# Minimal Change Nephrotic Syndrome and Graves' Disease in a Nigerian Child

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**ABSTRACT**

We report a 12 year old Nigerian boy with steroid sensitive nephrotic syndrome who developed Graves' disease 12 months after the diagnosis of nephrotic syndrome. He had two relapses of the nephrotic syndrome with early response to steroids on both occasions. Renal biopsy showed normal findings on light microscopy. Graves' disease is rare among black African children, minimal change nephrotic syndrome is also not commonly reported among them. The coexistence of these two disorders in our patient underscores possible similar immunologic mechanisms in the aetiology of both diseases.

**KEYWORDS:** *nephrotic syndrome, minimal change nephrotic syndrome, hyperthyroidism, Graves' disease, steroids*

## INTRODUCTION

Hyperthyroidism has rarely been reported in association with Nephrotic Syndrome (NS)[1-5]. Nephrotic syndrome in African children, is relatively common, [6, 7] while hyperthyroidism is rare[8].We report a 12 year old Nigerian boy with steroid sensitive NS who developed hyperthyroidism in the course of the nephrotic syndrome.

## CASE REPORT

A 12 year old boy presented at the University College Hospital Ibadan, Nigeria with facial oedema of 2 weeks and two day history of scrotal swelling and pedal oedema. He weighed 36kg (25$^{TH}$ centile for age), and height was156cm (75$^{th}$ centile for age), Blood pressure was 100/70mmHg and heart rate was 120/min. Laboratory data showed serum protein 6.2g/dL; serum albumin1.6g/dl, serum cholesterol 384mg/dL, Serum urea 39mg/dL and serum Creatinine 0.8mg/dl. Serum electrolytes were normal. HIV screening and HBsAg were negative. Dipstick urinalysis showed proteinuria of 4+ and trace of blood. Urine microscopy was normal and urinary protein excretion was 1 gram in 24 hours.

He was commenced on oral prednisolone at 50mg/day and went into remission 11 days after commencement of steroids. He had 17 days of daily steroid therapy and then 7months of alternate day steroids. At the end of steroid therapy serum protein was 7.5g/dL; serum albumin, 4.3g/dL and 24 hour urinary protein, 0.1g in 24 hours.

Twelve months after initial presentation and two months after discontinuation of alternate day prednisolone, he was noted to have a goiter, associated with proptosis and excessive sweating. Blood pressure was 120/ 70 mmHg and heart rate was 120/ minute. Thyroid gland ultrasound showed homogenous parenchymal echoes. The volume of the right lobe of the thyroid was at the upper limit of normal, while volume of the left lobe of the thyroid was normal. Total T3 was 8.3nmol/L (normal= 1.0-3.25), Total T4 was 244nmol/L (normal= 65-175) and TSH 0.1miu/L (normal=0.5-6.5). Three months later, he had a relapse of the nephrotic syndrome. Serum protein was 5.4g/dL, serum albumin 1.6g/dL, 24 hour urinary protein 4.1g and creatinine clearance 147ml/min. Serum urea was 33mg/dL, serum creatinine was 0.3mg/dl and the serum electrolytes were normal. The weight of 36kg at initial presentation had increased to 45 kg, while his height remained essentially unchanged at 158cm. He was recommenced on oral prednisolone. He went into remission on the 9$^{th}$ day of steroid therapy. He had

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14 days of daily prednisolone therapy and he was then changed to alternate day prednisolone.

The goiter however persisted with bilateral hand tremors, exophthalmos, warm moist palms and increased aggression. Repeat Thyroid function test, after 4 months of alternate day steroids, showed Total T3 5.4ng/ml (0.8-2ng/ml); Total T4 190ng/ml (45-115ng/ml);TSH <0.3µIU/ml(0.54-3.7 µIU/mL). He was then started on oral Carbimazole 10mg tds.

He had 9 months of alternate day steroids; 20 days after discontinuation of steroids he had a second relapse of nephrotic syndrome. He had a recurrence of oedema and dipstick urinalysis showed 4+ proteinuria, while the 24 hour urinary protein excretion was 4.8g in 24 hours. His serum urea was 34 mg/dL, while serum creatinine was 0.6mg/dl, his serum electrolytes remained normal. Renal biopsy, revealed normal findings on light microscopy. He was recommenced on daily prednisolone and achieved remission after the 6th day of daily steroids. Clinical and biochemical features of Graves' disease resolved with p.o carbimazole therapy.

## DISCUSSION

Autoimmune thyroid disorders have rarely been associated with nephrotic syndrome[1-5, 9-11]. Nephrotic syndrome has been associated with both hyperthyroidism[1-5]and hypothyroidism[12]. Initial reports were of membranous glomerulonephritis secondary to immune complex deposition of thyroid antigens[1, 12, 13]. More recently few reports of association of autoimmune thyroid disorders with minimal change nephrotic syndrome have been documented [2-5, 9, 11], with Graves' disease occurring in association with minimal change nephrotic syndrome[2-5]. Three of the reports of Graves' disease were in adults. In the only case reported in the paediatric age group the patient developed Graves' disease about 9 years after the diagnosis of minimal change nephrotic syndrome[5]. Our patient developed Graves' disease about 1 year after the development of minimal change nephrotic syndrome.

Minimal change nephrotic syndrome is suspected to be secondary to an abnormality in T Cell immunity[14]. The association of minimal change nephrotic syndrome with lymphoma, particularly the T cell disease 'mycosis fungoides', is well recognized[3]. Remission of minimal change nephrotic syndrome may coincide with measles infection[15]. Minimal change nephrotic syndrome largely responds to steroids and calcineurin inhibitors which modulate T cell immunity. A glomerular permeability factor (VPF) isolated from T cell hybridomas has been implicated in the pathogenesis of minimal change disease (MCD)[16]. Cytokine stimulation and inhibition of VPF production by T lymphocytes has been described in *in vitro* studies[17]. T cell subset changes and high IL 2R expression on peripheral lymphocytes may indicate the presence of stimulated T cells populations in MCD[18]. There are reports of reduction in VPF production in lymphocytes from patients with MCD who were treated with tacrolimus or cyclosporine[19].

Thyroid stimulating antibodies play a major role in Graves' disease and the extracellular domain of the thyrotropin receptor is the autoantigen. They are mainly produced by lymphocytes infiltrating the thyroid gland and their production is T cell dependent. Infiltrating T lymphocytes secrete interferon γ which stimulate the thyroid cells to express HLA class II molecules allowing the thyroid cells to present antigens such as the thyrotropin receptor to activated T cells[20, 21].

Autoimmune disorders tend to cluster together; either appearing simultaneously or consecutively in the same patient. Graves' disease has been documented in association with other autoimmune disorders such as Addisons disease, vitiligo and pernicious anaemia, which further emphasizes the autoimmune basis of Graves' disease[20].The association of Graves' disease with minimal change nephrotic syndrome suggests a common aetiology

Grave's disease occurs 5-10 times more frequently in women than in men, and is unusual in children. The prevalence of Graves' disease is similar among whites and Asians, and it is lower among blacks[20]. In a European study Graves' disease had an estimated incidence of 3 per 100,000 at puberty[22]. In Sub-Saharan Africa Graves' disease is rare in childhood, Laditan documented 3 cases of hyperthyroidism associated with exophthalmos over a 5 year period, accounting for 0.02 % of paediatric cases seen at at our centre between 1972 and 1976[8]. Minimal change nephrotic syndrome is also less common among Africans than among Caucasians. Among Americans, Asians and in Europe minimal change nephrotic syndrome accounted for 76.6% of cases of idiopathic nephrotic syndrome[23]. In a standard Paediatric nephrology text it was noted that 90% of children with idiopathic nephrotic syndrome may be steroid responsive[24]. In Nigeria

minimal change nephrotic syndrome occurred in 9.8% of 41 children with nephrotic syndrome. In Northern Africa, the histopathology of nephrotic syndrome shows a profile that is similar to the pattern in Europeans, however in other parts of Africa minimal change disease accounted for 18-56% of cases of nephrotic syndrome[6]. In Nigeria 25.5-60% of nephrotic syndrome patients are steroid sensitive[7, 25, 26]. The coexistence of these two relatively rare conditions in our patient further supports an immunologic link in the aetiology of both diseases rather than coincidence.

Features of nephrotic syndrome preceded those of hyperthyroidism in our patient. This association is probably secondary to some dysregulation in the T cell Lymphocyte population possibly producing vasoactive peptide and then thyroid stimulating antibodies[3]. Association of minimal change nephrotic syndrome and Graves' disease should perhaps be considered a syndrome.

The renal biopsy in our patient was analysed by light microscopy only and it showed normal findings. Immunofluorescence or electron microscopy was not carried out, but the frequent relapses of the nephrotic syndrome without impairment of renal function, and complete remission following steroid therapy together with normal findings on light microscopy of the kidney biopsy are in keeping with minimal change nephrotic syndrome[27].

Free T3, free T4, and anti thyroid antibodies were not estimated in our patient but with the clinical features of hyperthyroidism, the features of mild ophthalmopathy, a diffuse goitre, the elevated total T4 and T3, and depressed TSH which remained so over a 6 month period we made a diagnosis of Graves disease.

Though the development of Grave's disease in the course of nephrotic syndrome is not common, Graves' disease should be considered in patients with nephrotic syndrome with careful clinical evaluation for features of Grave's disease such as ophthalmopathy and goitre.

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