



ARTICLE ID: BTS0626001

BEYOND ASTHMA “THE ROLE OF SALBUTAMOL IN NEUROMUSCULAR DISORDER”

Kaviya S

PPG college of pharmacy, Tamilnadu, India.

Corresponding Mail ID: kavyiasubramaniam45@gmail.com

RECEIVED: 31 July 2025 | **REVISED & ACCEPTED:** 05 November 2025

KEYWORDS: Congenital myasthenic syndrome, Neuromuscular junction, Mutation, salbutamol, MUSK, DOK7 Therapy.

ABSTRACT:

Congenital myasthenic syndrome is a group of heterogeneous genetic disorder affecting the neuromuscular junction which leads to muscle weakness and fatigue. It is rare condition which occur due to genotype and phenotypical changes that mainly affecting neuromuscular transmission. Deficiency or mutation that occur in Musk and DOK7 protein mainly cause congenital myasthenic syndrome. There is no proper standardized therapy for congenital myasthenic syndrome. Identification of subtypes in congenital myasthenic syndromes will improve the treatment of the patient. Beta 2 adrenergic agonist class of drug salbutamol is mainly used to strengthen muscle weakness and also improves the stamina of the muscle which helps the patient of neuromuscular disorder to walk independently. Salbutamol works effectively in the therapy of patient with neuromuscular disorder mainly in congenital myasthenic syndrome. It cause gradual improvement in patient in their muscle strength, post synaptic defects and also in acetylcholine receptor. This review gives overview of Therapy, classification and mutations that occur in neuromuscular disorder.

INTRODUCTION:

Neuromuscular disorder is hereditary or genetic disease mainly affecting peripheral neuromuscular system especially anterior horn cells, nerve cells, muscles and neuromuscular junction [1]. Muscle weakness is the major clinical symptoms in hereditary neuromuscular disorder [2]. CMS is the neuromuscular disorder occur due to mutation in the DOK7 which cause fatigue and limb girdle weakness. Salbutamol, beta 2 adrenergic agonist used in neuromuscular

disorder which have less side effect in adult with high effectiveness. Nine children were treated with salbutamol orally after treating with drug it produces functional benefit and have progressive important in their medications. After drug treatment significantly improves the strength the children with neuromuscular disorder [4].

PHARMACOLOGY OF SALBUTAMOL

Salbutamol is selective beta 2 adrenergic agonist mainly acts on the beta 2 adrenergic

receptor which is located in bronchial smooth muscle. It triggers adenylyl cyclase enzyme activation and also increases the intracellular concentration of cyclic AMP. It leads to decrease in calcium ion concentration which cause smooth muscle relaxation, decreases vascular permeability and also inhibit mast cell release [6]. The mechanism through which salbutamol or other beta 2 adrenergic agonist improve the neuromuscular transmission in the patient with neuromuscular disorder. It mainly improves neurotransmission between the muscle in DOK7 congenital myasthenic syndrome through effective mechanism or through independent stabilization of the synaptic structure [7].

NEUROMUSCULAR DISORDER

Congenital myasthenic syndrome (CMS) are group of inherited neuromuscular disorder mainly characterized by fatigable muscle weakness [8]. It occurs due to mutation occur in DOK7, encoding for skeletal muscle protein [5]. CMS is also associated with neuromuscular junction [9]. It is treatable disorder [10]. DOK (Downstream of kinase) family of cytoplasmic protein has main role in signaling downstream of the receptor. Skeletal muscle receptor tyrosine kinase (MUSK) interacting with cytoplasmic protein of DOK7. It is useful to maintain synaptic structure. Treatment of congenital myasthenic syndrome with salbutamol is effective [12] with delay time of diagnosis and treatment. But it persistently improves the muscle strength of CMS [13].

CLASSIFICATION OF CMS

Congenital myasthenic syndrome is a heterogenous genetic disorder characterized

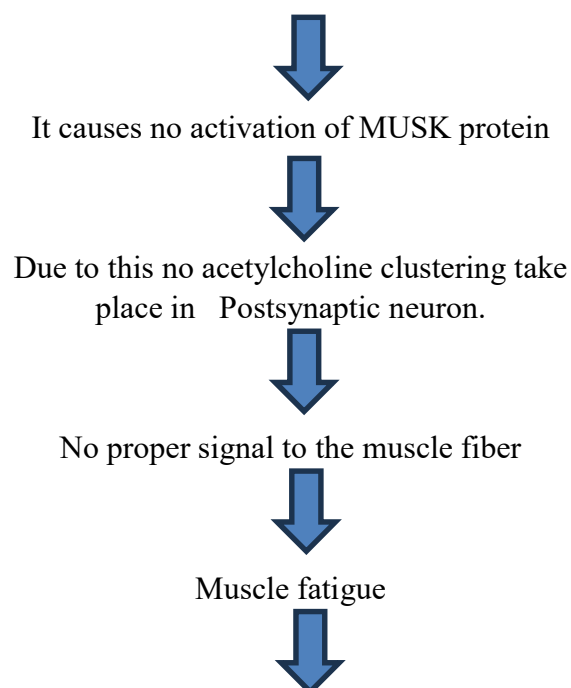
ARTICLE ID: BTS0626001
by comprised neuromuscular transmission of signal. They are classified into three various types depends on their primary location in neuromuscular junction [14].

1. Pre synaptic
2. Synaptic
3. Post synaptic

Pre synaptic congenital myasthenic syndrome caused by mutation in choline acetyltransferase (CHAT) gene generally caused by anomaly of Acetylcholine. Synaptic congenital myasthenic syndrome occur mostly due to deficiency of Acetylcholine. Post synaptic CMS are two categories. First category kinetic anomaly of Ach receptor and decreased number of Ach receptor in neuromuscular junction. Second category is Ach deficiency cause numerous mutations in Ach receptor subunit gene [10].

MECHANISM OF ACTION OF CMS

Mutation occurs in DOK7 protein





Weakness of muscle leads to congenital myasthenic Syndrome.

PATHOPHYSIOLOGY OF CONGENITAL MYASTHENIC SYNDROME

MUSK AND ITS MUTATION IN CMS:

MUSK (Muscle specific kinase) is a receptor of tyrosine kinase and key signaling molecule or protein which is responsible for formation of highly mature and functional neuromuscular junction. MUSK encode for protein which is responsible for maintenance, maturation and proper functioning of the end plate [16]. MUSK are activated by Agrin induced low lipoprotein receptor induced protein 4 (Lrp 4) [17]. Mutations in musk is rare and it manifest neuromuscular disorders such as CMS, proximal limb muscle weakness or bulbar, facial or ocular muscle weakness [16,17].

MUTATION IN DOK7:

DOK7 mutations leads to congenital myasthenic syndrome [12]. It is activated by musk. MUSK and DOK7 proteins are mainly required for neuromuscular synapsis if any changes in any one of these proteins cause neuromuscular disorder such as CMS. DOK7 mutation mainly occur due to frameshift mutation that cause loss of COOH group in DOK7 and also affect the musk activation [23]. Patient with DOK7 mutation have reduced post synaptic function with less acetylcholine deficiency. This leads to limb gridle weakness, facial and bulbar muscle weakness is frequent in the patient [24].

ARTICLE ID: BTS0626001

SALBUTAMOL IN DIFFERENT NEUROMUSCLAR DISORDER

1. Facioscapulohumeral muscle dystrophy
2. Spinal muscular dystrophy

Facioscapulohumeral muscle dystrophy is one of the inherited neuromuscular disorders it mainly affects the facial and shoulder gridle muscle. It has low rate of progression and has difficulty in walking. And no therapies modify this effect. Beta 2 agonist salbutamol or clenbuterol are used to enhance the muscle strength and mass [20].

Spinal muscular atrophy (SMA) is rare neuromuscular disorder that affecting the nerve cell in spinal cord. It is caused by mutation in motor neuron gene SMN1 [21].

Positive effect is detected in the patient with SMA by using salbutamol [22].

MECHANISM OF ACTION OF SALBUTAMOL IN CMS

Salbutamol works by enhancing neuromuscular junction by increasing release of acetylcholine and also increasing the sensitivity of post synaptic neurons. CMS occur due to mutations in DOK7. In some patients 3,4 DAP (3,4 Di-aminopyridine) is effective but muscle strength and its ability are improved by administration of salbutamol [12]. It improves function of the muscle in the patient with congenital myasthenic syndrome. It does not produce any side effects while using salbutamol. It also improves stamina and functions of the muscle. Patient with CMS can walk independently and has ability to walk after administration of salbutamol. Action of salbutamol is similar to action of ephedrine.



Beta 2 agonist improves the functions of inherited neuromuscular disorder [5].

THERAPY IN CONGENITAL MYASTHENIC SYNDROME

1. Acetyl cholinesterase inhibitor
2. Potassium channel blockers
3. 3,4 Di-aminopyridine
4. Salbutamol

Therapy of congenital myasthenic syndrome depends upon the defects in the neuromuscular disorder and genetic defect [18]. In CMS there is no need of immunosuppressive therapy but cholinesterase inhibitor is effective in CMS. 3,4 Di-aminopyridine has good mode of action in pre synaptic and sometimes more effective in pre and post synaptic CMS [16]. Drugs used in CMS are Acetylcholinesterase inhibitors, 3,4 Di-aminopyridine, Quinidine sulphate, Fluoxetine, Acetazolamide and ephedrine are effective in CMS [18]. ACE inhibitor administered for CMS therapy. Pyridostigmine which inhibit breakdown of Ach and 3,4 DAP potassium channel blockers increases release of acetylcholine. Beta 2 adrenergic receptor agonist such as ephedrine and salbutamol are widely prescribed in the treatment of congenital myasthenic syndrome [19].

FUTURE DIRECTIONS

In congenital myasthenic syndrome. Search can be done to improve the development of specific therapy in mutation and early detection of neuromuscular disorder through genetic screening method.

CONCLUSION

ARTICLE ID: BTS0626001

Mutation, therapy and classification description of neuromuscular muscular disorder which leads to an enhanced understanding of the disease. Salbutamol treatment for CMS patient gives good clinical recognition which led to improvement in muscle and better quality of life.

REFERENCE

1. Mary, P., Servais, L., & Vialle, R. (2017). Neuromuscular diseases: Diagnosis and management. *Orthopaedics & Traumatology Surgery & Research*, 104(1), S89–S95. <https://doi.org/10.1016/j.otsr.2017.04.019>
2. Tiffreau, V., Ledoux, I., Eymard, B., Thévenon, A., & Hogrel, J. (2007). Isokinetic muscle testing for weak patients suffering from neuromuscular disorders: A reliability study. *Neuromuscular Disorders*, 17(7), 524–531. <https://doi.org/10.1016/j.nmd.2007.03.014>
3. Volk, H. A., Shihab, N., & Matiassek, K. (2011). Neuromuscular Disorders in the CAT: Clinical Approach to Weakness. *Journal of Feline Medicine and Surgery*, 13(11), 837–849. <https://doi.org/10.1016/j.jfms.2011.09.005>
4. Burke, G., Hiscock, A., Klein, A., Niks, E. H., Main, M., Manzur, A. Y., Ng, J., De Vile, C., Muntoni, F., Beeson, D., & Robb, S. (2012a). Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations. *Neuromuscular Disorders*, 23(2), 170–175. <https://doi.org/10.1016/j.nmd.2012.11.004>
5. Lorenzoni, P. J., Scola, R. H., Kay, C. S., Filla, L., Miranda, A. P., Pinheiro, J. M., Chaouch, A., Lochmüller, H., & Werneck, H. (2012b). Salbutamol improves muscle strength in children with congenital myasthenic syndrome due to DOK7 mutations. *Neuromuscular Disorders*, 22(12), 1073–1078. <https://doi.org/10.1016/j.nmd.2012.09.005>



ARTICLE ID: BTS0626001

L. C. (2013). Salbutamol therapy in congenital myasthenic syndrome due to DOK7 mutation. *Journal of the Neurological Sciences*, 331(1–2), 155–157. <https://doi.org/10.1016/j.jns.2013.05.017>

6. Durrant, N. (2023d). Salbutamol: hero or villain? *Paediatrics and Child Health*, 33(4), 97–103.

<https://doi.org/10.1016/j.paed.2023.01.003>

7. Webster, R. G., Vanhaesebrouck, A. E., Maxwell, S. E., Cossins, J. A., Liu, W., Ueta, R., Yamanashi, Y., & Beeson, D. M. W. (2020). Effect of salbutamol on neuromuscular junction function and structure in a mouse model of DOK7 congenital myasthenia. *Human Molecular Genetics*, 29(14), 2325–2336.

<https://doi.org/10.1093/hmg/ddaa116>

8. Beeson, D., Higuchi, O., Palace, J., Cossins, J., Spearman, H., Maxwell, S., Newsom-Davis, J., Burke, G., Fawcett, P., Motomura, M., Müller, J. S., Lochmüller, H., Slater, C., Vincent, A., & Yamanashi, Y. (2006). DOK-7 mutations underlie a neuromuscular junction synaptopathy. *Science*, 313(5795), 1975–1978.

<https://doi.org/10.1126/science.1130837>

9. Palace, J., Lashley, D., Newsom-Davis, J., Cossins, J., Maxwell, S., Kennett, R., Jayawant, S., Yamanashi, Y., & Beeson, D. (2007). Clinical features of the DOK7 neuromuscular junction synaptopathy. *Brain*, 130(6), 1507–1515.

<https://doi.org/10.1093/brain/awm072>

10. Liewluck, T., Selcen, D., & Engel, A. G. (2011). Beneficial effects of albuterol in congenital endplate acetylcholinesterase deficiency and Dok-7 myasthenia. *Muscle &*

Nerve, 44(5), 789–794. <https://doi.org/10.1002/mus.22176>

11. Muller, J. S., Herczegfalvi, A., Vilchez, J. J., Colomer, J., Bachinski, L. L., Mihaylova, V., Santos, M., Schara, U., Deschauer, M., Shevell, M., Poulin, C., Dias, A., Soudo, A., Hietala, M., Aarimaa, T., Krahe, R., Karcagi, V., Huebner, A., Beeson, D., . . . Lochmüller, H. (2007).

Phenotypical spectrum of DOK7 mutations in congenital myasthenic syndromes. *Brain*, 130(6), 1497–1506.

<https://doi.org/10.1093/brain/awm068>

12. Klein, A., Pitt, M. C., McHugh, J. C., Nix, E. H., Sewry, C. A., Phadke, R., Feng, L., Manzur, A. Y., Tirupathi, S., DeVile, C., Jayawant, S., Finlayson, S., Palace, J., Muntoni, F., Beeson, D., & Robb, S. A. (2013). DOK7 congenital myasthenic syndrome in childhood: Early diagnostic clues in 23 children. *Neuromuscular Disorders*, 23(11), 883–891.

<https://doi.org/10.1016/j.nmd.2013.06.000>

13. Klein, A., Pitt, M. C., McHugh, J. C., Nix, E. H., Sewry, C. A., Phadke, R., Feng, L., Manzur, A. Y., Tirupathi, S., DeVile, C., Jayawant, S., Finlayson, S., Palace, J., Muntoni, F., Beeson, D., & Robb, S. A. (2013b). DOK7 congenital myasthenic syndrome in childhood: Early diagnostic clues in 23 children. *Neuromuscular Disorders*, 23(11), 883–891.

<https://doi.org/10.1016/j.nmd.2013.06.002>

14. Engel, A. G. (2007). The therapy of congenital myasthenic syndromes. *Neurotherapeutics*, 4(2), 252–257.

<https://doi.org/10.1016/j.nurt.2007.01.001>



ARTICLE ID: BTS0626001

15. Pugliese, A., Holland, S. H., Rodolico, C., Lochmüller, H., & Spendiff, S. (2023). Presynaptic Congenital Myasthenic Syndromes: Understanding Clinical Phenotypes through In vivo Models. *Journal of Neuromuscular Diseases*, 10(5), 731–759. <https://doi.org/10.3233/jnd-221646>
16. Finsterer, J. (2019). Congenital myasthenic syndromes. *Orphanet Journal of Rare Diseases*, 14(1). <https://doi.org/10.1186/s13023-019-1025-5>
17. Herbst, R. (2019). MuSK function during health and disease. *Neuroscience Letters*, 716, 134676. <https://doi.org/10.1016/j.neulet.2019.134676>
18. Schara, U., & Lochmüller, H. (2008). Therapeutic strategies in congenital myasthenic syndromes. *Neurotherapeutics*, 5(4), 542–547. <https://doi.org/10.1016/j.nurt.2008.07.003>
19. Thompson, R., Bonne, G., Missier, P., & Lochmüller, H. (2019). Targeted therapies for congenital myasthenic syndromes: systematic review and steps towards a treatatolome. *Emerging Topics in Life Sciences*, 3(1), 19–37. <https://doi.org/10.1042/etls20180100>
20. Payan, C., Hogrel, J., Hammouda, E., Lacomblez, L., Ollivier, G., Doppler, V., Eymard, B., Attarian, S., Pouget, J., Desnuelle, C., & Laforêt, P. (2009). Periodic salbutamol in facioscapulohumeral Muscular dystrophy: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, 90(7), 1094–1101. <https://doi.org/10.1016/j.apmr.2008.12.027>
21. Pera, M. C., Coratti, G., Pane, M., Masson, R., Sansone, V. A., D'Amico, A., Catteruccia, M., Agosto, C., Varone, A., Bruno, C., Messina, S., Ricci, F., Bruno, I., Procopio, E., Pini, A., Siliquini, S., Zanin, R., Albamonte, E., Berardinelli, A., . . . Briganti, E. (2024). Type I spinal muscular atrophy and disease modifying treatments: a nationwide study in children born since 2016. *EClinicalMedicine*, 78, 102967. <https://doi.org/10.1016/j.eclinm.2024.102967>
22. Pane, M., Staccioli, S., Messina, S., D'Amico, A., Pelliccioni, M., Mazzone, E. S., Cuttini, M., Alfieri, P., Battini, R., Main, M., Muntoni, F., Bertini, E., Villanova, M., & Mercuri, E. (2008). Daily salbutamol in young patients with SMA type II. *Neuromuscular Disorders*, 18(7), 536–540. <https://doi.org/10.1016/j.nmd.2008.05.004>
23. Hamuro, J., Higuchi, O., Okada, K., Ueno, M., Iemura, S., Natsume, T., Spearman, H., Beeson, D., & Yamanashi, Y. (2007). Mutations causing DOK7 congenital myasthenia ablate functional motifs in DOK-7. *Journal of Biological Chemistry*, 283(9), 5518–5524. <https://doi.org/10.1074/jbc.m708607200>



24. Vogt, J., Morgan, N. V., Marton, T., Maxwell, S., Harrison, B. J., Beeson, D., & Maher, E. R. (2009). Germline mutation in DOK7 associated with fetal akinesia deformatic e. *Journal of Medical Genetics*, 46(5), 338–340
<https://doi.org/10.1136/jmg.2008.065425>