

Case report:

Overt acquired primary hypothyroidism in a ten-year-old girl with perinatally-acquired HIV infection on HAART: A rare association.

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Abstract

Overt hypothyroidism is rare in human immunodeficiency virus (HIV)-infected children but can further compromise the child's quality of life. We report a case of a 10-year-old girl with perinatally-acquired human immunodeficiency virus (HIV) infection who subsequently developed overt acquired primary hypothyroidism. She has been on highly active antiretroviral therapy (HAART) for 9 years but developed goitre 2 years before presentation. Her thyroid gland was diffusely enlarged, firm, freely movable and non-tender. She had no symptoms of hypo- or hyperthyroidism. Physical examination revealed periorbital puffiness. Although her height was 139cm (50th percentile), it was significantly below the target centile range (152.5-169.5cm). Results of investigations showed very low free T4 and markedly elevated TSH level (31-fold increase above our laboratory reference value). Ultrasonography of the goitre showed multicystic nodules in both lobes. She was commenced on oral levo-thyroxine 100µg once daily. **Conclusion:** Physicians need to pay more attention to thyroid function in HIV-infected children on HAART, particularly in the presence of linear growth abnormalities.

Keywords: Acquired primary hypothyroidism, childhood, HIV, HAART, perinatal.

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Introduction

Abnormalities in thyroid function tests are common in human immunodeficiency virus (HIV)-infected children but overt hypothyroidism is rare^{1,2} Overt hypothyroidism in childhood may lead to growth failure, insidious onset of fatigue, weakness, and slowed mentation. Therefore, the additional development of overt hypothyroidism in a child with HIV infection further compromises the child's quality of life. In the paediatric age group, acquired primary hypothyroidism is most commonly due to Hashimoto thyroiditis (HT), a goitrous autoimmune thyroid disease³. The prevalence of HT peaks in early-to-mid puberty and a female preponderance of 2:1 has been reported⁴. The pathogenetic mechanisms causing HT include genetic predisposition interacting

with environmental triggers, such as infections, medications and possibly, stress³. In literature, the strong role played by genetic factor is well established and this is reflected in the frequent positive family history of autoimmune thyroid disease in affected individuals⁵. The potential mechanisms of thyroid dysfunction in HIV-infected individuals include autoimmune disease, concurrent infections, thyroid gland destruction by opportunistic infections and interreaction with drugs used in highly active antiretroviral therapy (HAART)⁶. The role of HAART was confirmed by a recent report that HAART interruption was associated with normalization of thyroid function tests⁷. Chen et al⁸, demonstrated that patients with lower CD4 count at baseline who experienced greater increments in the CD4 counts

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following HAART are more likely to develop autoimmune thyroid disease. One case of Hashimoto thyroiditis has been reported after initiation of HAART⁹. On the contrary, Quirino et al¹⁰ reported that hypothyroidism in HIV-infected patients is not associated with autoimmunity.

The results of a study among Indian children with HIV infection indicate that 16.7% of them had abnormalities in thyroid function¹. In that study, 6.7% and 10.0% of the children had sick euthyroid and subclinical hypothyroidism, respectively¹. In prevalence study involving 350 subjects, Beltran et al¹¹, found overt hypothyroidism 2.6%, subclinical hypothyroidism 6.6% and isolated low T4 6.8%. In another study the frequencies were overt hypothyroidism 2.5%, subclinical hypothyroidism 4.0% and non-thyroidal illness 17%². During follow up over a 3-year period, only 1.0% of the cases developed overt hypothyroidism [2]. In that study the authors made a strong case against routine screening for thyroid dysfunction in HIV-infected children². In contrast, Nelson et al¹², found a higher than expected incidence of overt hypothyroidism in patients receiving HAART and they recommended universal screening of subjects on therapy. The reported prevalence of autoimmune thyroid disease in HIV-infected patients was 0.69%, with 83.3% of them known to have HIV infection before the development of autoimmune disease¹³. The purpose of this case report is to highlight the need to pay more attention to thyroid function in HIV-infected children on HAART.

Case report

We report a case of a 10-year-old girl with perinatally-acquired human immunodeficiency virus (HIV) infection who subsequently developed overt primary hypothyroidism. She has been on highly

active antiretroviral therapy (HAART) consisting of Zidovudine, Lamivudine, and Nevirapine for 9 years with a good medication adherence. Her mother was also HIV-test positive and on HAART. She presented to the endocrinology clinic with a 2-year history of anterior neck swelling that has progressively increased in size. There are no associated symptoms of hypo- or hyperthyroidism. Mother has a similar small neck swelling but she is unaware of its presence. No history of use of anti-thyroid drugs. Her foods were usually prepared with iodized salt but eats foods made from processed cassava. She has been living in Benin City (a non-iodine deficiency belt) since birth. There was no delay in achieving developmental milestones. At present, she is in primary 4 with good academic performance. She is yet to achieve menarche. Her father is HIV negative. She is the youngest of 3 children and all are alive and are HIV negative. Her height was 139cm (50th percentile) but this was well below her target centile range (152.5-169.5). Both parents are tall. Her weight was 26kg (10th percentile) and the BMI 13.5kg/m² (5th percentile). On examination she was found to be dull-looking with peri-orbital puffiness and mild pallor. She had a swelling in the anterior triangle of the neck measuring 10 by 10cm. Her thyroid gland was diffusely enlarged, firm and freely movable. No bruit was heard over the mass. She has a sexual maturity rating of Tanner stage 1. The systemic examination was unremarkable. Neck ultrasound revealed that both thyroid lobes were enlarged with multiple cystic changes. There is displacement of adjacent vascular structures on the right and no cervical lymphadenopathy. Fasting blood sugar was 86mg/dl. The other laboratory findings are summarized in Tables 1 and 2

Table 1: Summary of thyroid function test results.

Thyroid function test 1			
	Results	Lab reference interval	Comments
Free T4(µg/dl)	1.6	4.8-10.8	Low
Free T3(ng/dl)	0.9	0.7-2.0	Within normal limits
TSH(µU/ml)	20.6	0.4-6.2	Very high
Thyroid function test 2 (4 months after test 1)			
Free T4(µg/dl)	0.91	4.8-10.8	Very low
Free T3(ng/dl)	1.12	0.7-2.0	Within normal limits
TSH(µU/ml)	193.33	0.4-6.2	Very high

T4 = Thyroxine; T3= Triiodothyronine; TSH = Thyrotropin stimulating hormone

Table 2: Summary of CD4 count tests.

CD4 count tests (cells/mm ³)	Results	Comments
CD4 count 1 (at age 11 months)	141	Evidence of severe suppression
CD4 count 2 (at age 2 years)	840	Evidence of moderate suppression
CD4 count 3 (at age 10 years; i.e., 2 months before presentation in UBTH)	1129	No evidence of suppression

A clinical diagnosis acquired primary overt hypothyroidism probably due to Hashimoto thyroiditis in a known HIV-infected child was made. She was commenced on Levo-thyroxine 50µg daily at the referral hospital. She discontinued the drug after 8 weeks due to perceived poor response (no reduction in size of goitre) to therapy and financial constraints. Following evaluation at the endocrinology clinic, UBTH, the dosage was increased 100µg daily and she is being followed up in the clinics (Endocrinology and HIV clinics).



Figure 1: The neck of a 10-year-old girl showing goitre.

Ethical Clearance:

This case report was submitted for publication after getting Ethical approval from the Ethics Committee of the University of Benin Teaching Hospital

Discussion

In our patient, the clinical diagnosis of overt acquired primary hypothyroidism was based on age (8 years) of onset of goitre, periorbital puffiness, height significantly below target centile range, very low serum levels of T4 and markedly elevated TSH levels. These are well recognized features of overt acquired primary hypothyroidism³. Epidemiologically,

Hashimoto thyroiditis is the most common cause of acquired primary childhood hypothyroidism [3,4]. We were unable to assay for antithyroid antibodies that would have strengthened our clinical suspicion of Hashimoto thyroiditis as the cause of the overt acquired primary hypothyroidism in our patient. The presence perinatally-acquired HIV infection was confirmed during infancy with positive HIV nucleic acid amplification testing (NAT) on two occasions. Our patient is currently receiving levothyroxine for the overt hypothyroidism. Such therapy is justified and it is aimed at preventing additional adverse effect of overt hypothyroidism on the quality of life of a child who is already HIV-infected. Therapy with levothyroxine is known to result in improvement in height¹⁴. However, we need to keep in mind that drug interactions between levothyroxine and protease inhibitors have been reported¹⁵. This drug interaction has been linked to the shared metabolic pathway of glucuronidation¹⁵. In addition, thyroid medication may influence the course of the various co-morbidities in HIV-infected individuals¹⁶.

As in previous reports^{2,11,12}, overt hypothyroidism was present in the index case. Various pathogenetic mechanisms have been postulated to explain the occurrence of overt hypothyroidism and other thyroid dysfunctions in HIV-infected individuals. These mechanisms include stress of the advanced disease, concomitant morbidities, destruction of the thyroid gland by opportunistic infections, autoimmune disease (resulting from immune reconstitution inflammatory syndrome), release of cytokines such as interleukin-6 and tumour necrosis factor and drug interactions^{6,12,17,18}. In the present report, we did not investigate for the possible mechanism(s) of overt hypothyroidism in our patient. This will be the subject of another study. Our patient's mother also has a goitre (relatively smaller in size), reflecting the possible role of genetic factor in the occurrence of thyroid disorder in our patient. Dittmir et al⁵, have reported increased familial clustering of autoimmune

thyroid diseases.

Some studies have shown that the risk of thyroid dysfunction was higher in HIV-infected individuals on HAART^{12,19,20}. With regard to occurrence of hypothyroidism, the contribution of individual drugs used in the regimen is not well established. The drugs present in the regimen of our patient included zidovudine, lamivudine and nevirapine. The report of a study in India revealed that out of 10 patients with hypothyroidism (overt and subclinical), both nevirapine and lamivudine were present in the regimen of all 10(100.0%) while zidovudine was present in the regimen of 3(30.0%)¹⁹. Although the regimen of the index case did not include Stavudine (protease inhibitor), this drug has been linked to

occurrence of hypothyroidism^{7,18}.

Conclusion: physicians need to pay more attention to thyroid function in HIV-infected children on HAART, particularly in the presence of linear growth abnormalities.

Conflict of interest: None declared

Authors' Contributions: Data gathering and idea owner of this study: Alphonsus N, Onyiriuka

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