Clinical Reasoning: Pes cavus and neuropathy

Think beyond Charcot-Marie-Tooth disease

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Section 1

An 18-year-old woman was referred to a neuromuscular clinic for neuropathy and tremors. She had been born full-term and had mildly delayed walking at 14 months. She was a toe-walker, clumsy, and when running, had difficulty keeping up with her peers. She was diagnosed with attention-deficit/hyperactivity disorder (ADHD) at age 7 and was found to have high arches and difficulty with heel-walking. EMG and nerve conduction studies (NCS) were performed, showing demyelinating neuropathy (table e-1, doi.org/10.5061/dryad.876r5m5). With her history and EMG/NCS findings, she was diagnosed with Charcot-Marie-Tooth (CMT) disease. Symptoms progressed over the next few years, characterized by tripping, occasional falls, and continued difficulty running. She could climb stairs without the use of a handrail, but was very cautious going down the stairs. She also developed tremors in the hands (left > right), which would worsen when she approached objects. There was no loss of sensation, paresthesias, bladder or bowel problems, or hearing or visual symptoms. She graduated from high school and was accepted into college. Family history was negative for neurologic disorders. Neurologic examination showed normal mental status and cranial nerves. There were no abnormal eye movements or corticobulbar findings (no brisk jaw jerk, gag reflex, dysarthria, or pseudobulbar palsy). She had ankle contractures and pes cavus. She had mild lower limb spasticity without atrophy or fasciculations, and 5−/5 weakness of distal extremity muscles, including bilateral abductor digiti minimi, first dorsal interossei, tibialis anterior, and extensor hallucis longus. Tendon reflexes were 2+ in the upper extremities and brisk (3+) in the lower extremities; plantars were extensor. Sensation was intact to light touch, pain, temperature, and proprioception, but vibration was mildly reduced at the toes. She had cerebellar intention tremors (left > right) and mild dysmetria on finger-to-nose testing without appreciable dysdiadochokinesia. Her gait was mildly wide-based and tandem gait was impaired.

Questions for consideration:

1. What are the differential diagnoses in this case?
2. What tests could narrow the differential diagnosis in this case?

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Section 2

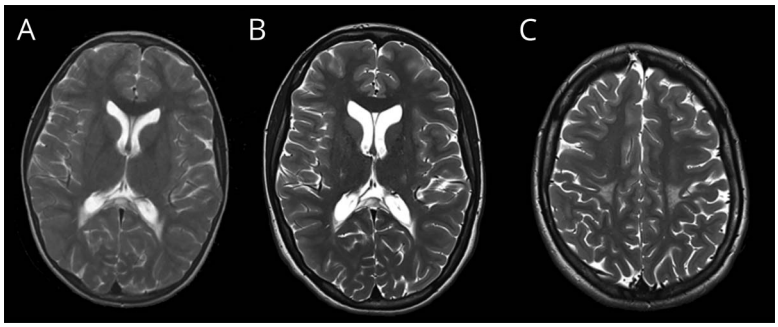
The patient had upper motor neuron (UMN) signs in the legs (spasticity, brisk reflexes, extensor plantar reflexes), cerebellar signs (intention tremors, dysmetria, impaired tandem gait), impaired vibration sensation, and pes cavus. Pes cavus is a fixed foot deformity causing high arches, which is frequently found in association with long-standing neuropathy (either inherited or acquired). It can be seen in patients with hereditary spastic paraplegia,[2] Friedreich ataxia (FA),[3] and some patients with spinal dysraphism (spina bifida, tethered cord syndrome). Though pes cavus is commonly seen in CMT, it would be unusual to have brisk reflexes in the demyelinating form of CMT. CMT most commonly causes distal weakness, atrophy, and sensory loss with arreflexia,[1] though rare CMT subtypes can have pyramidal features.[4] The localization might involve posterolateral cord (corticospinal tract + dorsal column), tremor circuit (bilaterally from the deep cerebellar nuclei, cerebellar outflow tracts to the contralateral ventral lateral nucleus of the thalamus), and demyelinating polyneuropathy or myeloneuropathy. Compressive myelopathy would be less likely given lack of pain, sensory level, or bowel/bladder involvement.

Genetic noncompressive myelopathies should be considered given the young age at symptom onset. Hereditary spastic paraplegias (HSP) are a group of genetic disorders with variable modes of inheritance resulting from a length-dependent axonopathy of corticospinal tracts causing UMN signs.[2] Clinically, HSP can be divided into "pure" type (prominent lower limb spasticity, hyperreflexia, extensor plantars, and sometimes urinary symptoms and impaired distal vibratory sensation) and "complex" types (neuropathy, seizures, parkinsonism, cognitive impairment, ataxia, amyotrophy, short stature, visual or hearing abnormalities). HSP can sometimes overlap with other disorders characterized by cerebellar ataxia, neuropathy, motor neuron disease, cognitive impairment, and leukodystrophy.[2] Our patient showed clinical features of complex HSP (lower limb pyramidal tract signs, cerebellar ataxia, neuropathy). Another condition to consider includes FA, which is the most common form of autosomal recessive ataxia caused by homozygous intronic GAA triplet expansion (70–1,000 GAA triplets) in 96% of cases.[5] The mean age at onset is 10–15 years with gait ataxia, pyramidal tract signs (spasticity and extensor plantar responses), and sensory axonal neuropathy (impairment of joint position and vibration sense, areflexia).[3,5] Some patients with FA can have retained reflexes but demyelinating neuropathy would be unusual. Female carriers of X-linked adrenoleukodystrophy can present with myeloneuropathy.[6] Intention tremors can be caused by multiple sclerosis, spinocerebellar ataxias, and various degenerative, metabolic, or neoplastic disorders affecting deep cerebellar nuclei and their outflow tracts.

In our patient, presence of upper and lower motor neuron and possibly cerebellar findings could suggest neurometabolic disorders like late-onset leukodystrophies. Leukodystrophies are a heterogeneous group of inherited disorders with highly variable phenotype and genotype.[6] Presence of demyelinating neuropathy could further narrow the differential diagnosis[6]: X-linked adrenoleukodystrophy (adrenomyeloneuropathy in female patients), Krabbe disease (KD), metachromatic leukodystrophy, cerebrotendinous xanthomatosis (treatable condition that should be screened by checking cholestanol levels even in absence of tendon xanthomas), and Pelizaeus-Merzbacher-like disease (no nystagmus).

Laboratory tests showed normal blood counts, vitamin levels (B_{12}, folate, E), lactate, glucose, renal, liver, and thyroid functions, C-reactive protein, homocysteine, methylmalonic acid, and copper. Treatable causes of myeloneuropathy due to B_{12} and copper deficiencies were ruled out; cholestanol levels were not checked. Very long-chain fatty acids were normal, making adrenomyeloneuropathy less likely, though it can be normal in female carriers. MRI spine performed during the first evaluation was normal so was not repeated. MRI brain showed nonenhancing, confluent, symmetrical callosal and periventricular white matter lesions without much progression from the previous MRI (figure). MRI changes could suggest leukodystrophies, though lack of progression was unusual. Lumbar puncture was not performed. NCS showed prolonged distal latencies and slow conduction velocities with

Figure MRI brain



Symmetrical T2 hyperintensities within the calossal and periatrial white matter (A, B) and corona radiata bilaterally (C; these changes were absent in the first scan). MRI scan in (A) was performed in 2007 and (B, C) in 2018.

preserved amplitudes of both the sensory and motor responses, similar to a previous study and consistent with demyelinating neuropathy (table e-1, doi.org/10.5061/dryad.876r5m5). Needle EMG showed mild chronic reinnervation changes in the tibialis anterior muscle. Electrodiagnostic features along with the clinical course were more consistent with hereditary demyelinating neuropathy rather than an acquired demyelinating neuropathy. Genetic panel for CMT, which included the following genes, was negative at first evaluation: *PMP22*, *Cx32*, *MPZ*, *ERG2*, *NFL*, *GDAP1*, *LITAF*, *MFN2*, *SH3TC2*, *FIG4*.

Question for consideration:

1. What is the next step to achieve a definite diagnosis?

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Section 3

As the differential diagnosis was broad at this stage (complex HSP, leukodystrophies), whole exome sequencing (WES) was performed as the next diagnostic step. In this case, WES identified 2 known pathogenic mutations in the galactocerebrosidase gene (*GALC*): maternally inherited deletion of exons 11–17 (3′end) and paternally inherited c. 857G>A, p.G286D. GALC enzyme activity was low in the plasma, thus confirming KD. Lysosomal enzyme screening test is useful in diagnosing KD. Genetic counseling was provided and the patient was referred to the Genetics and Metabolism clinic for further evaluation and management.

Discussion

KD (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by mutation of the *GALC* gene.[7,8] The deficiency of lysosomal enzyme GALC in KD leads to accumulation of galactoceramide and neurotoxic galactosylsphingosine (psychosine) in macrophages (globoid cells) as well as neural cells especially in oligodendrocytes (centrally) and Schwann cells (peripherally) which in turn leads to the damage of myelin.[7]

KD occurs in approximately 1 in 250,000 births in the United States. Clinically KD can be divided into 2 major phenotypes: infantile-onset (<12 months, 85%–90%) characterized by progressive neurologic deterioration in infancy and death before age 2 years and later onset (>12 months, 10%–15%) with slower disease progression.[8] Within the later-onset type, patients can be further subdivided into late infantile (up to 3 years), juvenile (3–8 years), or adulthood, which is clinically more heterogeneous and less severe.[7,8] Our patient fits into juvenile-onset KD.

Children older than 6 years often exhibit behavioral symptoms (ADHD and mood disorders) first, followed by motor difficulties.[8] They often decline rapidly after disease onset followed by more gradual progression over years[9]; survival has been reported up to 26 years.[10] Our patient presented around age 7 with ADHD symptoms with slow progression and preserved cognitive function. Pes cavus has been reported before the diagnosis of KD (as seen in our patient) and is suggestive of peripheral neuropathy.[10] Most patients with infantile-onset KD have abnormal NCS with disease severity correlating with degree of demyelinating neuropathy.[10] Our patient had demyelinating neuropathy at age 7, which remained stable over a decade. About half of the patients with later-onset KD have p.G286D mutation,[8] as was seen in our patient. However, it is difficult to predict the clinical course as there is significant variability within the same family.[10]

Treatment of KD depends on the age at diagnosis and stage of the disease.[8] For children <6 months with stage II/III infantile-onset KD, treatment is largely supportive. Asymptomatic newborns identified by prenatal testing (based on positive family history) or abnormal newborn screening followed by additional testing and confirmed infantile-onset KD are candidates for hematopoietic stem cell transplant (HSCT) before 14 days.[8] There is no consensus regarding HSCT in asymptomatic newborns with abnormal newborn screening results presumed to be at risk for later-onset KD.[8] Preclinical studies are conducted for several potential treatment options including enzyme replacement therapy, neural stem cell transplantation, substrate reduction therapy, and chemical chaperone therapy.[8]

It is important to think beyond CMT when there are atypical clinical findings and radiologic abnormalities in spite of the presence of pes cavus and demyelinating neuropathy.

Author contributions

P.S. Ghosh: study concept and design. J. Alderson: acquisition of data. J. Alderson and P.S. Ghosh: analysis and interpretation. P.S. Ghosh: critical revision of the manuscript for important intellectual content. P.S. Ghosh: study supervision.

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Disclosure

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