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Motor Delay– A Diagnostic Dilemma, Will Molecular Genetics Help? A Case Series

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Abstract:

Congenital muscle disorders are a group of clinically, genetically, and histologically heterogeneous diseases characterized by congenital or early-onset muscle weakness of varying degrees with a static or slowly progressive clinical course. These disorders involve a constellation of clinicopathological features typically involving a child with early-onset motor delay, especially with walking, together with normal to slightly elevated creatine phosphokinase levels and characteristic histopathological findings on muscle biopsy. Considering the invasive nature, technical complexity, and often inconclusive results, muscle biopsies have almost become obsolete. Molecular genetics even though costly, has now been increasingly used for the diagnosis due to their specificity. We present a case series of 5 children with gross motor delay where a definite etiology could not be obtained. One child had associated Vitamin D deficiency, another had hypothyroidism and significantly elevated creatine kinase and two of them had brain MRI findings. Due to the diagnostic and prognostic dilemma, parents were counseled regarding the need for genetic evaluation. Results identified various common genetic causes like Duchenne muscular dystrophy, Limb-girdle muscular dystrophy, and not-so-common causes like Bethlem myopathy and Central core disease. Parents were counseled for further management as appropriate. Hence it is desirable to identify genetic variations in muscle disorders where congenital cause is strongly suspected as it has the potential to improve family planning, aid in prognosis, and also start specific interventions, if any.

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Introduction:

Motor development is the ability to move which is essential in human development. It refers to the ability to improve our physical capabilities, both in the usage of lower (for locomotion and stability) and upper (for hand skills) limb extremities. Hence aberrations in motor development can affect the quality of life considerably. Isolated motor delay associated with several systemic conditions (PEM,

rickets, anemia) and benign hypotonia is usually self-limiting. However, diagnosis of motor delay associated with progressive or static weakness especially with elevated muscle enzymes is always a clinical dilemma. Considering the invasive nature, technical complexity, and often inconclusive results, muscle biopsies have almost become obsolete. A secure diagnosis based on molecular evidence has become possible for many syndromes previously only clinically defined, which has helped enormously in predicting children's-developmental progress, in allowing knowledgeable surveillance for potential associated health problems, in genetic counselling, and in prenatal diagnosis [2]. The discovery of new cytogenetic and molecular genetic techniques and principles has been explosive in recent years, resulting in ground breaking progress in the evaluation of rare diseases where genetic testing became helpful [3]. We present a case series of 5 children with predominant gross motor delay where a definite clinical etiology could not be obtained.

Subject and Method:

Children of the age group from 9 months to 5 years who came to child development centre. After detailed clinical evaluation, parents were counselled for genetic testing, blood samples were collected and sent for genetic analysis and results were interpreted.

CASES

Case 1

Master X born of non consanguineous marriage was seen at 10 months of age with concerns of no sitting. His assessment revealed hypotonia with developmental age of 3-4 months and unremarkable lab reports and was initiated on developmental therapy. By 2 years of age he had started walking but with a lordotic gait. Hence family was counselled for genetic testing for definite diagnosis. It revealed a heterozygous two base pair duplication in exon 239 of the TTN gene and heterozygous missense variant in exon 198 of the TTN gene suggestive of Limb Girdle Myopathy.

Case 2

A 5-year-old boy, 1st born of consanguineous marriage with normal cognition was brought with an abnormal gait and difficulty in getting up from a sitting posture at 5 years of age. Mother also gives a history of recurrent muscle cramps. Clinical examination revealed pseudohypertrophy of calf muscles with positive Gower sign s/o a proximal limb girdle weakness. His blood investigations showed significantly elevated creatine kinase,Aspartate transaminase, TSH with low Vitamin D levels pointing towards a chronic muscle weakness. He was started on symptomatic treatment and gentle physiotherapy. Considering his normal cognition, hypothyroidism was not considered clinically as the cause for calf pseudohypertrophy. Genetic testing sent was confirmatory of DMD with Hemizygous deletion of exon 44.

Case 3

Master Y born of non consanguineous marriage was detected to have hypotonia with no sitting sitting by 1 year of age. Imaging studies and blood investigations were non-contributory. This child started to walk with waddling gait by the age of 2 years following developmental with the help of therapy and foot orthosis.Whole exome sequencing and revealed heterozygous missense variant in exon 23 of the RYR1 gene suggestive of Congenital myopathy, concluding his diagnostic dilemma and helped in prognosis.

Case 4

A 3-year-old girl born of non consanguineous marriage with noncontributing family and birth presented with global developmental delay at 1 year of age. She had subtle dysmorphism and on examination she had peripheral hypotonia and sluggish deep tendon reflexes. Laboratory workup showed Vitamin D deficiency and high normal CPK. MRI Brain showed benign CSF space enlargement with normal myelination. She started walking with support, with an awkward wide based gait by 2 years of age. Suspecting genetic etiology, investigations sent. a rare cause of muscular dystrophy with heterozygous missense variation in exon 26 of the COL6A2 gene s/o Ullrich congenital muscular dystrophy-1 and Bethlem myopathy-1.

Case 5

A 2-year-old boy born out of non consanguineous marriage was brought at the age of 9 months with unprovoked seizure and global developmental delay. On examination he was found to have hypotonia, stereotyped behaviors, proximal and distal muscle weakness and hyperextensive joints. Imaging revealed nonmyelination of anterior limb of internal capsule in MRI and right posterior slowing on EEG. He didn't show much improvement despite developmental therapy.Whole exome sequencing revealed a heterozygous missense variation in exon 100 of the RYR1 suggestive of another another rare disorder, Central core disease.

Discussion:

Case 1**: Limb-girdle muscular dystrophy** is a term for a group of diseases that cause weakness and wasting of the muscles in the arms and legs. Signs and symptoms may first appear at any age and generally worsen with time, although in some cases they remain mild.[5]

Case 2 : **Duchenne muscular dystrophy (DMD**) affects both skeletal and heart muscle. Early signs may include delayed ability to sit, stand, or walk and difficulties learning to speak. Symptoms of this disease may start to appear in early childhood (2-11 years)[6]. It leads to progressively worsening disability, and most children with DMD need to use a wheelchair by the age of 12[7].

Case 3: **Congenital myopathy** is a term for any genetic muscle disorder that is typically noticed at birth and includes weakness and lack of muscle tone. Some symptoms may remain stable or progress slowly. There is no cure for congenital myopathy.[8]

Case 4**: Ullrich congenital muscular dystrophy (UCMD)** is a rare hereditary muscle condition that manifests at birth or a few months after birth. It belongs to a group of disorders called collagen type 6-related myopathies and characterized by abnormalities in collagen type 6, a major protein that supports skeletal muscles[9].**Bethlem myopathy** is a rare disease affecting the skeletal muscles and connective tissue. The disease is characterized by slowly progressive muscle weakness and joint stiffness (contractures). Signs and symptoms may begin before birth (with decreased fetal movements), shortly after birth (with low muscle tone or torticollis), in early childhood (with delayed motor skills, muscle weakness, and contractures), or in adulthood (with weakness, Achilles tendon, or finger contractures)[10]

Case 5: **Central core disease (CCD)** is an inherited condition that involves muscle weakness, skeletal abnormalities. Symptoms of this disease may start to appear from early childhood(around 2 years).Muscle weakness ranges from mild to severe and typically affects muscles in the trunk and upper legs[11]

Conclusion:

In the case of a child with motor delay, there is no single approach to diagnostic evaluation. The clarification of the etiological diagnosis is necessary in order to prognosticate, to consider the possibilities for therapeutic intervention and to assess the risk of recurrence. Families can be offered genetic counselling regarding the mode of inheritance and are supported to take informed family planning decisions, based on the implied risk of recurrence. To conclude, molecular genetics will alleviate the diagnostic dilemma to isolated motor delay. A reduction in the cost of next-generation sequencing will likely lead to its widespread use.

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Table 1: Summary of the cases

Case no	Age/ Gender	Consanguinity	Walking initiated by	Hypotonia, Muscle weakness	Other features	Para clinical findings	Genetic test	Diagnosis
1.	2years /boy	No	2 years	Hypotonia+, Proximal muscle weakness	Frontal bossing, lordotic walk	-	Heterozygous duplication in exon 239 and missense variant in exon 198 of the TTN gene	Limb Girdle myopathy
2	5 years /Boy	YES	1 year	Normal tine	Gower sign positive, pseudohypertrophy of calf +	Highly elevated CKMB, hypothyroidism, Vitamin D deficiency	Hemizygous deletion of exon 44	Duchenne Muscular dystrophy

3	2 years / boy	No	2 years	Hypotonia+	Frontal bossing +, Waddling gait + mild intellectual disability, macrocephaly	Increased CKMB, MRI normal	Heterozygous missense variant in exon 23 of the RYR1 gene	Congenital myopathy
4	3 years / girl	No	2 years	Hypotonia+	Floppy from at birth	Vitamin D deficiency, Benign CSF space enlargement, Myelination normal.	Heterozygous missense variation in exon 26 of the COL6A2 gene	Ullrich congenital Muscular Dystrophy, Bethlem myopathy
5	2 year / boy	No	2 years	Hypotonia+	Recurrent seizures, Hyperextensive joints, Autistic traits	Absence of myelination of anterior limb of internal capsule on MRI, right posterior slowing on EEG.	Heterozygous missense variation in exon 100 of the RYR1 gene	Central core disease.

Genetic Test Reports:

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
***TTN* (-)** (ENST00000589042.5)	Exon 239	c.44252_44253dup **(p.Lys14752LeufsTer13)**	Likely compound Heterozygous	Limb-girdle muscular dystrophy-10 (OMIM#608807)	Autosomal recessive	Pathogenic **(PVS1, PM2, PP3)**
	Exon 198	c.38755G>A **(p.Ala12919Thr)**				Uncertain Significance

Case 1:

Sl. No.	Deletions /Duplications	No. of exons deleted/duplicated †	MLPA probe ratio (Dosage quotient) #	Disease (OMIM)	Inheritance	Classification
1.	Hemizygous deletion	1 (Exon 44) '	0.00	Duchenne muscular dystrophy/Becker muscular dystrophy	X-linked recessive	Pathogenic

Case 2:

***RYR1* (+)** (ENST00000359596.8)	Exon 23	c.2812G>A **(p.Val938Met)**	Heterozygous	Congenital myopathy-1A with susceptibility to malignant hyperthermia (OMIM#117000)	Autosomal dominant	Uncertain Significance **(PM2)**

Case 3:

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
***COL6A2* (+)** (ENST00000300527.9)	Exon 26	c.2227A>T **(p.Asn743Tyr)**	Heterozygous	Ullrich congenital muscular dystrophy-1 (OMIM#254090) Bethlem myopathy-1 (OMIM#158810)	Autosomal dominant/ Autosomal recessive	Uncertain Significance

Case 4 :

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***RYR1* (+)** (ENST00000359596.8)	Exon 100	c.14420A>G **(p.Asn4807Ser)**	Heterozygous	Central core disease	Autosomal dominant / Autosomal recessive	Uncertain Significance

Case 5:

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