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Bartter's Syndrome in Pregnancy: A Case Report and Review

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Abstract: ***Bartter's syndrome is a rare autosomal recessive disorder characterized by hypokalemia, hyperaldosteronism, sodium wasting, normal blood pressure, hypochloremicalkalosis, and hyperplasia of the juxtaglomerular apparatus. We present a 28-year-old Indian nulliparous patient who was referred to our hospital at 16 weeks' gestation. Patient was known case of Hyperthyroidism diagnosed 18 months ago and was being treated with Propylthiouracil. She presented with Vomiting followed by ascending quadriparesis. She required increasing potassium supplementation. She developed hypomagnesemia which necessitated magnesium therapy. Patient suffered intrauterine death of her fetus. Bartter's syndrome, although extremely rare in pregnancy, requires prompt recognition and careful management, as it may have significant maternal and neonatal implications.***

Keywords: Bartter's syndrome; pregnancy; hypokalemia; hyperaldosteronism

1. Introduction

Bartter's syndrome is a rare autosomal recessive disorder with a reported prevalence of 1.2 per million. (1) It is characterized by hypokalemia, hyperaldosteronism, sodium wasting, normal blood pressure, and hypochloremic alkalosis; renal biopsy often demonstrates hyperplasia of the juxtaglomerular apparatus. (2)The disease is usually diagnosed in infancy or childhood, and several cases of fetal Bartter's syndrome have been reported. (3-5) However, there are only few cases of maternal Bartter's syndrome complicating pregnancy in the literature. (6-8) We present a case of maternal Bartter's syndrome complicating pregnancy and review the pathogenesis and clinical management of this disease in pregnancy.

2. Case Report

28 year old female, k/c/o Hyperthyroidism since 18 months 16 weeks pregnant (primigravida) On Tab Propylthiouracil 50mg TID Came with chief c/o Vomiting episodes 4 to 5 per day since 3 days Weakness in all 4 limbs more in lower limbs since 1 day. Illness started with history of vomiting episodes 4 to 5 per day associated with nausea and containing food particles. On 2nd day patient started having weakness in lower limbs which then progressed to upper limbs. Initially she was able to walk with support but weakness progressed rapidly and on 3rd day patient became bedridden. Proximal muscles were involved predominantly. On day of admission she was unable to move lower limbs in bed. At that time Arterial blood gas analysis showed presence ofmetabolic alkalosis with severe hypokalemia. ECG showed presence of ST depression and U waves s/o Hypokalemia. Creatinine: 0.7 mg/dl Na/K: 126/1.6 meq/l Thyroid Function Test: T3: 227 ng/dl (60-200)T4: > 30 ug/dl (4.5-12) TSH: <0.01 uIU/ml (0.3-5.5) suggestive of Severe Hyperthyroidism. In view of Hyperthyroidism keeping in mind possibility of Redistributive Hypokalemia patient was started on Propranolol 40mg TID and dose of Propylthiouracil increased to 200 mg TID.

In view of hypokalemia and presence of quadriparesis and Poor neck holding patient was started on intravenous and oral Potassium supplements with caution with 6 hourly monitoring (risk of rebound hyperkalemia) and samples for urinary electrolytes were obtained.

On 3rd day patients lower limb power improved to grade 3. Potassium level of 2.5 mEQ/l after continuous maximal intravenous infusions and oral Potassium supplements. Patient started having perioral tingling and episodes of carpopedal spasms s/o tetany. In view of development of tetany and inability to correct Potassium levels patient was further investigated. Serum Calcium: 7.5 mg% (8.8-10.6) Corrected Calcium: 8.3 mg % Ionised Calcium: 3.40 mg% (4.15-5.71) Suggestive of Hypocalcemia Serum Phosphorous: 2.52 mg% (3.5-5.5) Serum Magnesium: 0.7 mg% (1.6-2.2) Serum Chloride: 68 mEq/l (98-106) Urinary Electrolytes: Sodium: 82 mEQ/l Potassium: 16.4 mEQ/l Average 24 Urine Output: 2.5 to 3 lit Serum Intact PTH: 10.88 pg/ml (15-65 pg/ml) Serum osmolality : 273 mOsm/kg (285-295 mOsm /kg) Urine osmolality: 291.2 mOsm/kg (600 to 800 mOsm/kg) TTKG (Transtubular Potassium Gradient) = 9.6

Patient was treated with intravenous and oral potassiuminitially. Oral and intravenous Calcium Gluconate was used. Magnesium correction with intravenous MgSO4 was given. Oral Propylthiouracil and Propranolol was continued.

Patient improved dramatically after this.Advised further work up; serum renin, serum aldosterone but patient was not willing. Patient was discharged on tab spironolactone, sypksol, and oral Vit D, Calcium and Magnesium supplements. She isbeing followed up.

3. Discussion

There are numerous theories regarding the possible pathophysiology of Bartter's syndrome. (2) Each of the six abnormalities characteristic of Bartter's syndrome—juxtaglomerular hyperplasia, angiotensin resistance, altered bradykinin system, increased renalprostaglandin E2 production, hypokalemia, andrenal tubular dysfunction—could be the initiating cause of the disease. (2,9) The site of renal tubular biochemical dysfunction has been variably described as abnormal chloride transport in the thick ascending loop of Henle or abnormal sodium handling in the

proximal or distal tubule. (2,9-11) Juxtaglomerular hyperplasia is associated with increased renin production. However, normal feedback inhibition of renin release is prevented by angiotensin resistance, which results in further juxtaglomerular hyperplasia. Renin-stimulated angiotensin release results in elevated aldosterone and renal medullary production of prostaglandin E2 and kallikrein, which stimulates bradykinin formation. Increased production of the vasodilators bradykinin and prostaglandin E2 combined with angiotensin resistance results in normotension that is characteristic of Bartter's syndrome. Hypokalemia is responsible for most of the clinical signs and symptoms of Bartter's syndrome, including growth retardation, muscle weakness and cramps, polydipsia, polyuria, and alkalosis. Hypokalemia stimulates increased production of renin, prostaglandin E2, and bradykinin. The differential diagnosis of hypokalemia in a normotensive patient includes vomiting, inappropriate use of laxatives and diuretics, congenital chloride-wasting diarrhea, and cystic fibrosis. Low urinary excretion of chloride in the presence of excessive sodium and potassium loss is characteristic of abnormal gastrointestinal function. Surreptitious diuretic use may be distinguished from Bartter's syndrome by screening the urine for diuretics. Treatment of patients with Bartter's syndrome is directed at relief of symptoms caused by hypokalemia. It should be noted that symptoms are not directly correlated with serum potassium levels, and therefore treatment is aimed at symptomatic relief rather than a specific targeted potassium level. Furthermore, most patients never maintain normal serum potassium despite aggressive treatment. Treatment modalities include oral or intravenous potassium supplementation and potassium-sparing diuretics such as spironolactone and amiloride. Amiloride is classified as a Category B drug during pregnancy; however, there are only three case reports of its use during pregnancy. (12) Spironolactone is classified as a Category D drug during pregnancy due to potential feminization of male fetuses. (13)Angiotensin-converting enzyme inhibitors (such as captopril) have been used todecrease renin and aldosterone levels, as have prostaglandin synthetase inhibitors such as indomethacin. However, the efficacy of these agents is variable withregard to serum potassium levels. (8) Furthermore, in pregnancy angiotensin-converting enzyme inhibitors are contraindicated due to adverse fetal effects (14) and indomethacin use has been associated with premature closure of the ductusarteriosus and necrotizing enterocolitis in the neonate. (15) Propranolol also decreases plasma renin and aldosterone; however, this may be associated with hypotension in these patients. (11)Our patient, in addition to demonstrating derangement of potassium, sodium, and chloride balance, also had hypomagnesemia. Thirty-nine percent of patients with Bartter's syndrome exhibit renal magnesium wasting due to a defect in reabsorption in the loop of Henle. (16) Symptoms associated with hypomagnesemia include lethargy, confusion, tremor, ataxia, nystagmus, seizures, and tetany. Furthermore, hypomagnesemia may exacerbate hypokalemia. (16) Therapy is aimed at normalizing magnesium levels and decreasing symptoms, recognizing that oral magnesium therapy may be associated with diarrhea, which may exacerbate hypokalemia. The effect of pregnancy on the course of Bartter's syndrome is unknown due to limited reported cases in the literature. Pregnancy is associated with stimulation of the renin-angiotensin-aldosterone system,which could theoretically increase potassiumexcretion. (17) In fact, serum potassium decreases by approximately 0.5 mEq/L at midgestation. (18) Daily requirements of dietary magnesium increase during pregnancy from 280-320 mg per day. (19) This could partially explain the increase in magnesium supplementation required by our patient during pregnancy. Angiotensin resistance is also characteristic of normal pregnancy (17) and this may result in increased resistance to pressors in patients with Bartter's syndrome. This should be taken into consideration prior to the administration of regional anesthesia in these patients. (8)Other anesthetic considerations include avoidance of nephrotoxic drugs or drugs that require renal excretion, maintenance of perioperative fluid balance, and monitoring of end-tidal CO2 to prevent respiratory alkalosis.8 Metabolic alkalosis, which is characteristic of Bartter's syndrome, may interfere with binding of muscle relaxants to protein. In addition, frequent monitoring of serum potassium is required as is continuous cardiac monitoring during administration of anesthetic agents. (8)Patients with Bartter's syndrome are usually of short stature and this should be recognized prior to administration of regional anesthesia. The effect of maternal Bartter's syndrome on fetal and neonatal development is unknown. One report suggested intrauterine growth restriction, (7) . Neonates may exhibit transitory metabolic derangement; however, this should resolve if the infant is given balanced formula solution. There is a theoretical concern that neonatal electrolyte balance will be more difficult to maintain if the infant is breast fed with potassium depleted milk, but electrolyte measurements in breast milk of women with Bartter's syndrome have not been performed. There have been several reports of fetal Bartter's syndrome in the obstetrical literature. (3-5) This is characterized by fetal polyuria and polyhydramnios; the condition has been reported to recur in cases of parental consanguinity. (5) Measurement of amniotic fluid electrolytes does not facilitate prenatal diagnosis due to equilibration across the placenta. (3) Renin is not excreted in the urine and therefore measurement of amniotic fluid renin levels are also of little help in the diagnosis of fetal Bartter's syndrome. (3)

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