Treatment of Paramyotonia Congenita with Acetazolamide

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ABSTRACT: Treatment of paramyotonia congenita with acetazolamide has been shown to reduce myotonic symptoms but severe weakness has developed in some patients leading to a recommendation not to use the drug in this disorder. We studied a patient with the characteristic clinical and electrophysiological profile of paramyotonia congenita. Myotonia was effectively treated with a very low dose of acetazolamide and no weakness developed. We conclude that acetazolamide can be a safe and effective medication in paramyotonia congenita.

RÉSUMÉ: Traitement de la paramyotonie congénitale au moyen de l'acétazolamide Il a été démontré que le traitement de la paramyotonie congénitale au moyen de l'acétazolamide diminue les symptomes dus à la myotonie. Cependant, parce que certains patients ont développé une faiblesse importante lors de l'administration de ce médicament, il est recommandé de ne pas l'utiliser pour traiter cette maladie. Nous avons étudié un patient chez qui le tableau clinique et l'électrophysiologie étaient caractéristiques de la paramyotonie congénitale. Avec de très petites doses d'acétazolamide, la myotonie a été traitée efficacement sans apparition de faiblesse. Nous concluons que l'acétazolamide peut être une médication efficace et sûre dans le traitement de la paramyotonie congénitale.

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Paramyotonia congenita is a relatively benign autosomal dominantly inherited myotonic disorder. First described by Eulenburg in 1886,[1] it is characterized by paradoxical myotonia and increased stiffness and weakness following exposure to cold. Acetazolamide has been reported to reduce myotonia in this disorder, but due to the development of severe weakness in some patients after taking the medication[2,3] it has been recommended that it should be avoided in paramyotonia congenita.[4] We have had the opportunity to study a patient with paramyotonia congenita and to assess the effects of acetazolamide.

Case Report

Since early childhood this 26 year old woman had muscle stiffness made worse by exercise and cold. She had noted difficulty in releasing her grip particularly after a prolonged forceful contraction such as when releasing a baseball bat after hitting the ball. Her shoulder girdle muscles became stiff after carrying heavy objects and walking up stairs produced stiffness in her legs. Cold exacerbated her symptoms. She noted that placing her hands in cold water increased the stiffness. In the cold, movement of her facial muscles became difficult due to stiffness. Outdoor activities during winter months were limited by her symptoms. Actions such as shovelling snow brought on stiffness which progressed to significant weakness most marked in the upper extremities that persisted until after rewarming. Episodes of weakness unrelated to cold had not occurred.

One of the patient's brothers, her mother, maternal grandmother and great grandfather, two sons and one daughter all suffered from stiffness made worse by cold and weakness following exercise in the cold. An evaluation of her five year old daughter confirmed she suffered from the same disorder. Several other members of the kindred were affected which included male to male inheritance consistent with autosomal dominant inheritance.

Examination revealed no abnormal findings outside the neurological system. The patient's strength, reflexes and sensory exam were normal. Percussion myotonia was elicited over the thenar eminence and tongue. Grip myotonia was initially mild, but with repeated contractions became more severe. Myotonia of the orbicularis oculi muscles developed after repeated eye closure.

The serum K + ranged from 4.4 - 4.9 mM/L on three measurements during the patient's evaluation. Needle electromyography at room temperature demonstrated myotonic discharges and normal motor unit potentials. Motor unit activation remained normal after repeated forceful contractions. Cooling the patient's hand by immersion in ice water for 10 minutes produced marked stiffness and restriction of movement. Following a few seconds of repeated forceful contraction of the hand the grip became weak and flaccid. Needle examination while at rest after cooling showed that myotonic discharges could still be elicited by needle movement. After brief exercise motor unit potential activation was very reduced despite maximum effort.

Therapeutic trial. Due to the reports of flaccid quadriparesis in paramyotonia congenita treated with acetazolamide, the patient was admitted to hospital. Acetazolamide 125 mg was given orally, and the patient's strength and myotonia were monitored. After two hours no weakness had developed and repeated forceful hand gripping no longer produced noticable myotonia. After repeated forceful eye closure slight periorbital myotonia was seen, much less than prior to the medication. This improvement persisted for about 12 hours. The following day the patient was given acetazolamide 250 mg; however further improvement above that with 125 mg was not seen and there was no weakness. Needle electromyography at room temperature once again showed

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myotonic discharges and normal motor unit potentials. Immersion of her hand in ice water for 10 minutes resulted in mild grip myotonia with repeated contraction, much less than prior to treatment, and no weakness after repeated contraction. Myotonic discharges persisted on EMG following cooling of the muscle in ice water, but no fall out of motor unit potentials developed after repeated forceful contractions.

As satisfactory improvement in the patient's symptoms had been accomplished without any weakness, higher doses of acetazolamide were not attempted. The patient was discharged on acetazolamide 250 mg once daily. At follow-up after six months treatment the improvement in myotonia was still present without weakness. The patient found that despite the coldness of winter she was able to partake in several outdoor activities that had been previously very difficult because of myotonic symptoms and weakness induced by cold.

Discussion

Our patient's clinical and electrophysiologic findings are consistent with the diagnosis of paramyotonia congenita. Paramyotonia congenita is distinguished from other myotonic disorders by the presence of paradoxical myotonia and cold intolerance.[1,5] Unlike myotonia congenita, in which myotonia decreases after movement, the myotonia in paramyotonia congenita increases with exercise, a feature that can be quite disabling for affected patients, especially those frequently exposed to cold environments. Electrophysiologic features of paramyotonia congenita[6,7,8] include characteristic waxing and waning myotonic discharges induced by needle movement and muscle percussion. The size and shape of voluntary motor unit potentials are normal. Moderate cooling of the muscle results in spontaneous muscle activity with the appearance of fibrillations. These disappear with greater cooling. Intense exercise produces a drop out of voluntary motor unit potentials which is enhanced by moderate cooling. After deep cooling the drop out of motor unit potentials can be extreme, resulting in electrical silence associated with flaccid paralysis or cramp contracture. These electrophysiologic features parallel the clinical correlates of increased stiffness after exercise and weakness on exposure to cold environments.[6] Exercise enhanced fall out of motor unit potentials associated with flaccid weakness was documented in our patient during cooling. However, fibrillation and complete electrical silence were not seen. Intramuscular temperature was not recorded during the examination and muscles, therefore, may not have been examined at temperature levels necessary to see these changes.

The main conditions to be considered in the differential diagnoses of paramyotonia congenita are myotonia congenita and paramyotonia associated with periodic paralysis in warm environments. Myotonia congenita does not demonstrate the clinical and electrophysiologic features associated with exercise and cold that were seen in our patient and are characteristic of paramyotonia congenita.[6,7,8,9] The relationship between paramyotonia congenita and periodic paralysis is not clear. Some patients with paramyotonia have episodic weakness unrelated to cold but sometimes associated with hyperkalemia.[5,10,11,12] These patients may represent subgroups of paramyotonia congenita. Potassium loading and glucose and insulin infusions can help characterize these subgroups.[5] These were not performed in our patient. However, the lack of paralysis without cooling makes it unlikely that this patient falls into a subgroup of paramyotonia congenita with additional periodic paralysis.

Successful treatment of the myotonic symptoms in paramyotonia congenita has been documented with the use of tocainide[12,13] and acetazolamide.[14] Tocainide is a new antiarrythmic agent with properties similar to lidocaine. Though its toxicity is reported to be usually mild, dose related and affecting the central nervous system or gastrointestinal tract, up to 16% of patients in reported series have had to discontinue the medication due to toxicity.[15] Occasional serious adverse effects reported include agranulocytosis,[16] interstitial pneumonitis,[17] and possible hepatotoxicity.[18] A long experience with acetazolamide has been acquired through its use in other disorders. It is generally tolerated well and serious toxicity is unusual.[19] With the low dose of acetazolamide used in this patient, intolerance from paresthesiae and drowsiness and possibly the long term side effect of renal calculi[20] are less likely to occur. In paramyotonia congenita weakness developing in some patients treated with acetazolamide[2,3] has prompted the suggestion that it should be avoided in this disorder.[4] The factors that produce this serious side effect are unclear. The weakness can develop acutely, within the first two days of therapy in one patient.[3] Improvement in myotonia appears to occur in both those that develop weakness and those who do not. One patient responded favourably to acetazolamide 500 mg per day without developing weakness.[3] Patients reported to become weak have taken from 500 to 1000 mg per day.[2,3] Both of the patients suffering adversely from acetazolamide, however, had a history of episodic weakness not related to cold, suggesting they may belong to a subgroup of the disorder. Interestingly, weakness was provoked in a patient with hyperkalemic periodic paralysis treated with acetazolamide,[21] though this does not usually occur in that disorder. Potassium loading was normal in one patient with paramyotonia congenita who experienced acetazolamide induced weakness[3] and hence will not help identify which patients might suffer this complication.

Our patient responded promptly to acetazolamide with reduced clinical myotonia in warm and cold environments, reduced cold induced weakness and reversal of the cold induced drop in motor unit potential activation which had correlated with flaccid weakness. From this single case we can not conclude that acetazolamide is better than tocainide in the treatment of paramyotonia congenita and a double blind therapeutic trial in a larger number patients is needed to fully assess the benefit of low dose acetazolamide. However, this case demonstrates that acetazolamide can be beneficial in some patients and should be considered among the therapeutic options for paramyotonia congenita, particularly because of its relatively good tolerance by patients and low incidence of serious side effects. Initiating treatment at a low dose may decrease the risk of weakness but until the safety of low dose acetazolamide in paramyotonia congenita is more widely established, especially in those patients with a history of weakness induced with cooling, we recommend starting treatment in hospital.

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