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Muscular Dystrophy

Developed by Brittany Lissinna and Dr. Lyn Sonnenberg for PedsCases.com.
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Introduction

Hi, my name is Brittany Lissinna and I am a fourth year medical student at the University of Alberta. This podcast will discuss the topic of gross motor delay and muscular dystrophy in children, and was created in collaboration with Dr. Lyn Sonnenberg, a Neurodevelopmental Pediatrician with the Glenrose Rehabilitation Hospital and the Stollery Children's Hospital in Edmonton, Alberta, Canada.

Objectives:

After listening to this podcast, you will be able to:

1. Develop a differential diagnosis to gross motor delay in children
2. Identify key investigations in the work up of a child with gross motor delay
3. List key features in the presentation of Duchenne Muscular Dystrophy
4. Discuss the importance of an interdisciplinary approach in the management of children with Duchenne Muscular Dystrophy

Clinical Case:

Let's start with a clinical case: you are working in a community clinic on your pediatrics rotation. Your next patient is Shane, a 3.5 year old boy who is new to your clinic. You sit down with Shane and his mother and she tells you she is concerned because she recently noticed that her son is the only one in his playgroup who is still unable to jump. When you probe further about his motor development, she tells you that he was rolling front to back at 4 months, sitting without support around 7 months, and began walking without support at 23 months, which was later than his older sister. She also thinks Shane has been falling more than usual lately. She had assumed these falls were just because Shane was a clumsy kid, but now she's wondering if there's something more serious going on.

Other than these motor difficulties, Shane has been developing normally and has had no other health concerns. Pregnancy was uncomplicated and he was born via a spontaneous vaginal delivery at 39 weeks and his newborn screening was normal. His immunizations are up to date and he does not have any allergies. Other than vitamin D supplements, he is not taking any medications.

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On family history you find out that Shane's parents are healthy, as is his older sister. Shane's mom is not aware of any developmental delays or motor disorders in the family.

What, if anything, from this history is concerning for you?

If you were worried that Shane may not have been meeting his motor developmental milestones, you're right! This history is concerning for gross motor delay.

What is the differential diagnosis for gross motor delay?

The differential diagnosis of gross motor delay is broad but the most common neuromotor disability in childhood is cerebral palsy. Other diagnoses to consider include developmental coordination disorder (DCD), muscular dystrophy, spinal muscular atrophy, spina bifida, and global developmental delay. It is also important to keep in mind other causes for weakness and motor delay such as thyroid disease, congenital heart disease, metabolic disorders, genetic syndromes, and nutritional deficiencies.

Let's return to the case. Given you have some concerns about Shane, you know it will be important to complete a thorough physical exam, focusing on neurological and musculoskeletal systems.

Physical Exam

You begin your physical exam by simply observing Shane walking up and down the hallway. You notice that Shane's calves are quite large and you also notice that he has a slightly exaggerated lumbar lordosis. As he is walking, you think he has a slight Trendelenberg gait but the gait is symmetric and you don't notice a foot drop. He struggles to run quickly and in fact falls at the end of the hallway. When he rises from the floor he places his hands on his knees and then further up his thighs to help himself to a standing position again. His arm swing is symmetrical both while walking and trying to run. He is unable to jump.

When assessing range of motion, you find that his range is decreased bilaterally in his ankles, making it difficult to achieve complete dorsiflexion. However he does not have any clonus nor does he have increased tone. You find Shane's reflexes somewhat difficult to elicit, but the neurologist didn't seem to have any difficulties.

You examine his back and do not notice any abnormalities, specifically no tuft of hair or dimple over the sacrum. You don't notice any unusual markings on his skin or any dysmorphic facial features. Finally you pull up Shane's growth curves. He is near the 25th percentile for height and at the 50th percentile for weight and head circumference.

Now that you have completed your history and physical exam, how are you going to approach the workup of this case?

Diagnostic Tests
When working up a child with gross motor delay, the most important test for a community pediatrician to remember before referring on to a specialist is a CK.

Gross motor delay? Do a CK!

In addition to the CK, you order a CBC, TSH, ferritin, and electrolytes.
These tests can help rule in or out some more easily correctable factors that may be contributing to a child's delay. If the child is found to be hypothyroid, it would be important to treat this, as hypothyroidism can cause weakness in children. Ferritin and electrolyte analysis may reveal a nutritional deficiency that could be contributing to the child's presentation or hint at an underlying metabolic disorder. It's important to keep in mind that more than one thing can contribute to a child's presentation, and if these correctable factors have been resolved, and the child continues to show signs of motor delay and weakness, further investigation is necessary.

One more thing about testing a child's CK. If your initial blood work shows an abnormal CK, the test always needs to be repeated; sometimes the elevated CK is secondary to a traumatic blood draw, though that should only result in a mildly increased CK. The parents should also be told to go for bloodwork first thing in the morning so that the result is not falsely elevated by a child's activity throughout the day.

Back to the Case
You explain to Shane's mother that you are concerned about his motor development and some of the findings you have seen on physical exam, including calf muscle pseudohypertrophy, Gower's sign (using his hands on his legs when getting to standing), a Trendelenberg gait (weakness in the hip adductors causing a compensatory pelvic tilt), and the limited range of motion in his ankles. You explain that in order to determine what is causing Shane's delay, you will be ordering some blood work that includes looking for the muscle enzyme creatine kinase or CK. Once we have the results of the blood work back we will have a better sense of what's going on. Shane's mom thanks you for your time and says they will head over to the lab right away.

The next day you are back in the pediatric clinic and the report from Shane's blood work is back. His CK level is elevated, more than 50 times the normal limit. His other investigations, including TSH, ferritin, electrolytes and CBC came back normal. You phone Shane's mother and ask her to take Shane back to the lab, tomorrow morning so that the CK can be measured again, this time first thing in the morning, even though you know that the timing is unlikely to be a factor in Shane's significantly raised CK. The results from this second CK return and once again, Shane's CK is abnormally elevated.

Let's take a moment to put together all of the information we have gathered so far.

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Shane is a 3.5 year old boy presenting with gross motor delay. He does not demonstrate signs of an upper motor neuron disorder such as increased tone or spasticity and so we are less worried about a diagnosis of cerebral palsy. His normal head circumference and lack of dysmorphic facial features suggests this is unlikely a metabolic disorder. He has not lost any developmental milestones and he does not have any fasciculations suggesting this is less likely to be a neurodegenerative process or lower motor neuron disease, such as SMA. However he does demonstrate weakness particularly proximally in his lower extremities with the positive Gower sign; he has enlarged calf muscles, and his lab testing so far has been normal except for a repeat elevated CK 50x the normal limit.

Combining all of this information, what are you most concerned about for Shane?
If you were thinking about muscular dystrophy, you're on the right track!

What is Muscular Dystrophy?
Let's take a moment to learn a little bit more about muscular dystrophy.

Muscular dystrophy is a group of genetic disorders causing progressive muscle weakness and atrophy. Unlike other causes of weakness, muscular dystrophies cause changes in the skeletal muscle itself rather than impacting the nerve or neuromuscular junction such as is seen in Guillain Barre Syndrome or Spinal Muscular Atrophy. The two most common types of muscular dystrophy are Duchenne Muscular Dystrophy and Becker Muscular Dystrophy, both of which are labelled dystrophinopathies, as they result from defects in the dystrophin gene. Defects in the dystrophin gene lead to unstable sarcolemmas, which cause cellular proteins, such as CK, to escape from the damaged cell. In the short term, the muscle cells are able to regenerate, but long term there is muscle atrophy, which gets replaced with fatty and fibrous tissue. This replacement of healthy muscle tissue with fatty and fibrous tissue is what creates the characteristic calf muscle pseudohypertrophy.

Both Duchenne and Beckers are inherited in an X-linked recessive pattern, but there is a high spontaneous mutation rate with up to ⅓ of cases being attributed to new mutations. In Duchenne Muscular Dystrophy, the genetic defect results in no dystrophin being produced and thus usually presents with more severe symptoms and typical onset by 5 years of age. The genetic difference in Becker Muscular Dystrophy results in misshapen dystrophin being produced. Thus, the symptom profile is often milder than that seen in Duchenne's and the age of onset is older, between 10 and 20 years of age.

Duchenne Muscular Dystrophy typically presents in boys who are asymptomatic in early infancy and initially meet their developmental milestones. Occasionally some children present with global developmental delay or a delay in achieving early motor milestones. Around age 4, the symptoms from progressive skeletal muscle weakness begin to become apparent. This typically presents with a waddling gait, trouble climbing stairs, and toe walking due to contractures. Proximal pelvic girdle muscle weakness becomes evident, particularly as the children show difficulty rising from the floor. Gower's sign is

the classic physical exam finding where children walk their hands up their legs to help them return to a standing position. Generally, these boys lose the ability to walk before age 13, if left untreated.

Becker Muscular Dystrophy presents with a milder and slower deterioration. Children can present with severe cramps on exertion. Because these children experience later onset disease, they may remain ambulatory later into adolescence than in Duchenne's. Once children lose ambulation, progressive scoliosis and equinovarus deformities of the feet are common. Weakening intercostal muscles results in a progressive, restrictive respiratory failure and nocturnal hypoventilation. Duchenne Muscular Dystrophy also causes a primary dilated cardiomyopathy, the incidence of which increases into adolescence. Patients with Duchenne Muscular Dystrophy rarely survive beyond the age of 30. In contrast, patients with Becker Muscular Dystrophy typically survive to a mean age of 45, with the commonest cause of mortality being heart failure from dilated cardiomyopathy, though some patients survive into late adult life. Boys with muscular dystrophy are also more likely to present with intellectual disability.

Children with muscular dystrophy will show a dramatic elevation in CK, often 50 to 100 times the normal value. These children can also present with elevation in other muscle enzymes such as AST and ALT. It is important to remember that elevated transaminases are not always caused by a hepatic source.

After repeat abnormal CK's, it is necessary to refer these children on to a neuromuscular specialist and genetic analysis should be completed to look for mutations. If the CK returns normal, this makes muscular dystrophy much less likely and therefore an alternative diagnosis should be considered.

In the past, muscle biopsies played an important role in diagnosing muscular dystrophy. Recent advancements in genetic analysis techniques have made it so that biopsy is no longer routinely required. It may also be tempting to consider an EMG in the work up of these children, but EMG changes in muscular dystrophy are nonspecific and do not add further information to an already complete workup.

There are a number of other, more rare, muscular dystrophies including Congenital Muscular Dystrophy, Myotonic Dystrophy, Limb Girdle Muscular Dystrophy and Emery-Dreifuss Muscular Dystrophy. The genetics and presentations of these disorders vary slightly from Duchenne and Becker, but the specific details of each are beyond the scope of this podcast.

Management

Now that we know a little bit more about muscular dystrophy, let's explore its management.

Care for patients with muscular dystrophy requires a multidisciplinary team. Throughout a child's course with muscular dystrophy, in addition to their general pediatrician, their care team may include: pediatric neurology, physiatry, respirology, cardiology, mental

health, physiotherapy, occupational therapy, orthopedics, plastic surgery, and endocrinology. While this is not an exhaustive list, it gives you a bit of a picture of how caring for a child with muscular dystrophy could quickly become overwhelming for a parent.

While a cure for muscular dystrophy has yet to be discovered, corticosteroids have been proven to extend the number of years a child can ambulate. Steroids, and in particular diflazacort, have also been shown to increase life expectancy, on average, into a patient's thirties when coupled with extensive rehabilitative care. Side effects of steroids should be closely monitored, particularly cataracts.

Routine health surveillance for children with muscular dystrophy requires close attention to their nutrition and bone health, as well as annual pulmonary function testing, ECGs and cardiac echos. As these children often develop osteopenia due to their reduced mobility, it is recommended that they take daily vitamin D and calcium supplements.

Rehabilitation focuses on promoting and maintaining ambulation, with interventions including but not limited to: physical therapy, occupational therapy, orthotic devices, night splints and surgical tendon lengthening. Boys are encouraged to participate in regular moderate aerobic activity, which prevents muscle atrophy from lack of use, as well as excessive weight gain and social isolation. As the disease progresses, and a child's needs become more complex, the multidisciplinary team will also need to adapt the goals and care plan.

Newer approaches to treatment of Duchenne Muscular Dystrophy include clinical trials looking at gene modification therapies, such as nonsense read-through and exon skipping drugs. At the current time, however, the cornerstone of management of muscular dystrophy remains corticosteroids and intensive multidisciplinary rehabilitative care.

Back to the Case
Let's get back to the case.

Shane and both of his parents have returned to the pediatric clinic for a follow up appointment. They are anxious to hear about the results of the blood work. Together with your preceptor you share with the family that Shane's CK is quite elevated and given this, along with his history and physical exam, makes you suspicious for muscular dystrophy. You discuss the probable diagnosis of muscular dystrophy and Shane's parents ask you what the next steps are. You explain that a referral has been sent to a pediatric neuromuscular specialist and genetic analysis will be completed in order to further confirm the diagnosis. Until they are able to see the specialist, they should continue to encourage Shane to be active while making sure the home is safe and Shane is not at risk for significant falls. You acknowledge that this is likely an overwhelming appointment for the family and encourage them to call the clinic or book another appointment if they have any questions or concerns.

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Conclusion

That's all for muscular dystrophy! Let's review some take home points from the podcast:

1. The differential diagnosis of gross motor delay is broad and includes things such as cerebral palsy, muscular dystrophy, spinal muscular atrophy, as well as thyroid disease, congenital heart disease and metabolic disorders.
2. Gross motor delay, do a CK, if you ever have a concern! And if the first test returns abnormal it is important to repeat the CK again, first thing in the morning.
3. Duchenne muscular dystrophy is an X-linked recessive disorder causing progressive weakness in skeletal muscles. It often presents with weakness seen in the proximal muscles first, which can include symptoms such as difficulty using stairs, difficulty running or walking, more frequent falls, and a positive Gower's sign. It can also present with calf pseudohypertrophy, though this may be more subtle at a young age.
4. Management of muscular dystrophy includes a multidisciplinary team that changes as the disease progresses and the child's needs become more complex. On average, children with Duchenne Muscular Dystrophy do not survive beyond the third decade of life, while children with Becker Muscular Dystrophy have a longer life expectancy.
5. There is no definitive treatment for muscular dystrophy but the progression of the disease can be slowed with the use of daily corticosteroids and prolonging physical activity.

That's all for today. You should now be able to:

1. Develop a differential diagnosis to gross motor delay in children
2. Identify key investigations in the work up of a child with gross motor delay
3. List key features in the presentation of Duchenne Muscular Dystrophy
4. Discuss the importance of an interdisciplinary approach in the management of children with Duchenne Muscular Dystrophy

Thanks for listening!

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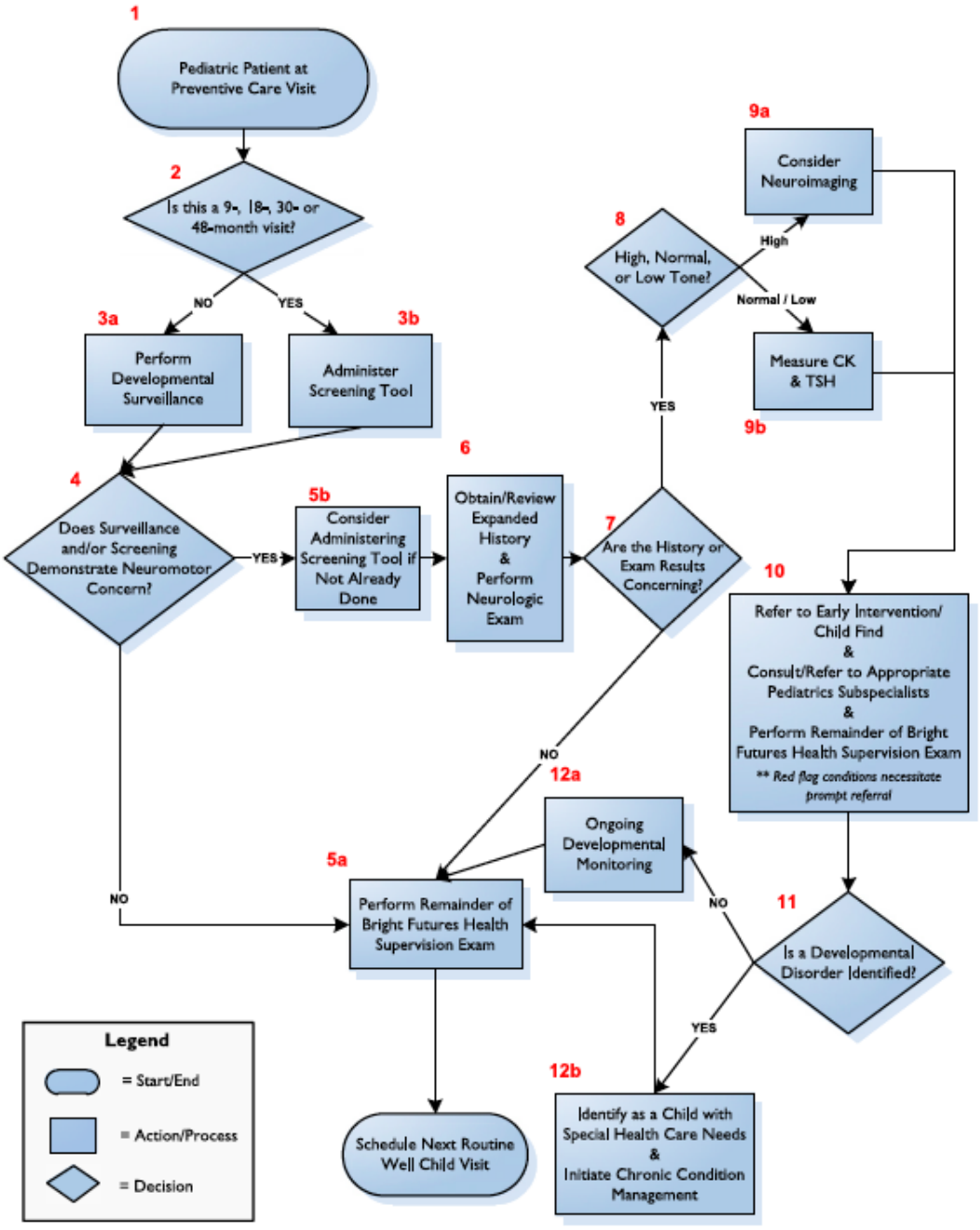

Figure 1: Approach to Child with Motor Delays (Noritz & Murphy (2013))

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