

Summary – Pain

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Pain is a very common feature of any chronic disease and patients with mitochondrial disease frequently suffer from different types of pain. Almost any organ or system may be involved in patients with Mito, and thus they may have a variety of pains.

Pediatric pain in particular is a very difficult area, as it is very hard for physicians to watch children suffering. Up until a few years ago there was not much information on how to approach and assess pain in children who are very young or those who are nonverbal. However, research now indicates that the best gauge of pain in both children and adults is patient (or parent) report, and that children should be treated for suspected pain.

What types of pain or pain syndromes are most frequently seen in children and in adults with Mito?

I. Headaches are very common. Patients may suffer from migraines, tension headaches, chronic daily headaches and combinations of these.

Are mechanisms of these headaches different from those in patients who don't have mitochondrial disorders? No one can answer this question with 100% certainty.

My approach to the treatment of headaches in individuals with mitochondrial disease is not that much different from our approach to headache in other patients with several exceptions:

- Treatment is based on frequency and severity of the headaches. For example, if they occur once or even twice a month, it is probably not worth treating the patient with prophylactic medicine. Prophylactic or preventive approach means that the patient takes medication every day. If the headaches are infrequent we often use abortive drugs; these are medications taken only if one develops headache.
- In patients experiencing migraines who do not have mitochondrial disease, the most commonly used abortive medications are Triptans. This medication class is very effective, very popular, used very widely and at some point, made a revolution in migraine treatment. Unfortunately, they are not fully approved for use in kids. Neurologists do use them in patients with migraines who are older than 12; however, most child neurologists do not feel comfortable treating mitochondrial disease patients with triptans. Unfortunately, our patients with Mito are deprived of this very effective treatment. We still can use Motrin and Tylenol.

- As far as prophylactic medications are concerned, we child neurologists love medicine called Periactin. It is a very benign medicine and its main side effect is appetite increase. As many kids with Mito have poor appetites, it is loved by the parents as well.
- Medications such as tricyclic antidepressants (Pamelor, Elavil) and even antiseizure medication Topamax can be used too. Depakote, widely used for migraine prophylaxis is contraindicated for kids with Mito. We usually try to maximize supplement such as CoQ 10 and Carnitine and vitamin B2. Hydration is very important.
- Headaches are very resistant to treatment not only in kids with mitochondrial disease but in general. They are more difficult to treat in kids with Mito, because these kids have a lifelong underlying condition, which is directly related to headaches, and which is not going to go away. However, even in patients with Mito there is a chance that the headache may get better.
- Triggers for headaches or migraines are often difficult to pinpoint, particularly in children. Illness, heat, and dehydration, may provoke headaches, while food triggers are seen very infrequently.

Other "nondrug approaches" can be used successfully and should be considered when treating pain. For example, at Children's Hospital in Boston acupuncture in older kids and acupressure in younger ones has been helpful. Biofeedback, relaxation treatments are additional options.

II. Neuropathic pain is pain coming from the nerves due to nerve damage. These types of nerve problems are called **neuropathies**, and are considered a characteristic feature of mitochondrial disease. In some cases, neuropathies may develop during the course of a treatment - such as DCA (dichloroacetate that may be used in children with high lactate levels). Neuropathies can also develop with time as a result of vitamin deficiency, malnutrition and other factors.

Neuropathic pain can be continuous (deep, burning, aching), paroxysmal (sudden, lancinating, like electric shocks or sharp stabs) and abnormal cutaneous sensitivity. Paresthesias with the sensation of bugs crawling under the skin could be present and frequently is felt in the hands and feet. NCS (nerve conduction studies) are not always a valuable tool in pain assessment and if normal does not exclude neuropathic pain. NCS are good only for testing large nerve fibers, while pain is usually caused by small nerve involvement.

Medications that are used for chronic neuropathic pain are slightly different from those used for migraines, although tricyclic antidepressants may be used. We frequently use medicine called Neurontin; now there is a new medicine Lyrica that is becoming more and more popular. In the past, anticonvulsants such as Tegretol and Dilantin were used.

III. Muscle pains and aches are of course very common in patients with Mito due to the muscle's involvement in the process of OXPHOS as part of energy production. Pain in the muscles may be exacerbated by exercise, exertion, and dehydration. Physicians are careful to try to ensure that there is no significant break down of muscle tissue, particularly with exercise. Some Mito patients may have so-called **rhabdomyolysis**, a process where muscles get destroyed and the breakdown products are eliminated by the kidneys. This is seen more frequently in metabolic muscle disorders other than Mito, but this could be present in some mitochondrial disorders as well. Rhabdomyolysis is a dangerous condition because kidneys could be damaged; therefore, we pay a lot of attention to muscle aches and pains. Hydration is a very important way of treating these conditions.

Treatment for muscle pain also consists of painkillers, such as Tylenol and Motrin. Tricyclic antidepressants may be used too. Medications belonging to a muscle relaxant group such as Flexeril and Soma may be used. In some situations even steroids can be used, but of course with great caution, because prolonged use of steroids may produce muscle weakness.

Many patients with MD experience **spasticity and dystonia** due to the lesions in the brain, especially in the area called basal ganglia. We see that quite often in young children, especially those with Leighs Disease. Spasticity and dystonia may produce muscle spasms and cause pain due to muscle contractions. The medications that are used in such situations are different. For dystonia the most commonly used medications are Artane and cogentin. For spasticity, Baclofen, Valium, Klonopin and even Botox may be used. I follow several patients with Mito who receive regular Botox injections

IV. Abdominal pain is commonly related to problems with gut motility. There are some forms of Mito when gastrointestinal complaints are a presenting feature, and again are very hard to assess. Stomach pain may be accompanied by nausea, vomiting, constipation, and diarrhea. It is generally a rule in pediatrics not to treat abdominal pain with pain killers, because they may mimic serious and potentially very dangerous problems, such as appendicitis, however, this is being reconsidered and many pain specialists advocate early use of analgesics in abdominal pain. Further evaluation from gastroenterologists is necessary, as well as use of medications that improve gastric motility, or relieve other symptoms.

Assessing Pain

We are frequently confronted by a question of whether the child or adult who cannot express him or herself, but who is known to have a neuropathy (based on the nerve conduction studies) has pain caused by his or her neuropathy. This is a hard question to answer, because some of the neuropathies are painful and some are not. In a newborn

or infant with neuropathy it is almost impossible to answer. Child may be irritable for different reasons and may be in pain that is hard to assess.

This is true not only about the neuropathies, but about other types of pain in children, especially if they are very young, delayed and nonverbal. How do we know what a child or nonverbal patient experiences? Research has shown that nurses and physicians tend to underestimate pain. There is a consensus about adult patients that the mainstay of pain assessment is the patient's self-report; intensity of pain is whatever the experiencing person says it is. But what do we do with children who frequently are not able to express themselves and to report the pain that they have?

We usually try to give our patients the benefit of doubt and presume that they do have pain, particularly if they are irritable or appear to be in distress. In addition, some indirect signs such as increases in heart rate and blood pressure may be clues that the person has pain. However, the main sign in children is irritability; therefore, pain should always be considered when a child is fussy, irritable, or crying without obvious reason.

Pain rating scales are widely used by pain specialists. It is not correct to think that delayed or cognitively impaired patients are not able to use them. Even very young children understand the idea. For them, it is not the numbers but the pictures with sad and smiling faces that can be used.

There is also plenty of data now suggesting that chronic pain adversely affects their cognitive development in children and contribute to depression in adults. Obviously, minimizing pain is important!

Myths about Pain

Pain management is a difficult area. It is especially difficult in patients with chronic diseases and especially with such complex disorders like mitochondrial disease. There are many misconceptions about pain. I will mention few of them. This relates to both children and adults:

1. The best judge of the experience of severity of pain is the physician or nurse caring for patient. **The patients' self-report is the most reliable indicator of the existence and intensity of pain. Obviously in the case of young children parental report is very important.**
1. There is no reason for patients to experience pain when no physical cause for pain can be found. **In many cases no obvious cause for pain can be found. This is**

particularly true about patients with Mito, who frequently feel much worse than they look.

1. Patients should not receive analgesics until the cause of pain is diagnosed. **Symptomatic relief of pain should be provided, while the cause of pain is investigated.**
1. Physical signs of pain may help with assessment its severity. **Lack of pain expression does not mean lack of pain. Different patients have different pain tolerance. Also pain expression may reflect cultural differences.**

As physicians we frequently order procedures and studies in our patients that may be associated with pain, such as blood draws, brain MRI, etc. Some of these common procedures may require sedation which requires IV placement, which is another source of pain, not to mention more invasive tests (skin, muscle biopsies, spinal taps). We have to be very critical and decide whether tests and procedures are indeed necessary in order to try to spare patients painful experiences that they do not need to have.

As neurologists of course, we deal with patients having pain on a daily basis, but we frequently ask our colleagues from the pain service to assist us in management of patients with pain.

Nondrug approaches should not be a substitute for drugs, but should be complementary.

It may have not only emotional, but also physiologic effects. Some of these techniques may decrease stimulation of sympathetic nervous system, produce muscle relaxation and thus reduce pain. They also may cause release of endorphins in the body, substances that provide analgesic effect.

Several no drug approaches have been used successfully to manage pain:

1. Cognitive-behavioral techniques. Distraction, playing games, blowing bubbles and other methods.
2. Music therapy provides distraction and relaxation
3. Controlled breathing and Imagery
4. Hypnosis
5. Mindful meditation, paying attention to the present moment without thinking about what has happened or will happen in the future.

Biophysical techniques

1. Cold and heat therapy
2. Massage therapy reduces muscle tension, improves flexibility, produces relaxation and improves sleep. Can be focused on muscle trigger points
3. TENS (transcutaneous electrical nerve stimulation) non-painful electrical stimulus interferes with transmission of pain by altering spinal cord gating mechanism, may cause endorphin release.
4. acupuncture seems to alter spinal cord gating mechanisms and causes release of endorphins
5. therapeutic exercise

MitoAction would like to thank Dr. Anselm for her involvement in supporting patients with mitochondrial disease!