A Case of Nephrotic Syndrome with Gitelman’s Syndrome

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Abstract
Nephrotic syndrome, though common in children, association of it with Gitelman’s syndrome (GS) is a rare occurrence. Very few cases have been reported in the medical literature so far. Here we report a case of nephrotic syndrome with frequent relapses and remissions on intermittent steroid and diuretic therapy. Patient was restarted on steroids and frusemide. Puffiness of face, bipedal edema and oliguria improved but patient developed tingling numbness in both limbs, perioral numbness and carpopedal spasm. On investigation she was found to have proteinuria, metabolic alkalosis, hypokalemia, hypocalcemia, hypomagnesemia and hyperreninemia with normal blood pressure.

Introduction
Gitelman syndrome, discovered in 1966 by Gitelman, Graham and Welt, is an autosomal recessive renal tubular disorder and is characterised by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria. It is milder than other sub-types of Bartter’s syndrome. Patients with GS usually present during childhood or adolescence. Clinically characterised by tetanic episodes, muscle cramps, muscle paralysis, tingling numbness, perioral tingling sensation, salt craving and nocturia. Most cases of GS result from inactivating mutations to the SLC12A3 gene, which encodes the thiazide-sensitive Na-Cl cotransporter (NCC) on the apical membrane of distal convoluted tubule (DCT) cells. A minority of GS patients have mutations in the basolateral chloride channels (CLCNKB). The defect in thick ascending loop of Henle (TALH) or distal convoluted tubule (DCT) results in a failure to reabsorb chloride and sodium, that leads to excessive sodium and chloride delivery to the distal tubules, resulting in excessive salt and water loss from the body. The renin-angiotensin-aldosterone system (RAAS) is a feedback system activated with volume depletion. Long-term stimulation of the renin-angiotensin-aldosterone system may lead to hyperplasia of the juxtaglomerular complex. Angiotensin II also produces a counterregulatory rise in vasodilating prostaglandin E (PGE) level. High prostaglandin E level is associated with growth inhibition in children. Concurrence of nephrotic syndrome with Bartter or Gitelman syndrome is very rare. The possible association between these two entities is still unclear. Hitherto few such cases have been reported out of which one is by DAI Yu-wen from China and another by Hanevold C from U.S.A.

Case Report
A 19 year old unmarried female born of non-consanguineous marriage, diagnosed as a case of nephrotic syndrome at the age of 3 years, was admitted with complaints of puffiness of face, bipedal edema, oliguria and generalized weakness since 2 months and multiple tetanic episodes in form of carpopedal spasm and perioral numbness since 4 days. Nephrotic syndrome was diagnosed on the clinical and laboratory parameters. Patient was started on steroids at the time of diagnosis from the peripheral hospital for a period of 2 months. Her symptoms subsided but she relapsed twice every yearly in between till the time of present admission to our hospital. With each episode of relapse she was started on short course of steroids (Tab Prednisolone 1mg/kg of body weight for 2–3 weeks) and diuretic along with potassium supplements and her symptoms used to subside with that only to recur at the time of next relapse. This time she again presented with relapse and multiple tetanic episodes. She denied any history of continuous diuretic, laxative, any street drug abuse or multiple episodes of nausea, vomiting, diarrhea, heat intolerance, excessive perspiration and changes in bowel habits before this. Menstrual history was normal.

On admission her physical examination showed pallor, periorbital and bipedal edema. Vital parameters were normal. But Chvostek and Trousseau signs were positive. Arterial blood gas analysis showed metabolic alkalosis (pH = 7.558, HCO3- = 33.9 mmol, PCO2 = 38, PO2 = 93.3 and SaO2 = 95.9), hypokalemia (Sr. K+ = 2.3 mEq/L), hypocalcemia (Corrected Sr.Ca = 7.8 mEq/L), hypomagnesemia (Sr.Mg = 0.7 mEq/L), hypoalbuminemia (Total protein = 5.2 gm/dl, Albumin = 2.6 gm/dl, globulin = 2.6 gm/dl), hypercholesterolemia (Sr. Cholesterol = 451mg/dl), 24 hour urinary protein = 1.445 gm/day, 24 hour urinary calcium excretion was 180 mg/day (within normal limit). Urine routine and microscopy showed trace proteins and no casts or calculi. Ultrasonography showed bilateral bulky kidneys with no evidence of nephrocalcinosis. Serum 25-OH vitamin D3 level was low (5.12, N.R = 9–37.6 ng/ml) and serum PTH (Intact) hormone level was low normal. Plasma renin level was elevated (14.96 ng/ml/hour, N.R = 0.95–2.33 ng/ml/hour). Rest of the other investigations such as complete blood count, blood sugar, renal, liver and thyroid function test, serum cortisol level and ECG were within normal limits. ANA and dsDNA were negative.

In view of proteinuria, patient was started on steroids (Tab Prednisolone 20mg daily along with milk) as per 1mg/kg of body weight, potassium sparing diuretic (Tab. Spironolactone 25mg bid), ACE inhibitor (Tab. Enalapril 2.5 mg od) along with calcium, magnesium (Tab Magnical) and potassium supplements. Patient was also given Inj . Arachitol (vitamin D3) 6 lac I.U on day of receiving Vitamin D3 report with second dose repeated after 7 days. Serum K+ level became normal. Tetanic episodes decreased. Puffiness of face and bipedal edema decreased. Renal biopsy was deferred as patient went into remission after starting steroid.

Discussion
GS due to NCC mutations is often described as a mild variant of the salt-losing tubular disorders. Both sexes are equally affected. Often there will be a history of patient’s sibling with GS and parents basically never have the disease. Patients with...
GS usually present the clinical symptoms during childhood or adolescence.1 Our patient lies in the adolescent age – group and presented with tetanic episodes, perioral numbness, Chvostek’s and Trousseau’s sign which are the cardinal manifestations of GS. However, some patients remain asymptomatic while others develop severe symptoms, including muscle paralysis. As reported by Cruz el al., approximately 6% of GS patients present with hypokalemic paralysis.2 In fact, GS patients presenting with profound hypokalemic paralysis have been reported increasingly in Asia.6, 7 Our patient first presented with nephrotic syndrome at 3 years of age and now with features of GS consistent with the case report by DAI Yu-wen from China.4 The possible association between these two entities is still unclear. Though there are reports regarding glomerular changes in Bartter syndrome/GS such as proliferative nephritis, diffuse mesangial hypercellularity and focal segmental glomerulosclerosis8,9 there is no information regarding severity of proteinuria. However recent studies indicate that long term stimulation of Renin angiotensin aldosterone system (RAAS) due to volume depletion may contribute to renal damage through release of transforming growth factor β, tumor necrosis factor-α, and other cytokines.10

Renal biopsy was not done in our patient. But considering clinical and biochemical parameters diagnosis of nephrotic syndrome and Gitelman syndrome was made. Patient was restarted on steroids , ACE inhibitor, K+ sparing diuretic, potassium, calcium and magnesium supplements. Puffiness of face, bipedal edema and tetanic episodes decreased.

**Conclusion**

Whether the association of nephrotic syndrome and Gitelman syndrome is coincidental in our patient or is it due to any glomerulotubular defect as questioned by DAI Yu-wen in his similar case report . Also one should keep an high index of suspicion in nephrotic syndrome patient about the co existence of Bartter/ Gitelman syndrome and vice – versa. We should also search at molecular level to find out the exact cause or defect so that we can treat the disease in a better way as some of these patients (Bartter/ Gitelman syndrome ) with proteinuria have been reported to progressed to renal failure.11

**References**