Patient report

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Migratory polyarthritis as an adverse effect of thiamazole use in a 13-year-old girl with Graves' disease

Abstract: Graves' disease is the most prevalent cause of hyperthyroidism in children. The treatment commonly involves antithyroid therapy using a thionamide. We present a case of a 13-year-old girl with the antithyroid arthritis syndrome, presenting as a migratory polyarthritis, after the initiation of thionamide treatment for Graves' disease. Antithyroid arthritis syndrome warranted immediate cessation of thionamide. Improvement of the arthritis was seen in subsequent days. As there are no other reversible treatment modalities for Graves' disease in children, definitive treatment with radioactive iodine was needed to control the hyperthyroidism in this child. Antithyroid arthritis syndrome presenting as a migratory polyarthritis is a severe adverse effect of a common pediatric disease and should therefore be recognized by pediatricians.

Keywords: adverse reaction; antithyroid arthritis syndrome; Graves' disease; thionamide.

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Introduction

Graves' disease is the most common cause of hyperthyroidism in children. Thionamide therapy is the first-line therapy in The Netherlands. If antithyroid therapy using thionamide fails, other options are surgery or radioactive iodine therapy (1). Many adverse effects of thionamide, most commonly skin reactions, gastrointestinal effects,

and arthralgias, have been observed to occur in approximately 5% of the cases. The most frequent severe adverse effect is agranulocytosis, which occurs in 0.1%–0.5% of patients (2). Less common adverse effects include hypoglycemia, anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis, and polyarthritis (3). Adverse effects of thiamazole are dose-related, whereas those of the thionamide propylthiouracil (PTU) are less clearly related to dose (3). PTU has no place in the treatment of Graves' disease in children due to possibility of fatal liver failure (3). This case report describes a girl with autoimmune thyroiditis who experienced antithyroid arthritis syndrome due to therapy with thiamazole.

Case

A 13-year-old Caucasian Dutch girl was presented to the outpatient clinic of our pediatric department with a 2-month history of nausea, headache, increased hunger sense, and neck swelling. Further specific questions revealed hyperactivity, insomnia, hoarseness, flushes, and heart palpitations. The patient's medical history was otherwise unremarkable. Family history was significant for the patients' mother who had Graves' disease in adolescence. Upon physical examination, the patient seemed agitated, with a blood pressure of 148/55 mm Hg and a pulse of 116 beats/min in rest. There was no exophthalmos, the thyroid gland was diffusely enlarged without nodules. Heart auscultation revealed a systolic ejection murmur grade II/VI. There were no other remarkable findings.

Laboratory results revealed a thyroid-stimulating hormone (TSH) <0.010 mU/L (ref. 0.4–4.0) and a free serum thyroxine >96 pmol/L (ref. 8–22). Additional laboratory tests confirmed Graves' disease, proven by the presence of stimulating antibodies against the TSH receptor. The TSH receptor antibody level was 36 U/L (ref. <1 U/L). The patient was started on the antithyroid drug thiamazole

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15 mg two times a day, as well as propranolol 10 mg three times a day to treat high blood pressure, tachycardia, and agitation.

Two weeks after starting the thiamazole, the patient presented at the emergency department. She experienced an urticarial rash on her body as well as facial angioedema. This is a known minor adverse effect of thiamazole, so thiamazole was continued. Two antihistamines were started (cetirizine 10 mg and hydroxyzine 25 mg). Two days later, she presented again to the emergency department with malaise and pain in the left ankle, which prevented her from walking. She did not experience fever. Upon physical examination, the patient was afebrile, her left ankle was warm, swollen and tender, and her left hip joint was painful during endo- and exorotation. There was still mild angioedema of the eyelids and her skin showed mild dermatographia. An ultrasound of the left ankle showed fluid in the intra-articular space, ultrasound of the left hip showed no abnormalities. Since our patient did not experience fever, we did not perform a joint aspiration as the suspicion of a septic/bacterial arthritis was less evident.

Further laboratory tests were done to exclude common causes of the combination of arthritis and arthralgia such as connective tissue disease, reactive arthritis, bacterial arthritis, immunodeficiency associated arthritis, and antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis, where arthralgia is often the first symptom (4, 5).

Antinuclear antibody (ANA), ANCA, anti-proteinase 3 (anti-PR3), anti-myeloperoxidase (anti-MPO), throat culture, and Parvovirus were negative. Other viral and bacterial diagnostic tests such as for varicella zoster, hepatitis B, rubella, shigella, salmonella, campylobacter, and chlamydia trachomatis were not done since there was no history of specific symptoms such as rash or gastrointestinal complaints.

Complement C3 was 989 mg/L (ref. 700–1500), complement C4 127 mg/L (ref. 100–400), IgG 11.1 g/L (ref. 7.30–16.0), IgE 513 U/mL (ref. <100), aspartate aminotransferase (AST) 200 IE/mL, anti-DNAse 300 IE/mL (ref. <300), and C-reactive protein (CRP) 21 mg/L (ref. <10). Because of the combination of arthritis and arthralgia, we suspected an impending migratory polyarthritis due to an adverse reaction of thiamazole. The thiamazole was discontinued immediately.

Diclofenac 25 mg thrice a day and prednisolone 25 mg once daily was started; propranolol was continued. However, a migratory polyarthritis developed and persisted for 2 weeks, localized in ankles, knees, shoulders, and wrists lasting for several hours up to a maximum of 1 day. After 2 weeks the arthritis disappeared completely. Following cessation of the thiamazole, there was a rapid

increase of the free thyroxine level, for which treatment with radioactive iodine therapy was performed, resulting in definitive treatment of the hyperthyroidism. A year later, she was doing well on thyroid hormone replacement therapy.

Pathogenesis

Polyarthritis as an adverse effect of thionamide is known as the “antithyroid arthritis syndrome”. This occurs in 1%–2% of the patients treated with antithyroid drugs (3). Swelling and erythema are unusual, but may be present. This is the reason why the development of arthralgias, while classified as a “minor” reaction, should prompt drug discontinuation as this symptom may be a harbinger of a severe transient migratory polyarthritis (3).

Antithyroid arthritis syndrome usually resolves within 8 weeks after cessation of the thionamide (6). Little is known about the pathogenesis of arthritis induced by thionamide therapy. Some authors claim that a deficit in copper-binding capacity allows free copper to bind to the thionamide. This complex affects glutathione metabolism and induces the release of interleukins, which can cause synovial inflammation (5). Another theory is that binding of antithyroid drugs to macromolecules induces auto-antibody production. However, this theory is less likely to be the cause in our patient because there was a negative ANA (5). Patients with an autoimmune disease such as Graves’ disease have a higher chance of developing other autoimmune diseases such as juvenile idiopathic arthritis; however, the symptoms in our patient were not typical for juvenile idiopathic arthritis. Our patient had been using three different medications before the arthritis started. Neither propranolol has any reported cases of arthritis as an adverse effect nor cetirizine or hydroxyzine.

Conclusion

Only a few case reports have described arthritis as an adverse effect of the antithyroid drug thiamazole in children. The development of arthralgia is classified as a “minor” reaction”; however, it requires prompt thionamide cessation as this symptom could develop into severe transient migratory polyarthritis. As this a serious adverse effect, it is important that pediatricians recognize this immediately so that thionamide can be withdrawn and proper alternative therapy (radioactive iodine or surgery) can be initiated.

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