Austin Journal of Musculoskeletal Disorders

Open Access

Austin Publishing Group

Case Report

Beneficial Effect of Pregnancy on Hyperkalemic Periodic Paralysis

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Received: April 30, 2017; **Accepted:** May 22, 2017; **Published:** May 30, 2017

Abstract

Background: Reduction of intensity, duration and frequency of attacks of muscle weakness in hyperkalemic periodic paralysis (hyperPP), also known as Gamstorp's disease, has been reported only once. Here we report the second case.

Case Report: A 30yo Caucasian female with hyperPP due to the mutation c.2111C>T in the SCN4A gene became pregnant for the first time. Shortly after onset of pregnancy she experienced marked reduction of frequency and intensity of attacks, such that she experienced only 4 severe attacks during the 9 months of pregnancy compared to approximately 1/week before pregnancy. After delivery the attacks returned to the pre-gestational level. The beneficial effect was attributed to hormonal changes during pregnancy.

Conclusion: duration, intensity, and frequency of episodic attacks of muscle weakness in hyperPP may decline during pregnancy. Contrary to previous reports pregnancy may have a beneficial effect on disease severity in certain hyperPP patients.

Keywords: Periodic Paralysis; Pregnancy; Gestagens; Treatment; Scna4; Potassium Channel; Chanelopathy

Introduction

Hyperkalemic periodic paralysis (hyperPP) is a genetic, autosomal dominant disorder due to mutations in the muscle sodium channel gene *SCN4A*. Hyper PP is phenotypically characterised by recurrent episodes (attacks) of sudden-onset, mild to severe, flaccid muscle weakness lasting between a few seconds and several hours [1]. Weakness usually involves the limb, axial, and bulbar muscles. Respiratory muscles are spared [1]. Attacks may be mild or of such a degree that patients become unable to move and require medical support [2,3]. Attacks are usually associated with hyperkaliemia. Intake of potassium-rich food, potassium-containing drugs, or alcohol, cold, emotional stress, fasting, strenuous exercise, general anesthesia, corticosteroids, or pregnancy are generally regarded as triggers of attacks in hyperPP [1,4,5,6]. Onset of attacks is usually in the first decade of life. Frequency and severity of attacks increase over time with a nadir at around age 50y to decrease thereafter. In addition to transient muscle weakness, half of the patients develop interictal myotonia of the facial, lingual, or hand muscles. Myotonia may be enhanced by cold (paramyotonia) or exercise [1]. In the advanced stage of the disease myopathy of lower limb and pelvic girdle muscles with permanent weakness may develop. Patients without interictal myotonia more likely develop myopathy with permanent weakness than those with myotonia. Attacks may be prevented or weakness during an attack relieved by mild exercise or intake of carbohydrates immediately at onset of an arising attack, inhalation of salbutamol, or application of calcium intravenously in form of calcium-gluconate [2]. Drugs known to decrease serum potassium levels and thus being preventive include thiazide diuretics. acetazolamide, and dichlorphenamide [1,2,3]. Life expectancy of hyperPP patients is not reduced. A beneficial effect of pregnancy on the frequency, duration, and intensity of attacks in hyperPP has been reported previously only once [7]. In this previous case, attacks of hyperPP resolved completely during pregnancy [7]. Here we report a second female with hyperPP who experienced significant relief of her manifestations during her first pregnancy.

Case Presentation

The patient is a 30yo, Caucasian female, height 150cm, weight 55kg, with a family history of hyperPP due to the mutation c.2111C>T in the *SCN4A* gene in her 57yo mother. The mother had experienced typical episodes of muscle weakness since age 3.5y. She was recommended by her treating physician to avoid pregnancy and to undergo tubal ligation because they feared deterioration of hyperPP during pregnancy. However, the patient became pregnant despite a contraceptive coil and there was no deterioration of hyperPP. She was told to eat low potassium food, to avoid heavy work and cold, and to take Na-polystyrensulfonate (15g) three times a week and salbutamol on demand. She was also on a long-term therapy with acetazolamide.

The index patient became apparent to her mother for attacks of muscle hypotonia of the upper limbs when learning to walk at age 1y. After hyperPP was diagnosed in the mother, these attacks of muscle weakness or hypotonia were attributed to suspected hyperPP in the index case as well. The attacks occurred with a frequency of 1-2/d and lasted between 15min and maximally 3h. Severity of weakness during these attacks was highly variable. Mild attacks manifested as gait disturbance without losing the ability to walk unaided or inability to move a single or several fingers preventing her from lifting heavy weights. Severe attacks manifested with dropped head, inability to

Citation: Finsterer J. Beneficial Effect of Pregnancy on Hyperkalemic Periodic Paralysis. Austin J Musculoskelet Disord. 2017; 4(2): 1047.

walk and to turn around in bed, inability to move the hands, and heaviness of the tongue resulting in impaired speech. So far, she had never experienced involvement of the respiratory muscles. Attacks could be triggered by alcohol occurring 1-2h after consumption. From age 3y to age 13y she was taking acetazolamide, without effect. Attacks could be occasionally prevented by regular intake of food every 4h. Additionally, she restricted intake of fruits and vegetables and took calcium orally. Mild attacks could be relieved by walking. At age 29y she recognised that intake of carbohydrates shortly after onset of an attack prevented further deterioration or even stopped an incipient attack. Since then she was eating a chocolate, drank cola, or went for urination or defecation when she recognised an upcoming attack. Disadvantage of carbohydrates was that she gained weight. Clinical neurologic exam between the attacks at age 28y was normal.

Clinical exam during these attacks revealed severe flaccid muscle weakness (M1) with right-sided predominance particularly of the legs with weakness (M4) of the upper limbs. Serum potassium was normal between the attacks but increased up to 8.3mmol/l (n, 3.4-4.5mmol/l) during the attacks. Creatine-kinase was normal. The ECG during the attacks showed typically heightened T-waves. Needle electromyography during the interval revealed positive sharp waves during slight voluntary activation, some prolonged motor unit action potentials (MUAPs), and single oscillations respectively reduced interference pattern during maximal voluntary contraction. Severity and duration of the attacks became less with increasing age. The diagnosis was genetically confirmed at age 29y.

In August 2015 she became pregnant and already two weeks after the positive pregnancy test she experienced a marked reduction of intensity, duration and frequency of her attacks. During pregnancy she experienced only mild attacks with a frequency of one per week. She did not require carbohydrates for mitigating attacks during the entire pregnancy because they remained low in frequency, duration, and intensity until birth. Even immediately after birth she remained attack-free but when the new-born was brought to her for the first time she again experienced a severe attack, which resulted in general muscle weakness during two days. After delivery of a so far healthy child at term, frequency and intensity of attacks increased to the pre-gestational level. Clinical neurologic exam at age 30y, two years after pregnancy, was normal, except for apparent calf hypertrophy. Neither wasting or tremor, nor clinical myotonia could be registered.

Discussion

A beneficial effect of pregnancy on the severity and frequency of attacks from hyperPP has been previously reported in a single patient with hyperPP due to the mutation p. T704M in the *SCN4A* gene [7]. Though the cause of the beneficial effect of pregnancy on hyperPP remains unknown, several speculations can be raised to explain the phenomenon. The first explanation for the relief of attacks in hyperPP during pregnancy could be hyperglycemia due to hormonal changes during pregnancy. An argument against this hypothesis, however, is that none of the two females experiencing improvement during pregnancy had developed gestational diabetes or elevated blood glucose levels during pregnancy. Neither of the two was diabetic prior to onset of pregnancy. Whether the beneficial effect will also occur in a second pregnancy remains speculative since neither of the two had become pregnant again. The second explanation could be a direct effect of gestagens on sodium channels since treatment of Xenopus laevis oocytes with progesterone resulted in complete abolishment of transmembrane sodium currents [8]. A third explanation for the relief of clinical manifestations of hyperPP during pregnancy could be that hormonal changes during gestation induce hypokalemia [7]. An argument against this hypothesis, however, is that reduction of potassium in hyperPP frequently does not influence the clinical manifestations of an attack. A fourth explanation could be improved contractility induced by gestagens. An argument against this hypothesis, however, is that gestagens reduce contractility of smooth muscle cells [9] by reducing transmembrane calcium-currents [10]. Whether this effect also occurs in the striated muscles remains unknown. It is also unknown which factors may enhance or reduce the beneficial effect of pregnancy on attacks on hyperPP. Factors that potentially influence the beneficial effect of pregnancy could be age, co-medication, or type of underlying mutation.

Conclusion

In conclusion, this case shows that pregnancy can reduce duration and intensity of episodic attacks of muscle weakness in hyperPP. Though the cause of this spontaneous improvement remains speculative, there are indications that metabolic changes during pregnancy may cause the beneficial effect.

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