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CASE REPORT

Chronic stridor as an early presentation of congenital myasthenic syndrome due to *RAPSN* mutation

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Abstract:
The Congenital Myasthenic Syndromes (CMS) are a group of rare genetic disorders affecting neuromuscular transmission and often presents within first year of life. A high index of suspicion is usually required as clinical manifestations can be variable and non specific. RAPSN mutations are likely to be one of the common causes for CMS in patients of Indo-European ethnic origin. Clinical phenotype includes arthrogryposis, respiratory crises, transient torticollis at birth, facial deformities and weakness. Chronic stridor as an early manifestation of CMS has not been described before.

Key words: Congenital myasthenic syndromes, RAPSN mutation, clinical phenotype
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Introduction

Congenital myasthenic syndromes (CMS) are inherited disorders of neuromuscular transmission caused by various genetic defects at presynaptic, synaptic or postsynaptic levels [1]. They are characterized by fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood. Despite recent advances in the understanding of molecular genetics and distinctive phenotypes, CMS continue to pose diagnostic and management challenges, particularly in childhood [2]. The recent discovery of mutations in the *RAPSN* gene [1,3,4] for postsynaptic rapsyn proteins which plays an essential role in the clustering of AChR at the motor endplates are of significant clinical relevance given their worldwide frequency and a distinct early onset clinical phenotype.

We describe a 5 years old female child, who initially presented with chronic stridor, failure to thrive and recurrent apnoea at two months of age.

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Case Report

Our patient was a Caucasian girl born to healthy non consanguineous parents. She was born at term and weighed 3.2 kg following an uneventful pregnancy. She first presented at the age of 8 weeks with recurrent apnoeic episodes, poor weight gain, and stridor. The apnoeic episodes continued and 5 weeks later required ventilation and admission to paediatric intensive care for a

lower respiratory tract infection. On extubation she was noted to have marked generalized hypotonia with poor sucking reflex. Bulbar functions were impaired and swallowing was uncoordinated. She had poor visual behaviour and inconsistent fixing and following. There was no ptosis though she had persistent stridor. On further enquiry mother reports left congenital talipes, which improved with time. She didn't have any arthrogryposis or dysmorphic features.

Extensive neurometabolic workup, neuroimaging and muscle biopsies were negative. Trial of neostigmine led to marked clinical improvement with increased alertness and visual responsiveness, stronger vocalizations along with improved tone and posture. Molecular testing confirmed the presence of an N88k deletion in *RAPSN* gene along with deletion at exon 7 of the same gene.

She is now 5 years old and has had repeated admissions to the hospital with apnoeic episodes and chest infections. The frequency of apneic episodes has decreased with age. Bronchoscopy and extensive imaging in view of stridor have been non-contributory. She had a tracheostomy and needs non invasive ventilation overnight. She has motor developmental delay but her social skills are relatively spared. The stridor has persisted, though less marked and fluctuant. She has been tried on neostigmine, 2, 3 Diaminopyridine and is currently on neostigmine.

Discussion

CMS are currently classified based on site of defect as presynaptic, synaptic based lamina associated, and postsynaptic [1]. This is based on 205 patients investigated at the Mayo clinic with the most common site being postsynaptic. To date 10 different genes are implicated to cause CMS and include, presynaptic choline acetyltransferase gene *CHAT*, the gene *COLQ* encoding the synaptic protein ColQ, genes for postsynaptic acetylcholine receptor (*CHRNA1, CHRNB1, CHRND, CHRNE*), the genes for postsynaptic proteins rapsyn (*RAPSN*), muscle specific receptor tyrosine kinase (*MUSK*), postsynaptic sodium channel (*SCN4A*) and downstream of kinase 7 protein *(DOK7)* [6-10].

RAPSN is one of most frequently mutated genes in recessive CMS in people of indo European origin [11,12]. Rapsyn is a 43 kDa post-synaptic protein involved in development and maintenance of the specialized postsynaptic structures at the neuromuscular junction, and specifically in AChR clustering. No fewer than 21 mutations in *RAPSN* have been identified to date in the coding region. The missense mutation N88K has been identified in all individuals with mutations in the translated region in at least one allele. In CMS with rapsyn deficiency, the *RAPSN* N88K mutation is always found either as homozygous or heteroallelic state, with a carrier rate of 1% as found in the studies on general population. Our patient was heterozygous with two mutations (including the common N88K mutation) in the *RAPSN* gene. It has been hypothesized that the mutation derives from ancient Indo-European founder, which explains why it's widely distributed in Europe and North America [12].

Burke et al described two distinct phenotypes in patients with *RAPSN* mutations, early-onset and late-onset [13]. Patients with these mutations generally present with sudden episodes of generalised muscle weakness, hypotonia and respiratory insufficiency requiring assisted ventilation (occasionally misdiagnosed as SIDS), although the phenotypic expression can be highly variable. It is often associated with arthrogryposis multiplex congenital and structural abnormalities of the jaw and palate [13]. Milone et al described the clinical phenotype in patients with *RAPSN* mutation and found that 24 out of 39 patients presented immediately after birth. Weak cry/suck and respiratory distress were the common symptoms at birth. One patient had only limb-girdle weakness and eight were born with arthrogryposis [5]. These patients often respond dramatically to anticholinesterases and recognition of this genotype can prevent early death in a condition which is easily treatable with a good long-term outcome [14].

Kinali [15] et al described the phenotype of 46 children with CMS. Their cohort had 6 children who were noted to have stridor and included four with *DOK7* and one with *CHAT* mutation.

Table 1. Features of 29 patients with RAPSN deficiency investigated at Mayo clinic	
Genotype–phenotype Correlation	Mild course and strong facial deformities with homozygous E-box mutations in Near-Eastern Jews. Increased frequency of arthrogryposis with truncating mutations. No phenotype correlation for other mutations
Onset	At birth, 17; early infancy, 8; childhood, 2; third decade, 2 (both carry –38A/G)
AChR deficiency	Relatively mild (20–50% of normal mean)
EMG decrement	Can be mild or absent
Malformations	Arthrogryposis at birth, 7; transient torticollis at birth, 1; facial deformities, 9 (8 carry E-box mutation)
Effect of febrile illness	Worsening in 15, including respiratory insufficiency or apneic episode in 9
Response to therapy	All respond to AChE inhibitor; 3 derived further benefit from 3,4-DAP

AchE: Acetylcholinesterase; 3,4-DAP: 3,4- Diaminopyridine

Interestingly stridor, which was an early feature in our patient, has not been reported as a major manifestation in the cohort of CMS patients described so far with *RAPSN* mutation. Table 1 summarizes clinical features of 29 patients with *RAPSN* mutations investigated at Mayo clinic.

Conclusion:

Our case highlights the fact that in any infant or young child with stridor and associated respiratory symptoms, possibility of a myasthenic disorder must be considered. With the availability of molecular genetic analyses, this group of conditions can now be more clearly delineated and targeted treatment can be initiated, thus preventing morbidity and mortality.

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