Title: Cerebral Palsy is not a diagnosis; a case report of a novel atlastin-1 mutation

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Introduction

The term ‘cerebral palsy’ (CP) describes a group of developmental disorders of movement and posture attributed to disturbances occurring in the fetal or infant brain due to a static insult⁽¹⁾. The symptoms and signs may change over time, even though the underlying insult does not. We present a girl given the label of CP as an infant. This case highlights the need to never accept a “diagnosis” of cerebral palsy without a search for the underlying cause, especially if the course is suggestive of a progressive disorder.

Case report

A Caucasian female was born to non-consanguineous parents by normal vaginal delivery at term, after an uncomplicated pregnancy and no known exposure to teratogens. The perinatal period was normal. Her parents noted stiffness in her limbs and fisting of her hands in her first months of life, and by nine months sought medical attention for her motor delay. A paediatrician noted findings consistent with spastic quadriplegic CP, with otherwise normal development.

Her motor development was hindered by hypertonia and contractures, but with physical therapy and interventions including serial casting, splinting, botulinum toxin injections and surgical tendon releases, the patient began walking with a walker at 3 years of age (Gross Motor Function Classification System level IV) with ongoing normal cognitive and social development.

At age seven years, distal hypotonia and muscle wasting in her lower limbs became apparent. There was also a deterioration in strength and function of her upper limbs and she developed bulbar dysfunction with intermittent gagging on solid food. Hyperhidrosis was noted. She never achieved continence with bladder or bowel function. She had periods of increased hypertonia with pain, particularly while sleeping, requiring treatment with diazepam. She took no other medications.

There was a family history of intellectual disability in a half-brother, spina bifida occulta in the maternal grandmother and Factor V Leiden mutation in the mother. There was no family history of CP or neuromuscular disorders.

On examination, the patient was interactive with normal cognition. Her weight was on the 75th centile, her height on the 3rd centile and head circumference on the 90th centile throughout her life. Her cranial nerve examination was normal. She had no scoliosis. From early infancy she had significant spasticity and hyperreflexia with upgoing plantar responses. By the age of seven years, large joint contractures were noted at her shoulders, elbows, hips and knees, with distally-predominant muscle atrophy most marked in the hands and feet. An unusual posture was noted in the hands, with prominently adducted thumbs, and in the feet, with everted planovalgus deformity and overlapping toes. There was no sensory deficit.

Extensive assessments by multiple specialists were arranged by her primary paediatrician due to her unusually severe but isolated motor disorder. Reviews by a geneticist, two metabolic physicians and three paediatric neurologists were obtained. Magnetic resonance imaging (MRI) of the brain was performed at two, four and six years, and MRI of the spine was obtained at six years. All of these studies were normal. Her full blood count, electrolytes, liver function tests, thyroid function tests, creatine kinase and metabolic screening (including serum amino acids, lactate, pyruvate, urine amino and organic acids) were normal, as were her CSF glucose, cell count, lactate, amino acids and neurotransmitters.

Due to the presence of distal weakness and muscle atrophy, nerve conduction and electromyography performed at seven years demonstrated a length-dependant, chronic primarily axonal sensorimotor polyneuropathy. Muscle biopsy demonstrated mild fibre size variation with no structural abnormality on direct or electron microscopy and were felt to reflect secondary neuropathic changes. A sural nerve biopsy showed significant axonal loss without evidence of active degeneration or demyelination.

Genetic causes were pursued: a microarray and *SMN* gene testing were normal. The patient was then tested with a next generation sequencing gene panel including 277 known genes associated with neuromuscular disorders. A novel *de novo* mutation was identified in exon 12

of the *ATL1* gene, with a heterozygous T to C nucleotide substitution at position 1202 (c.1202T>C; p.Leu401Pro). This is a significant change in amino acid chemistry, occurring in the functional domain of the atlastin protein. This variant is absent from the Exome Aggregation Consortium database, a reference exome data set which excludes severe paediatric diseases, and on the basis of its predicted effect on the protein structure it was felt to be pathogenic. A diagnosis of hereditary spastic paraplegia (HSP) type 3A was made.

The patient remains under the care of a multi-disciplinary team, but has experienced a continued slowly progressive deterioration in her function.

Discussion

CP is the most common motor disability in children, affecting two in every 1000 live births⁽²⁾. However, as demonstrated in our case, this label should be used with caution and the underlying cause should be pursued. A careful history and examination, looking for suggestions of a non-CP diagnosis such as regression, peripheral neuromuscular findings, changing neurological signs over time, or decompensations during periods of metabolic stress should be sought in every patient with apparent CP⁽³⁾.

The presence of non-motor symptoms should be pursued including vision or hearing deficits, cranial nerve dysfunction and a history of epilepsy. In this child, the presence of severe and progressive motor disabilities in the absence of other CNS involvement and normal CNS imaging led the clinicians involved to pursue the extensive investigations performed.

The depth of investigation in CP should be informed by the history and examination. MRI is the highest yield investigation in CP, with around 89% of children with CP having an abnormal MRI⁽⁴⁾. Genetic testing should be considered⁽⁵⁾ as an abnormality can be found on a chromosomal microarray in 7-20% of all CP^(6,7) and 31% of cryptogenic CP⁽⁸⁾, while whole exome sequencing can find single gene disease causing variants in 14% of all CP⁽⁹⁾.

Metabolic investigations have lower yields in general (<4%), and are not routinely recommended. Nerve conduction studies are normally undertaken on suspicion of peripheral nervous system dysfunction and are not routine in the work up of CP, but were prompted in

this case by the findings of distally-predominant weakness, wasting and areflexia, which ultimately led to her genetic diagnosis.

Atlastin, or *ATL1*, plays a role in axon elongation in neuronal development⁽¹⁰⁾, and has been associated with an autosomal dominant (AD) sensory neuropathy (type ID) and an AD HSP (type 3A). HSP type 3A is typically a pure/uncomplicated HSP. A concomitant neuropathy has been described, but in previous cases has been a pure motor neuropathy. This is the first report of a sensorimotor axonal neuropathy in association with an *ATL1* mutation.

For the family of this child, completion of their diagnostic journey was as important as the diagnosis itself. Whilst this diagnosis did not alter management of this child's condition, a genetic diagnosis may prompt disease-specific treatment with an impact on clinical outcome, and can inform genetic and prognostic counselling, including prenatal testing where appropriate. The knowledge that this condition was caused by a *de novo* mutation in the patient was reassuring for the extended family. It is important for patients that the clinicians looking after children with CP do not lose sight of the fact that CP is by definition secondary to an underlying neurological disorder and is not a diagnosis in itself. When the cause of CP is uncertain it is important to revisit diagnostic testing.

Learning points

- Cerebral palsy is a disorder of movement, posture and tone due to a static insult to the developing brain
- The label cerebral palsy does not define the underlying cause of the symptoms
- A number of conditions can mimic cerebral palsy, including hereditary spastic paraplegia
- The clinician looking after children with cerebral palsy should always consider what the underlying diagnosis may be and uncertainty about that diagnosis should prompt further investigation and referral

Multi-Choice Questions

- 1) A 3 year old boy presents with gross motor delays, hyperreflexia and spasticity in the lower limbs with scissoring of the legs but an otherwise normal neurological exam. Pregnancy history and perinatal history is unremarkable and cognitive development is normal. His maternal uncle has a diagnosis of diplegic cerebral palsy but his mother is thought to be normal. What is the most likely diagnosis causing these findings?
- a) Spastic diplegic cerebral palsy
 - b) X linked spinocerebellar ataxia
 - c) Hereditary spastic paraplegia
 - d) Worster-Drought syndrome
 - e) Tethered cord syndrome

Answer c)

- a) This is not a diagnosis.
 - b) While the inheritance pattern may fit an X-linked disorder, the absence of ataxia or other abnormalities on cranial nerve examination makes this unlikely
 - c) Penetrance in dominantly inherited HSP is 70-90% with variable expressivity seen. HSP can also be X-linked so the absence of known symptoms in the mother should not dissuade clinicians from this diagnosis
 - d) Presents with mild spastic diplegia or tetraplegia with pseudobulbar palsy
 - e) Can present with spasticity in context of cord ischaemia, but usually presents with atrophy and hyporeflexia without family history.
- 2) When hereditary spastic paraplegia is suspected, what investigation is likely to be most helpful in determining the specific subtype?
- a) Brain and spine MRI
 - b) Chromosome microarray
 - c) Spastin gene sequencing
 - d) Hereditary spastic paraplegia multigene panel
 - e) NCS/EMG

Answer d)

- a) Neuroimaging is typically normal in HSP. Although thinning of the corpus callosum or white matter abnormalities are seen in some subtypes, these changes are unlikely to suggest a specific subtype
 - b) Microarray testing only detects duplications, deletions and regions of homozygosity and will miss most significant mutations in HSP which are intragenic
 - c) Sequential genetic testing based on mode of inheritance and additional clinical findings is a reasonable approach to disease detection. Spastin mutations represent only 30-40% of autosomal-dominant HSP.
 - d) Multi-gene panels are relatively new in clinical practice but are particularly helpful on conditions with considerable genetic heterogeneity. Where HSP is considered, referral to a clinical geneticist for panel testing will be helpful.
 - e) A finding of a neuropathy in the context of HSP is helpful to refine the list of likely genetic aetiologies. However, at least seven of the 56 currently identified subtypes of HSP are associated with neuropathy.
- 3) Which of the following investigations is the most useful first line test in a child with CP of an unknown aetiology?
- a) Nerve conduction studies
 - b) MRI brain
 - c) Urine metabolic screen
 - d) Chromosome microarray
 - e) EEG

Answer b)

- a) Nerve conduction studies and EMG are generally normal in children with CP
- b) MRI brain is abnormal in around 90% of patients with CP, and is recommended in the evaluation of children with idiopathic CP.
- c) Metabolic causes of CP are infrequent (<4%), but can mimic CP, particularly dystonic CPs, so a urine metabolic screen is a useful (and cheap) test to consider

- d) Microarray has a yield of ~7% in all cases of CP
- e) EEG is primarily useful for investigating epilepsy, and is rarely diagnostically helpful in CP.

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