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Severe and persistent thyroid dysfunction associated with tetracycline-antibiotic treatment in youth

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Abstract

Thyroid dysfunction in adolescents treated with minocycline for acne has been previously described as transient effect and/or associated with autoimmune thyroiditis. We report non-immune-mediated thyroid dysfunction associated with minocycline/doxycycline in three adolescents whose clinical courses suggest an adverse effect that may be more common, serious, and persistent than realized previously.

Keywords

minocycline; thyroiditis; tetracycline; doxycycline; hyperthyroidism; hypothyroidism; acne vulgaris; thyroid dysfunction

Tetracycline antibiotics, including minocycline and doxycycline, are prescribed commonly for adolescents to treat acne vulgaris. An association of tetracycline-class antibiotic treatment with thyroid abnormalities was first reported in 1976, when the autopsy of a 69-year-old man treated with minocycline revealed black pigmentation of the thyroid grossly, pigment aggregates in follicular cells and colloid, interstitial fibrosis, and pyknotic nuclei suggesting epithelial damage.¹ The association with black pigmentation without alteration in thyroid gland function has been firmly established by autopsy studies.^{2–4} In contrast, thyroid dysfunction due to tetracycline-class drugs is rarely reported in adults and only two cases of minocycline-induced thyroid dysfunction have been described in the pediatric population. In both of these cases, thyroid dysfunction was associated with concomitant autoimmune thyroiditis⁵ or other autoimmunity.⁶ Severity of thyroid dysfunction was mild and transient in one case and impossible to evaluate in the other due to definitive treatment with thyroid ablation. In contrast, we report three pediatric patients treated with tetracycline-class

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antibiotics who developed non-immune-mediated thyroid dysfunction that was severe and/or persistent.

Methods

Cases were selected from the electronic medical record. Inclusion criteria: Patients aged <18 years evaluated by pediatric endocrinologists at the University of Wisconsin Hospital and Clinics between 2000–2014 who had an abnormal TSH (thyroid stimulating hormone) result coinciding temporally with tetracycline-class drug prescription. Exclusion criteria: autoimmune thyroid disease, congenital thyroid disease, thyroid cancer, and sick euthyroid syndrome.

Results

Twenty-one patients met inclusion criteria. Of these, 17 were excluded due to autoimmune thyroid disease (n=14), congenital thyroid disease (n=1), thyroid cancer (n=1), and sick euthyroid syndrome (n=1). Four patients remained; one was removed due to potentially confounding valproate therapy for seizures. The remaining three patients all had acne vulgaris and came to attention at 16 years of age with hyperthyroidism, negative anti-thyroid antibodies, and low uptake on radioiodine thyroid uptake scan.

Case 1

A 16-year-old female developed diplopia, headache and fatigue 3 months after starting oral doxycycline for treatment of acne vulgaris. Free T4 (free thyroxine) was elevated (2.1 ng/dL (reference range 0.9–1.7 ng/dL), thyrotropin suppressed (0.009; reference range 0.500–5.500 μ IU/mL) and thyroid scan showed low uptake (2.9%; reference range 10%–35%). TPO (thyroid peroxidase), TSI (thyroid stimulating immunoglobulin) and thyroglobulin antibodies were negative. There was no known family history of thyroid or autoimmune disease. Doxycycline was discontinued and hyperthyroidism resolved.

Case 2

A 16.5-year-old male developed polydipsia, headache, weight loss and fatigue 23 months after starting oral minocycline therapy for treatment of acne vulgaris. Free T4 was elevated (7.57 ng/dl ; reference range 0.75–1.54), thyrotropin was suppressed (<0.03 μ IU/mL; reference range 0.36–4.57), and thyroid scan showed low uptake (0.30%; reference range 10–35%). TPO, TSI, TRAb (TSH receptor antibodies), thyroglobulin antibodies were negative. Mother had a benign thyroid nodule and the maternal grandmother had celiac disease and multiple sclerosis. Minocycline was discontinued and hyperthyroidism was treated with propranolol and methimazole for 1 month. He experienced transient compensated hypothyroidism (TSH 7.56 μ IU/mL; reference range 0.36–4.57) and then thyroid function normalized.

Case 3

A 16.2-year-old male developed polydipsia, headache, night sweats and fatigue 9 months after starting oral minocycline therapy for treatment of acne vulgaris. Free T4 was elevated

(3.26 ng/dL; reference range 0.70 – 1.45), TSH suppressed (0.01 μ IU/ml; reference range 0.36 – 4.20), and thyroid scan showed low uptake (0.50%; reference range 10–35%). TPO, TSI, TRAb (TSH receptor antibodies), thyroglobulin antibodies were negative. A maternal aunt had a history of radioactive iodine ablation, but no other known family history of thyroid or autoimmune disease. Hyperthyroidism was initially treated with methimazole (5 days) and propranolol (1.5 months). Minocycline was discontinued. Hypothyroidism (TSH 19.3 μ IU/ml; reference range 0.36 – 4.20) then developed and persists to the present (>4.5 years), treated with levothyroxine replacement 68.5mcg/day.

Patients' presentation, laboratory and imaging findings, treatment, and clinical course are summarized in the Table.

Discussion

Tetracycline, first marketed by Lederle Laboratories in 1953, was frequently prescribed for treatment of acne vulgaris. Due to clinical advantages over tetracycline (e.g. simpler dosing schedule and improved digestive tolerability)⁷ doxycycline (1967) and minocycline (1972) became preferred, although their own adverse effects include gastrointestinal symptoms, photosensitivity, and pigment accumulation in nails, skin, sclerae and teeth. In addition, minocycline can induce autoimmune conditions including systemic lupus erythematosus, autoimmune hepatitis and less commonly, serum sickness and vasculitis^{8–10}; doxycycline also can induce autoimmune hepatitis.¹¹

Although black pigmentation of the thyroid appears to occur commonly with exposure to minocycline or doxycycline, thyroid dysfunction manifesting as hyper- or hypothyroidism has been reported rarely. Proposed mechanisms include (1) competitive inhibition of TPO-induced iodination of tyrosine moieties in thyroglobulin, (2) inhibition of TPO-catalyzed coupling of iodotyrosine residues, (3) cytotoxic damage to follicular cells leading to release of preformed thyroid hormone, (4) indirect or direct antibody-mediated destruction of follicular cells.^{6, 12, 13}

Proposed mechanisms of tetracycline-class drug-induced pigmentation accumulation include (1) degradation from drug interaction with lipofuscin, (2) oxidation of the drug, (3) interaction via TPO with tyrosine metabolism (needed for melanin and neuromelanin), and (4) lysosomal dysfunction.^{14–16} Pigmentation seems to occur rapidly and is enduring.¹⁴ Although black discoloration often is considered pathognomonic for minocycline exposure, less common etiologies include cystic fibrosis, ochronosis, mucoviscidosis, ceroid storage disease, bruising, hemorrhage, hemochromatosis and effects of other drugs including doxepin, lithium, and tricyclic antidepressants (via lysosomal accumulation).^{17–20}

One in vitro study of minocycline effects on thyroid hormone synthesis found that only the combined presence of minocycline and TPO led to black pigmentation changes as well as disruption of synthesis steps. Specifically, minocycline appeared to inhibit TPO-catalyzed iodination at a potency similar to or greater than¹³ the anti-thyroid drugs methimazole and propylthiouracil. Inhibition of iodination was dose-dependent; at low concentrations (25 μ M), minocycline competitively inhibited of TPO-induced iodination, whereas at high

concentrations (100uM), it acted reversibly to inhibit iodination independent of inactivation of TPO.

The three cases described herein illustrate that minocycline and doxycycline can result in more severe thyroid dysfunction in children and adolescents than previously demonstrated. Prior pediatric cases have been associated with evidence of autoimmunity.^{5, 6} The second novel observation from our cases is that concurrent autoimmunity is not a necessary component of tetracycline-induced clinical and laboratory-evident thyroid dysfunction. Thus, thyroiditis from minocycline in these cases appears to be a non-autoimmune chemical thyroiditis resulting in cytotoxic damage sufficient to cause marked release of thyroid hormone and, in some cases, subsequent persistent hypothyroidism. That being said, this chart review also found that it is not uncommon for tetracycline-antibiotic treated adolescents to have evidence for autoimmune thyroid dysfunction. It is possible that family history of autoimmunity in two of the three cases could point to a latent familial predisposition without detectable autoimmunity in the individual.

In spite of these potential clinically significant effects on thyroid function, a warning about thyroid dysfunction is not included in the package insert for doxycycline,²¹ and is mentioned only as “cases of abnormal thyroid function have been reported” for minocycline.²² Routine clinical and laboratory evaluation of thyroid function is not currently recommended when prescribing these medications for treatment of acne.

Tetracycline antibiotic-induced thyroid dysfunction may be more common, serious, and persistent than previously realized and should be considered in the differential diagnosis for pediatric cases of antibody-negative thyroid dysfunction. Minocycline and doxycycline can cause a non-immune chemical thyroiditis leading to severe hyperthyroidism. Following removal of offending antibiotics, this chemical thyroiditis can evolve into persistent hypothyroidism. Although doxycycline and minocycline are commonly prescribed to youth for treatment of acne vulgaris, the frequency of non-autoimmune thyroiditis related to minocycline or doxycycline is unknown. It is likely that the majority of cases escape clinical detection and diagnosis and therefore prospective studies are needed to determine the prevalence, clinical significance and severity of cases. Additional investigation is needed to determine whether routine screening of thyroid function in youth receiving long-term treatment with these antibiotics is warranted.

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Abbreviations

TSH	thyroid stimulating hormone
TPO	thyroid peroxidase
TSI	thyroid stimulating immunoglobulins
Free T4	free thyroxine

TRAb TSH receptor antibodies

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Table 1

Summary of three pediatric cases of tetracycline-induced hyperthyroidism without autoimmunity, one of which was severe and persistent.

TETRACYCLINE-INDUCED THYROID DYSFUNCTION	Mild	Severe	Severe & Persistent
Age (yrs) / Sex	16.0 / Female	16.5 / Male	16.2 / Male
Tetracycline-class oral acne medication (Total mg/day)	(minocycline, 200mg) [#] doxycycline, 150mg for 3 months	minocycline, 200mg for 23 months	minocycline, 200mg for 9 months
Presentation	Fatigue , headaches, weakness, decreased endurance, puffy eyes, diplopia	Fatigue , headaches, polydipsia, heat intolerance, weight-loss, sleep difficulties, palpitations, frequent stools	Fatigue , polydipsia, heat intolerance, night sweats, coordination difficulties
Antibodies TPO, TSI, TRAb, Thyroglobulin	Negative	Negative	Negative
Evidence of Hyperthyroidism	TSH 0.013 (nl 0.5–5.5 µIU/mL) free T4 2.4 (nl 0.9–1.7 ng/dL) total T3 2.53 (nl 0.8–1.6 ng/mL)	TSH <0.03 (nl 0.36–4.57 µIU/mL) free T4 7.57 (nl 0.75–1.54 ng/dL) free T3 23.5 (nl 2.0–4.9 pg/mL)	TSH 0.01 (nl 0.36–4.20 µIU/mL) free T4 3.26 (nl 0.7–1.45 ng/dL) free T3 15.5 (nl 2.3–4.8 pg/mL)
Evidence of Subsequent Hypothyroidism	TSH 3.04 (nl 0.5–5.5 µIU/mL)	TSH 7.56 (nl 0.36–4.57 µIU/mL)	TSH 19.3 (nl 0.36–4.20 µIU/mL)
Radioiodine thyroid uptake scan (nl 10–35%)	2.9%	0.30%	0.5%
Treatment of Hyperthyroidism after drug cessation	None	Methimazole + propranolol	Methimazole + propranolol
Subsequent Hypothyroidism?	No	Yes, transient	Yes, persistent

TPO: thyroid peroxidase antibody, TSI: thyroid stimulating immunoglobulin, TRAb: Thyroid Stimulating Hormone receptor antibody.

[#] This patient recently switched from minocycline to doxycycline. Previous minocycline duration unknown.

nl = normal reference range