.; Swanson M.S. **Reversal of RNA missplicing and myotonia after muscleblind overexpression in a mouse poly(CUG) model for myotonic dystrophy.** *Proc Natl Acad Sci USA Aug* 1 103:11748-53, 2006.

Mahadevan M.S.; Yadava R.S.; Yu Q.; Balijepalli S.; Frenzel-McCardell C.D.; Bourne T.D.; Phillips L.H. **Reversible model of RNA toxicity and cardiac conduction defects in myotonic dystrophy.** *Nature Genet* 38: 1066-70, 2006.

Machuca-Tzili L.; Thorpe H.; Robinson T.E.; Sewry C.; Brook J.D. **Flies deficient in muscleblind protein model features of myotonic dystrophy with altered splice forms of Z-band associated transcripts.** *Hum. Genet* 120: 487-99, 2006.

Dansithong W.; Paul S.; Comai L.; Reddy S. **MBNL1 is the Primary Determinant of Focus Formation and Aberrant Insulin Receptor Splicing in DM1.** *JBC* 280: 5773-80, 2005.

Jiang H.; Mankodi A.; Swanson M.S.; Moxley R.T.; Thornton C.A. **Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscleblind proteins and deregulated alternative splicing in neurons.** *Hum. Molec. Genet* 13: 3079-88, 2004.

Kanadia R.N.; Johnstone K.A.; Mankodi A.; Lungu C.; Thornton C.A.; Esson D.; Timmers A.M.; Hauswirth W.W.; Swanson M.S. **A muscleblind knockout model for myotonic dystrophy.** *Science* 302: 1978-80, 2003.

Fardaei M.; Rogers M.T.; Thorpe H.M.; Larkin K.; Hamshere M.G.; Harper P.S.; Brook J.D. **Three proteins, MBNL, MBLL and MBXL, co-localize in vivo with nuclear foci of expanded-repeat transcripts in DM1 and DM2 cells.** *Hum Mol Genet* Apr 1 11:805-14, 2002.

Mankodi A.; Urbinati C.R.; Yuan Q.-P.; Moxley R.T.; Sansone V.; Krym M.; Henderson D.; Schalling M.; Swanson M.S.; Thornton C.A. **Muscleblind localizes to nuclear foci of aberrant RNA in myotonic dystrophy types 1 and 2.** *Hum. Molec. Genet* 10: 2165-70, 2001.

Ladd A.N.; Charlet-B. N.; Cooper T.A. **The CELF family of RNA binding proteins is implicated in cell-specific and developmentally regulated alternative splicing.** *Molec. Cell. Biol* 21: 1285-96, 2001.

Miller J.W.; Urbinati C.R.; Teng-umnuay P.; Stenberg M G.; Byrne B.J.; Thornton C.A.; Swanson M.S. **Recruitment of human muscleblind proteins to CUG(n) expansions associated with myotonic dystrophy.** *EMBO J* 19: 4439-48, 2000.

Mankodi A.; Logigian E.; Callahan L.; McClain C.; White R.; Henderson D.; Krym M.; Thornton C.A. **Myotonic dystrophy in transgenic mice expressing an expanded CUG repeat.** *Science* 289:1769-72, 2000.

Timchenko, L. T. **Myotonic dystrophy: the role of RNA CUG triplet repeats.** *Am. J. Hum. Genet* 64: 360-4, 1999.

Philips A.V.; Timchenko L.T.; Cooper T.A. **Disruption of splicing regulated by a CUG-binding protein in myotonic dystrophy.** *Science* 280: 737-41, 1998.

Davis B.M.; McCurrach M.E.; Taneja K.L.; Singer R.H.; Housman D.E. **Expansion of CUG trinucleotide repeat in the 3' untranslated region of myotonic dystrophy protein kinase transcripts results in nuclear retention of transcripts.** *Proceedings of the National Academy of Sciences* 94: 7388-93, 1997.

Roberts R.; Timchenko N.A.; Miller J.W.; Reddy S.; Caskey C.T.; Swanson M.S.; Timchenko L.T. **Altered phosphorylation and intracellular distribution of a (CUG)n triplet repeat RNA-binding protein in patients with myotonic dystrophy and in myotonin protein kinase knockout mice.** *Proc. Nat. Acad. Sci* 94: 13221-6, 1997.

Timchenko L.T.; Miller J.W.; Timchenko N.A.; DeVore D.R.; Datar K.V.; Lin L.; Roberts R.; Caskey C.T.; Swanson M.S. **Identification of a (CUG)n triplet repeat RNA-binding protein and its expression in myotonic dystrophy.** *Nucleic Acids. Res* 24: 4407-14, 1996.

Wang J.; Pegoraro E.; Menegazzo E.; Gennarelli M.; Hoop R.C.; Angelini C.; Hoffman E.P. **Myotonic dystrophy: evidence for a possible dominant-negative RNA mutation.** *Hum. Molec. Genet* 4: 599-606, 1995.

Fu Y-H.; Friedman D.L.; Richards S.; Pearlman J.A.; Gibbs R.A.; Pizzuti A.; Ashizawa T.; Perryman M.B.; Scarlato G.; Fenwick R.G.Jr.; Caskey C.T. Decreased expression of myotonin protein kinase messenger RNA and protein in adult form of myotonic dystrophy. *Science* 260: 235-8, 1993.

Hull K.L. Jr; Roses A.D. Stoichiometry of sodium and potassium transport in erythrocytes from patients with myotonic muscular dystrophy. *J Physiol Jan* 254:169-81, 1976.

Somatic Mosaicism

Foiry L, Dong L, Savouret C, Hubert L, Riele HT, Junien C, Gourdon G. **Msh3 is a limiting factor in the formation of intergenerational CTG expansions in DM1 transgenic mice.** *Hum Genet* 119: 520-6, 2006.

Fortune MT, Vassilopoulos C, Coolbaugh MI, Siciliano MJ, Monckton DG. **Dramatic, expansion-biased, age-dependent, tissue-specific somatic mosaicism in a transgenic mouse model of triplet repeat instability.** *Hum Mol Genet* 9: 439-45, 2000.

Gomes-Pereira M, Fortune MT, Ingram L, McAbney JP, Monckton DG. **Pms2 is a genetic enhancer of trinucleotide CAG/CTG repeat somatic mosaicism: implications for the mechanism of triplet repeat expansion.** *Hum Mol Genet* 13: 1815-25, 2004.

Martorell L, Martinez JM, Carey N, Johnson K, Baiget M. **Comparison of CTG repeat length expansion and clinical progression of myotonic dystrophy over a five year period.** *J Med Genet* 32: 593-596, 1995.

Martorell L, Monckton DG, Gamez J, Baiget M. **Complex patterns of male germline instability and somatic mosaicism in myotonic dystrophy type 1.** *Eur J Hum Genet* 8: 423-30, 2000.

Monckton DG, Wong LJC, Ashizawa T, Caskey CT. **Somatic mosaicism, germline expansions, germline reversions and intergenerational reductions in myotonic dystrophy males: small pool PCR analyses.** *Hum Mol Genet* 4: 1-8, 1995.

van den Broek WJ, Nelen MR, Wansink DG, Coerwinkel MM, te Riele H, Groenen PJ, Wieringa B. **Somatic expansion behaviour of the (CTG)_n repeat in myotonic dystrophy knock-in mice is differentially affected by Msh3 and Msh6 mismatch-repair proteins.** *Hum Mol Genet* 11: 191-8, 2002.

Savouret C.; Brisson E.; Essers J.; Kanaar R.; Pastink A.; te Riele H.; Junien C.; Gourdon G. **CTG repeat instability and size variation timing in DNA repair-deficient mice.** *EMBO J* May 1 22:2264-73, 2003.

Khajavi M.; Tari A. M.; Patel N. B.; Tsuji K.; Siwak D.R.; Meistrich M.L.; Terry N.H.A.; Ashizawa T. **'Mitotic drive' of expanded CTG repeats in myotonic dystrophy type 1 (DM1).** *Hum. Molec. Genet* 10: 855-63, 2001.

Gomes-Pereira M.; Fortune M.T.; Monckton D.G. **Mouse tissue culture models of unstable triplet repeats: in vitro selection for larger alleles, mutational expansion bias and tissue specificity, but no association with cell division rates.** *Hum. Molec. Genet* 10: 845-54, 2001.

Martorell L.; Monckton D.G.; Gamez J.; Johnson, K.J.; Gich I.; Lopez de Munain A.; Baiget M. **Progression of somatic CTG repeat length heterogeneity in the blood cells of myotonic dystrophy patients.** *Hum. Molec. Genet* 7: 307-12, 1998.

Lia A.-S.; Seznec H.; Hofmann-Radvanyi H.; Radvanyi F.; Duros C.; Saquet C.; Blanche M.; Junien C.; Gourdon G. **Somatic instability of the CTG repeat in mice transgenic for the myotonic dystrophy region is age dependent but not correlated to the relative intertissue transcription levels and proliferative capacities.** *Hum. Molec. Genet* 7: 1285-91, 1998.

Wong L.J.; Ashizawa T.; Monckton D.G.; Caskey C.T.; Richards C.S. **Somatic heterogeneity of the CTG repeat in myotonic dystrophy is age and size dependent.** *Am J Hum Genet* Jan 56:114-22, 1995.

López de Munain A.; Cobo A.M.; Hugué E.; Martí Massó J.F.; Johnson K.; Baiget M. **CTG trinucleotide repeat variability in identical twins with myotonic dystrophy.** *Ann Neurol* Mar 35:374-5, 1994.

Thornton CA, Johnson K, Moxley RT 3rd. **Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than in leukocytes.** *Ann Neurol* Jan 35:104-7, 1994.

Lavedan C.; Hofmann-Radvanyi H.; Shelbourne P.; Rabes J.-P.; Duros C.; Savoy D.; Dehaupas I.; Luce S.; Johnson K.; Junien C. **Myotonic dystrophy: size- and sex-dependent dynamics of CTG meiotic instability, and somatic mosaicism.** *Am. J. Hum. Genet* 52: 875-83, 1993.

Anvret M.; Ahlberg G.; Grandell U.; Hedberg B.; Johnson K.; Edstrom L. **Larger expansions of the CTG repeat in muscle compared to lymphocytes from patients with myotonic dystrophy.** *Hum. Molec. Genet* 2: 1397-400, 1993.

Ashizawa T.; Dubel J.R.; Harati Y. **Somatic instability of CTG repeat in myotonic dystrophy.** *Neurology* Dec 43:2674-8, 1993.

Anticipation

Yang J.; Freudenreich C.H. **Haploinsufficiency of yeast FEN1 causes instability of expanded CAG/CTG tracts in a length-dependent manner.** *Gene* May 15 393:110-5, 2007.

Dean N.L.; Loredó-Ostí J.C.; Fujiwara T.M.; Morgan K.; Tan S.L.; Naumova A.K.; Ao A. **Transmission ratio distortion in the myotonic dystrophy locus in human preimplantation embryos.** *Eur J Hum Genet* 14:299-306, 2006

Savouret C, Garcia-C, Megret J, te Riele H, Junien C, Gourdon G. **MSH2-dependent germinal CTG repeat expansions are produced continuously in spermatogonia from DM1 transgenic mice.** *Mol Cell Biol* 2004 Jan 24:629-37, 2004.

De Temmerman N.; Sermon K.; Seneca S.; De Rycke M.; Hilven P.; Lissens W.; Van Steirteghem A.; Liebaers I. **Intergenerational instability of the expanded CTG repeat in the DMPK gene: studies in human gametes and preimplantation embryos.** *Am J Hum Genet* Aug 75:325-9, 2004.

- Martorell L.; Monckton D.G.; Sanchez A.; Lopez de Munain A.; Baiget M. **Frequency and stability of the myotonic dystrophy type 1 premutation.** *Neurology* 56: 328-35, 2001.
- Seznec H.; Lia-Baldini A.-S.; Duros, C.; Fouquet C.; Lacroix C.; Hofmann-Radvanyi H.; Junien C.; Gourdon G. **Transgenic mice carrying large human genomic sequences with expanded CTG repeat mimic closely the DM CTG repeat intergenerational and somatic instability.** *Hum. Molec. Genet* 9: 1185-94, 2000.
- Cohen H.; Sears D.D.; Zenvirth D.; Hieter P.; Simchen G. **Increased instability of human CTG repeat tracts on yeast artificial chromosomes during gametogenesis.** *Mol Cell Biol* Jun 19:4153-8, 1999.
- Simmons Z.; Thornton C.A.; Seltzer W.K.; Richards C.S. **Relative stability of a minimal CTG repeat expansion in a large kindred with myotonic dystrophy.** *Neurology* 50: 1501-4, 1998. Magee, A.C.; Hughes, A.E. **Segregation distortion in myotonic dystrophy.** *J. Med. Genet* 35:1045-6, 1998.
- Gourdon G.; Radvanyi F.; Lia A.-S.; Duros C.; Blanche M.; Abitbol M.; Junien C.; Hofmann- Radvanyi H. **Moderate intergenerational and somatic instability of a 55-CTG repeat in transgenic mice.** *Nature Genet* 15: 190-2, 1997.
- Leeflang, E.P.; McPeck, M.S.; Arnheim, N. **Analysis of meiotic segregation, using singlesperm typing: meiotic drive at the myotonic dystrophy locus.** *Am. J. Hum. Genet* 59: 896-904, 1996.
- Jansen G.; Willems P.; Coerwinkel M.; Nillesen W.; Smeets H.; Vits L.; Höweler C.; Brunner H.; Wieringa B. **Gonosomal mosaicism in myotonic dystrophy patients: involvement of mitotic events in (CTG)n repeat variation and selection against extreme expansion in sperm.** *Am J Hum Genet* Apr 54:575-85, 1994.
- Jansen G.; Willems P.; Coerwinkel M.; Nillesen W.; Smeets H.; Vits L.; Howeler C.; Brunner H.; Wieringa B. **Gonosomal mosaicism in myotonic dystrophy patients: involvement of mitotic events in (CTG)n repeat variation and selection against extreme expansion in sperm.** *Am. J. Hum. Genet* 54: 575-85, 1994.
- Abeliovich D, Lerer I, Pashut-Lavon I, Shmueli E, Raas-Rothschild A, Frydman M. **Negative expansion of the myotonic dystrophy unstable sequence.** *Am J Hum Genet* Jun 52:1175-81, 1993.
- Lavedan C, Hofmann-Radvanyi H, Shelbourne P, Rabes JP, Duros C, Savoy D, Dehaupas I, Luce S, Johnson K, Junien C. **Myotonic dystrophy: size- and sex-dependent dynamics of CTG meiotic instability, and somatic mosaicism.** *Am J Hum Genet* May 52:875-83, 1993.
- Sutherland G.R.; Richards R.I. **Anticipation legitimized: unstable DNA to the rescue.** *Am J Hum Genet* Jul 51:7-9, 1992.
- Harper P.S.; Harley H.G.; Reardon W.; Shaw D.J. **Anticipation in myotonic dystrophy: new light on an old problem.** *Am J Hum Genet* 1992 Jul 51:10-6. Erratum in: *Am J Hum Genet* Oct 51:942, 1992.

MULTISYSTEMIC FEATURES

Skeletal Muscle

Benders A.A., Timmermans J.A., Oosterhof A., Ter Laak H.J., van Kuppevelt T.H., Wevers R.A., Veerkamp J.H. **Deficiency of Na⁺/K⁺-ATPase and sarcoplasmic reticulum Ca²⁺-ATPase in skeletal muscle and cultured muscle cells of myotonic dystrophy patients.** *Biochem J* Jul 1 293:269-74, 1993.

Benders A.A.G.M., Groenen P.J.T.A., Oerlmans F.T.J.J., Veerkamp J.H., Wieringa B. **Myotonic dystrophy protein kinase is involved in the modulation of the Ca²⁺ homeostasis in skeletal muscle cells.** *J. Clin. Invest* 100: 1440-7, 1997.

Casanova G., Jerusalem F. **Myopathology of myotonic dystrophy: a morphometric study.** *Acta Neuropath (Berlin)* 45: 213-40, 1979.

de Swart B.J., van Engelen B.G., van de Kerkhof J.P., Maassen B.A. **Myotonia and flaccid dysarthria in patients with adult onset myotonic dystrophy.** *J Neurol Neurosurg Psychiatry* 75:1480-2, 2004.

Drachman D. B., Fambrough D. M. **Are muscle fibers denervated in myotonic dystrophy?** *Arch. Neurol* 33: 485-8, 1976.

Dubowitz Z. (1995) **Muscle Disorders in Childhood**, 2 ed. W.B. Saunders Co, London.

Kalkman J.S., Schillings M.L., van der Werf S.P., Padberg G.W., Zwarts M.J., van Engelen B.G., Bleijenberg G. **Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I.** *J Neurol Neurosurg Psychiatry* 76:1406-9, 2005.

Kurihara T. **New Classification and Treatment for Myotonic Disorders.** *Internal Medicine* 44: 1027-32, 2005.

Logigian E.L., Ciafaloni E., Quinn L.C., Dilek N., Pandya S., Moxley R.T. 3rd, Thornton C.A. **Severity, type, and distribution of myotonic discharges are different in type 1 and type 2 myotonic dystrophy.** *Muscle Nerve* Apr 35:479-85, 2007.

Logigian E.L., Blood C.L., Dilek N., Martens W.B., Moxley R.T. 4th, Wiegner A.W., Thornton C.A., Moxley R.T. 3rd. **Quantitative analysis of the "warm-up" phenomenon in myotonic dystrophy type 1.** *Muscle Nerve* 32:35-42, 2005.

Logigian E.L., Moxley R.T., IV, Blood C.L., Barbieri C.A., Martens W.B., Wiegner A.W., Thornton C.A., Moxley R.T., 3rd. **Leukocyte CTG repeat length correlates with severity of myotonia in myotonic dystrophy type 1.** *Neurology* 62: 1081-9, 2004.

Lovell M.E., Morcuende J.A. **Neuromuscular disease as the cause of late clubfoot relapses: report of 4 cases.** *Iowa Orthop J* 27:82-4, 2007.

Lueck J.D., Mankodi A., Swanson M.S., Thornton C.A., Dirksen R.T. **Muscle chloride channel dysfunction in two mouse models of myotonic dystrophy.** *J Gen Physiol* Jan 129:79-94, 2007.

Mankodi A., Takahashi M.P., Jiang H., Beck C.L., Bowers W.J., Moxley R.T., Cannon S.C., Thornton C.A. **Expanded CUG repeats trigger aberrant splicing of CIC-1 chloride channel pre-mRNA and hyperexcitability of skeletal muscle in myotonic dystrophy.** *Mol Cell* 10:35-44, 2002.

Mounsey J.P., Xu P., John J.E. 3rd, Horne L.T., Gilbert J., Roses A.D., Moorman J.R. **Modulation of skeletal muscle sodium channels by human myotonin protein kinase.** *J Clin Invest* May 95:2379-84. 1995.

Orngreen M. C., Olsen D. B., Vissing J. **Aerobic training in patients with myotonic dystrophy type 1.** *Ann. Neurol* 57: 754-7, 2005.

Reddy S., Smith D. B., Rich M. M., Leferovich J. M., Reilly P., Davis B. M., Tran K., Rayburn H., Bronson R., Cros D., Balice-Gordon R. J., Housman D. **Mice lacking the myotonic dystrophy protein kinase develop a late onset progressive myopathy.** *Nature Genet* 13: 325-35, 1996.

Streib E.W., Sun S.F. **Distribution of electrical myotonia in myotonic muscular dystrophy.** *Ann Neurol* 14:80-2, 1983.

Timchenko N.A., Iakova P., Cai Z.J., Smith J.R., Timchenko L.T. **Molecular basis for impaired muscle differentiation in myotonic dystrophy.** *Mol Cell Biol* Oct 21:6927-38, 2001.

Trip J., Drost G., van Engelen B.G., Faber C.G. (2006) **Drug treatment for myotonia.** Cochrane Database Syst Rev CD004762.

van der Kooi E.L., Lindeman E., Riphagen I. (2005) **Strength training and aerobic exercise training for muscle disease.** Cochrane Database Syst Rev CD003907.

Whittaker R.G., Ferenczi E., Hilton-Jones D. **Myotonic dystrophy: practical issues relating to assessment of strength.** *J Neurol Neurosurg Psychiatry* 77:1282-3, 2006.

Cardiovascular

Bassez G., Lazarus A., Desguerre I., Varin J., Laforet P., Becane H.M., Meune C., Arne-Bes M.C., Ounnoughene Z., Radvanyi H., Eymard B., Duboc D. **Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1.** *Neurology* 63:1939-41, 2004.

Bhakta D., Lowe M.R., Groh W.J. **Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type I.** *Am Heart J* 147:224-7, 2004.

Duboc D., Eymard B., et al. *Cardiac management of myotonic dystrophy.* **Myotonic dystrophy: present management, future therapy** P. S. Harper, B. M. G. Van Engelen, B. Eymard and D. E. Wilcox. New York, Oxford University Press 85-93, 2004.

Gregoratos G., Abrams J., Epstein A.E., Freedman R.A., Hayes D.L., Hlatky M.A., Kerber R.E., Naccarelli G.V., Schoenfeld M.H., Silka M.J., Winters S.L., Gibbons R.J., Antman E.M., Alpert J.S., Gregoratos G., Hiratzka L.F., Faxon D.P., Jacobs A.K., Fuster V., Smith S.C. Jr., American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for Pacing and Electrophysiology Committee to Update the 1998 Pacemaker Guidelines. **ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the American College of Cardiology/American Heart Association task force on practice guidelines.** *Circulation* 106:2145-61, 2002.

Harper P.S. **Myotonic Dystrophy.** 3rd ed, W.B. Saunders, London 2001.

Klompe L., Lance M., Woerd D., van der Scohy T., Bogers A.J.J.C. **Anaesthesiological and ventilatory precautions during cardiac surgery in Steinert's disease: a case report.** *J Card Surg* 22:74-5, 2007.

Kilic T., Vural A., et al. **Cardiac resynchronization therapy in a case of myotonic dystrophy (Steinert's disease) and dilated cardiomyopathy.** *Pacing Clin Electrophysiol* 30(7): 916-20, 2007.

Lazarus A., Varin J., et al. **Relationships among electrophysiological findings and clinical status, heart function, and extent of DNA mutation in myotonic dystrophy.** *Circulation* 99(8): 1041-6. 1999.

Lazarus A., Varin J., Babuty D., Anselme F., Coste J., Duboc D. **Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: A multicenter diagnostic pacemaker study.** *J Am Coll Cardiol* 40:1645-52, 2002.

Phillips M.F., Harper P.S. **Cardiac disease in myotonic dystrophy.** *Cardiovasc Res* 33:13-22, 1997.

Schoser B.G., Ricker K., Schneider-Gold C., Hengstenberg C., Durre J., Bultmann B., Kress W., Day J.W., Ranum L.P. **Sudden cardiac death in myotonic dystrophy type 2.** *Neurology* 63:2402-4, 2004.

Sovari A.A., Bodine C.K., et al. **Cardiovascular manifestations of myotonic dystrophy-1.** *Cardiol Rev* 15(4): 191-4, 2007.

Vignaux O., Lazarus A., et al. **Right ventricular MR abnormalities in myotonic dystrophy and relationship with intracardiac electrophysiologic test findings: initial results.** *Radiology* 224(1): 231-5, 2002.

Respiratory System

Souayah N.; Tick Chong P.S.; Dreyer M.; Cros D.; Schmahmann J.D. **Myotonic dystrophy type 1 presenting with ventilatory failure.** *J Clin Neuromuscul Dis* Sep 9:252-5, 2007.

Klompe L.; Lance M.; van der Woerd D.; Scohy T.; Bogers A.J. **Anaesthesiological and ventilatory precautions during cardiac surgery in Steinert's disease: a case report.** *J Card Surg* 22:74-5, 2007.

Laub M.; Berg S.; Midgren B. **Symptoms, clinical and physiological findings motivating home mechanical ventilation in patients with neuromuscular diseases.** *J Rehabil Med* Jul 38:250-4, 2006.

- Fodil R, Lofaso F, Annane D, Falaise L, Lejaille M, Raphaël JC, Isabey D, Louis B. **Upper airway calibre and impedance in patients with Steinert's myotonic dystrophy.** *Respir Physiol Neurobiol* Nov 30 144:99-107, 2004.
- Nishi M.; Itoh H.; Tsubokawa T.; Taniguchi T.; Yamamoto K. **Effective doses of vecuronium in a patient with myotonic dystrophy.** *Anaesthesia* 59:1216-8, 2004.
- Rosenbaum H.K.; Miller J.D. **Malignant hyperthermia and myotonic disorders.** *Anesthesiol Clin North America* 20, 385-426, 2002.
- Aquilina A.; Groves J. **A combined technique utilising regional anaesthesia and target-controlled sedation in a patient with myotonic dystrophy.** *Anaesthesia* 57:385-6, 2002.
- Nugent A.M.; Smith I.E.; Shneerson J.M. **Domiciliary-assisted ventilation in patients with myotonic dystrophy.** *Chest* Feb 121:459-64, 2002.
- Shneerson J.M.; Simonds A.K. **Noninvasive ventilation for chest wall and neuromuscular disorders.** *Eur Respir J* Aug 20:480-7, 2002.
- Ahmadian J.L.; Heller S.L.; Nishida T.; Altman K.W. **Myotonic dystrophy type 1 (DM1) presenting with laryngeal stridor and vocal fold paresis.** *Muscle Nerve* Apr 25:616-8, 2002.
- Nitz J.; Burke B. **A study of the facilitation of respiration in myotonic dystrophy.** *Physiother Res Int* 7:228-38, 2002.
- Imison A.R. **Anaesthesia and myotonia--an Australian experience.** *Anaesth Intensive Care* 29:34-7, 2001.
- Calabrese P.; Gryspeert N.; Auriant I.; Fromageot C.; Raphaël J.C.; Lofaso F.; Benchetrit G. **Postural breathing pattern changes in patients with myotonic dystrophy.** *Respir Physiol* Aug 122:1-13, 2000.
- Ugalde V.; Breslin E.H.; Walsh S.A.; Bonekat H.W.; Abresch R.T.; Carter G.T. **Pursed lips breathing improves ventilation in myotonic muscular dystrophy.** *Arch Phys Med Rehabil* Apr 81:472-8, 2000.
- Keller C.; Reynolds A.; Lee B.; Garcia-Prats J. **Congenital myotonic dystrophy requiring prolonged endotracheal and noninvasive assisted ventilation: not a uniformly fatal condition.** *Pediatrics* 101: 704-6, 1998.
- Mathieu J.; Allard P.; Gobeil G.; Girard M.; De Braekeleer M.; Begin P. **Anesthetic and surgical complications in 219 cases of myotonic dystrophy.** *Neurology* 49:1646-50, 1997.
- Moxley R.T. 3rd. **Carrell-Krusen Symposium Invited Lecture-1997. Myotonic disorders in childhood: diagnosis and treatment.** *J Child Neurol* 12:116-29, 1997.
- Mathieu, J, Allard, P, Gobeil, G, Girard M.; De Braekeleer M.; Begin P. **Anesthetic and surgical complications in 219 cases of myotonic dystrophy.** *Neurology* 49:1646-50, 1997.
- Robin N.H.; Curtis M.T.; Mulla W.; Reynolds C.A.; Anday E.; Rorke L.B.; Zackai E.H. **Non-immune hydrops fetalis associated with impaired fetal movement: a case report and review.** *Am. J. Med. Genet* 53: 251-4, 1994.

Lehmann-Horn F.; Iazzo P.A. **Are myotonias and periodic paralyses associated with susceptibility to malignant hyperthermia?** *Br J Anaesth* 1990; 65:692-7, 1990.

Aldridge L.M. **Anaesthetic problems in myotonic dystrophy. A case report and review of the Aberdeen experience comprising 48 general anaesthetics in a further 16 patients.** *Br J Anaesth* 57:1119, 1985.

Mudge B.J.; Taylor P.B.; Vanderspek A.F. **Perioperative hazards in myotonic dystrophy.** *Anaesthesia* 35:492-5, 1980.

Moulds R.F.; Denborough M.A. **Letter: Myopathies and malignant hyperpyrexia.** *Br Med J* 3:520, 1974.

Saidman L.J.; Havard E.S.; Eger E.I. 2nd. **Hyperthermia during anesthesia.** *JAMA* 190:1029-32, 1964.

Bellini M., Alduini P., Costa F., Tosetti C., Pasquali L., Pucciani F., Tornar A., Mammini C., Siciliano G., Maltinti G., Marchi S. **Gastric emptying in myotonic dystrophic patients.** *Dig Liv Dis* 34: 484-488, 2002.

Gastrointestinal System

Bellini M., Biagi S., Stasi C., Costa F., Mumolo M.G., Ricchiuti A., Marchi S. **Gastrointestinal manifestations in myotonic muscular dystrophy.** *World J Gastroenterol* Mar 28 12:1821-8, 2006.

Brunner H.G., Hamel B.C.J., Rieu P., Howeler C.J., Peters F.T.M. **Intestinal pseudoobstruction in myotonic dystrophy.** *J. Med. Genet* 29: 791-3, 1992.

Costantini M., Zaninotto G., Anselmino M., Marcon M., Iurilli V., Boccu C., Feltrin G.P., Angelini C., Ancona E. **Esophageal motor function in patients with myotonic dystrophy.** *Dig Dis Sci* 41 : 2032-8, 1996.

Garrett J.M., DuBose T.D. Jr., Jackson J.E., Norman J.R. **Esophageal and pulmonary disturbances in myotonia dystrophica.** *Arch Intern Med* 123: 26-32, 1969.

Horowitz M., Maddox A., Maddern G.J., Wishart J., Collins P.J., Shearman D.J. **Gastric and esophageal emptying in dystrophia myotonica. Effect of metoclopramide.** *Gastroenterology* 92: 570-577, 1987.

Kerr T.P., Robb S.A., Clayden G.S. **Lower gastrointestinal tract disturbance in congenital myotonic dystrophy** *Eur J Pediatr* Aug 161:468-9, 2002.

Lecointe-Besancon I., Leroy F., Devroede G., Chevrollier M., Lebeurier F., Congard P., Arhan P. **A comparative study of esophageal and anorectal motility in myotonic dystrophy.** *Dig Dis Sci* 44:1090-99, 1999.

Marchi S., Polloni A., Bellini M., Costa F., Tumino E., Masi M.C., Rossi B., Siciliano G., Maltinti G. **Gastrointestinal manifestations in myotonic muscular dystrophy: a review.** *Acta Cardiologica* 1: 151-8, 1989.

Modolell I., Mearin F., Baudet J.S., Gamez J., Cervera C., Malagelada J.R. **Pharyngo- esophageal motility disturbances in patients with myotonic dystrophy.** *Scand J Gastroenterol* 34: 878-882, 1999.

Motlagh B., MacDonald J.R., Tarnopolsky M.A. **Nutritional inadequacy in adults with muscular dystrophy.** *Muscle Nerve* 31:713-8, 2005.

Nowak T.V., Ionasescu V., Anuras S. **Gastrointestinal manifestations of the muscular dystrophies.** *Gastroenterology* 82: 800-10, 1982.

Ronnblom A., Forsberg H., Danielsson A. **Gastrointestinal symptoms in myotonic dystrophy.** *Scand J Gastroenterol* 31:654-7, 1996.

Sartoretti C., Sartoretti S., DeLorenzi D., Buchmann P. **Intestinal non-rotation and pseudoobstruction in myotonic dystrophy: case report and review of the literature.** *Int J Colorectal Dis* 11:10, 1996.

Siegel C.I., Hendrix T.R., Harvey J.C. **The swallowing disorder in myotonia dystrophica.** *Gastroenterology* 50:541-50, 1966.

Takhar A.S., Thaper A., Byrne A., Lobo D.N. **Laparoscopic cholecystectomy in a patient with myotonic dystrophy.** *J R Soc Med* Jun 97:284-5, 2004.

Siegel C.I., Hendrix T.R., Harvey J.C. **The swallowing disorder in myotonia dystrophica.** *Gastroenterology* 50: 541-50, 1966.

Central Nervous System

Akiguchi I., Nakano S., Shiino A., Kimura R., Inubushi T., Handa J., Nakamura M., Tanaka M., Oka N., Kimura J. **Brain proton magnetic resonance spectroscopy and brain atrophy in myotonic dystrophy.** *Arch. Neurol* 56: 325-30, 1999.

Annane D., Moore D.H., Barnes P.R., Miller R.G. **Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy.** *Cochrane Database Syst Rev* 2006, 3:CD003218.

Antonini G., Morino S., Fiorelli M., Fiorini M., Giubilei F. **Selegiline in the treatment of hypersomnolence in myotonic dystrophy: a pilot study.** *J Neurol Sci* 147:167-9, 1997.

Antonini G., Soscia F., Giubilei F., De Carolis A., Gragnani F., Morino S., Ruberto A., Tatarelli R. **Health-related quality of life in myotonic dystrophy type 1 and its relationship with cognitive and emotional functioning.** *J Rehabil Med* 38:181-5, 2006.

Ashizawa T. **Myotonic dystrophy as a brain disorder.** *Arch Neurol* 55:291-3, 1998.

Censori B., Provinciali L., Danni M., Chiamoni L., Maricotti M., Foschi N., Del Pesce M., Salvolini U. **Brain involvement in myotonic dystrophy: MRI features and their relationship to clinical and cognitive conditions.** *Acta Neurol. Scand* 90: 211-7, 1994.

Damian M.S., Bachmann G., Koch M.C., Schilling G., Stoppler S., Dorndorf W. **Brain disease and molecular analysis in myotonic dystrophy.** *Neuroreport* 5:2549-52, 1994.

- Delaporte C. **Personality patterns in patients with myotonic dystrophy.** *Arch. Neurol* 55: 635-40, 1998.
- Gaul C., Schmidt T., Windisch G., Wieser T., Muller T., Vielhaber S., Zierz S., Leplow B. **Subtle cognitive dysfunction in adult onset myotonic dystrophy type 1 (DM1) and type 2 (DM2).** *Neurology* 67:350-2, 2006.
- Gibbs J.W. 3rd, Ciafaloni E., Radtke R.A. **Excessive daytime somnolence and increased rapid eye movement pressure in myotonic dystrophy.** *Sleep* 25:662-5, 2002.
- Harper P.S. **Myotonic Dystrophy.** Third ed. W.B. Saunders, London. 2001.
- Krishnan A.V., Kiernan M.C. **Axonal function and activity-dependent excitability changes in myotonic dystrophy.** *Muscle Nerve* 33:627-36, 2006.
- Laberge L., Begin P., Montplaisir J., Mathieu J. **Sleep complaints in patients with myotonic dystrophy.** *J Sleep Res* 13:95-100, 2004.
- Logullo F., Censori B., Danni M., Del Pesce M., Di Bella P., Provinciali L. **Peripheral neuropathy in myotonic dystrophy: electrophysiological and clinical features.** *Electromyogr Clin Neurophysiol* 32:515-20, 1992.
- Maurage C.A., Udd B., Ruchoux M.M., Vermersch P., Kalimo H., Krahe R., Delacourte A., Sergeant N. **Similar brain tau pathology in DM2/PROMM and DM1/Steinert disease.** *Neurology* 65: 1636-8, 2005.
- MacDonald J.R., Hill J.D., Tarnopolsky M.A. **Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy.** *Neurology* 59:1876-80, 2002.
- Meola G., Sansone V. **Cerebral involvement in myotonic dystrophies.** *Muscle Nerve* 36:294-306, 2007.
- Meola G., Sansone V., Perani D., Colleluori A., Cappa S., Cotelli M., Fazio F., Thornton, C.A., Moxley, R.T. **Reduced cerebral blood flow and impaired visual-spatial function in proximal myotonic myopathy.** *Neurology* 53:1042, 1999.
- Modoni A., Silvestri G., Pomponi M.G., Mangiola F., Tonali P.A., Marra C. **Characterization of the pattern of cognitive impairment in myotonic dystrophy type 1.** *Arch Neurol* 61:1943-7, 2004.
- Olson N.D., Jou M.F., Quast J.E., Nuttall F.O. **Peripheral neuropathy in myotonic dystrophy. Relation to glucose intolerance.** *Arch Neurol* 35:741-5, 1978.
- Oyamada R., Hayashi M., Katoh Y., Tsuchiya K., Mizutani T., Tominaga I., Kashima H. **Neurofibrillary tangles and deposition of oxidative products in the brain in cases of myotonic dystrophy.** *Neuropathology* 26:107-14, 2006.
- Park J.D., Radtke R.A. **Hypersomnolence in myotonic dystrophy: demonstration of sleep onset REM sleep.** *J Neurol Neurosurg Psychiatry* 58:512-3, 1995.
- Rubinsztein J.S., Rubinsztein D.C., Goodburn S., Holland A.J. **Apathy and hypersomnia are common features of myotonic dystrophy.** *J Neurol Neurosurg Psychiatry* 64:510-5, 1998.
- Sansone V., Gandossini S, Cotelli M., Calabria M., Zanetti O., Meola G. **Cognitive impairment in adult myotonic dystrophies: a longitudinal study.** *Neurol Sci* 28:9-15, 2007.

Sergeant N., Sablonniere B., Schraen-Maschke S., Ghestem A., Maurage C.-A., Wattez A., Vermersch P., Delacourte A. **Dysregulation of human brain microtubule-associated tau mRNA maturation in myotonic dystrophy type 1.** *Hum. Molec. Genet* 10:2143-55, 2001.

Spranger M., Spranger S., Tischendorf M., Meinck H.M., Cremer M. **Myotonic dystrophy. The role of large triplet repeat length in the development of mental retardation.** *Arch Neurol* 54:251-4, 1997.

Talbot K., Stradling J., Crosby J., Hilton-Jones D. **Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy.** *Neuromuscul Disord* 13:357-64, 2003.

Turnpenny P., Clark C., Kelly K. **Intelligence quotient profile in myotonic dystrophy, intergenerational deficit, and correlation with CTG amplification.** *J. Med. Genet* 31:300-5, 1994.

Winblad S., Lindberg C., Hansen S. **Cognitive deficits and CTG repeat expansion size in classical myotonic dystrophy type 1 (DM1).** *Behav Brain Funct* May 15 2:16, 2006.

Winblad S., Lindberg C., Hansen S. **Temperament and character in patients with classical myotonic dystrophy type 1 (DM-1).** *Neuromuscul Disord* 15:287-92, 2005.

Wintzen A.R., Lammers G.J., van Dijk J.G. **Does modafinil enhance activity of patients with myotonic dystrophy?: a double-blind placebo-controlled crossover study.** *J Neurol* Jan 254:26-8, 2007.

Reproductive and Endocrine

Rakocevic-Stojanovic V.; Savic D.; Pavlovic S.; Lavnica D.; Stevic Z.; Basta I.; Romac S.; Apostolski S. **Intergenerational changes of CTG repeat depending on the sex of the transmitting parent in myotonic dystrophy type 1.** *Eur J Neurol* 12:236-7, 2005.

Rudnik-Schoneborn S.; Zerres K. **Outcome in pregnancies complicated by myotonic dystrophy: a study of 31 patients and review of the literature.** *EJOG* vol 114: 44-53, 2004.

Savkur R.S.; Philips A.V.; Cooper T.A.; Dalton J.C.; Moseley M.L.; Ranum L.P.; Day J.W. **Insulin receptor splicing alteration in myotonic dystrophy type 2.** *Am J Hum Genet* Jun 74:1309-13, 2004.

Sarkar P.S.; Paul S.; Han J.; Reddy S. **Six5 is required for spermatogenic cell survival and spermiogenesis.** *Hum. Molec. Genet* 13: 1421-1431, 2004.

Johansson A.; Ahrén B.; Forsberg H.; Olsson T. **Testosterone and diurnal rhythmicity of leptin, TNF-alpha and TNF-II receptor in insulin-resistant myotonic dystrophy patients.** *Int J Obes Relat Metab Disord* Oct 26:1386-92, 2002.

Magee A.C.; Hughes A.E.; Kidd A.; Lopez de Munain A.; Cobo A.M.; Kelly K.; Dean J.; Nevin N.C. **Reproductive counseling for women with myotonic dystrophy.** *J Med Genet* 39: e15, 2002.

Savkur R.S.; Philips A.V.; Cooper T.A. **Aberrant regulation of insulin receptor alternative splicing is associated with insulin resistance in myotonic dystrophy.** *Nat Genet* 29:40-7, 2001.

- Rudnik-Schoneborn S.; Nicholson G.A.; Morgan G.; Rohrig D.; Zerres K. **Different patterns of obstetric complications in myotonic dystrophy in relation to the disease status of the fetus.** *Am. J. Med. Genet* 80: 314-21, 1998.
- Bergoffen J.; Kant J.; Sladky J.; McDonald-McGinn D.; Zackai E.H.; Fischbeck K.H. **Paternal transmission of congenital myotonic dystrophy.** *J. Med. Genet* 31: 518-20, 1994.
- Roig M.; Balliu P.-R.; Navarro C.; Brugera R.; Losada M. **Presentation, clinical course, and outcome of the congenital form of myotonic dystrophy.** *Pediat. Neurol* 11: 208-13, 1994.
- Vazquez, JA, Pinies, JA, Martul, P, De los Rios A.; Gatzambide S.; Busturia M.A. **Hypothalamic-pituitary-testicular function in 70 patients with myotonic dystrophy.** *J Endocrinol Invest* 13:375, 1990.
- Middleton P.G.; Posen S.; Shannon G. **Hyperparathyroidism in a patient with myotonic dystrophy.** *J R Soc Med Apr* 82:227, 1989.
- Banerjee D.; McClintock J.; Silver M.M.; Hudson A.J. **Monocyte IgG-Fc receptors in myotonic dystrophy.** *Clin Exp Immunol* Dec 50:572-8, 1982.
- Moxley R.T. 3rd; Livingston J.N.; Lockwood D.H.; Griggs R.C.; Hill R.L. **Abnormal regulation of monocyte insulin-binding affinity after glucose ingestion in patients with myotonic dystrophy.** *Proc Natl Acad Sci USA Apr* 78:2567-71, 1981.
- Larsen B.; Johnson G.; van Loghem E.; Marshall W.H.; Newton R.M.; Pryse-Phillips W.; Skanes V. **Immunoglobulin concentration and Gm allotypes in a family with thirty-three cases of myotonic dystrophy.** *Clin. Genet* 18: 13-9, 1980.
- Takeda R.; Ueda M. **Pituitary-gonadal function in male patients with myotonic dystrophy- serum luteinizing hormone, follicle stimulating hormone and testosterone levels and histological damage of the testis.** *Acta Endocrinol (Copenh)* Feb 84:382-9, 1977.
- Seay A.R.; Ziter F.A.; Hill H.R. **Defective neutrophil function in myotonic dystrophy.** *J. Neurol Sci* 35: 25-30, 1978.
- Webb D.; Muir I.; Faulkner J.; Johnson G. **Myotonia dystrophica; obstetric complications.** *Am. J. Obstet. Gynec* 132: 265-70, 1978.
- Sarnat H.B.; O'Connor T.; Byrne P.A. **Clinical effects of myotonic dystrophy on pregnancy and the neonate.** *Arch Neurol* 33:459-65, 1976.
- Sagel J.; Distiller L.A.; Morley J.E.; Isaacs H.; Kay G.; van der Walt A. **Myotonia dystrophica: studies on gonadal function using luteinising-releasing-hormone (LRH).** *J. Clin. Endocr. Metab* 40: 1110, 1975.
- Harper P.S.; Dyken P.R. **Early-onset dystrophia myotonica: evidence supporting a maternal environmental factor.** *Lancet II* 53-55, 1972.
- Wochner R.D.; Drews G.; Strober W.; Waldmann T.A. **Accelerated breakdown of immunoglobulin G (IgG) in myotonic dystrophy: a hereditary error of immunoglobulin catabolism.** *J. Clin. Invest* 45: 321-9, 1966.

Bruyland M., Lissens W., De Waele M., Demanet C. **Hypo-IgG in myotonic dystrophy is due to a selective reduction of the IgG1-subclass serum level.** *Muscle Nerve* Oct 17:1233-4, 1994.

Cigliano B., Baltogiannis N., De Marco M., Faviou E., Settimi A., Tilemis S., Soutis M., Papandreou E., D'Agostino S., Fabbro M.A. **Pilomatricoma in childhood: a retrospective study from three European paediatric centres.** *Eur J Pediatr* 164:673-7, 2005.

Chuang C.C., Lin H.C. **Pilomatrixoma of the head and neck.** *J Chin Med Assoc* Dec 67:633-6, 2004.

Day J.W., Ricker K., Jacobsen J.F., Rasmussen L.J., Dick K.A., Kress W., Schneider C., Koch M.C., Beilman G.J., Harrison A.R., Dalton J.C., Ranum L.P. **Myotonic dystrophy type 2: molecular, diagnostic and clinical spectrum.** *Neurology* Feb 25 60:657-64, 2003.

Geh J.L., Moss A.L. **Multiple pilomatrixomata and myotonic dystrophy: a familial association.** *Br J Plast Surg* 52:143-5, 1999.

Hubbard V.G., Whittaker S.J. **Multiple familial pilomatrixomas: an unusual case.** *J Cutan Pathol.* Mar 31:281-3, 2004.

Kim J., Hayton W.L., Robinson J.M., Anderson C.L. **Kinetics of FcRn-mediated recycling of IgG and albumin in human: pathophysiology and therapeutic implications using a simplified mechanism-based model.** *Clin Immunol* Feb 122:146-55, 2007.

Kudva G.C., Maliekal K., Kim H.J., Naunheim K.S., Stolar C., Fletcher J.W., Puri S. **Thymoma and myotonic dystrophy: successful treatment with chemotherapy and radiation: case report and review of the literature.** *Chest* Jun 121:2061-3, 2002.

Nakamura A., Kojo T., Arahata K., Takeda S. **Reduction of serum IgG level and peripheral T-cell counts are correlated with CTG repeat lengths in myotonic dystrophy patients.** *Neuromuscul Disord* May 6:203-10, 1996.

Pan-Hammarström Q., Wen S., Ghanaat-Pour H., Solders G., Forsberg H., Hammarström L. **Lack of correlation between the reduction of serum immunoglobulin concentration and the CTG repeat expansion in patients with type 1 dystrophia [correction of Dystrofia] myotonica.** *J Neuroimmunol* Nov, 144:100-4, 2003.

Reimund J.M., Duclos B., Chamouard P., Warter J.M., Weill J.P., Baumann R. **Intestinal carcinoid tumor and myotonic dystrophy. A new association?** *Dig Dis Sci* Dec 37:1922-5, 1992.

Saponaro A.E., Marini M.A., Rossi G.C., Casas J.G. **Multiple basal cell carcinomas in a patient with myotonic dystrophy type 1.** *Int J Dermatol* Jan 45:87-8, 2006.

Schara U., Schoser B.G. **Myotonic dystrophies type 1 and 2: a summary on current aspects.** *Semin Pediatr Neurol* Jun,13:71-9, 2006.

Terrence C.F. **Myotonic dystrophy and multiple sclerosis.** *J Neurol* Oct 4 213:305-8, 1976.

Vandecaveye V., Verswijvel G., Colla P., Verhelst H., VanRobaey J., Palmers Y. **Cystic insulinoma of the pancreas in a patient with myotonic dystrophy: correlation of imaging and pathologic findings.** *JBR-BTR* Sep-Oct 86:268-71, 2003.

Waldmann T.A., Polmar S.H., Balestra S.T., Jost M.C., Bruce R.M., Terry W.D. **Immunoglobulin E in immunologic deficiency diseases. II. Serum IgE concentration of patients with acquired hypogammaglobulinemia, thymoma and hypogammaglobulinemia, myotonic dystrophy, intestinal lymphangiectasia and Wiskott-Aldrich syndrome.** *J Immunol* Aug 109:304-10, 1972.

Waldmann T.A., Strober W., Blaese R.M., Terry W.D. **Immunoglobulin metabolism in disease.** *Birth Defects Orig Artic Ser.* 11:87-94, 1975.

Vision

Arsenault M.-E., Prévost C., Lescault A., Laberge C., Puymirat J., Mathieu J. **Clinical characteristics of myotonic dystrophy type 1 patients with small CTG expansions.** *Neurology* 66: 1248-50, 2006.

Baig K.M., Discepolo M. **Recurrent capsular opacification after Nd:YAG laser treatment in myotonic dystrophy.** *Can J Ophthalmol* 42:489-490, 2007.

Bollinger K.E., Kattouf V., Arthur B., et al. **Hypermetropia and esotropia in myotonic dystrophy.** *J Aapos* 12:69-71, 2008.

Harper PS. **Myotonic Dystrophy.** Third ed, W.B. Saunders, London 2001.

Medica I., Teran N., Volk M., Pfeifer V., Ladavac E., Peterlin B. **Patients with primary cataract as a genetic pool of *DMPK* protomutation.** *J Hum Genet* 52:123-8, 2007.

Schein O.D., Katz J., Bass E.B., Tielsch J.M., Lubomski L.H., Feldman M.A., Petty B.G., Steinberg E.P. **The value of routine preoperative medical testing before cataract surgery. Study of medical testing for cataract surgery.** *N Engl J Med* Jan 20 342:168-75, 2000.

Shaunak S., Orrell R., Henderson L., Kennard C. **Saccades and smooth pursuit in myotonic dystrophy.** *J Neurol* 246:600-606, 1999.

Versino M., Rossi B., Beltrami G., et al. **Ocular motor myotonic phenomenon in myotonic dystrophy.** *J Neurol Neurosurg Psychiatr* 72:236-240, 2002.

NOTES



MYOTONIC
DYSTROPHY
FOUNDATION

1259 El Camino Real, #150
Menlo Park, CA, 94025
Phone: 86-myotonic (866-968-6642)
Email: info@myotonic.org

www.myotonic.org