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Graves' disease as a manifestation of immune reconstitution inflammatory syndrome in an HIV-1-infected adolescent patient: A case report

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ABSTRACT

Introduction: Although Graves' disease (GD) is the most common cause of hyperthyroidism in adolescents, it is very rare for it to result from the production of thyroid-stimulating hormone (TSH) receptor autoantibodies due to Graves' immune reconstitution inflammatory syndrome (IRIS). Especially for paediatric patients, very little is known about the aetiology and complete pathogenesis of Graves' IRIS. Furthermore, details of a valid treatment plan are severely lacking. The case report presented here is only the third for paediatric patients worldwide.

Case presentation: We report on a Caucasian female adolescent who initially presented with non-specific complaints about discomfort and tightness in the anterior part of the neck and thyroid enlargement. Based on clinical, laboratory and thyroid ultrasound findings, she was diagnosed with GD. However, after several months of outpatient treatment, the patient's GD could still not be fully managed with conservative therapy alone. Only when the patient was hospitalized for the third time was it discovered that she had previously been diagnosed with human immunodeficiency virus infection and had received highly active antiretroviral therapy (HAART) for the previous 29 months. Consequently, the production of autoantibodies to TSH receptors and abnormal changes in thyroid hormones had led to the development of GD and her final diagnosis was established as Graves' IRIS. Ultimately, a total thyroidectomy was performed.

Discussion/conclusion: This case report demonstrates how fundamentally important it is to have full access to a patient's complete anamnesis and results of all previous investigations. Clinicians should be made aware of the potential existence of thyroid dysfunction and other autoimmune or infectious processes in paediatric patients initiating or reinitiating HAART. Further research is needed to optimize the treatment for such paediatric patients.

1. Introduction

An autoimmune process by nature, Graves' disease (GD) remains a challenge for modern endocrinology as long-term remissions by non-invasive methods can be as low as 15% [1]. Although GD is the main cause of hyperthyroidism in children and adolescents, epidemiological data are very limited with a high probability of inaccurate data indicating lower numbers than those occurring in reality [2,3]. One of the few studies analysing hyperthyroidism in children recently reported an incidence of 4.58 per 100,000 person-years (2.91/100,000 person-years in children under 15 years), with an incidence peak during adolescence [4]. Furthermore, there is evidence showing that the incidence is rising [5]. Despite this rising occurrence rate, there are still no international consensus guidelines available regarding the treatment for childhood-onset GD [6] and so treatment plans usually follow the recommendations for adults. However, Japan has recently published its national treatment guidelines specifically for paediatric GD patients [7].

GD development as a result of human immunodeficiency virus (HIV) infection treatment is extremely rare. A phenomenon known as immune reconstitution inflammatory syndrome (IRIS) (ORPHA disease code:

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98004 – rare immune disease) emanates from the immune system being reactivated when highly active antiretroviral therapy (HAART) is initiated [8]. This results in overactivation of the immune system that, amongst other autoimmune phenomena, can lead to the onset of GD (termed Graves' IRIS) [9]. It is thought to be caused by late naïve CD4 cell repopulation [9]; however, multiple risk factors may be involved, such as deep immunosuppression at the time of therapy initiation, rapid immunologic improvement, etc. [9]. GD as a manifestation of IRIS is exceptionally rare in the adult population and even more so in children. To date, there are only two paediatric cases described in the literature [10,11]. With such little information available, there is a large uncertainty about how this syndrome presents in children and how effective our current treatment strategies are.

In this case report, we present a paediatric case of Graves' IRIS. To the best of our knowledge, this is the first paediatric case of Graves' IRIS in Europe.

2. Case Presentation

2.1. Development of Graves' disease

A Caucasian girl aged 14 years and 9 months presented to her general practitioner in June 2019 with complaints of discomfort and tightness in the anterior part of the neck, thyroid enlargement and tachycardia. Ultrasonography of her thyroid revealed signs of inflammation and an increase in volume (46.4 mL). In September 2019, she was admitted to the Children's Clinical University Hospital in Riga. The patient presented with a two-month history of discomfort and tightness in the anterior part of the neck, an increase of a mass in the lower part of the neck and difficulties with swallowing and breathing. The patient had lost 11 kg in weight over the previous three months. She also reported polyphagia, an increased frequency of defaecation and an irregular menstrual cycle. The patient also had a history of child cerebral palsy, mild mental disability, spastic diplegia and hallux valgus foot deformity. There was no information about previous thyroid diseases. Her thyroid-stimulating hormone (TSH) level measured in May 2018 was normal (0.62 mU/L; normal range 0.27–4.2 mU/L). There was no known family history of thyroid or autoimmune diseases.

At this juncture, the patient's height was 153 cm (−1.5 SDS), weight 39.8 kg (−2.2 SDS) and BMI 17 kg/m^2 (11th percentile). Physical examination by inspection and palpation estimated goitre grade III. Hypertension was present. Laboratory investigations determined the following: a low TSH level of 0.05 mU/L (0.27–4.2 mU/L) (Fig. 1); elevated levels of free T3 (45.63 pmol/L; 3.7–7.7 pmol/L) and free T4 (99.75 pmol/L; 13.6–23.2 pmol/L); an elevated TSH receptor antibody level of 170.6 IU/L (<1.58 IU/L); the absence of anti-thyroid peroxidase and anti-thyroglobulin antibodies.

During hospitalization, the patient was examined by an ophthalmologist, gynaecologist and haemato-oncologist. Ultrasonography of the abdomen, X-ray examination of the oesophagus with barium contrast agent, echocardiography, electrocardiography and additional laboratory investigations were performed; however, no pathologies were detected. Based on the clinical, laboratory and thyroid ultrasound findings, the patient was diagnosed with GD. Complete blood tests and liver function tests were done prior to starting Tab. Thiamazole as treatment (they all showed normal results). She was started on Tab. Thiamazole 30 mg daily (0.75 mg/kg/daily); however, after one week of therapy she complained about nausea, fatigue and diarrhoea, and blood tests revealed neutropenia. Subsequently, the dosage was decreased to 20 mg daily. The patient was also administered Tab. Propranolol 30 mg daily. Her general health improved and she was discharged from hospital in October 2019.

The patient returned for monthly follow-up ambulatory visits with the paediatric endocrinologist. Regular blood work was done and the therapeutic medication was adjusted when required; minor improvements over the course of the disease were observed. The patient's and legal guardian's attitude towards treatment was lackadaisical. Specifically, the patient did not attend scheduled outpatient appointments even after repeated invitations and the control blood work assigned by the general practitioner and endocrinologist was not done. Consequently, no data concerning the patient's thyroid function are available between hospitalizations.

Eight months later (May 2020), the patient was hospitalized in the same hospital. She had difficulties with swallowing and breathing, her heart rate was 130 bpm and blood pressure 132/66 mmHg, and her general health condition was deemed serious. Palpatory evaluation revealed her thyroid was dense and painful, goitre had enlarged to grade IV, there was a distinct systolic bruit directly over the thyroid gland and a carotid bruit on auscultation, and pulsation of blood vessels in the neck. Endocrinological tests showed the following: a TSH level of 0.006 mU/L (0.27–4.2 mU/L) (Fig. 1); free T3 and T4 levels of 13.75 pmol/L (3.7–7.7 pmol/L) and 36.16 pmol/L (13.6–23.2 pmol/L), respectively; a TSH receptor antibody level of 31 IU/L (<1.58 IU/L). A follow-up thyroid ultrasound detected increased vascularization and signs of autoimmune thyroiditis, thyroid growth, and an increase in volume to 52 mL (Fig. 2). Duplex scanning of the brachiocephalic arteries with colour dopplerography and spectrum analysis detected stenosis of the right superior thyroid artery with a flow rate of up to 4 cm/sec, with a mild increase of flow rate in both ACC (*arteria cerebri*) in the proximal and middle thirds due to compression.

The Doctors Council of the Children's Clinical University Hospital came to the decision that a total thyroidectomy was indicated according to the patient's current condition, relapse following antithyroid drug therapy for Graves' hyperthyroidism, goitre grade IV, persistent complaints of discomfort and pain in the neck, developmental delay, and signs of right superior thyroid artery stenosis. The definitive therapy decision also took into account the previous 18–24 months throughout which the patient and legal guardian poorly adhered to the therapy and

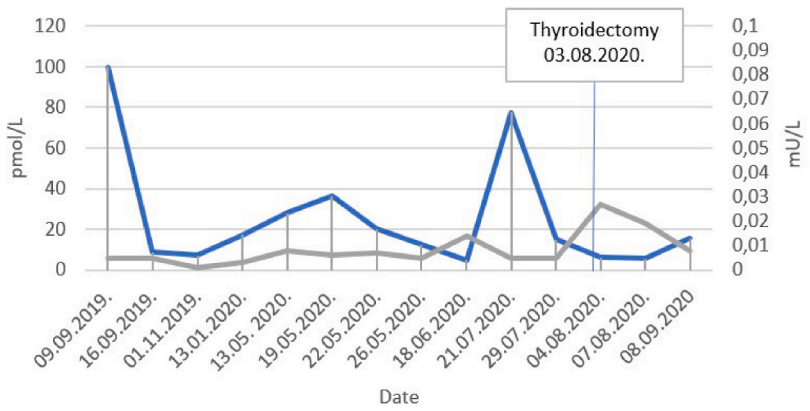

Fig. 1. Thyroid laboratory tests from September 2019 through to September 2020.
Fig. 1. Legend text. Three episodes of thyrotoxicosis are shown in the graph (September 2019, May 2020 and July 2020). Iatrogenic post-thyroidectomy hypothyroidism was observed shortly after the total thyroidectomy on August 3, 2020. One month later, the patient's free T4 (FT4) level was within the normal reference range: 15.53 pmol/L (13.6–23.2 pmol/L).

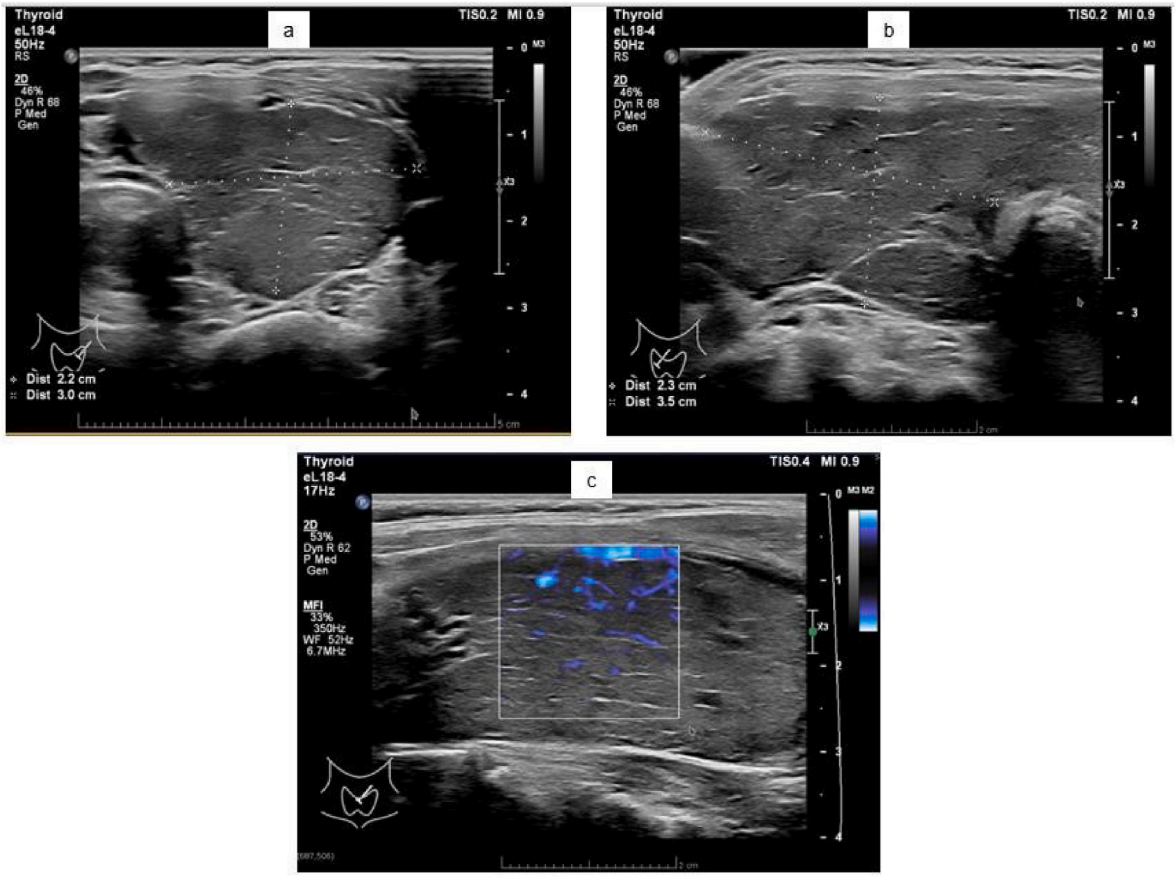

Fig. 2. Thyroid ultrasound in May 2020.
Fig. 2. Legend text. Transverse views of both enlarged thyroid lobes are shown in images a (left lobe) and b (right lobe). Increased vascularization detected during Doppler ultrasound investigation is shown in image c.

refused to administer the prescribed Tab. Thiamazole dosage. Furthermore, the inability to achieve euthyroidism due to the patient's tolerated dosage and progressive thyroid enlargement reinforced the decision. The patient continued on Tab. Thiamazole 20 mg daily (she declined to administer the maximal dosage of 30 mg daily due to concerns about previously experienced side effects) and Tab. Propranolol 10 mg daily. Over the following 10 days, the patient's health condition stabilized and she was discharged from hospital.

Two months later (July 2020), the patient was hospitalized for the scheduled elective surgery. Although her general health condition was stable, the control analysis showed low TSH and high free T4 levels (Fig. 1). It was therefore decided that surgery at this time was contraindicated and would be postponed until a time when her thyroid hormones had returned to normal levels. The patient was duly admitted to the Endocrinology Department for conservative treatment.

2.2. Human immunodeficiency virus

On the third day of the patient's hospitalization, a nurse became aware that the patient was hiding HAART usage. Her relatives were immediately contacted and they eventually revealed that the patient was HIV-1 positive, stage 3 (considered to be congenital). They justified their failure to inform medical personnel of her HIV status through fear of social stigma and possible discrimination. It was disclosed that a few months after the patient's mother was diagnosed with HIV-1 infection, the patient was also diagnosed with HIV-1 infection at the age of 12 years and 4 months (February 2017). At the time of diagnosis, the patient's CD4 T cell count was 3–1% cell/mL and HIV-1 viral load was 3.98×10^5 copies/mL, indicating severe immunocompromisation; the initial blood count also revealed neutropenia. Herpes simplex and herpes zoster infections were also present. Therapy with Raltegravir + Lamivudine/Zidovudine (RAL + 3CT/AZT) was initiated. Later, in October 2018, her therapy was changed to Raltegravir + Tenofovir/Emtricitabine (RAL + TDF/FTC). The patient was not treated with protease inhibitors nor non-nucleoside reverse transcriptase inhibitors.

2.3. Total thyroidectomy

Upon stabilization of the patient's free circulating thyroid hormone levels, a total thyroidectomy was performed on August 3, 2020. Histological examination revealed no signs of cell atypia. Histological changes characteristic of GD were observed (Fig. 3).

2.4. Immune reconstitution inflammatory syndrome

The patient's final diagnosis was Graves' IRIS (classification by SSK-10 D89.3, by ORPHA 98004 (rare immune disease)). Twenty-nine months after HAART had been initiated to treat her HIV-1 infection, the consequent production of autoantibodies to TSH receptors led to the development of GD. In February 2017 when the patient was diagnosed with HIV-1 infection and before HAART administration, she had a very low CD4 T cell count and a very high HIV-1 viral load. In June 2019 when the first signs and symptoms of hyperthyroidism were presenting, immune regeneration had occurred with her number of CD4 T cells significantly increasing to 568 cells/mL. Furthermore, the last time her HIV-1 viral load was checked (July 2017) it was markedly lower (245 copies/mL). In January 2020, her CD4 T cell count was 476 cells/mL.

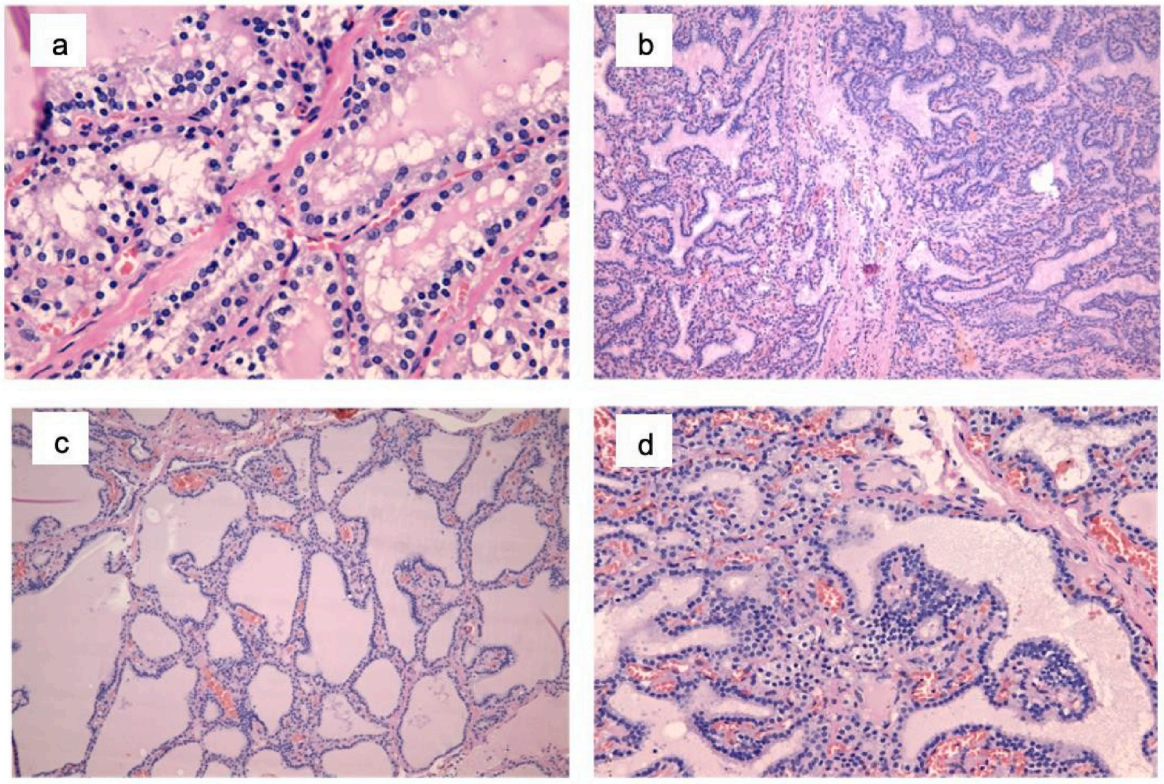

Fig. 3. Histological examination results in August 2020.
Fig. 3. Legend text. Histological examination revealed cytoplasmic vacuolization (image a), stromal tissue fibrosis (image b), and compactly arranged irregularly shaped follicles with a small quantity of light colloid and optically blank vacuoles (image c). Image d shows small papillary structures within follicles without signs of cell atypia characteristic of thyroid papillary cancer.

2.5. Postoperative period

There were no complications during the early postoperative period. Four days after the total thyroidectomy, laboratory tests indicated iatrogenic post-thyroidectomy hypothyroidism (Fig. 1). Hormone substitution with Tab. Levothyroxine 50 μg PO daily was started on the second postoperative day. Replacement with Levothyroxine was started at a low dose because the patient had tachycardia three days post operation. Upon general improvement of her condition, she was discharged from hospital with a plan for further outpatient supervision and continuation of Tab. Levothyroxine replacement 100 μg PO daily and calcium supplementation. One month after the total thyroidectomy, the patient had no complaints and positive weight dynamics. Moreover, her heart rate was 87 bpm and blood pressure 121/74 mmHg. Thyroid laboratory tests revealed biochemical euthyroidism (Fig. 1).

3. Discussion

Management of the Graves' IRIS case presented here was initially hampered by incomplete anamnesis regarding the patient's HIV-1 infection. Additionally, as the patient's levels of TSH and thyroid autoantibodies (TPOAb, TRAAb) were not measured prior to HAART initiation, comparison of this case with ones previously described in the literature is more difficult. However, we believe this case to be of importance as currently there are only two previously described Graves' IRIS cases in children. Moreover, to the best of our knowledge, this is the first report of a paediatric case of Graves' IRIS in Europe.

In 1998, Gilquin et al. were the first to describe Graves' IRIS (three patients) [12]. Conducting a systematic literature review, Katusiime identified only 212 reported cases of autoimmune IRIS in HIV-infected patients (from 1998 to 2018) [11]. Of these cases, Graves' IRIS was the most prevalent condition – 74 cases – and only two were paediatric patients (both from USA) [11]. Furthermore, Katusiime found Graves' IRIS to be slightly more common amongst women with a median age of 39.5 years and was reported only very rarely in children [11].

The signs and symptoms of thyroid dysfunction typically occur 8–33 months after the start of HAART in HIV-infected patients, mostly corresponding with the attainment of plateau levels of CD4 T cells [11,13]. In our patient, the first symptoms were observed 29 months after the initiation of therapy. Pérez et al. detailed the case of an 11-year-old African American boy with Graves' IRIS and reported that the clinical manifestations of GD occurred 30 months after starting HAART [10]. Their patient's baseline CD4 T cell count was 1 cell/uL and at the time of IRIS diagnosis it was 689 cells/mL [10]. Our patient's baseline CD4 T cell count was 1–3% cell/ml and at the time of IRIS diagnosis it was 568 cells/mL. Katusiime reported that the median baseline CD4 T cell count for adult patients was 15 cells/uL (IQR: 3–59) and at the time of IRIS diagnosis it was 383 cells/uL (IQR: 300–513) [11]. Our patient was diagnosed with HIV-1 infection at the age of 12, whereas Pérez et al.'s male patient was diagnosed at the age of 9 (both had perinatally transmitted HIV). Our patient received Raltegravir and Lamivudine/Zidovudine while Pérez et al.'s patient received Efavirenz and Lamivudine/Zidovudine [10], suggesting that different treatments can initiate Graves' IRIS in children (as has been described in adults). The clinical course of disease and laboratory findings were similar for the two paediatric patients; both were profoundly immunosuppressed before the start of HAART and both showed good T cell recovery prior to the onset of GD. Furthermore, the first signs and symptoms indicating thyroid dysfunction were similar; both displayed weight loss in the previous few months, tachycardia, polyphagia and goitre. No family or individual history of thyroid disease was found. Thyroid function laboratory findings showed decreased TSH, increased free T4 and elevated

TSH receptor antibody levels [10].

First-line treatment for symptomatic GD as a manifestation of IRIS is antithyroid drugs for 12–18 consecutive months [14]. Thyroidectomy for GD is recommended in cases of recurrent disease, drug intolerability or uncontrolled fluctuating course of disease [14]. For our patient, antithyroid drug therapy did not achieve remission of GD. Therefore, iodine-131 therapy was indicated and offered, but the patient and her legal guardian categorically refused the procedure and consequently surgery was performed. In the case of Pérez et al.'s patient, he underwent thyroid ablation treatment with iodine-131; however, there is no further information about how successful this treatment was [10]. Of note, at the present time, thyroidectomy is not the treatment of choice for adult and adolescent patients.

According to the European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy (2019), it is recommended that TSH is measured in all patients before the start of HAART. If TSH is abnormal, it is also recommended to measure free T3 and free T4 [14]. In our clinical case, this was not done before HAART initiation. The guidelines do not recommend measuring thyroid autoantibodies (TPOAb, TRAb), as there is no good evidence that these data are valuable in determining the risk of developing thyroid dysfunction [14]. They also recommend assessment of TSH while patients are receiving therapy; however, there is no clear guidance on how often this assessment is necessary [14]. Ibrahim et al. recently recommended measuring thyroid function every 12–24 months for HIV-infected patients [15]. From our patient's medical history, we know that her TSH level was 0.62 mU/L (0.27–4.2 mU/L) in May 2018 (15 months after HAART initiation).

Dhasmana et al. described the main risk factors that are associated with IRIS: low CD4 T cell count when initiating HAART, rapid increase in CD4 T cell count, rapid decline in viral load after introduction of HAART, HAART naïve – all these factors were evident in our patient [9]. Factors that are not involved in IRIS are the type of HAART and race [16]. Nevertheless, there have been reports that Graves' IRIS may be associated with the group of non-nucleoside reverse transcriptase inhibitor HAART medications, particularly Efavirenz [15,16]. Thus, further investigation is needed.

This case report raises a couple of important issues. First, we strongly recommend thyroid function testing (TSH, free T3, free T4 measurements) in HIV-infected children with signs/symptoms of thyroid dysfunction and also HIV testing in children with severe and recurrent GD. Graves' IRIS must be considered in the differential diagnosis for HIV-infected children with viral suppression and relevant immune restoration resulting from HAART initiation in the previous months. Secondly, a universal health information system would facilitate the work of clinicians between different hospitals and between paediatric and adult patients. If this system had been in place, our patient's Graves' IRIS diagnosis would have been confirmed sooner. At present, there are no treatment guidelines for children with Graves' IRIS; however, the existing therapy recommended for adults can achieve satisfactory results for control of the disease.

4. Conclusion

Case reports like this one impart relevant and important information for clinicians. Early identification of those who are HIV infected, especially in paediatric practice, would be helpful with regard to timely treatment of their HIV infection and other comorbidities/complications. Clinicians should be made aware of the potential existence of thyroid dysfunction and other autoimmune or infectious processes in paediatric patients initiating or reinitiating HAART. Further case reports are needed to better understand the pathogenesis of paediatric Graves' IRIS and to evaluate the effects and results of different treatments.

Statements

Statement of ethics

The published article complies with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The authors state that the subject and their guardian(s) have given written informed consent to publish their case (including publication of images).

Consent was obtained from the patient and her parents after a full explanation of the purpose and nature of all procedures used.

Conflict of interest statement

The authors declare no conflicts of interest. The authors alone are responsible for the content and the writing of the manuscript.

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Author contributions

Iveta Dzivite-Krisane: Conceptualization, Data curation, Investigation, Supervision, Writing – review and editing. Liga Kornete: Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft. Sintija Sausa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Ruta Terauda: Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. Ivars Melderis: Investigation. Valentina Sitkare: Investigation, Writing – review and editing. Davis Rudolfs Zakis: Methodology, Resources, Visualization, Writing – original draft. Baiba Rozentale: Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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