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Management Challenges of Co-Existing Sickle Cell Disease, Graves' Disease and Thyroid Cancer in a Resource Poor Setting: A Case Report

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Abstract:
Background:
Sickle cell disease (SCD) is the most common autosomal recessive inherited haemoglobin (Hb) disorder found worldwide, with reported high prevalence of 2 – 3% in Nigeria[1,2] while Graves' disease (GD), an acquired autoimmune thyroid disorder is the commonest cause of hyperthyroidism, with reported global prevalence of 0.5 – 2%; and Thyroid Cancer (TC), a rare cause of hyperthyroidism, is also the commonest endocrine cancer globally[3,4,5],. These disorders are common causes of life threatening medical emergencies, chronic disability and major distress and drain on family resources[3,4,6,7,8,9,10]. The high costs and limited availability of current recommended standard diagnostic and monitoring work-up ancillary investigation tests for SCD, GD and TC markers; and treatment facilities for these disorders were major management challenges because of low national health insurance service (NHIS) coverage. Thyroid disorders are rare in SCD, with few reported cases of autoimmune thyroid disease[11], there is paucity of reports on co-existing SCD, GD and TC in Nigeria. We report the co-existing SCD, GD and TC in a 33 years old female patient in order to highlight the management challenges in a resource poor setting and the imperatives for wider NHIS coverage in Nigeria and strongly recommend inclusion of GD management in the NHIS for timely diagnosis and treatment to mitigate the deleterious effects of coexistence of the trio disorders.
Keywords: *Sickle Cell Disease, Graves' Disease, Thyroid Cancer, Hyperthyroidism, Co-existing.*
Written informed consent for use of her history and investigation results were obtained from the patient as well as ethical approval from the institutional research ethics review board (IRB) of University of Abuja Teaching Hospital, Gwagwalada, FCT, Nigeria.

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I. Introduction:

Sickle Cell Disease (SCD) is the most common autosomal recessive inherited haemoglobin disorder found worldwide. SCD is characterized by varying degree of chronic haemolytic anaemia, recurrent episodic acute pain and progressive multiorgan dysfunction. Nigeria has the highest prevalence, affecting 2% - 3% of the population[1,2,6]. Graves' disease (GD), the most common cause of hyperthyroidism is an autoimmune thyroid disorder caused by acquired thyrotropin receptor autoantibodies (TRAbs) induced stimulation of thyroid stimulating hormone receptors (TSHRs) on thyroid gland leading to increased thyroid hormones (T_3 and T_4) production and release into the circulation; suppression of thyroid stimulating hormone (TSH) production by the pituitary and low or undetectable serum TSH. This is associated with varying degree of clinical manifestation such as hyperthyroidism; orbitopathy and diffuse thyroid gland enlargement. The presence of TRAbs is pathognomonic of GD but can be negative in very mild GD and studies showed that TPOAbs and TGAbs are secondary to the TRAbs immune response. TC, a rare cause of hyperthyroidism is the commonest endocrine cancer globally, with an estimated worldwide prevalence rate of 0.5% – 2% and 90% of endocrine cancers. Studies have shown that differentiated thyroid cancer (DTC) cells express TSHRs like normal thyroid cells. And TRAbs may play a role in stimulation of growth, invasiveness and angiogenesis of DTC through the TSHRs, upregulation of vascular endothelial factor, placenta growth factor and their receptors via the same TSHRs pathway. Studies have reported coexistence of GD and TC with a prevalence of 17% and papillary thyroid cancer being the most common, both disorders are more common in females with a male to female ratio of 1:5.[1,2,5,12].

Thyroid hormones have influence on every tissue and organ system in mammals, the hormones are essential for development and growth by regulating many cellular genes expression. The non-genomic activities of the hormones also regulate many physiological functions in the body. Clinical features of GD include: goitre; orbitopathy (photophobia, lid lag, lid retraction, stare, and exophthalmos); Gastrointestinal (nausea and vomiting, diarrhea); Cardiovascular (palpitation, tachycardia, atrial fibrillation, angina cardiovascular collapse, congestive heart failure); Central nervous system (insomnia, anxiety, nervousness, inability to concentrate, muscle weakness, easy fatigability, irritability, tremors); increased sensitivity to heat, excessive sweating; pruritus, fine brittle hair, thinning of the skin, peripheral (pretibial) oedema, clubbing osteoporosis, bone pain; menstrual disorder, infertility and gynecomastia, pre-eclampsia, abortion, premature birth and low birth weight in pregnancy. Biochemical derangements like hypocholesterolemia, hypercalcaemia, hypokalaemia, hyperglycemia[3],[4],[12]. Thus, both SCD and GD affects every organ and tissues in the body and manifest with similar clinical features except for enlarged thyroid, orbitopathy, tremors and pruritus.

Diagnostic work-up GD include: TFTs – TSH, T_4, and T_3; Autoimmune antibodies - TRAbs, TPOAbs and TGAbs. Radioactive iodine-123 or technetium-99m uptake; Doppler ultrasonography; Chest X-ray; CT scan; MRI; fine needle aspiration (FNA) electrocardiography (ECG); echocardiogram (ECO); FBC; Serum electrolytes; urea and creatinine[3],[5].

Management of hyperthyroidism is subject to the aetiology, comorbidity, patient's age and treatment choice. The three main treatment modalities are: Antithyroid drugs (ATDs); Radioactive iodine and Surgery (thyroidectomy). Others include, immunotherapy (rituximab); and adjuvants like glucocorticoids and nonselective beta blockers[3],[12],[12]. Studies reported 50% relapse rate within four years of antithyroid drugs withdrawal and iatrogenic permanent hypothyroidism requiring lifelong treatment with levothyroxine (caused by thyroidectomy or radioiodine therapy)[13]. Management of SCD is based on current understanding of its pathophysiology, which incude disease modification through early diagnosis (counseling and neonatal screening), systematic /routine clinical follow-up, immunization and penicillin prophylaxes against infections, lifelong folic acid and micronutrient suppplimentation; hydroxyurea; adequate treatment of specific crises and complications[1],[6].

Thyroid disorders are rare in sickle cell disease (SCD) patients, with few reported cases of immunotherapy associated hyperthyroidism[11]. There is paucity of published reports of coexistence of SCD, GD, TC. We report this rare case of co-existing SCD, GD and TC in a 33 years old female patient in order to highlight the management challenges and the importance of timely diagnosis and treatment to mitigate the deleterious effects of GD and TC on the natural clinical courses of SCD in a resource poor setting like Nigeria.

II. Case Report:

A 33 years old female SCD patient was seen at the Haematology clinic with complaints of anterior neck swelling, bulging of the eyeballs, weight loss, excessive sweating, joint and lower back pain of one month duration. She was gravida 3^{+1}, 2 alive, last child birth 21 months and last menstrual period 3 weeks prior to presentation. On examination the positive findings were: Body mass index 17.5; bilateral proptosis; pale; jaundiced; symmetrically enlarged thyroid gland; respiratory rate – 18/min, pulse rate – 110 bpm, regular, large volume, blood pressure 120/70mmHg, heart sounds - 1^{st}, 2^{nd} + pan systolic murmur. Other systems were essentially normal. Baseline investigations: Ultrasound scan showed enlarged thyroid, right lobe measuring 4.64 X 1.94cm and left lobe 4.58 X 1.74 with uniform parenchymal echogenicity. TFTs: elevated serum T_3 and T_4; thyroid autoantibodies: TPOAbs, TGAbs (table 1 below). Full blood count showed low haemoglobin; mildly elevated ESR, normal serum electrolytes, urea and creatinine (tables 2, 3 & 4 below). Both clinical and laboratory findings were consistent with the diagnosis of GD in SCD. She was placed on carbimazole 15mg bd, propranolol 40mg bd X 1/12; folic acid 5mg, Paludrine 100mg daily; and Tramadol 50mg bd for 5/7.

Two weeks after commencement carbimazole she discovered that she was pregnant and abruptly discontinued carbimazole. She developed thyroid storm which was appropriately treated with intravenous fluids and carbimazole, she had spontaneous abortion two weeks after discharge. There was remarkable improvement in the presenting symptoms and signs; with reduction in serum free T_3, T_4 and raised Hb and TSH values (table 1 and 2) on subsequent follow-up visits. Patient got pregnant which necessitated reduction of carbimazole dose from 15mg to 10mg bd. Her antenatal care was punctuated by several severe vasooclusive crises which were appropriately managed with morphine and intravenous fluids and she eventually gave birth to a healthy male baby during the course of management. She had successful total thyroidectomy performed 2½ years after the onset of GD due to failure to achieve euthyroid status with carbimazole (table 1), requiring consult to endocrinologist, who placed her on high dose steroid (dexamethasone) prior to surgery. Histologic examination of the excised thyroid revealed papillary thyroid cancer. She has been placed on lifelong tablets Levothyroxine, folic acid and Paludrine. She is also on top-up blood transfusion due to low haemoglobin below her normal steady state value of 7.3g/dl post thyroidectomy despite being on regular routine medication (table 2). Follow-up post-thyroidectomy neck ultrasonographies are normal.

III. Discussion:

SCD, Graves' disease and thyroid cancer are common causes of life threatening medical emergencies, chronic disability and major distress and drain on family resources[3,4,1,6,7,8,9,10], especialy in resoure poor countries like Nigeria. The shared common (similar) clinical features of these disorders may lead to misdiagnosis and/or delay in diagnosis of thyrotoxic patients who have no obvious enlarged thyroid gland or associated sudden weight loss and polyphagia. Timely accurate diagnosis and appropriate treatment of these disorders are crucial for prevention of their complications[1],[2],[3]. Despite the reported high prevalence of these disorders in Nigeria, most tertiary health institutions lack the requisite ancillary laboratory tests facilities required to perform current recommended standard diagnostic work-up for the markers of these disorders and monitor their treatment. Although Methimazole is the first ATD of choice for treatment of GD disease, and propylthiouracil in first trimester of pregnancy respectively[3], both drugs are rarely available in Nigeria. She was treated with Carbimazole for 24 months, but did not achieve euthyroid status. Pregnancy, lactation and thyroid cancer are some of the contraindications for Radioactive iodine treatment[3]. Thus, she had total thyroidectomy and histologic examination of the excised thyroid gland revealed papillary carcinoma. Studies reported 50% relapse rate within four years of antithyroid drugs withdrawal and iatrogenic permanent hypothyroidism requiring lifelong treatment with levothyroxine caused by thyroidectomy or radioiodine therapy. She has been placed on lifelong levothyroxine to replace thyroid hormones and suppress production TSH thereby inhibiting the potential growth stimulus of TSH on any remaining cancer cells[12],[13],[14].

Inherited persistent Hb F is one of genetic modulator of the clinical course of SCD[4]. Patient has high HbF (15%), and thus, mild SCD clinical course, she rarely had crises, except during pregnancy. Bone pain is one of the symptoms of both SCD and GD (hyperthyroidism), while pregnancy has been associated with precipitation and/or aggravation of GD and SCD crises[1,4,5,12,15]. Our patient had several hospital admissions on account of VOC that was attributed to the coexisting SCD and GD, exacerbated by pregnancy. Thyroid hormones have been shown to be essential in haemopoiesis, The reported stimulation and inhibition of erythropoietin production by elevated and low thyroid hormones respectively[16],[17],[18] may have accounted for the observed significantly raised haematocrit value from her normal steady state of 22% to 29% within five months of the onset of GD and low haematocrit of 17% within six months post-thyroidectomy. Although not unmindful of the reported significant risk of cancer recurrence and adverse tumour characteristics associated with intake of medium to high folic acid[19], she is currently placed on the recommended folic acid 5 mg daily supplementation because of the increased erythropoiesis and high red blood cell turnover in SCD patient to ameliorate the worsening anaemia and top-up blood transfusion when required[20]. Although irregular menstruation and infertility are some of the clinical features and complications of GD and SCD, these were not seen in this patient. The recommended routine follow-up repeat TFTs and neck ultrasonography for monitoring treatment and cancer recurrence[3,21] were done. However, she could not do TRAbs, TPOAbs, TGAbs and thyroglobulin (Tg)[3,14,] due to the high costs of these tests.

IV. Conclusion:

We report co-existing SCD, GD and thyroid Cancer in a 33-year-old female patient to highlight the deleterious effects of GD and thyroid cancer on the natural clinical courses of SCD, the challenges of managing these disorders in a resource poor setting and the imperatives for wider NHIS coverage in Nigeria, towards effective and efficient healthcare delivery required to achieve the Sustainable Development Goal by 2030. Based on the reported high prevalence of thyroid disorders and SCD in Nigeria from studies cited in our review above, we strongly recommend inclusion of GD management in the NHIS for timely diagnosis and treatment to mitigate the deleterious effects (morbidity and mortality from the life-threatening complications) of coexistence of the trio disorders. Its noteworthy that long standing goitre can undergo malignant transformation, thus surgeons working in endemic areas should endeavour thyroidectomy early.

Conflict of interest: The authors have no conflict to declare.

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Table 1: Thyroid function tests (T3, T4, TSH) Thyroid Antibodies

	T3	T4	TSH	TPOAbs	TgAbs
Baseline	4.8ng/ml (0.49 - 2.02ng/ml)	17.5µg/dl (4.8 - 11.6µg/dl)	0.01 mIU/ml (0.39 - 6.16 mIU/ml)	2500 IU/ml (< 60 IU/ml)	648 IU/ml (< 60 IU/ml)
Pre-Op Follow-up	2.08 ng/ml (0.49 - 2.02 ng/ml)	12.5 µg/dl (4.8 - 11.6µg/dl)	0.33mIU/ml (0.39 6.16 mIU/ml)		
Pre-Op Follow-up	4.8 ng/ml (0.49 2.02 ng/ml)	17. 9µl/dl (4.8 - 11.6µg/dl)	0.01mIU/ml (0.39 - 6.16 mIU/ml)		
Pre-Op Follow-up	4.1ng/ml (0.49 2.02 ng/ml)	16.8 µg/dl (4.8 - 11.6µg/dl)	0.01mIU/ml (0.39 -6.16 mIU/ml)		
Post-OpFollow-up	2.05 ng/ml (0.49 - 2.02 ng/ml)	12. 3µl/dl (4.8 - 11.6µg/dl)	0.31mIU/ml (0.39 -6.16 mIU/ml		
Post-Op Follow-up	2.08 ng/ml (0.49 2.02 ng/ml)	12.5µl/dl (4.8 - 11.6µg/dl)	0.33mIU/m (0.39 -6.16mIU/ml)		

Table 2: Full Blood Count (FBC) and Erythrocyte Sedimentation Rate (ESR)

FBC	Baseline	Pre-Op	Pre-Op 2	Per-Op 3	Post-Op 1	Post-Op 2	Ref values
Total WBC Count	10.9 x 10^9/L	9.5 x 10^9/L	9.0 x 10^9/L	9.5 x 10^9/L	10.62 x 10^9/L	8.7 x 10^9/L	4.0 - 11.0 x 10^9/L
Neut.	7.1 x10^9/L	5.6 x 10^9/L	5.2 x 10^9/L	5.4 x 10^9/L	6.5 x 10^9/L	4.8 x 10^9/L	2.0 - 7.0 x 10^9/L
Lymp.	3.0 x 10^9/L	3.3 x10^9/L	3.1 x 10^9/L	3.5 x 10^9/L	3.5 x 10^9/L	3.3 x 10^9/L	1.0 - 3.0 x 10^9/L
Mono.	0.5 x 10^9/L	0. 3 x 10^9/L	0.38 x 10^9/L	0.3 x 10^9/L	0.3 x 10^9/L	0.3 x 10^9/L	0.2 - 1.0 x 10^9/L
Eos.	0.28 x 10^9/L	0.28 x 10^9/L	0.3 x 10^9/L	0.28 x 10^9/L	0.3 x 10^9/L	0.28 x 10^9/L	0.02 - 0.5 x 10^9/L
Baso.	0.02 x 10^9/L	0.02 x 10^9/L	0.02 x 10^9/L	0.02 x 10^9/L	0.02 x 10^9/L	0.2 x 10^9/L	0.02- 0.1 x 10^9/L
Hb	7.4 g/dl	9.0 g/dl	9.2 g/dl	9.0 g/dl	7.0 g/dl	15.5 g/dl	11 - 16 g/dl
PCV	22%	29%	29%		20%	17%	33 - 48%
ESR	27 mm/hr Westergren						5 - 20 mm/hr

Table 3: Haemoglobin Phenotype Quantitation (High Performance Liquid Chromatography/ HPLC)

Hb A	Hb A2	Hb S	Hb F
0.00%	3.0 (2.5)	75% (0.0%)	15% (0.5)

Table 4: Baseline Serum Electrolytes, Urea and Creatinine

Serum Electrolytes	Urea	Creatinine
Na 140mmol/L (136 -148mmol/L)	5.9 mmol/L (2.1 - 7.1 mmol/	76 Pmol/L (40 - 90 Pmol/L)
K 3.5mol/L (3.0 - 5.0 mml/L)		
Cl 100 mmol/L (98 - 110 mol/L)		
HCO 23 mmol/L (20 - 30mmol/L)		