Acetazolamide can improve symptoms and signs in ion channel related congenital myopathy

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Introduction

Sarcolemmal voltage gated sodium and calcium ion channels are essential for generating action potentials and excitation contraction coupling required for muscle contraction. Autosomal dominant sodium and calcium ion channel gene disorders cause episodic symptoms of periodic paralysis (PP) and myotonia[1]. Acetazolamide treatment improves these symptoms [2]. Recently recessive congenital myopathies due to compound heterozygous or homozygous ion channel gene mutations have been described with fixed muscle weakness and disability [3;4].

In case series we previously reported, two individuals with ion channel related congenital myopathy had additional discrete episodic or fluctuant weakness causing added morbidity [3;4]. Here we delineate the long term benefit of treatment with acetazolamide for these individuals and discuss the implications for genetic diagnosis and management of future cases.

Case one: a 16 year old female with compound heterozygous *SCN4A* gene mutations (Fig 1B) [3]. Reduced foetal movements were noted during pregnancy with a breech presentation at birth. Features of congenital myopathy included neonatal hypotonia, weak cry, talipes, thin muscle build and weak suck requiring nasogastric tube feeding for 12 days. With maturity significant proximal and axial weakness occurred with difficulties running, going upstairs, rising from the floor and walking long distances. Due to respiratory insufficiency, she required nocturnal BiPAP from age six. Progressive scoliosis required surgical fixation at age 12.

From age 12 she reported new episodic symptoms. The most severe occurred during a viral illness when she had profound leg weakness and was unable to walk without assistance for

two days. Subsequently she reported daily (up to 10min) episodes of leg weakness after exercise or prolonged sitting and diurnal episodes of fatigue after school.

Genetic diagnosis was made at age 14. On the basis that one of her *SCN4A* mutations, R1135C, had been previously described in periodic paralysis[5] and that she reported discrete episodic exacerbations in limb strength she was started on acetazolamide 125mg BD at age 15, increased incrementally to 250mg BD. Subjectively she reported a reduction in episodic weakness and fatigue. Objectively her functional scores, timed function test and respiratory function improved between approximately 20 and 30% (Fig 1A).

Case two: a 10-year-old boy with compound heterozygous *CACNA1S* mutations (Fig 1C)[4]. Reduced foetal movements were noted during pregnancy. At birth neonatal hypotonia with hip, knee and ankle contractures was observed. He had bulbar and facial weakness, ophthalmoplegia, ptosis and high arched palate. He required nocturnal BiPAP from age seven. He has never been able to walk but can sit independently. From age five his parents reported periodic episodes lasting up to an hour where he loses head control, and develops slurred speech communicating using gestures. These were triggered by rest, hot weather, fasting, and illness. They occurred at least three times a week often in the morning and he frequently missed school. They were also prominent at night, waking him from sleep feeling weak and dribbling saliva. This resulted in marked fluctuation in his swallow causing recurrent aspiration and lung collapses requiring frequent prolonged hospitalisation and escalation of pressures for non-invasive ventilation.

One of his *CACNA1S* gene mutations E100K was predicted to share biophysical properties with other periodic paralysis mutations. Due to this and the reported episodic symptoms he was started on acetazolamide 125mg BD, increased to 250 mg BD. Periodic symptoms resolved completely and he consistently attended school. Respiratory and bulbar function

improved such that he no longer aspirated or required hospitalisation and ventilator pressures were weaned.

Discussion: Periodic paralysis causes episodes of profound muscle weakness or paralysis due to prolonged muscle membrane depolarisation. PP gene mutations of the skeletal muscle voltage gated sodium or calcium channels share a common pathomechanism of disrupting bonds between positively charged amino acid residues in the channel voltage sensor (S4) and negative charges in the interacting S1 to 3 segments (Fig 1D) to introduce an anomalous inward ionic leak current across the sarcolemma [1].

Acetazolamide is used to treat periodic paralysis. We have observed it to also have benefit in congenital myopathy for children with compound heterozygous mutations in ion channel genes where one of their mutations is identified as sharing biophysical features with a PP mutation (Fig 1D).

Congenital myopathies are a heterogeneous group of disorders and ion channel related congenital myopathy is only relatively recently recognised. Disability in congenital myopathy is usually regarded as fixed with supportive treatment being the only available intervention. Genetic testing can be prolonged due to the number of possible genetic diagnoses and in some countries cost can be prohibitive. Our cases demonstrate however that there is a reversible component to some ion channel related congenital myopathy and genotype may predict this. This has important implications for children presenting with congenital myopathy. We propose it is essential to pursue a genetic diagnosis and those with an ion channel gene mutation predicted to act in a biophysical fashion similar to PP mutations and who have episodic or fluctuant symptoms warrant a trial of acetazolamide.

Author contributions:

E. M.: drafting the manuscript for content, analysis or interpretation of data, study concept

L.H.: revising the manuscript for content, analysis or interpretation of data, study concept

R.S.: revising the manuscript for content, analysis or interpretation of data

M.G.H.: revising the manuscript for content, analysis or interpretation of data

F. M.: revising the manuscript for content, analysis or interpretation of data, study concept

P.M.: revising the manuscript for content, analysis or interpretation of data, study concept

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Figure title

Figure 1: Outcome measures, family trees and pictorial representation of skeletal muscle voltage gated sodium and calcium channels with mutations marked

Figure legend

Fig 1A: Summary of functional and respiratory measures pre and post acetazolamide treatment in case one **1B:** Family tree and *SCN4A* mutations identified in case one. **1C:** Family tree and *CACNA1S* mutations identified in case two. **1D:** Pictorial representation of a voltage gated skeletal muscle sodium and calcium channel. Each has four transmembrane domains (DI to DIV) comprised of six segments (S1 to S6). The fourth segment in both channels contains an abundance of positive charge and is denoted the voltage sensor. These positive charges interact with negative charges in the S1 to S3 segments. Protein position of sodium channel mutations in case one represented by red circles. R1135C replaces a positive charge in the voltage sensor. Protein position of calcium channel mutations in case two represented by yellow circles. E100K replaces a negative charge in an S2 segment.