Care Guide for Patients with Mucolipidosis Type IV

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Common Questions:

What is Mucolipidosis Type IV (MLIV)?

MLIV is a genetic disorder that affects the function of lysosomes. Lysosomes are small organelles within all cells that are responsible for degrading biological molecules. When lysosomes are not functioning correctly, molecules that are normally degraded accumulate and cause cells to become dysfunctional. In patients with MLIV, lysosomal dysfunction mainly affects cells in the brain, eye, stomach, and kidney.

MLIV is caused by mutations in *MCOLN1*, the gene encoding the lysosomal cation channel, TRPML1. The role of TRPML1 in regulating lysosomal function is not completely understood. However, complete or partial loss of TRPML1 is sufficient to cause MLIV.

How is MLIV inherited?

MLIV is inherited in an autosomal recessive manner. Everybody has two copies of each gene in their body. One copy is inherited from their father and the other from their mother. Most parents of children with MLIV have one normal copy of *MCOLN1* and one abnormal copy. Having one normal copy is enough to prevent symptoms. Most children with MLIV inherit two abnormal copies of *MCOLN1* (one from their mother and one from their father) leaving them with little or no functional TRPML1 protein.

In rare cases, a disease causing mutation in MCOLN1 may have occurred spontaneously during early development, rather than being inherited from a parent.

Are some patients with MLIV more severely affected than others?

Some patients with MLIV are less severely affected than others. Part of this variation is explained by how severely different mutations in *MCOLN1* affect the function of TRPML1. Some *MCOLN1* mutations completely abolish the function of TRPML1. Patients with two copies of these mutations are typically the most severely affected. Other *MCOLN1* mutations leave TRPML1 partially functional. Patients with these mutations tend to be less severely affected.

How is MLIV diagnosed?

Most patients with MLIV are first brought to medical attention because of delayed development, low muscle tone, abnormal eye movements, or visual impairment within the first two years of life. These are not specific to MLIV and can be seen in other neurodevelopmental disorders, often leading to a delay in diagnosis. A cloudy appearance of the cornea (the clear tissue overlying the eye) or visual impairment accompanying low tone and developmental delay is more suggestive of MLIV and often leads to the correct diagnosis.

The diagnosis of MLIV can be confirmed in three different ways. First, the identification of two known, disease causing mutations in the MCOLN1 gene. If a mutation that has not previously been associated with MLIV is identified, the patient must also have the correct clinical symptoms to confirm the diagnosis. The second mode of diagnosis involves a tissue biopsy (usually skin or cornea). If cells from the biopsy show abnormal accumulation of material in lysosomes consistent with MLIV, a diagnosis is confirmed. The third manner of diagnosis is detection of elevated gastrin levels in a patient who has symptoms consistent with MLIV. Gastrin is a hormone that signals for more acid secretion in the stomach. Because the cells that secrete stomach acid are dysfunctional in MLIV, gastrin levels are elevated in a futile effort by the body to increase acid production.

What resources are available to patients and caregivers?

1. ML4 Foundation Website: http://ml4.org/
2. ML4 Foundation Facebook Community: https://www.facebook.com/ML4Foundation/
3. Mucolipidosis type IV Gene Reviews: https://www.ncbi.nlm.nih.gov/books/NBK1214/

Medical Management of MLIV (For Caregivers):

MLIV mainly affects the nervous system, eyes, stomach, and kidneys. While there is no cure for MLIV, symptoms should be monitored and managed with standard treatment options. To ensure comprehensive care, patients with MLIV should be seen by a pediatrician, geneticist, neurologist, physical medicine and rehabilitation physician (**PMR**), physical therapist, occupational therapist, speech and language pathologist, gastroenterologist, ophthalmologist, nephrologist (renal), dentist, and palliative care specialist.

Core Care Team:

1. **Pediatrician**: Manages standard medical care including vaccinations, treatment of routine infections, monitoring growth and nutrition, and managing iron deficiency anemia. The standard frequency of "well child visits" may be recommended or an increased frequency of visits if a medical problem is actively being managed.

2. **Geneticist**: Helps establish the genetic diagnosis of MLIV and explains the implications for further family planning. After diagnosis, a geneticist will act as the primary care coordinator for patients, providing referral to specialists when appropriate and monitoring a patient's overall medical management plan. Routine visits typically occur on a yearly basis.

3. **Neurologist**: Monitors neurodevelopmental progress and severity of neurological symptoms (muscle weakness/tightness, muscle wasting, seizures, tremor, sleep issues). A neurologist will diagnose and manage seizures (if necessary), muscle tightness (often in collaboration with a PMR specialist), and sleep issues. Routine visits typically occur on a yearly basis.

4. **PMR**: Physical medicine and rehabilitation physicians (a.k.a physiatrists) aim to improve the functional ability and quality of life of patients with physical disabilities. A PMR may prescribe medicines for muscle tightness (orals, injectables, or spinal pumps), braces/orthotics, or other adaptive medical devices (walker, wheelchair, stander, etc.). PMR specialists work closely with physical therapists, occupational therapists, and orthotists to coordinate care. Routine visits typically occur every 6 months to year.

5. **Physical therapist**: Works with patients and caregivers to improve muscle tone, strength, and mobility. Most insurance plans will provide a limited number of visits per targeted issue (i.e. poor head control, impaired leg strength, etc.). Treatment plans (exercises, stretches, etc.) are then continued at home by caregivers. If a new issues arises or an existing issue worsens, a referral for an additional course of treatment should be provided.

6. **Occupational therapist**: Works with patients to improve fine motor skills (finger coordination, reaching, etc.) and may provide adaptive equipment to aid with tasks of daily living (adaptive utensils, communication devices, etc.).

7. **Speech and language therapist**: Monitors a patient's ability to safely and effectively chew and swallow food. If your therapist suspects aspiration (food or liquid going into the lungs when swallowing) a swallow study may be ordered. Thickening of liquids and selective food consistencies may also be recommended. A speech and language therapist may work in collaboration with a dietician to ensure a patient is safely consuming the necessary calories and

nutrients for age. Routine visits usually occur on a yearly basis or when issues with chewing/swallowing worsen. It is important to obtain a new assessment if your child is coughing or choking when eating or drinking.

8. **Ophthalmologist**: Monitors degree of visual impairment from retinal degeneration and corneal clouding. May prescribe lubricating eye drops to help with eye pain. Once visual function reaches a nadir in adolescence, monitoring may be discontinued.
9. **Nephrologist**: Monitors kidney function and manages chronic or acute kidney failure. While kidney involvement in MLIV is poorly understood, a fraction of patients develops acute on chronic renal failure after the second decade of life. We recommend establishing care with a nephrologist by early adolescence to begin monitoring.
10. **Pediatric Dentist**: Children with any neurodevelopmental condition are at an increased risk of cavities and gingival (gum) inflammation from poor oral hygiene. Visits with a pediatric dentist on yearly basis, or more frequently if recommended, will help prevent dental decay.
11. **Palliative Care Specialist**: This is **NOT hospice.** Palliative care specialists help patients and family members define the goals of medical treatment to optimize quality of life goals. Engaging a specialist early in life provides continuity of care and ongoing discussions around treatment goals across the lifespan.

Additional Specialists (referred as needed):

12. **Gastroenterologist**: Diagnoses and treats stomach pain, reflux, constipation, or diarrhea. A gastroenterologist may also test the body's ability to digest and absorb nutrients if a problem is suspected.
13. **Hematologist**: If your pediatrician feels uncomfortable managing iron supplementations for iron deficient anemia, you may be referred to a blood specialist.
14. **Ears, Nose, and Throat (ENT)**: If excessive drooling is not adequately managed with conservative means or oral medications, and it is impacting quality of life, an ENT specialist may offer Botox injections into the salivary glands to temporarily decrease the production of saliva.

Medical Issues Associated with MLIV:

Muscle weakness and tightness (hypertonicity) in the arms and legs:

Patients with MLIV experience muscle weakness and tightness which primarily results from problems in the central nervous system. Because the communication between brain and muscle is impaired, patients cannot fully activate their muscles resulting in weak voluntary movements. Muscle tightness in MLIV is complex and arises from poor communication between the brain, spine, and muscles (spasticity) as well as abnormal coordination of muscle tone (rigidity or dystonia). Spasticity is characterized by an increase in resistance to movement that can be appreciated when passively moving an arm or leg around a joint (i.e. the elbow). The faster the limb is moved, the more resistance is felt. Spasticity can show mild fluctuations throughout the day, but for the most part it is present and persistent. Rigidity is characterized by an increase in resistance to passive movement across a joint that does not change

when varying the speed of movement. Rigidity can be variably present. Dystonia is an involuntary muscle contraction that may be brief or last for minutes to hours. In patients with MLIV, dystonia may manifest as extension of the legs with inward rotation of the feet, flexion at the elbow and wrist, twisting of the neck or trunk, or curling of the fingers or toes.

Monitoring: Muscle tightness should be monitored by a neurologist, PMR, and physical therapist. Muscle tightness typically worsens with time in patients with MLIV, though the rate of progression is variable and may be slower in some patients than other. There are two main indications to medically treat muscle tightness. First, if muscle tightness is preventing the development of gross or fine motor functions. For example, Botox injections to the muscles around the ankle may increase flexibility and allow proper foot placement when standing or ambulating with an assisted walker. Second, if muscle tightness is severe enough to cause discomfort or structural damage (i.e. hip dislocation), treatment may improve quality of life.

Treatment options:

1. Stretching and bracing: Your PMR specialist and physical therapist may recommend any of the following if appropriate:
    a. Daily stretching routine to elongate the affected muscle groups.
    b. Braces at the ankles to promote flexibility.
    c. Braces or padding to open the hands and fingers.
2. Oral medications: All medication options have side effects. The goal of treatment is to determine whether there is a dose of medication that offers benefits that significantly outweigh side effects. The medications below may all improve muscle tightness of the arms and legs.
    a. **Baclofen**: May treat spasticity and dystonia. Side effects include decreased muscle tone of the neck and trunk, drowsiness and vomiting.
    b. **Gabapentin**: May treat dystonia and have some effect on spasticity. Side effects include dizziness, drowsiness and incoordination.
    c. **Clonazepam**: May treat dystonia and have some effect on spasticity. Side effects include drowsiness, aggression or dizziness.
    d. **Sinemet (carbidopa/levodopa)**: May treat dystonia. This has been tried in one patient with MLIV who showed prominent rigidity, dystonia, and tremor with some benefit after treatment; however, treatment was stopped due to side effects. Sinemet will not treat spasticity. Side effects include low blood pressure, nausea, constipation, decreased appetite.
3. Botox Injections: Can be used to treat both spasticity and dystonia. Botox has the advantage of targeting specific muscle groups without systemic effects. Benefits typically last 3-4 months after which redosing is required.
4. Phenol injections: Similar to Botox injections except that the effects are irreversible.

Low muscle tone affecting the trunk and scoliosis:

While muscle tone is increased in the arms and legs of patients with MLIV, it is typically decreased in the trunk and neck. This may manifest as poor head control or difficulty maintaining posture when sitting or standing. Because the trunk muscles are responsible for keeping the spine aligned, low muscle tone in the trunk may lead to scoliosis (abnormal curvature of the spine).

Monitoring: Low trunk muscle tone and scoliosis should be monitored by a neurologist and PMR specialist. If scoliosis becomes severe, you may be referred to an orthopedic surgeon.

Treatment options: An exercise regimen designed by a physical therapist may increase the strength of the neck and trunk muscles and enhance the support they provide. A trunk support brace may be used to provide comfort, however, they are not used to correct scoliosis in children with progressive neurological conditions. If the degree of scoliosis affects the internal organs or ability to breath, surgical correction may be indicated.

Impaired ability to stand and walk:

Few patients with MLIV develop the ability to walk independently. This is due to a combination of low trunk muscle tone, weakness, and muscle tightness in the arms and legs. There may be a positive correlation between the amount of physical therapy a patient receives and the maximum mobility they achieve. Because all patients are unique, families should work with their medical care providers to determine an appropriate therapy regimen on an individual basis.

Monitoring: The ability to stand and walk should be monitored by a neurologist, physical medicine and rehabilitation physician, physical therapist and occupational therapist.

Treatment options: A physical therapist may design an exercise regimen to increase strength and coordination. Supportive equipment may include a prone stander and a walker that provides truncal support. Assuming a standing position for some amount of time on a daily basis will help promote strength, bone density, and joint flexibility.

Corneal Clouding:

All patient with MLIV have clouding of the cornea, the clear layer of tissue covering the eye. Clouding may be apparent as early as the first year of life. Anecdotal observations suggest that clouding may improve with age and become less apparent in the second and third decades of life. Though corneal clouding can impair vision by blocking the entry of light into the eye, it likely plays a smaller role in visual impairment than degeneration of the retina at the back of the eye.

Monitoring: Corneal clouding should be assessed by an ophthalmologist or corneal specialist.

Treatment options: Though corneal transplant and corneal scrapping have been tried in MLIV patients, the benefits are not permanent. This is because the patient's own cells will repopulate the treated area leading to recurrent clouding. Because these treatment options require surgery and may be painful, a thoughtful discussion with your ophthalmologist about the risks and benefits is warranted.

Retinal degeneration:

Patient with MLIV experience a rapid, irreversible degeneration of the retina over the first 2 decades of life. The retina is located at the back of the eye and is composed of cells that detect light and cells that transmit information from light detecting cells to the brain. Retinal cells are extremely sensitive to the lysosomal dysfunction in MLIV and rapid retinal degeneration is seen in even the least affected patients.

Monitoring: Retinal function should be evaluated by your ophthalmologist. They may use a combination of tests including optical coherence tomography, electroretinograms and/or visual evoked potentials.

Treatment options: Unfortunately, there are no treatment options for degeneration of the retina in MLIV at this time. Development of gene replacement therapies may offer options in the future.

Episodes of eye pain:

Severe attacks of eye pain accompanied by tearing and facial flushing have been frequently reported in patients with MLIV. These attacks may occur without provocation or occur after accidentally bumping or touching the eye. The cause of these episodes is uncertain but there are two strong possibilities to consider:

1. Pain caused by damage to the cornea: Some evidence suggests that the corneas of MLIV patients may be more susceptible to damage. Because the cornea has many pain fibers associated with it, frequent "micro damage" to the cornea could underlie these painful episodes.

2. Headache variants: Paroxysmal Hemicrania, SUMA and SUNCT are headache variants that present with brief, severe pain episodes, tearing, and facial flushing. Given the description of pain episodes and that they may occur spontaneously without physically touching the eye may suggest one of these headache variants.

Treatment options:

Because the cause of these episodes is uncertain the following may be tried:

1. Start with frequent eye lubrication and see if the episodes respond. We recommend using **preservative free** eye drops and instilling 1-2 drops in each eye 6 times per day and a **preservative free** lubricating gel or ointment at night. Only use **preservative free** drops, gels or ointment. Please consult with your ophthalmologist before starting any treatment regimen.

2. If the eye lubrication regimen is unsuccessful in decreasing the frequency of the eye pain episodes, consult your neurologist and ask about discussing the possibility of a headache variant. Potential treatment regimens include a course of indomethacin or lamotrigine.

Difficulty chewing and swallowing:

Oromotor function (chewing and tongue movement) are severely impaired in patients with MLIV. Patients typically lack rotary jaw movement when chewing and have difficulty moving food to the back of the mouth where it can be swallowed. As a result, patients require longer amounts of time to finish meals. Fortunately, aspiration (allowing liquids or food to enter the lungs) is uncommon in children with MLIV, though it becomes more frequent in the age range of 20 years and older.

Monitoring: Risk of aspiration should be assessed by a speech and swallow pathologist. If your child is coughing or gagging while drinking or eating, an assessment is medically necessary. A barium swallow study is typically used to assess for aspiration. During the study, a patient will swallow radio opaque liquids of various thickness and passage down the esophagus or trachea will be assessed with x-ray images.

Treatment: If aspiration is occurring, the consistency of liquids can be altered to prevent aspiration. This can be achieved with different starches and gums added to liquids. In the most severe cases, a g-tube may be necessary to deliver nutrition. In the oldest MLIV patients (>30 years) placement of a tracheostomy tube has been necessary to prevent aspiration of oral secretions.

Excessive drooling:

Excessive drooling in patients with MLIV arises from the inability to effectively move and swallow saliva. This is a common symptom that can be medically managed.

Monitoring: Excessive drooling can be treated by a pediatrician, neurologist or physical medicine and rehabilitation physician. If more invasive means of treatment are necessary, an Ears, Nose and Throat (ENT) physician should be consulted.

Treatment options: Treatment is initiated with oral medications and escalated to targeted invasive therapies if indicated. The goal of treatment is to promote comfort and hygiene.

1. Oral atropine drops: Atropine is a medication that will decrease production by the salivary glands. Atropine drops should be administered locally under the tongue. If atropine is absorbed into the circulation, patients may experience slow heart rate, dilate pupils, and worsen constipation and urinary retention. Over time, patients may build tolerance to atropine and require increasing doses to obtain benefit.
2. Glycopyrrolate (Rubinol): Administered in oral liquid or per g-tube to decrease production of saliva. Careful monitoring and dosage adjustments may be needed as oral secretions may become thickened and more difficult to clear from the airway.
3. Botox injections to the salivary glands: If medical management is inadequate, targeted injection of Botox to the salivary glands can decrease saliva production. The procedure is performed by an ENT specialist. Effects typically last 3-4 months after which re-dosing is necessary.
4. Surgical removal of salivary glands: If excessive drooling cannot be managed by medications or Botox injections, surgical removal of salivary glands by an ENT specialist offers a definitive treatment option. In the mouth, saliva is produced by several different glands: the parotid,

submandibular and sublingual. Surgical resection only targets a subgroup of glands to reduce overall production but leaves the patient with the ability to produce saliva.

Dental care:

Cavities are a common occurrence in children with MLIV. This is not a direct cause of MLIV but is instead related to poor management of salivary secretions. Saliva typically coats the teeth and plays an important role in preventing cavities. MLIV patients are unable to adequately coat their teeth with saliva due to impaired control of the tongue and oral musculature.

Monitoring: All patients with MLIV should be seen by a dentist on an annual basis or more frequently if indicated.

Treatment options: Teeth are typically cleaned and repaired under sedation. Consult your pediatrician to identify a dentist who is trained in treating patients with disabilities.

Iron deficiency anemia:

In patients with MLIV, iron deficiency anemia results from poor absorption of dietary iron. This occurs because the stomach pH is altered as a consequence of impaired stomach acid production. Fortunately, anemia is usually well tolerated in patients. Supplementation with oral iron may help but repletion to normal levels is rarely achieved.

Monitoring: Iron levels should be monitored by your pediatrician. Treatment should be considered in all patients that exhibit symptoms of anemia: fatigue, shortness of breath, and/or fainting.

Treatment options: Supplementation with oral ferrous sulfate is first line treatment. If ineffective, intra venous iron repletion may be recommended. Goals of treatment may vary between individuals and should be discussed with your physician.

Seizures:

Seizures are rare in MLIV. Some patients have experienced absence seizures (petite mal) or staring spells. Absence seizures are characterized by unresponsiveness to verbal or physical cues and may be accompanied by lip smacking, blinking, or repeated, unintentional movements. If you suspect your child may be having an absence seizure, physically touch your child to get their attention. If they remain unresponsive, consult your neurologist. Capturing an episode on video will be extremely helpful in facilitating a conversation with your neurologist.

Monitoring: If your child is having episodes of unresponsiveness, consult your neurologist. An electroencephalogram (EEG) may be recommended to monitor your child's brain activity. EEG studies typically last 45 minutes to an hour. If an episode occurs while the EEG is being performed, a definitive diagnosis can be made. If an episode is not captured on EEG, the presence of a specific types of abnormal brain activity may support the diagnosis in the proper clinical context. Importantly, most MLIV patients will have an abnormal EEG though few will have seizures. As such, the results of any EEG must

be discussed with a neurologist and carefully considered in the context of your child's clinical presentation.

Treatment options: Choice of antiseizure medications depends on the type of seizure being treated. Examples of medications include ethosuximide, valproic acid and lamotrigine. Medication side effects and monitoring should be discussed with your neurologist. To our knowledge, patients with MLIV generally tolerated anti-seizure medications well and there are no anti-seizure medications contraindicated in this patient population.

Impaired kidney function:

A fraction of patients with MLIV will also experience kidney failure in their 20's to 30's. This appears to be a direct consequence of MLIV but is poorly understood. Unfortunately, there are no effective treatments and rapidly progressive kidney failure can limit life span.

Monitoring: Chronic kidney failure may manifest as a gradual decline in level of activity/energy, muscle wasting, loss of appetite, or decreased production of urine. Acute kidney failure may present as a sudden decrease in level of alertness, vomiting, decreased urine production, and fluid retention. Acute kidney injury may be precipitated by an acute illness such as infection.

Kidney function should be monitored by a renal specialist. The age at which kidney failure becomes an issue is not known, but it is reasonable to start monitoring when a patient reaches 10 years of age. Kidney function is typically monitored with levels of creatinine within the blood. If the kidneys are not working properly, creatinine will not be filtered from the blood and levels will rise. Elevations in blood creatinine levels correlate with worsening kidney function.

In patients with MLIV, blood creatinine levels may not accurately reflect kidney function. Baseline levels of creatinine in the blood depend on overall muscle mass. Because patients with MLIV have decreased muscle mass, their baseline creatinine levels may be lower than a healthy individual of similar age. As such, a blood creatinine level within the range of "normal" may actually represent an elevated level within a patient with MLIV. We recommend monitoring **cystatin C levels** in the blood as an alternative to creatinine. Levels of cystatin C are not dependent on muscle mass and more accurately represent kidney function in patients with MLIV.

Reflux:

Reflux typically presents with episodes of stomach/chest pain, burping, coughing, regurgitation of food or bile, persistent hiccups and/or difficulty swallowing. Reflux is difficult to diagnose in patients who lack expressive language but consulting with a primary care doctor or a gastrointestinal (GI) specialist is important if you suspect your child may have reflux. While reflux usually results from the regurgitation of stomach acid, patients with MLIV likely experience regurgitation of bile (yellow digestive juices from the initial part of the small intestine) because all MLIV patients appear to develop achlorhydria. Achlorhydria is the absence of stomach acid that results from dysfunction of parietal cells, the cells in the stomach that produce acid. When consulting with your primary care doctor or GI specialist about reflux, it is important to discuss the universal presence of achlorhydria in MLIV, because the treatment

of bile reflux differs from the treatment of acid reflux. Bile reflux will not respond to antiacids, histamine receptor blockers or proton pump inhibitors.

Monitoring: A primary care doctor or GI specialist should be consulted if you suspect your child is experiencing reflux. A GI specialist my recommend further testing which could include an upper GI tract endoscopy or measurements of the esophageal and stomach pH.

Treatment options: Your doctor may recommend medications that sequester or improve the flow of bile.

Sleep issues:

Patients with MLIV may experience trouble falling asleep or staying asleep throughout the night. Currently, we have a poor understanding of the types of sleep issues that occur in MLIV. Because degeneration of the retina occurs in all patients, sleep issue may be related to a disorder called Non-24 sleep disorder. Daylight plays an important role in telling the brain when to remain awake and when to prepare for sleep. When the amount of sunlight decreases in the evening, the lack of blue light signals your brain to make a hormone called melatonin that prepares the brain for sleep. When the retina degenerates, the brain no longer receives this signal, melatonin production is disrupted, and the wake/sleep cycle is altered. If your child is experiencing trouble falling asleep or staying asleep, consult with your primary care doctor or a neurologist that specializes in sleep medicine.

Monitoring: Your neurologist may ask you to keep a consensus sleep diary to characterize your child's sleep issues. They may also recommend a polysomnogram (sleep study).

Treatment options:

Conservative measures:

1. Eliminate daytime naps.
2. Take a hot bath or shower immediately before bed.
3. Lower bedroom temperature at night to 69-70 degrees Fahrenheit.
4. Decrease screen time (phone or TV) 2-3 hours before bed (relevance depends on amount of visual function).
5. Increase daytime physical activity.

Medication options:

1. Melatonin: 2-5mg every night ~3 hours before bedtime (over the counter).
2. Remelteon: This is the only FDA approved treatment for Non-24. It works by activating melatonin receptors (prescription only).

Small stature/restricted growth

Patients with MLIV typically exhibit small stature and weight for age. The reason behind this is unknown and not consistent across all patients. Possible causes may include insufficient nutritional intake,

inability to absorb nutrients (usually presents with chronic diarrhea or change in stool), or hormonal imbalances.

Monitoring: Nutritional intake should be monitored with your pediatrician. A referral to a clinical dietician may be suggested. If the inability to absorb nutrients is suspected, seek a referral to a gastroenterologist. If a nutritional/GI cause has been ruled out, seek a referral to an endocrinologist who can assess the production of growth hormone.

Treatment: Ensuring sufficient nutritional intake and absorption are the most important aspects of care. Hormonal supplementation could be used in cases of hormone deficiency; however, the benefits should be weighed against the complications of caring for a larger, neurologically disabled patient later in life.

What is the life expectancy in patients with MLIV?

Life expectancy in MLIV is not well defined and can vary significantly. In the most severely affected patients, we have cared for patients up to 40 years in age. The life expectancy of mildly affected patients is unknown.

Unfortunately, MLIV is a progressive degenerative disorder. By the 30's to 40's, worsening weakness and muscle tightness prevent the majority of volitional movement and patients are typically bed bound. Pneumonia, skin ulcerations and infection may be life limiting.

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Routine MLIV Clinic Visits at MGH:

Neurological Assessment

1. Neurological Evaluation: All patients are evaluated by a neurologist or pediatric neurologist. During the appointment a full history and neurological examination are conducted. We routinely use the following validated scales to evaluate neurological function and level of disability (Please see attachment for copy of scales):
    a. Brief Assessment of Motor Function Scales
        i. Gross Motor Function
        ii. Upper Extremity Gross Motor Function
        iii. Fine Motor Function
        iv. Articulation
        v. Deglutition
    b. Gross Motor Function Classification System (GMFCS) score
    c. Gross Motor Function Measure (GMFM) 88 score
    d. Modified Ashworth Scales (assessment of muscle tone)

2. Lab Work: The following blood work is routinely obtained at our visits.
    a. Iron and Iron binding studies
    b. Ferritin
    c. CBC with differential
    d. Comprehensive metabolic panel
    e. Cystatin C
    f. CPK
    g. ESR/CRP
    h. Gastrin
    i. Vitamin D

3. Brain magnetic resonance imaging (MRI): Patients with MLIV typically have a brain MRI performed during their initial work diagnostic work up. Because studies require sedation, they are not routinely performed unless clinically indicated. Clinical indications for performing a brain MRI include a new weakness, increased hyper reflexivity, worsening high muscle tone, emergence of seizures, or any new neurological deficit. The following MRI sequences are typically included in our studies (please see attachment for full description):
    a. Sagittal 3D Bravo
    b. Axial DWI
    c. Axial DTI (86 Direction)
    d. Sagittal CUBE FLAIR
    e. Sagittal CUBE T2
    f. Sagittal DWI

4. Electromyogram (EMG) and Nerve Conduction Studies (NCS): These are not routinely performed but should be considered in the setting of worsening leg weakness or decreased responsiveness to pain

and temperature. EMC/NCS are difficult to perform in non-verbal patients and can be uncomfortable. Studies are performed by a neurologist specializing in neuromuscular disease.

5. Electroencephalogram: Only performed if there is a suspicion for seizure. Seizures in patients with MLIV usually present staring episodes in which the patient is unresponsive to verbal or physical cues for seconds to minutes at a time.