Clinical Reasoning: A 6-Year-Old Girl With Progressive Toe Walking

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*Neurology*® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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Contributions:
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Ahmed Ibrahim: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Number of characters in title: 67

Abstract Word count: 26

Word count of main text: 1492

References: 10

Figures: 1

Tables: 1

Supplemental: Patient consent to disclose form. CARE Form


Acknowledgements: None

Study Funding: The authors report no targeted funding

Disclosures: The authors report no disclosures relevant to the manuscript.
Section 1:

A 6-year-old girl presented to clinic for evaluation of progressive gait abnormality of 3 years duration.

Following an uneventful perinatal history. She first started walking around 18 months, and gait was appropriate for age. By 3 years of age, she was able to run, and ride a tricycle. She was on target in fine motor, speech, and social milestones.

Around the age of 3 years, she started walking on her tip toes (plantar flexion at the ankles) and had in-toeing (toes point towards midline instead of straight ahead). These abnormalities became more obvious and persistent overtime. She started having difficulty walking and was tripping frequently. She had to use a walker or a wheelchair for longer distances. She intermittently complained of leg pain and back pain. Her symptoms would partially improve after sleep and would get worse in the afternoon to the point where she would crawl on her knees. Her symptoms continued to progress despite physical therapy, braces, and casting.

She had no other neurological symptoms, including change in bowel or bladder habits, and no tingling or numbness. She had no regression in cognitive, speech, or fine motor skills. There was no concern for autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), or learning disability.

She had no chronic medical illnesses, no previous surgeries, and was not on medications. She had no siblings, and no family history of a similar condition.

Her general exam was normal, and showed no skeletal deformities, no limited range of motion, no sacral dimple, and no neuro-cutaneous stigmata. She was alert and oriented and had fluent speech. Cranial nerves were intact. She had normal tone and 2+ deep tendon reflexes (DTR) in the upper extremities (UE). Tone was mildly increased at both knees and increased at both ankles. DTR were 3+ at both patellae and both ankles, with down going toes. Strength was 5/5 throughout, and sensation was intact to light touch, vibration, and proprioception throughout. She had no ataxia, and no dysmetria. Her feet were plantar flexed, and her toes were turned inwards, but could be manipulated passively. She had to use a walker to ambulate, and her heels were not touching the floor. Her right leg appeared slightly shorter than the left while walking. (Video 1, part1)
Questions for consideration:

What is the differential diagnosis for TW?
What are some of the red flags for pathological TW?
Which parts of neurological history and exam are relevant when evaluating TW?

Section 2:

TW is defined as lack of heel strike during the stance phase of gait cycle. It is a common variation of normal gait development. Persistent TW past 2–3 years of age warrants further evaluation. Differential diagnosis for pathological TW is wide, and includes neurological, developmental, and orthopedic problems. (Table 1).

TW affects around 2% of normally developing children, and 40% of children with a neuropsychiatric diagnosis or developmental delay \(^1\).

Of patients referred to neurology clinic for TW, around 60% are found to have a neurological etiology \(^2\). The most common etiologies include idiopathic TW, diplegic cerebral palsy (DCP), and neurodevelopmental conditions \(^2\). Red flags for pathological TW include onset after a period of normal walking, asymmetry, and abnormal neurological exam.

Detailed history and physical exam help narrow the differential diagnosis and guide further evaluation. This includes details of perinatal and early developmental history, and onset and progression of the gait abnormality. Relevant neurological symptoms include cognitive regression, muscle weakness, sensory deficits, back pain, and bowel and bladder issues. Other family members may have been diagnosed with neurological conditions or be known to have an abnormal gait. A full general as well as neurological exam is warranted, including back and lower extremities.

Questions for consideration:

How does the information provided in the history and exam above help narrow your differential diagnosis?
Section 3:

The conditions listed in Table 1 may present with TW, but each has characteristic symptoms and exam findings. Patients with DCP typically have history of brain injury in the perinatal period, gait abnormality is noted when they first start walking, and gait usually improves with therapy. For our patient, uneventful perinatal history, onset of TW after a period of normal walking, and progressive worsening despite physical therapy made DCP unlikely.

TW is more prevalent in patients with neuropsychiatric conditions, and unlike our patient, the neurological exam usually shows normal or decreased tone and normal DTR. Peripheral neuropathies are typically associated with abnormal sensation and decreased or absent DTR. Myopathies and muscular dystrophies present with muscle atrophy, pseudohypertrophy, or muscle weakness. McArdle is a rare type of Glycogen Storage Disease that could present with TW. Patients have fatigue, muscle pain and cramps during the first few minutes of exercise, and a “second wind phenomenon” which denotes a marked improvement in exercise capacity after a period of rest. Patients have characteristic musculoskeletal variations and elevated creatine kinase (CK). Musculoskeletal and orthopedic disorders present with skeletal deformities, limited range of motion, and or contractures. None of these symptoms or signs were present in our patient.

Dystonia is an abnormal muscle tone leading to abnormal posture. It can be due to acquired or genetic disorders. Various types of genetic dystonia are classified based on their distribution (focal, segmental, generalized, etc), associated symptoms, mode of inheritance, and molecular genetic data. Dystonia may only be present during certain tasks and with certain positions. Observing the patient in various positions helps differentiate dystonia from spasticity which tends to be present in all positions. It helps to ask patients to walk in a long hallway, and observe while walking on their tiptoes, their heels, walking backwards, and running if possible. It is important to ask about specific triggers, exacerbating and alleviating factors. Our patient had more sustained posture of her feet while walking compared to when she was sitting. She reported diurnal variations of her symptoms with improvement after sleep. This raised concern for a genetic dystonia disorder.

Hereditary spastic paraplegia (HSP) is a heterogeneous group of genetic conditions characterized by progressive lower limb spasticity and weakness. Various types can be inherited as autosomal recessive or autosomal dominant, and genetic panels are available to test for known mutations. Exam shows upper motor neuron signs.
in the LE, including spasticity, hyper reflexia, and positive Babinski’s sign. Uncomplicated forms mainly cause gait abnormality. Complicated forms may be accompanied by other neurological symptoms including dystonia, dysarthria, cognitive impairment, ataxia, and peripheral neuropathy. We considered the possibility of HSP causing dystonia, but the patient did not have spasticity, had no other neurological symptoms, and her toes were down going.

Spinal cord pathologies may cause progressive gait abnormality, back pain, and hypertonia and hyper-reflexia in the LE. The overall incidence of tethered cord in patients presenting with toe walking is low (0.6 %) but it should be considered since it is a treatable cause. The absence of bowel and bladder issues made it less likely.

**Questions for consideration:**
What investigations would you consider?

**Section 4:**
Lower limb x-rays were normal. Brain and lower spine MRIs were normal. The report of diurnal variation of symptoms raised concern for a specific type of genetic dystonia called Dopa- Responsive Dystonia (DRD). A trial of L-Dopa led to dramatic response within few days of starting the medication. (Video 1, part2).

**Questions for consideration:**
How do you confirm the diagnosis?
Describe the long-term management and outcome of this condition?

**Section 5:**
A comprehensive dystonia panel showed a pathogenic heterozygous variant (c.509+1_509+3delinsTGTGAG) in the GCH1 gene. It affects a donor splice site in intron 3 of the gene, is expected to disrupt RNA splicing, and likely results in an absent or disrupted protein product. This confirmed the diagnosis of DRD. The patient continued L-Dopa 10mg/kg/day and has been doing well.

**Discussion**
Dopa-responsive dystonia (DRD, also known as Segawa’s disease, or DYT5) should be considered on the differential diagnosis of progressive TW, even in the
absence of positive family history of a similar condition. Mutations in the GCH1 gene are the most common cause of DRD, but it may result from mutations in the TH or SPR gene\textsuperscript{7}. DRD is estimated to affect 1 per million people worldwide but is likely underdiagnosed or misdiagnosed because it can present with mild symptoms. Symptoms typically start in early childhood with the development of equinovarus foot posturing and impaired walking and balance\textsuperscript{7}. Patients characteristically report diurnal variation of their symptoms, with improvement after sleep. Neurological exam may show normal or increased DTR. Patients are at risk of other co morbidities including sleep disturbances\textsuperscript{8} and mood disorders, and one study showed that 64\% of patients had cognitive impairment\textsuperscript{9}. Patients show dramatic and sustained response to L-dopa therapy, even if diagnosis is delayed. Treatment is life-long\textsuperscript{10}.

**Conclusion:**

TW can be the presenting symptom of various neurological, developmental, and orthopedic disorders. A detailed neurological history and physical exam can narrow the differential diagnosis and guide further evaluation and management. Treatable causes of toe walking should be considered, even if the presentation is atypical.

Video 1-http://links.lww.com/WNL/B692

**References:**


Table 1: Differential diagnosis of toe-walking:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Idiopathic TW</td>
<td>-Uneventful history</td>
</tr>
<tr>
<td></td>
<td>-Normal neurological exam</td>
</tr>
<tr>
<td></td>
<td>-No red flags</td>
</tr>
<tr>
<td>-Diplegic cerebral palsy (CP)</td>
<td>-H/o of perinatal brain injury.</td>
</tr>
<tr>
<td></td>
<td>-Static symptoms.</td>
</tr>
<tr>
<td></td>
<td>-UMN signs in the lower extremities</td>
</tr>
<tr>
<td>-Neurodevelopmental disorders (ASD, ADHD)</td>
<td>-Symptoms of these conditions.</td>
</tr>
<tr>
<td></td>
<td>-Neurological exam essentially normal.</td>
</tr>
<tr>
<td>-Dystonia including Dopa-Responsive dystonia (DRD)</td>
<td>-Progressive symptoms</td>
</tr>
<tr>
<td></td>
<td>-Diurnal variation</td>
</tr>
<tr>
<td></td>
<td>-Positive family history</td>
</tr>
<tr>
<td></td>
<td>-Dystonic posture of the limbs</td>
</tr>
<tr>
<td>-Hereditary Spastic Para paresis (HSP)</td>
<td>-Progressive symptoms</td>
</tr>
<tr>
<td></td>
<td>-Positive family history</td>
</tr>
<tr>
<td></td>
<td>-UMN signs in the lower extremities</td>
</tr>
<tr>
<td>Condition</td>
<td>Symptoms</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Tethered cord, spinal cord tumors              | - Progressive symptoms  
- Back pain, bowel or bladder symptoms.  
- UMN signs in the lower extremities          |
| Charcot Marie Tooth (CMT)                      | - Progressive symptoms  
- Positive family history  
- Feet deformities  
- Decreased sensation  
- LMN signs in the lower extremities           |
| Duchenne Muscular Dystrophy (DMD)              | - Progressive symptoms  
- Positive family history  
- Muscle weakness and pseudohypertrophy  
- Elevated CK                                   |
| Glycogen Storage Diseases (GSD) McArdle disease| - Muscle cramps  
- “second wind” phenomenon.  
- Elevated CK                                   |
| Musculoskeletal disorders: short Achilles tendon, hip dislocation, etc. | - Skeletal deformities  
- Contractures  
- Neurological exam essentially normal.        |

Video 1
Clinical Reasoning: A 6-Year-Old Girl With Progressive Toe Walking
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*Neurology* published online December 8, 2021
DOI 10.1212/WNL.0000000000013183

This information is current as of December 8, 2021

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