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

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Video

Section 1

A 6-year-old girl presented to the clinic for evaluation of progressive gait abnormality of 3 years duration. She had an uneventful perinatal history. She first started walking around 18 months, and gait was appropriate for age. By age 3 years, she was able to run and ride a tricycle. She was on target in fine motor, speech, and social milestones.

Around age 3 years, she started walking on her tiptoes (plantar flexion at the ankles) and had intoeing (toes point toward midline instead of straight ahead). These abnormalities became more obvious and persistent over time. 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 neurologic 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, attention deficit hyperactivity disorder, 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 examination was normal and showed no skeletal deformities, no limited range of motion, no sacral dimple, and no neurocutaneous stigmata. She was alert and oriented and had fluent speech. Cranial nerves were intact. She had normal tone and 2+ deep tendon reflexes (DTRs) in the upper extremities. Tone was mildly increased at both knees and increased at both ankles. DTRs were 3+ at both patellae and both ankles, with downgoing 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 inward, 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, part 1).

Questions for Consideration:

1. What is the differential diagnosis for toe walking (TW)?
2. What are some of the red flags for pathologic TW?
3. Which parts of neurologic history and examination are relevant when evaluating TW?

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Section 2

Toe walking (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 pathologic TW is wide and includes neurologic, developmental, and orthopedic problems (Table). TW affects around 2% of normally developing children and 40% of children with a neuropsychiatric diagnosis or developmental delay.[1]

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

Table Differential Diagnosis of Toe Walking

Etiology	Characteristic features
Idiopathic toe walking	Uneventful history Normal neurologic examination No red flags
Diplegic cerebral palsy (CP)	H/o of perinatal brain injury Static symptoms UMN signs in the lower extremities
Neurodevelopmental disorders (ASD and ADHD)	Symptoms of these conditions Neurologic examination essentially normal
Dystonia including dopa-responsive dystonia (DRD)	Progressive symptoms Diurnal variation Positive family history Dystonic posture of the limbs
Hereditary spastic paraparesis (HSP)	Progressive symptoms Positive family history UMN signs in the lower extremities
Tethered cord, spinal cord tumors	Progressive symptoms Back pain and 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 (GSDs) McArdle disease	Muscle cramps Second wind phenomenon Elevated CK
Musculoskeletal disorders: short Achilles tendon, hip dislocation, etc.	Skeletal deformities Contractures Neurologic examination essentially normal

Abbreviations: ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder.

Detailed history and physical examination 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 neurologic symptoms include cognitive regression, muscle weakness, sensory deficits, back pain, and bowel and bladder issues. Other family members may have been diagnosed with neurologic conditions or be known to have an abnormal gait. A complete general and neurologic examination is warranted, including back and lower extremities.

Question for Consideration:

1. How does the information provided in the history and examination above help narrow your differential diagnosis?

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Section 3

The conditions listed in the Table may present with TW, but each has characteristic symptoms and examination findings. Patients with DCP typically have a 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 neurologic examination 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.[3] 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. 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.[4] 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. Patients should be observed while walking on their tiptoes, their heels, and walking backwards. This is best done in a long hallway. It is important to ask about specific triggers, exacerbating and alleviating factors. Our patient had more sustained posture of her feet while walking compared with 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,[5] and genetic panels are available to test for known mutations. Examination shows upper motor neuron signs in the LE, including spasticity, hyperreflexia, and positive Babinski sign. Uncomplicated forms mainly cause gait abnormality. Complicated forms may be accompanied by other neurologic 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 and had no other neurologic symptoms, and her toes were downgoing.

Spinal cord pathologies may cause progressive gait abnormality, back pain, and hypertonia and hyperreflexia in the lower extremities. The overall incidence of tethered cord in patients presenting with TW is low (0.6%),[6] but it should be considered because it is a treatable cause. The absence of bowel and bladder issues made it less likely.

Question for Consideration:

1. What investigations would you consider?

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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, part 2).

Questions for Consideration:

1. How do you confirm the diagnosis?
2. Describe the long-term management and outcome of this condition.

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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 10 mg/kg/d and has been doing well.

Discussion

Dopa-responsive dystonia (DRD, also known as Segawa 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.[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.[7] Patients characteristically report diurnal variation of their symptoms, with improvement after sleep. Neurologic examination may show normal or increased DTR. Patients are at risk of other comorbidities including sleep disturbances[8] and mood disorders, and 1 study showed that 64% of patients had cognitive impairment.[9] Patients show dramatic and sustained response to L-Dopa therapy, even if diagnosis is delayed. Treatment is lifelong.[10]

Conclusion

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

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Appendix Authors

Name	Location	Contribution
Amal Abu Libdeh, MBBS	Department of Neurology Charlottesville, University of Virginia, Virginia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Ahmed Ibrahim, MBBCH	Department of Neurology Charlottesville, University of Virginia, Virginia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

References

1. Ruzbarsky JJ, Scher D, Dodwell E. Toe walking: causes, epidemiology, assessment, and treatment. *Curr Opin Pediatr.* 2016;28(1):40-46.
2. Haynes KB, Wimberly RL, VanPelt JM, Jo C-H, Riccio AI, Delgado MR. Toe walking: a neurological perspective after referral from pediatric orthopaedic surgeons. *J Pediatr Orthop.* 2018;38(3):152-156.
3. Pomarino D, Martin S, Pomarino A, Morigeau S, Biskup S. McArdle's disease: a differential diagnosis of idiopathic toe walking. *J Orthop.* 2018;15(2):685-689.
4. Zorzi G, Carecchio M, Zibordi F, Garavaglia B, Nardocci N. Diagnosis and treatment of pediatric onset isolated dystonia. *Eur J Paediatr Neurol.* 2018;22(2):238-244.
5. Lallemant-Dudek P, Durr A. Clinical and genetic update of hereditary spastic paraparesis. *Rev Neurol (Paris).* 2021;177(5):550-556.
6. Cho K, Sinner A. Incidence of tethered cord in toe walking: single center experience at gillette children's specialty healthcare. *PM R.* 2016;8(9S):S152.
7. Wijemanne S, Jankovic J. Dopa-responsive dystonia—clinical and genetic heterogeneity. *Nat Rev Neurol.* 2015;11(7):414-424.
8. Brüggemann N, Stiller S, Tadic V, et al. Non-motor phenotype of dopa-responsive dystonia and quality of life assessment. *Parkinsonism Relat Disord.* 2014;20(4):428-431.
9. López-Laso E, Sánchez-Raya A, Moriana JA, et al. Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease. *J Neurol.* 2011;258(12):2155-2162.
10. Lee W-W, Jeon BS. Clinical spectrum of dopa-responsive dystonia and related disorders. *Curr Neurol Neurosci Rep.* 2014;14(7):461.

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