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GFPT1 gene related congenital myasthenic syndrome: A treatable disorder mimicking limb girdle muscular dystrophy

Bhawna Sharma[1]; Kadam Nagpal[2]*; Swayam Prakash[3]; Ashok Panagariya[4]

[1]Neurology, Professor Neurology, Sawai Man Singh Medical college, Jaipur, Rajasthan

[2]Neurology, Consultant Neurology, Manipal Hospital, Dwarka, New Delhi, India

[3]Director and HOD – Neurology, Balaji Healthcare, Siliguri, West Bengal

[4]Neurology Professor Emeritus - Neurology, Sawai Man Singh Medical college, Jaipur, Rajasthan

***Corresponding Author(s): Kadam Nagpal**

Neurology, Consultant Neurology, Manipal Hospital, Dwarka, C-86 South Extension Part-II, New Delhi, India-110049

Tel: +91-995-808-5544;
Email: kadamnagpal@gmail.com

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Introduction

The Congenital Myasthenic Syndromes (CMS) are a group of neuromuscular diseases caused by genetic defects of muscle endplate. Symptoms are present at birth but may go unrecognized until adolescence or adulthood when clinical manifestations are mild and progression is gradual. Autosomal recessive inheritance account for all genetic forms except for slow channel syndrome having an autosomal dominant mode of inheritance. Two major features that distinguish CMS from acquired autoimmune myasthenia gravis are a positive family history and absence of AChR (acetylcholine-receptor) antibodies. Along with that clinical, electrophysiological assessment with genetic studies establish diagnosis of congenital myasthenic syndromes. We report a case of CMS without any positive family history, pyridostigmine responsive; who was initially misdiagnosed as muscular dystrophy after a muscle biopsy.

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Case report

17 year old born out of a non-consanguineous marriage with a normal birth and developmental history came with progressive weakness in all four limbs which started at the age of 2 years of age. He initially had difficulty in walking, getting up from a seated or squatted position and used to have repeated falls. Simultaneously he also had weakness in both the arms and had difficulty in raising arms or doing overhead tasks. The weakness kept on progressing to an extent that at the age of 12 years patient was wheelchair bound. He only said that during mornings he could turn in his bed but it progressed and became difficult during the course of day. There was no history of dysphagia, double vision, twitching of muscles, numbness in any limbs, drooping of eyelids, breathing difficulty and there was no family history of similar illness. On examination patient was bed bound and required assistance for daily chores. He was conscious, oriented, cranial nerve examination was normal. Hypotonia was present and he had significant proximal muscle and truncal muscle weakness. Plantars were flexor and there were no sensory, cerebellar or meningeal signs. Patient was subjected to routine blood investigations and CPK levels previously which were normal and Electrophysiology tests including Nerve conduction studies and Electromyography which were suggestive of a myopathic pattern. Patient in the past already underwent muscle biopsy at 3 ½ years of age which revealed that there was focal degeneration of myofibres with longitudinal splitting and scattered eosinophilic myofibres with moderate fatty infiltration suggesting a possibility of muscular dystrophy -likely Duchenne muscular dystrophy. After 15 years of ailment with biopsy suggestive of muscular dystrophy, but subtle fluctuation as mentioned by the patient in his symptoms, a Repetitive nerve stimulation study was done which showed decremental response and thereafter a Neostigmine test was done after which patient showed a miraculous recovery and significant improvement. A diagnosis of congenital myasthenia gravis was therefore established. Immediately, he underwent acetylcholine receptor antibodies and anti-MuSK antibodies which were negative and contrast enhanced CT scan of chest was done to look for thymoma which was normal as well. Patient was put on pyridostigmine to which he responded with a significant benefit. Subsequently, in due course a genetic analysis was done for CHRNE gene which was negative. After Sanger sequencing c.332 G>A, a novel sequence change in GFPT1 gene was confirmed further establishing a diagnosis of congenital myasthenia gravis, thereby explaining responsiveness to pyridostigmine as well. After 5 years of follow up, patient is now ambulatory completed his graduation and does not require any assistance or support and he is on pyridostigmine 60mg thrice a day.

Discussion

Congenital Myasthenic Syndromes (CMS) comprise of a heterogenous group of rare inherited disorders in which the neuromuscular transmission in motor endplate is compromised [1]. CMS can be classified according to pattern of inheritance, based on altered protein involved in motor endplate or by taking into account the site of neuromuscular junction (pre-synaptic, synaptic or post synaptic as shown in Table I [2,3,4]. The diagnosis in the recent times is been facilitated by whole exome sequencing which has helped in identifying around 20 new CMS disease related genes. Infantile onset hypotonia or juvenile onset neuromuscular disorder, CMS should be considered as an important differential diagnosis as many presentations could betreatable and reversible. Furthermore, different patterns of inheritance seen in CMS also emphasize an important role of genetic counselling in this variety of disorders.

Table 1

I	**Pattern of inheritance**	
	Autosomal dominant(gain-of-function)	*Slow Channel syndrome, SNAP25B*, SYT2**
	Autosomal recessive(loss-of-function)	*All other subtypes*
II	**Site of defect & molecular targets at neuromuscular junction**	
	Presynaptic defects	ChATdeficiency, SNAP25B deficiency, synaptogamin-2 deficiency
	Acetylcholine receptor defect	Primary deficiency, Slow channel syndrome (CHRNA1,CHRNB,CHRND,CHRNE,CHRNG), fast-channel syndrome (CHRNA,CHRND,CHRNE)
	Synaptic basal lamina defects	Acetylcholinesterase deficiency (ColQ),B2-laminin deficiency
	Endplate development &maintenance congenital defect	Argin deficiency, MuSK deficiency, LRP4 deficiency, rapsyn deficiency, COL12A1 mutations
	Metabolic & Mitochondrial disorders	Congenital disorders of glycosylation, SLC25A1 mutations
	Others	Congenital myopathies with secondary neuromuscular transmission compromise (MTM1, RYR1, DNM2, TPM3, BIN1); PREPL deletion; plectin deficiency

Variable clinical features of CMS include ophthalmoparesis, ptosis and mild facial paresis, present in most of the cases in infancy. Some children develop respiratory weakness or episodic respiratory crisis may occur. Generalized fatigue is common, but most often limb weakness in usually mild as compared to ophthalmoplegia. Skeletal deformities like high arched palate,facial dysmorphism, arthrogryposis and scoliosis are frequently seen. Cholinesterase inhibitors, sometimes in high doses improve limb girdle weakness. The weakness in some children respond to 3, 4-DAP(diaminopyridine). Clinical clues with specific CMS subtypes can be seen in Table II [5].

Table 2

Phenotypic features	CMS subtypes
Myopathic	
Limb girdle muscular dystrophy -type	COLQ, DOK7, MUSK, GFPT1, ALG2, ALG14, DPAGT1
Respiratory insufficiency	SLC18A3, SYB1, COLQ, LAMB2, CHRNB1, CHRND, CHRNE, CHRNG, MUSK, NYO9A, LRP4, COL13A1,SCN4A,RAPS
Episodic apnea	CHAT, MUSK, SCL5A7, SCL25A1, RAPSN, COLQ
Head Drop	AGRN
Myopathic EMG	CHRNB1, ALG2, PLEC1, GMPPB
Double Response	CHRNE, COLQ, SCCMS, ACHE-deficiency, CHRNA1, CHRNB1, CHRND
Non Myopathic	
Cognitive dysfunction	SLC25A7, DPAGT1, SNAP25, COL13A1, MYO9A, CHRNB1, CHRND
Facial tics	LAMA5
Cerebral atrophy	SCN4A,ALG14
Epilepsy	ALG14, SLC25A1, MUNC13-1
Facial dysmorphism	SYB1, RAPSN, SCN4A, COLQ
Myopia	LAMA5
Hyperacusis	SLC25A1,SYT2
Vocal cord paralysis	COLQQ,DOK-7
Neuropathy	SYT2,SLC25A7
Arthrogryposis	SLC5A7,CHRNG
Contractures	SNAP25, VAMP1, CHRNA1, ALG2, ALG14, RAPSN, CHRND, CHRNG, CHAT
Scoliosis	COLQ, CHRNE, VAMP1
Hyperlordosis, hyperkyphosis	SCNA4, RAPSN, SYB1
Adduction deformity of knees	SCN4A
Cubitus valgus	PLEC1
Foot deformity	SYT2, RAPSN, CHRNG, SLC25A1, COLQ
Hyperlaxity of joints	SYT2, VAMP1, COL13A1
Cutaneous blisters	PLEC1
Pterygia	CHRNG
Systolic dysfunction	SLC18A3
Pierson syndrome	LAMB2
Cerebellar ataxia	SNAP25
Laryngospasm	SCN4A
Hip dysplasia	SYT2
Cryptorchism	CHRNG
Arachnodactyly	CHRNG
Microcephaly	MUNC13-1

Out of these syndromes, pyridostigmine-responsive phenotypes are with mutations in GFPT1, SCN4A, CHAT deficiency, fast channel syndrome, AchR deficiency, PREPL, ALG2, GMPPB and RAPSN.

Our patient had a presentation with a limb girdle type of weakness which showed pyridostigmine responsiveness. Genetic analysis confirmed a GFPT1 gene related CMS, in which patients usually present with easy fatiguability and limb -girdle weakness [6,7]. Maintenance of neuromuscular junctions is dramatically impaired with loss of post-synaptic junctional fold and evidence of denervation-reinnervation processes affecting NMJ, therefore it is usually pyridostigmine responsive and in some the effect is usually dramatic [8,9]. Usually muscle biopsy in all CMS is normal apart from GFPT1 gene related CMS wherein signs of tubular aggregates in sarcoplasmic reticulum or vacuolar autophagic myopathy are seen. The muscle biopsy in our patient was abnormal but did not show any of features mentioned. And interestingly our patient had a EMG suggestive of myopathic variant, which is usually not seen in GFPT1 related. Follow up and long term outcome of such patients is usually lacking in literature. As per literature, DOK7 has got the worst outcome in terms of morbidity and mortality [10]. However as far as GFPT1 variant in our patient is concerned, he had a significant benefit over a period of 5 years on medications without any phases of intermittent worsening and without the need of increasing doses any further.

To conclude, congenital myasthenic syndromes are usually overlooked and under diagnosed especially in context of limb

girdle syndrome in early childhood without any family history. Atypical presentations should always warrant a clinician to look for congenital myasthenic syndromes and diagnose it by a genetic analysis, as many syndromes might be treatable and having a favorable long term follow up.

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