Clinical Reasoning: A child with arthrogryposis

Congenital myasthenic syndrome-*CHRNA1* mutation

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Section 1

A 5-year-old girl was evaluated for arthrogryposis. She was born at 34 weeks complicated by polyhydramnios and reduced fetal movements. She had symmetric growth parameters at birth. She had respiratory distress after birth requiring intubation, feeding difficulties and aspirations requiring nasojejunal feeding and subsequently gastrostomy tube, and stridor, for which she underwent supraglottoplasty. She had bilateral talipes equinovarus at birth and underwent surgical correction at 9 months. There were also mild contractures of the wrists, which did not require surgical interventions. She had paucity of facial movements, ptosis, and hypotonia noticed after birth. She had delayed motor milestones and was always slower compared to other children in terms of walking, running, and climbing stairs. She needed to hold on to the railing while climbing stairs and support to get up from the floor. She was mostly gastrostomy tube fed. She tired easily with physical activities and there was history of diurnal fluctuation of her ptosis. Her social and cognitive functions were grossly intact. Parents were first cousins and there was no family history of similar disorder. On examination, she had vertical and horizontal ophthalmoparesis, bilateral ptosis and frontalis overactivity, marked facial weakness (open mouth), high-arched palate, nasal dysarthria, proximal limb weakness, and 1–2+ tendon reflexes.

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

Presence of polyhydramnios, reduced fetal movements, and arthrogryposis multiplex congenita might suggest an underlying disorder of the motor system. Presence of respiratory distress, stridor, and feeding difficulties suggested respiratory and bulbar muscle involvement. With relatively preserved cognition, lack of spasticity, and hyperreflexia on examination, a neuromuscular disorder seemed more likely rather than CNS involvement. Presence of ptosis and ophthalmoparesis, facial weakness, fatigability, and diurnal fluctuation of ptosis pointed to a neuromuscular junction (NMJ) dysfunction. Among the NMJ disorders present since birth, congenital myasthenic syndrome (CMS) should be considered. Other differentials include genetic myopathies: congenital myopathy (CM), congenital muscular dystrophy (CMD), and congenital myotonic dystrophy (congenital presentation of myotonic dystrophy type 1 with hypotonia, respiratory and feeding difficulties at birth). CMs are genetically heterogeneous disorders presenting with hypotonia, muscle weakness, varying degrees of facial, ocular, and bulbar weakness, usually normal creatine kinase (CK), and nondystrophic muscle biopsy (characteristic histologic features are nemaline rod, central core, and central nuclei). CMDs are also genetically diverse (merosinopathies, collagen VI–related myopathies, dystroglycanopathies) and characterized by progressive muscle weakness, usually high CK, and dystrophic muscle biopsy.[1] Due to multisystem involvement and arthrogryposis, a genetic syndrome was considered initially. Another consideration was congenital cranial dysinnervation disorder due to facial weakness and ocular findings.

The patient had extensive metabolic testing and negative MRI brain and magnetic resonance spectroscopy, which ruled out most of the neurometabolic disorders and structural malformations. Chromosomal microarray showed multiple areas of homozygosity consistent with parental consanguinity. CK was normal, thus ruling out most of the muscular dystrophies. EMG revealed normal motor and sensory responses, ruling out neuropathies; repetitive nerve stimulation (RNS) was not performed so myasthenia could not be ruled out. Needle EMG showed myopathic motor unit potentials, ruling out anterior horn cell disorders; no myotonic discharges or fibrillations were recorded. Muscle biopsy was not performed.

Question for consideration:

1. What additional testing would you consider to obtain a diagnosis?

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Section 3

As there was no unifying diagnosis, whole exome sequencing (WES) was performed. It showed homozygous variant of unknown significance of the *SUCLG1* gene (c.110, G > C, p.G37A). This disorder is known to cause mitochondrial DNA depletion syndrome, which is associated with lactic acidosis, seizures, basal ganglia involvement, hepatic dysfunction, and early mortality,[2] none of which was present in our index case. Thus this genetic mutation was considered of unknown clinical significance. Reanalysis of WES was performed after 2 years. It showed homozygous mutation of the *CHRNA1* gene (c.257 G > A, p.R86H). The *CHRNA1* gene codes for the α1 subunit of acetylcholine receptor (AChR) and has been implicated in CMS.[3] Though this mutation was not previously reported, the patient's clinical features seemed to be consistent with the genetic diagnosis of CMS. The family did not wish to pursue another EMG test with RNS to show evidence of NMJ defect. She was started on oral pyridostigmine. The dose was adjusted gradually to the maximum dose of 7 mg/kg/d, which she was tolerating well. Her parents noticed that she was more active, fatigued less, and walked better. Her ptosis improved to a certain extent, she was able to close her mouth partially, and her voice was clearer.

Discussion

Arthrogryposis multiplex congenita (AMC) is a syndrome rather than a specific disease entity. It is characterized by fixed position of multiple joints in the body. Distal joints are more frequently affected than the proximal joints; talipes equinovarus and flexion deformities of the wrists are the most common manifestations.[4] Although about 50% of patients with AMC have congenital anomalies of multiple organs including CNS, AMC can be due to nonsyndromic disorders of the peripheral nervous system.[4,5]

Clinicians should carefully look for the clinical features that may provide clues to the peripheral nervous system as the underlying etiology of AMC. Our patient had ocular, bulbar, and facial weakness, diurnal variation of ptosis, and fatigability, pointing to myasthenia as the potential etiology of her symptoms. CMS are a rare group of inherited disorders caused by mutations in the genes encoding proteins involved in the integrity of neuromuscular transmission.[6] About 30 CMS disease genes have been identified to date, many in the last 5 years.[6] CMS typically presents early in life with considerable phenotypic variability. AMC has been reported in various CMS subtypes caused by mutation of the genes involved in the presynaptic, endplate, and postsynaptic sites of the NMJ (table). Choline acetyltransferase deficiency is caused by the *CHAT* gene, which catalyzes the synthesis of acetylcholine (Ach) from choline and acetyl-CoA in the presynaptic nerve terminal. The hallmark clinical manifestation of this condition is sudden apneic spells; AMC can be a rare presentation.[5] The most common CMS subtype associated with AMC is due to mutation of the *RAPSN* (receptor-associated protein at the synapse) gene.[7] Rapsyn protein is present in the synaptic endplate and plays a critical role in the clustering of ACh receptors. The early-onset phenotype (commonest type) presents at birth or in infancy with arthrogryposis, hypotonia, apnea, bulbar, neck, and proximal limb weakness.[7]

Another CMS subtype involved in endplate development and maintenance is Dok-7 deficiency. Patients commonly present with a limb girdle phenotype mimicking myopathy but can present in the neonatal–infantile period with stridor.[4,6]

Postsynaptic mutations affecting AChR account for the majority of CMS.[3,6] These mutations can lead to either deficiency of AChR or kinetic abnormalities of AChR (fast and slow channel syndromes). Adult AChR consists of 5 subunits (α1 [2 subunits], β1, δ, and ε), which are encoded by the following genes: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNG*, and *CHRNE*, respectively. Fetal AChR differs from adult AChR by the presence of γ unit instead of ε subunit. This class switch happens around 33 weeks of gestation.[8] AChR deficiency due to ε subunit mutation is the most common subtype; the high frequency of *CHRNE* mutations compared to other subunits is attributable to the phenomenon of phenotypic rescue.[3] As a result, patients with CMS caused by homozygous mutations of the non-ε subunits are more severely affected and have high mortality early in life.[3] This explains why our patient with *CHRNA1* mutation had a severe neonatal–infantile course.

When AMC is associated with pterygia (webbing) of the neck, elbows, or knees, it is called multiple pterygium syndrome. Other associated features are short stature and multiple anomalies of various organ systems (craniofacial, skeletal, cardiac, genital).[9] Multiple pterygium syndrome is genetically heterogeneous and can be transmitted as autosomal recessive, dominant, or X-linked

Table Arthrogryposis in congenital myasthenic syndrome

Congenital myasthenic syndrome	Site of defect	Gene mutation
Choline acetyltransferase deficiency	Presynaptic	*CHAT*
Rapsyn deficiency (most commonly associated with arthrogryposis)	Endplate	*RAPSN*
Dok-7 deficiency	Endplate	*DOK7*
Acetylcholine receptor deficiency	Postsynaptic	*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNG*, *CHRNE*

inheritance.[9] Interestingly, several genes associated with NMJ have been implicated in this multiple pterygium syndrome (Escober type): *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNG*, *RAPSN*, *DOK7*.[9,10] The severe, lethal form of multiple pterygium syndrome overlaps with fetal akinesia deformation sequence characterized by AMC, fetal akinesia, intrauterine growth restriction, pulmonary hypoplasia, several congenital anomalies, hydrops fetalis, and in utero death.[9] Homozygous mutations of *CHRNA1* cause autosomal recessive lethal multiple pterygium syndrome. The genes involved in NMJ present a diverse phenotype, from severe presentation with intrauterine death to AMC and other manifestations of CMS.

The mainstay of medical treatment in most CMS subtypes is AChE inhibitor (pyridostigmine), which prolongs synaptic response to ACh.[3,6] It is, however, contraindicated in AChE deficiency and slow channel syndrome and may worsen symptoms in Dok-7 myasthenia.[3,6] 3,4-Diaminopyridine is a potassium channel blocker that facilitates release of ACh from presynaptic terminal and is used as an adjunctive treatment with pyridostigmine. β2 agonists (oral albuterol, ephedrine) improve neuromuscular transmission by stabilizing the postsynaptic membrane.[3] They are effective in Dok-7 and AChE deficiency as well as adjunctive treatment in other CMS subtypes.[3,6] Clinical response to these agents may take weeks to months, unlike pyridostigmine and 3,4-diaminopyridine, which act faster.[6] Fluoxetine and quinidine are effective in slow channel syndrome.[3]

CMS should always be considered in the differential diagnosis of infants with arthrogryposis when there is ocular, facial, or bulbar weakness. Identification of CMS is crucial because many of the subtypes are amenable to treatment. Sometimes the diagnosis may not be apparent after initial workup and reevaluation of the laboratory and diagnostic testing are necessary to arrive at a diagnosis. This was exemplified in our case, where the diagnosis was made after reanalysis of the WES.

Author contributions

Dr. Ghosh: study concept and design, critical revision of the manuscript for important intellectual content, study supervision. Dr. Irumudomon: acquisition of data. Dr. Irumudomon and Dr. Ghosh: analysis and interpretation.

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