Reversible Left Recurrent Laryngeal Nerve Palsy in Pediatric Graves’ Disease

abstract

Vocal cord paralysis associated with goiter usually indicates the presence of a malignancy. Pediatric patients retain significant thymic tissue that regresses only later in life. This thymic tissue can develop significant hyperplasia during an acute autoimmune process. We describe a case of a 17-year-old girl who presented with a goiter secondary to severe Graves’ disease and a 2-month history of hoarseness, choking on liquid intake, and small-volume vomiting especially after eating. She demonstrated a left vocal cord paralysis probably secondary to a unilateral left recurrent laryngeal nerve palsy. A marked enlargement of the thymus was discovered on thoracic imaging. Treatment was initiated with methimazole, with near complete remission of her vocal cord paralysis within 3 months. Given the immunomodulatory effects of methimazole, a potential mechanism of the left recurrent laryngeal nerve palsy was autoimmune hyperstimulation of the thymus and consequent hyperplasia, resulting in distension of the nerve. Attenuation of the hyperactive immune process with methimazole may have resulted in regression of the mass effect of the thymus and associated reduction of the nerve distension. This case illustrates the unique risk of left recurrent laryngeal nerve palsy in pediatric patients with an acute immune stimulation and hyperplasia of the thymus and the reversibility in the context of mitigation of the immune hyperactivity. Methimazole may be an optimal initial treatment choice in pediatric patients with Graves’ disease and left recurrent laryngeal nerve palsy. Pediatrics 2013;132:e1704–e1708

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KEY WORDS
pediatric Graves’ disease, laryngeal nerve palsy, vocal cord paralysis, methimazole, reversible

ABBREVIATIONS
CT—computed tomography
T3—triiodothyronine
T4—thyroxine
TSH—thyroid-stimulating hormone
TSI—thyroid-stimulating immunoglobulin

Dr Chiu provided the endocrinology consultation for the patient, conceptualized the significance of the case report, and drafted the initial manuscript; Dr Ledbetter provided the general surgery consultation for the patient and reviewed and revised the manuscript; Dr Richter provided the initial medical evaluation for the patient and reviewed and revised the manuscript; Dr Iyer contributed a radiology assessment of the patient’s imaging and reviewed and revised the manuscript; Dr Merati provided the otolaryngology consultation for the patient and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Periodic nausea, decreased appetite, difficulty swallowing saliva, infrequent small-volume postprandial vomiting, and a sensation of “thick phlegm” in her throat developed.

Other symptoms included a remarkable unintentional weight loss, dyspnea limiting activity, fatigue, progressive weakness, and diarrhea. She denied any new rash, bruising, mucosal bleeding, or fever. Her past medical history was unremarkable. She took no medications. Her mother was diagnosed with Graves’ disease within the previous year.

On physical examination, she appeared generally well but tachycardic (pulse 112–128 beats/minute) and hypertensive (blood pressure 130–153/97–98 mm Hg). Her height was 69.7 kg (86.5th percentile), a significant decrease from a weight of 83.2 kg 3 months earlier, and her height was 166.0 cm (67.5th percentile) for a correlate BMI of 22.5 kg/m² (65.1th percentile). She had a weak, raspy voice and a weak cough. Cranial nerves II to XII were intact except as noted later. Oral examination demonstrated 4+ tonsillary hypertrophy with thick mucoid postnasal drainage. The adenoïds were small on mirror examination. No lymphadenopathy was appreciated. A diffuse symmetric goiter was present. On indirect laryngoscopy, she was noted to have left vocal cord paralysis with no mucosal lesions.

Laboratory studies demonstrated a normal leukocyte count (7.2 K/mm³), a slight normocytic anemia (hemoglobin 11.5 g/dL), and normal platelets (162 K/mm³). Tumor markers were undetectable, specifically the β-human chorionic gonadotropin (<1 mIU/mL) and α-fetoprotein (<0.9 ng/mL). Her thyroid studies demonstrated marked hyperthyroidism, with an undetectably low thyroid-stimulating hormone (TSH <0.02 mIU/L) and exceedingly high levels of thyroxine (total T4 >24.9 µg/dL, free T4 >7.0 ng/dL) and triiodothyronine (T3 7.22 ng/mL [1.00–2.10]) (Table 1). A markedly elevated thyroid-stimulating immunoglobulin (TSI 5.8 [≤1.3]) level confirmed a diagnosis of severe Graves’ disease.

Neck and thoracic computed tomography (CT) imaging demonstrated borderline enlarged cervical lymph nodes but no other mediastinal or hilar adenopathy. A homogeneous soft tissue mass in the anterior mediastinum (Fig 1) extended from the manubrium to the right atrial appendage, measuring 9.4 cm transversely and 2.8 cm in the anterior–posterior diameter. No adjacent vascular invasion or other aggressive features were noted, and the structure was assessed to represent enlarged thymic hyperplasia. Mild asymmetric left laryngeal ventricular dilation and loss of the left subglottic arch supported the clinical diagnosis of left vocal cord paralysis (Fig 2).

A swallowing and feeding evaluation revealed a weak laryngeal elevation and swallow for thin liquids, with a consistent concomitant cough. Oral nectar-thick liquids and regular solids were well tolerated.

On a diagnosis of Graves’ disease, the patient was started on methimazole 10 mg every morning, 5 mg midday, and 10 mg every evening (0.4 mg/kg per day).
A 4-week course of nadolol 40 mg/day was provided for symptomatic treatment. After 9 weeks, her hoarseness was subjectively better, as noted by the patient and her friends, and she was able to yell. Laboratory studies demonstrated a slightly elevated TSH (6.662 mIU/L, reference range [0.360–5.800]), a low T4 (2.8 μg/dL, reference range [5.1–10.0]), and a normal T3 (8.1 ng/mL, reference range [8.0–20.0]). Her methimazole was reduced to 15 mg once daily (0.2 mg/kg per day). After 9 1/2 weeks, a video-fluoroscopic swallowing study demonstrated intermittent mild supraglottic penetration without aspiration during the swallow of thin liquids and mild pharyngeal phase dysphagia.

After 14 weeks, she was able to “gulp down” liquids without problems. Her initial choking sensations had resolved, although the goiter size was unchanged. Her “voice [was] back” as her hoarseness disappeared. With overt hypothyroidism (TSH 20.843 mIU/L [0.450–5.100], T4 2.3 μg/dL [4.7–11.3]), the methimazole was decreased to 7.5 mg once daily (0.1 μg/kg per day). By 17 weeks of therapy, under videoendoscopic flexible fiberoptic laryngoscope assessment, the left vocal cord was noted to have recovered to 90% of normal motion, with excellent closure and symmetric vibration. After 20 weeks, her TSI had decreased to 3.29 [<1.23].

**DISCUSSION**

Graves’ disease is a prevalent condition, with a population frequency of 0.6%. Our patient presented with Graves’ disease, goiter, left vocal cord immobility, and an enlarged thymus. After treatment with methimazole for 3 months, her voice recovered. Her left vocal cord immobility was probably secondary to compromise of recurrent laryngeal nerve innervation. One mechanism may have been nerve compression by the goiter and the associated acute thyroiditis. With attenuation of the acute inflammation of the Graves’ disease, the compressive effects may have abated. However, given the extreme rarity of associated vocal cord paralysis with Graves’ disease and the fact that her goiter size did not appear to change with recovery of vocal cord function, additional explanations for this patient’s course seem necessary. Perhaps her markedly enlarged thymus and decreasing TSI provide a potential mechanism. The thymus is a large organ in the anterior thoracic cavity that grows until puberty and thereafter slowly regresses into 2 long fatty bodies. In the pediatric population, the thymus abounds with lymphocytes that have migrated from the bone marrow to generate T-cell receptors. Within the thymus, thymic stroma, antigen-presenting cells, and nurse cells develop T cells to recognize self-antigens for self-tolerance. Thyrotropin receptors are present in the thymus and, when stimulated by the anti-thyrotropin receptor antibodies present in Graves’ disease, may result in thymic hyperplasia, which has been described in pediatric Graves’ disease. In vivo data suggest an immunologic effect of antithyroid drugs such as methimazole. Use of an antithyroid drug...
depletes intrathyroidal lymphocytes and decreases serologic levels of thyrotropin receptor antibodies, the immunomodulating intracellular adhesion molecule-1, cytokines such as interleukin-1β and soluble interleukin-2 and interleukin-6 receptors. Overall active T-cell numbers and helper T-cell and natural killer cell activity decrease. In vitro data suggest effective dosages of antithyroid drugs between 10⁻²⁴ and 10⁻²⁵ mol/L, but in vivo the intrathyroidal concentrations are unlikely to exceed 5 × 10⁻⁵ mol/L. Thus, an extra-thyroidal site of the immune modulation of antithyroid drugs is likely, and the central role of the thymus in autoimmune immunity suggests a site of action. Indeed, a significant decrease in thymic size has been demonstrated with antithyroid drug treatment. Interestingly, a case of a 34-year-old patient with Graves’ disease and thymic enlargement that did not decrease in size in response to antithyroid drug therapy has also been described. The differences in response to antithyroid drug intervention may reflect innate differences in thymic dynamics with younger age as compared with a more static thymus with older age, as suggested by studies that demonstrate a decreasing susceptibility to cytokine dynamics with increasing age.

The left recurrent laryngeal nerve branches off of the left vagus in the superior mediastinum, passes inferior to the aortic arch, and then courses superiorly through the tracheoesophageal groove to innervate the intrinsic left laryngeal muscles. Conversely, the right recurrent laryngeal nerve passes inferiorly around the right subclavian artery and then courses superiorly to innervate the intrinsic right laryngeal muscles, never entering the thoracic cavity. A mass effect in the thoracic cavity, such as from thymic enlargement secondary to severe Graves’ disease, could distend the lengthy left recurrent laryngeal nerve, with compromise of left vocal cord mobility, but leave the right recurrent laryngeal nerve unscathed. In this case, CT imaging demonstrated significant hyperplastic thymic extension inferiorly to the level of the aortic arch (Fig 1) that may have effected such nerve distension. The pediatric population may be especially susceptible given the large thymus. A therapeutic intervention on the thyroid that compromises the remaining intact right recurrent laryngeal nerve to cause bilateral vocal cord paralysis may have devastating consequences, such as airway compromise. Such a risk of injury to the recurrent laryngeal nerve is a well-recognized risk of thyroid surgery but has been even described with radioiodine therapy. Thus the use of methimazole for Graves’ disease to modulate the immune stimulation of thymic hyperplasia becomes especially attractive in cases of recurrent laryngeal palsy as a primary intervention before other definitive therapies.

CONCLUSIONS

Our report describes a case of pediatric Graves’ disease that presented with reversible left recurrent laryngeal nerve...
palsy and thymic hyperplasia. Treatment with methimazole potentially ameliorated immune hyperstimulation of the thymus and resulted in remission of her left vocal cord palsy. Methimazole should be considered as an initial op-

tion in pediatric patients presenting with Graves’ disease and vocal cord palsy.

REFERENCES


9. Sprent J, Lo D, Gao E-K, Ron Y. T cell se-

10. Sprent J, Lo D, Gao E-K, Ron Y. T cell se-


14. Beck JS, Young RJ, Simpson JG, et al. Lymphoid tissue in the thyroid gland and thymus of patients with primary thyrotoxi-

15. Hardisty CA, Fowles A, Munro DS. The effect of radioiodine and antithyroid drugs on serum long acting thyroid stimulator pro-


18. Tsatsouls A, Vlachojannopoulos PG, Dalekos GN, Johnson EO, Moutsopoulos HM. Increased serum interleukin-1 beta during treatment of hyperthyroidism with anti-

related effect on the serum concentrations of soluble class I major histocompatibility complex antigens, soluble interleukin-2 re-


21. Tötterman TH, Karlsson FA, Bengtsson M, Mendel-Hartvig I. Induction of circulating activated suppressor-like T cells by methi-


mic hyperplasia in patients with Graves’ disease. Identification of thyrotropin recep-

26. Desforges-Bullet V, Petit-Aubert G, Collet-


30. Anthony DC, Bolton SJ, Fearn S, Perry VH. Age-related effects of interleukin-1 beta on polymorphonuclear neutrophil-dependent increases in blood-brain barrier perme-

31. Friedrich T, Steinitz M, Keitel R, Sattler B, Schönfelder M. Incidence of damage to the recurrent laryngeal nerve in surgical

32. Echeverri A, Flexon PB. Electrophysiologic nerve stimulation for identifying the recur-

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