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CONGENITAL MYASTHENIA-RARE CASE REPORT IN NORTH-WEST INDIA WITH MODERATE RESPONSE TO CHOLINERGIC DRUGS-

Neurology

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ABSTRACT

Strategies for therapy are based on whether a given CMS modified the synaptic response to acetylcholine .At the same time we should rule out polymyositis, stiffperson syndrome ,neuromyotonia and myopathic disorders.

We are presenting a case of young male bornout of nonconsanguineous marriage who presented with progressive limb –girdle weakness without family history.

Abbreviation –CMS-congenital myasthenic syndrome.

KEYWORDS

INTRODUCTION

Myasthenia gravis in infancy and childhood fall into two major groups i.e. acquired autoimmune and congenital. The congenital group comprises a number of phenotypically and genetically heterogeneous disorders which are familial and lack autoantibodies against acetylcholine receptors (AChR)(2). Specific diagnosis of a CMS is important as some medications that benefit one type of CMS can be detrimental in another type. In some CMSs, strong clinical clues point to a specific diagnosis. In other CMSs, morphologic and in vitro electro physiologic studies of the neuromuscular junction, determination of the number of acetylcholine receptors (AchRs) per junction, and molecular genetic studies may be required for a specific diagnosis.

CASE REPORT

A 19 yr hindu male born out of nonconsanguineous marriage with normal birth history and developemantal milestones presented with Progressive difficulty in walking and getting up from squatting position age of two yrs and progressive weakness of both upper limbs.

As the patient was asymptomatic upto the age of ,2 yrs ,his father noticed that his son gradually started having difficulty in getting up from the floor,for which he had to take support of nearby objects eg.bed,wall. Whenever he had to getup by himself he would take support of both hands over his thighs .After 3 yrs later when the child started going to school , his father noticed that he started difficulty in carrying school bags and difficulty in lifting these bags over his shoulders. However parents did not notice any difficulty in holding common objects with hands.

Gradually as the child grownup, he noticed that during initial morning hours in school ,he was able to climbup the stairs upto 2nd floor with help of holding the railing.,after which he had to take rest for few minutes to proceed further activities .However his other friends were able to do similar activities very well without taking rest. As the day progresses , his all the activities becomes worst as compare to morning hours. Weakness was gradually progressive in nature without any history of numbness/tingling sensations,twitching movements , thinning of limbs. His father did not notice any breathing difficulty , drooping of eyelids,double vision, chewing or swallowing difficulty, change in voice or facial expressions .

Since at the age of 10 yr , he became nonambulatory as. he was not able to move his body on the bed without support. He could not stand without support of one person and if he would stand with support ,he was able to maintain the erect posture and could walk for few steps and then he would fall.

Since then he also started difficulty in holding neck during getting up from lying position also.

There was no h/o double vision, vision impairement, drooping of eyelids, breathing difficulty ,change in voice/swallowing difficulty, sensory symptoms, musculoskeletal deformities,fixed joint deformities, abnormal twitching movements, thinning of limbs or diurnal variation.Family history was not significant upto 3 generations.

On examination higher mental function ,speech,cranial nerves were normal except atrophy and neck flexors weakness .on motor system examination there was atrophy of pectralis muscles and medial part of deltoid on both sides. Tone was decreased in all four limbs.Power was 2/5 proximally and 5/5 distally in both upper and lower limbs.Deep tendon reflexes were normal .sensory examination was normal.He was not able to stand and walk even with support .

His routine Investigations eg. hemoglobin ,ESR , blood sugar , blood urea, s.creatinine, liver function test ,CRP,RA factor,serum ANA , DsDNA were negative . Serum CPK , PTH ,calcium ,TSH , chest X ray, CT thorax, nerve conduction study were normal. HIV was nonreactive. EMG showed myopathic pattern. RNST was POSITIVE FOR 20 %DECREMENTAL RESPONSE AT 3 HZ.NEOSTIGMINE TEST was positive showed improvement in power proximally from 2/5 to 4-/5. He became ambulatory with minimal support. Ach receptor antibody-was negative. Anti musle specific kinase antibody-.003 nmol/L-was negative(<.05). MUSCLE BIOPSY showed –focal degeneration ,infiltration,with regeneration, longitudinal splitting of myofibres. No fibrosis with moderate fatty infiltration .

Genetic study for post synaptic congenital myasthenia- CHRNE mutation was negative.

He was discharged on pyridostigmine 60mg three times a day and 180 mg at night. After followup for 1 yr ,he had 40-50% improvement in his daily activities with medications.now he could getup with his own effort and able stand and walk with minimal support.

DISCUSSION –

Congenital myasthenic syndromes (CMSs) form a heterogeneous group of genetic diseases characterized by a dysfunction of neuromuscular transmission. This dysfunction causes muscle weakness, which is increased by exertion and usually starts during childhood.(3). Acetylcholinesterase deficiency was the first CMS identified, based on the lack of the enzyme at neuromuscular junctions [3]. Progressively, the pathophysiological heterogeneity of CMS was demonstrated: besides synaptic CMS caused by acetylcholinesterase deficiency, pre- and postsynaptic CMS were described.(3). .Knowledge of the mechanisms underlying CMS has increased considerably in the past years, because of the pioneering work undertaken by the group of Engel et al.(3).classification of congenital myasthenia is given below in table1.

Table 1 (1)
Classification of CMS
A. Pre synaptic defects :

1. Defects in ACh resynthesis or packaging (familial infantile myasthenia)
2. Paucity of synaptic vesicles and reduced quantal release.

B. Pre and post synaptic defects :

1. **End plate AChE deficiency**

C. Post synaptic defects :

1. Kinectic abnormalities of AChR with AChR deficiency.

a. Classic slow channel syndrome.

b. Epsilon subunit mutation.
c. AChR deficiency with short channel operation.
2. Kinetic abnormalities of AChR without AChR deficiency.
a. High conductance fast channel syndrome.
b. Abnormal interaction of ACh with AChR.

C. Partially characterised syndromes :
1. CMS resembling LEMS.
2. AChR deficiency with paucity of secondary synaptic clefts.
3. Other AChR deficiencies.
4. Familial limb girdle myasthenia.
5. Benign CMS with facial malformations

The various CMSs share a common clinical presentation.The onset is in general early. Late appearance of the symptoms during adolescence, or even in the adult,is more rarely reported. Some clinical signs suggest an anomaly of neuromuscular transmission: ophthalmoplegia and ptosis, dysphonia and swallowing disturbance, facial paresis, and muscle fatigability(3). In the young child, the ptosis is not easy to recognize because hypotonia, poor mimicry, suction disorders, and weakness of the cry are in the foreground. The occurrence of bouts and worsening by exertion are characteristics of the disease.(3)The favourable effect of cholinesterase inhibitors is a significant argument in favour of a myasthenic syndrome.

However, two types of CMS are worsened by cholinesterase **inhibitors:** slow channel syndrome and acetylcholinesterase deficiency.(3).

The diagnosis of CMS can be confirmed by molecular analyses in the eight genes whose mutations are so far known to cause CMS: four genes encoding the various acetylcholine receptor subunits (CHRNE, CHRNA1,CHRNB1, CHRND), the genes encoding rapsyn (RAPSN), the collagen tail of acetylcholinesterase (COLQ), choline acetyltransferase (CHAT), and the sodium channel (SCN4A).

In our case patient had progressive limb-girdle weakness since the age 2 yrs without diurnal variation, episodic apnoea, ophthalmoplegia, bulbar or respiratory dysfunction or family history. After investigations eg. decremental response in repetitive nerve stimulation test , positive neostigmine test and absence of Ach R ab and Musk-ab, he was diagnosed as congenital myasthenia. Looking to his symptoms and response to pyridostigmine, we investigated for postsynaptic molecular gene mutation of AchR subunit –CHRNE,which was negative.

In our case it is possible to have other postsynaptic gene mutation as mentioned above or it may be incompletely characterized congenital myasthenic syndrome, described on clinical or histological grounds, whose molecular origin and more generally their pathophysiology remain unknown in the absence of an exhaustive exploration.

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