Case Report

Muscle eye brain disease – A rare case of congenital muscular dystrophy

Vellusamy Subramaniam, Sakthimeena Ramanathan

From Professor and Head, Student, Department of Pediatric Neurology, Stanley Medical College, Chennai, Tamil Nadu, India

ABSTRACT

Congenital muscular dystrophies are a distinct group of inherited muscle disorders that manifest within the 1st year of life accompanied by weakness, hypotonia, and developmental delay. A distinguishing feature of congenital muscular dystrophy from other muscular dystrophies is an increased association with brain malformations, particularly disorders of cortical development such as lissencephaly, pachygyria, and polymicrogyria. Moreover, some subtypes of congenital muscular dystrophies (CMDs) such as muscle eye brain disease and Walker-Warburg syndrome are more commonly associated with structural eye abnormalities apart from brain malformations. The inheritance of CMD is usually autosomal recessive except for CMD with spinal rigidity and lamin A/C abnormality and Ullrich CMD.

Key words: Congenital muscular dystrophy, Hypotonia, Muscle eye brain disease, Polymicrogyria, Walker-Warburg syndrome

Congenital muscular dystrophies are a distinct group of inherited muscle disorders with early onset of symptoms often in the 1st year of life. Children with congenital muscular dystrophies (CMDs) present with symptoms such as weakness, hypotonia, and developmental delay. Hypotonia and muscle weakness manifest as decreased motor ability, joint, or spinal deformities. Infants often have contractures or arthrogryposis at birth. Ullrich type of CMD is closely related to congenital contractures of the elbow due to defect in collagen type VI genes. Muscle weakness is stable at initial stages for a short period which may later take a more severe course.

Table 1 major categories of CMDs include dystroglycanopathies (such as Walker-Warburg syndrome, muscle eye brain disease, and Fukuyama CMD), merosinopathies, and collagenopathies. Muscle eye brain disease is an autosomal recessive disorder that is predominantly found in Finland with an incidence of 1:50,000 [1] and few studies showing a prevalence of 0.68–2.5/100,000 [2] around the world whereas there is hardly any information about the incidence/prevalence of this disease in India. The disease is known for its rarity and is hence being reported here.

CASE HISTORY

A 9-month-old, first-born, female baby born out of 2nd degree consanguineous parents presented with chief complaints of global developmental delay since birth. There was a history of slipping easily between hands. No history of recurrent aspirations/feeding difficulties/seizures was noted. Antenatal, natal, and postnatal periods were uneventful.

On examination, the infant had microcephaly, dysmorphic facies in the form of hypertelorism, anti-mongoloid slant of eyes, and plagiocephaly. She was not able to visually fixate on objects. Extraocular movements were full with occasional eye movements. There was marked hypotonia, diminished reflexes, and paucity of movements in all four limbs. Bilateral equivocal plantars were present.

Investigations revealed the following: Serum creatinine phosphokinase (CPK) levels were elevated – 1969 U/L (normal range: 10–80 U/L). ECHO was normal (to rule out dilated cardiomyopathy/mitral valve regurgitation/mild conduction defect, which is a rare association) [3]. Magnetic resonance imaging (MRI) brain (Fig. 1) showed bilateral white matter hyperintensity and polymicrogyria/pachygyria complex in the frontoparietal region and bilateral cerebellar cysts.

DISCUSSION

MEB disease is an autosomal recessive disorder that is predominantly found in Finland with an incidence of 1:50,000 [1] with few studies showing a prevalence of 0.68–2.5/100,000 [2] around the world. CMD can be classified into one of the four major groups based on genes involved and the predicted localization and formation of their protein products [4] : Abnormalities of α-dystroglycan glycosylation and defects in other membrane receptors, abnormalities of extracellular matrix proteins (LAMA2, COL6A1, COL6A2, and COL6A3) [5], abnormalities of nuclear

Access this article online	
Received - 23 February 2021 Initial Review - 30 May 2021 Accepted - 04 June 2021	Quick Response code
DOI: 10.32677/IJCH.2021.v08.i06.007	

Correspondence to: Dr. Sakthimeena Ramanathan, B4, Ivory Apartments, 141, PH Road, Kellys, Chennai - 600 010, Tamil Nadu, India. E-mail: sakthimeenaram@gmail.com

Table 1: Dystroglycanopathies – clinical and imaging features

Type	Eye	Cortex	Cerebellum	Brain stem	Hydrocephalus	Intellectual disability/epilepsy
Walker-Warburg syndrome	Severe	Cobblestone lissencephaly	Very hypoplastic	Severely hypoplastic	Constant	Severe
Muscle eye brain disease	Common	Frontoparietal pachygyria, polymicrogyria	Vermis hypoplasia, cysts	Usually hypoplastic	Common	Severe
Fukuyama CMD	Variable/mild	Variable	Hypoplasia, cysts, polymicrogyria	Usually normal	Rare	Moderate

CMDs: Congenital muscular dystrophies

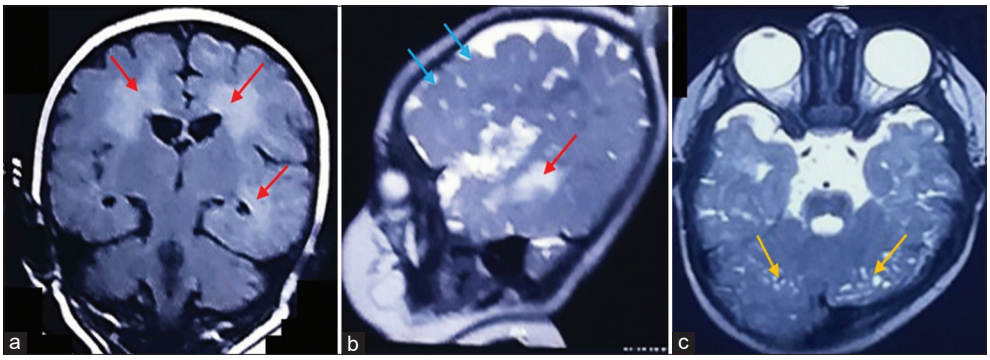

Figure 1: (a) Magnetic resonance imaging (MRI) brain T1-weighted flair coronal image shows bilateral frontal and left temporal white matter hyperintense signals (red arrows) suggesting hypomyelination of white matter. (b) MRI brain T2 sagittal image reveals anterior frontal polymicrogyria (blue arrows) and white matter hyperintense signals in the temporal region (red arrow). (c) MRI brain T2-weighted axial image shows bilateral cerebellar cysts (yellow arrows)

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
POMGNT1 **(-)** (ENST00000371992.1)	Intron 11	c.1027-1G>A **(3' splice site)**	Homozygous	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies; congenital muscular dystrophy-dystroglycanopathy with mental retardation; limb-girdle muscular dystrophy-dystroglycanopathy	Autosomal recessive	Pathogenic

Figure 2: Molecular genetic testing report

proteins (lamin A/C and nesprin), and abnormalities at the level of endoplasmic reticulum.

MEB disease occurs due to POMGnT1 mutations that lead to complete loss in its enzymatic activity, which is responsible for modification of α-dystroglycan after the phosphorylation process by catalyzing the addition of N-acetylglucosamine residue to O-linked mannose. The average life expectancy of MEB disease is around 10–30 years. This disease was first reported by Santavuori *et al*. in 1978.

Eye manifestations can include either unilateral or bilateral microcornea, microphthalmia, hypoplastic or absent optic nerve, and colobomas that may involve the retina. Anterior chamber malformations include cataract, iris hypoplasia, and shallow anterior chamber angle which can lead to glaucoma. Retinal dysplasia or detachment can also occur. In babies with milder manifestations of dystroglycanopathies, high myopia or optic disc pallor might be the only ocular manifestation.

Brain MRI shows structural abnormalities such as hydrocephalus, brain stem hypoplasia, cerebellar cysts, or abnormalities in neuronal migration through cobblestone lissencephaly or polymicrogyria [6]. Hindbrain malformations can include atrophy of the cerebellar vermis, flattening of pons and brainstem, partial absence of corpus callosum, hypoplasia of pyramidal tracts, and obstructive hydrocephalus requiring a shunt. White matter changes may regress with time [7].

Walker-Warburg syndrome [8] is the most severe brain malformation compared to other forms of CMDs which present with symptoms of lissencephaly type II, hydrocephalus, occipital

encephalocele, fusion of cerebral hemispheres, absence of corpus callosum, and hypoplasia of cerebellum as well as brainstem. Ocular findings include congenital cataract, microphthalmia, buphthalmos, and Peter's anomaly. Merosinopathies have white matter changes but with absence of structural eye abnormalities. Extraocular movement abnormalities may be present particularly during an upward gaze.

Diagnosis is usually made by muscle biopsy [9], which shows dystrophic features and on immunohistochemistry, there will be absence of dystroglycan staining. However, muscle biopsy is uncommon nowadays as it is an invasive procedure and genetic testing is confirmatory in establishing diagnosis [10] (Fig. 2). It has prognostic importance and is also useful in counseling parents for future pregnancies. Serum CPK levels are markedly elevated in dystroglycanopathies and merosinopathies but not in collagenopathies.

No definitive treatments exist but multidisciplinary medical care can improve the quality of life. Physical therapy and stretching exercises can help promote mobility and prevent contractures. The patient was advised to undergo physiotherapy. Mechanical-assisted devices may be of help at times. Surgical intervention [11] for foot deformities, joint contractures, and scoliosis may be necessary.

CONCLUSION

The muscle eye brain disease is a rare disorder and very few cases have been reported from India with no solid evidence on the incidence of cases, suggesting that this disease may be underreported or misdiagnosed. It is essential to determine the number of cases and lay down statistics to prevent misdiagnosis when a child presents with persistent hypotonia and developmental delay. Although there is no exact treatment for complete recovery, accurate diagnosis may help in giving proper supportive or conservative treatment and appropriate genetic counseling.

REFERENCES

1. Diesen C, Saarinen A, Pihko H, Rosenlew C, Cormand B, Dobyns WB, *et al*. POMGnT1 mutation and phenotypic spectrum in muscle-eye-brain disease. J Med Genet 2004;41:e115.
2. Bertini E, D'Amico A, Gualandi F, Petrini S. Congenital muscular dystrophies: A brief review. Semin Pediatr Neurol 2011;18:277-88.
3. Pane M, Messina S, Vasco G, Foley AR, Morandi L, Pegoraro E, *et al*. Respiratory and cardiac function in congenital muscular dystrophies with alpha dystroglycan deficiency. Neuromuscul Disord 2012;22:685-9.
4. Muntoni F, Voit T. The congenital muscular dystrophies in 2004: A century of exciting progress. Neuromuscul Disord 2004;14:635-49.
5. Sparks SE, Quijano-Roy S, Harper A, Rutkowski A, Gordon E, Hoffman, EP. Poster Session. Annual SMA Conference, Santa Clara, CA, 2010.
6. Kirschner J, Bönnemann CG. The congenital and limb-girdle muscular dystrophies: Sharpening the focus, blurring the boundaries. Arch Neurol 2004;61:189-99.
7. Louhichi N, Triki C, Quijano-Roy S, Richard P, Makri S, Méziou M, *et al*. New FKRP mutations causing congenital muscular dystrophy associated with mental retardation and central nervous system abnormalities. Identification of a founder mutation in Tunisian families. Neurogenetics 2004;5:27-34.
8. Willer T, Lee H, Lommel M, Yoshida-Moriguchi T, de Bernabe DB, Venzke D, *et al*. ISPD loss-of-function mutations disrupt dystroglycan O-mannosylation and cause Walker-Warburg syndrome. Nat Genet 2012;44:575-80.
9. Wang CH, Bönnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, *et al*. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol 2010;25:1559-81.
10. Allamand V, Merlini L, Bushby K. Consortium for Collagen VI-Related Myopathies. Naarden, The Netherlands: Neuromuscul Disord; 2009.
11. Quijano-Roy S, Mbieleu B, Bönnemann CG, Jeannet PY, Colomer J, Clarke NF, *et al*. *De novo* LMNA mutations cause a new form of congenital muscular dystrophy. Ann Neurol 2008;64:177-86.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Subramaniam V, Ramanathan S. Muscle eye brain disease – A rare case of congenital muscular dystrophy. Indian J Child Health. 2021; 8(6):231-233.