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CLINICAL REPORT

Pediatric Graves' Disease: Surgical Interventions in a Single Institution – A Comprehensive Case Series

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Abstract

Introduction Graves' disease (GD) is the most common cause of hyperthyroidism in children and adolescents. Data regarding pediatric GD in Indonesia are limited and pose challenges to diagnosing and treating the patients. In many aspects the clinical presentation of GD in children and adolescents resembles that of the adult population. There are three treatments for pediatric GD: anti-thyroid drugs, radioiodine ablation, and thyroidectomy. Although surgery is gaining acceptance as the definitive first-line treatment for children with GD, several studies examining pediatric populations have shown high complication rates. This study aims to describe a series of pediatric GD cases from a tertiary care center over an eight-year period.

Presentation of Cases Retrospective data of five patients with hyperthyroidism diagnosed with GD between 2014 and 2022 were reviewed. Clinical presentation, diagnosis, therapies, and short-term postoperative outcomes of GD were analyzed. All five GD patients presented with neck lumps. Low TSH levels and elevated FT4 levels were found in all patients preoperatively. Total thyroidectomy was performed in all patients, while one patient had lymphadenectomy concurrently. Histopathologic examination confirmed a diagnosis of GD in all patients. All patients in this study experienced postoperative complications such as hoarseness, while only three patients had hypocalcemia as a complication.

Discussion Total thyroidectomy in pediatric patients remains challenging. The euthyroid condition in patient prior to surgery is recommended to avoid the risk of thyroid storm during surgery, but a few studies have revealed that there is no difference in outcomes for hyperthyroid individuals. Close postoperative surveillance for complications of total thyroidectomy is necessary.

Conclusions Results of this study showed that pediatric GD patients had the same symptoms of hyperthyroidism as adults with all patients complained of neck lumps. Total thyroidectomy is the definitive therapy for GD in pediatrics as well as in adults. The minority of patients will experience transient and benign morbidities, with hoarseness of the voice being the most common transient postoperative morbidity. In performing total thyroidectomy, meticulous surgery and good anatomical recognition are required to avoid postoperative complications. So that, follow-up of post-total thyroidectomy in pediatric GD patients needs to be done.

Keywords Graves' Disease · Pediatric · Total Thyroidectomy

Introduction

Graves' disease (GD) – an autoimmune disorder in which antibodies stimulate thyroid-stimulating hormone receptors to promote synthesis and release of thyroid hormones, signaling thyroid gland growth; occurs less frequently in childhood than in adults, affecting from 0.1 per 100,000 children and 3.0 per 100,000 adolescents per year. GD can occur at any age in childhood and peaks in adolescence. It is much more common in females than males [1–3].

In children, the clinical manifestations of GD always presents with a goiter [3, 4]. It is also characterized by some

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key distinguishing features, such as much lower remission rates and a higher prevalence of adverse effects of antithyroid drugs (ATD). The majority of pediatric patients with GD eventually require definitive radioactive iodine (RAI) therapy or total thyroidectomy (TT) [2].

Surgery is gaining acceptance as the definitive first-line treatment for GD in adults. Still, several studies examining pediatric populations have shown that pediatric complication rates are high and outcomes depend on the surgeon's experience and volume [5]. Side effects noted during surgery were intraoperative parathyroid autotransplantation, postoperative hemorrhage, transient and permanent Recurrent Laryngeal Nerve (RLN) paralysis, transient and permanent hypoparathyroidism, transient hypocalcemia, and transient hoarseness of voice [6, 7].

Data regarding surgical treatment for pediatric GD profiles in Indonesia are still limited. This case series aims to describe pediatric GD`s clinical manifestations, diagnosis, management, and outcome over 8 years from a single institution.

Presentation of Cases

This was a single retrospective study and case series of all patients with Graves' Disease (GD) treated in the Surgical Oncology Clinic of Cipto Mangunkusumo General Hospital, Jakarta, between 1st January 2014 and 31st of December 2022. Medical records of patients diagnosed with GD and treated by surgical procedures were reviewed. This case series has been reported in line with the PROCESS Guideline.

Five patients were identified with a median age of 17 years (15–18 years), and all were female. All patients had a chief complaint of neck lump that felt to be increasing in size. Complaints of palpitations and tremors were felt in 60% of cases. Hyperhidrosis was observed in two patients. Significant weight loss was found in two patients.

Low TSH level was noted in all patients preoperatively. Elevated FT4 level was found in all patients preoperatively, with a median of 10.66 ng/dL (2.36 − 38.8 ng/dL). All patients received methimazole as initial medication preoperatively, with a median consumption duration of four years and five months (5 months – 13 years). The pediatric specialist found that all patients failed medication therapy and were then consulted with the surgeon for surgery. All patients in our case series underwent neck US examination, and only one patient had a thyroid scan.

Surgery was performed by our attending surgical oncologists. Four patients had total thyroidectomy, while one patient had total thyroidectomy and lymphadenectomy simultaneously. A frozen section sample was taken from one patient, and the result was that none of the lymph node spread was found. Histologically, all five patients showed characteristics corresponding to GD. All patients had a surgical complication which is hoarseness. After the surgical treatment, the serum calcium level laboratory testing was performed. Hypocalcemia was biochemically evident in three patients, with symptoms of hypocalcemia i.e. tingling sensations and muscle cramps. The median serum calcium level was 7.67 mg/dL (7.6–7.7 mg/dL). Calcium carbonate ($CaCO_3$) was given to elevate the serum calcium level with a median consumption duration of 1.6 months (1–2 months) and symptoms of hypocalcemia disappeared after calcium supplementation. The hypocalcemia that occurred in all three patients was temporary.

At present, all patients are known to be alive. GD-related complaints are no longer occur in all patients. However, post-surgical complications such as hoarseness and poorly heard voice occurred in one patient. Complaints were felt for approximately 8 months, and the patient was doing rehabilitation at the medical rehabilitation clinic (Table 1).

Discussion

The overall incidence of GD in children and adolescents is about 4.58/100,000 per year, but the incidence in those under 15 years of age is lower, between 1 and 2.91/100,000 per year [8]. According to a study in Japan, females have a significantly higher incidence than males, with reported males-to-females ratios of around 1:3 to 1:6 [9]. Various symptoms include tremors, weight loss, tiredness/exhaustion, behavioral changes, and heat intolerance. Symmetrical thyroid enlargement, accelerated growth, and bone maturation were also found. Thyroid eye disease (TED) is a potentially sight-threatening autoimmune disease most commonly associated with GD [10–12].

In our study, all GD patients in the pediatric group were female, with a median age of 17. All of them had a chief complaint of an enlarged thyroid gland. Other complaints included palpitations, tremors, excessive sweating, and significant weight loss.

The diagnosis of GD has also been made by finding elevated free triiodothyronine (FT3) and free thyroxine (FT4) concentration, a subnormal serum thyrotropin (TSH) level,

Table 1 Graves' Disease cases in paediatric with sex, age, laboratory examination, imaging examination, biopsy, surgery performed, histopathology results after surgery and postoperative complications

		Case 1	Case 2	Case 3	Case 4	Case 5
Sex		Female	Female	Female	Female	Female
Age		18	16	18	15	18
Clinical symptoms		Neck lump, palpitations, tremors, hyperhidrosis for six years	Neck lump, palpitations, tremor, hyperhidrosis, hoarseness for six months	Neck lump, significant weight loss for two years	Neck lump for 13 years	Neck lump, palpitations, tremor, significant weight loss for two years
Onset		2015	2020	2019	2009	2018
TSH level (mIU/L) [N: 0.5-5.0]	Initial	< 0.0025	< 0.003	0.005	< 0.003	< 0.003
	Pre	0.001	0.001	0.013	0.005	< 0.003
FT4 level (ng/dL) [N: 0.93–1.7]	Initial	38.8	3.77	4.29	2.36	4.11
	Pre	0.99	2.25	0.71	2.22	0.66
Calcium level (mg/dL) [N: 8.4–10.2]	Pre	9.0	8.4	8.7	9.1	9.5
	Post	7.7	7.6	7.7	9.7	9.3
Preoperative Imaging		**US**: Diffuse thyroid gland enlargement with heterogeneous echogenicity and increased intraparenchymal vascularization suggestive of Grave's disease. Left level II coli lymphadenopathy. **Thyroid scan**: Bilateral diffuse struma with increased total thyroid uptake (40.3%).	**US**: This may correspond to Graves' disease with prominent vascularization. Multiple lymph nodes in the neck region bilaterally with the largest short axis diameter of 1 cm.	**US**: Large thyroid size with heterogeneous parenchyma and impression of increased vascularity on color flow which may correspond to grave disease.	**US**: Right thyroid size 3.15 × 2.14 × 6 cm, left thyroid 3.36 × 2.37 × 5.84, multiple cysts of various sizes in both thyroids	**US**: Size of right thyroid 3.37 × 3.41 × 3.84 cm left thyroid 3.19 × 2.56 × 3.79 cm
Preoperative medications		Methimazole, propranolol	Methimazole, propranolol, dexamethasone	Methimazole, propranolol, lugol	Methimazole	Methimazole, propranolol
Surgery		Total thyroidectomy and lymphadenectomy	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy
Histopathology results		Histologically consistent with Graves' disease. Left neck non-specific chronic lymphadenitis.	Histologically consistent with treated Graves' disease.	Histologically consistent with treated grave's disease	Histology may be consistent with Graves' disease	Histology may be consistent with Graves' disease
Postoperative GD's clinical symptoms		None	None	None	None	None
Postoperative complications		Hoarseness of voice, hypocalcemia	Hoarseness of voice, hypocalcemia	Hoarseness of voice, hypocalcemia	Hoarseness of voice	Hoarseness of voice
Duration of postoperative complications		2 months	2 months	8 months	2 weeks	2 weeks
Postoperative medications		Levothyroxine, CaCO3	Levothyroxine, CaCO3	Levothyroxine, CaCO3	Levothyroxine	Levothyroxine
Duration of $CaCO_3$ consumption		2 months	2 months	1 month	-	-

anti-TSH receptor antibodies concentration greater than 1 IU/L, and high titers of thyrotropin receptor antibodies (TRAbs) [13, 14]. All patients in our study underwent biochemical examinations of TSH and FT4. The results of the TSH examination showed undetectable levels. In contrast, the FT4 examination found an increase in serum levels.

Ultrasound examination of the thyroid gland can help distinguish GD from other causes of thyrotoxicosis. Two sonographic features, hypoechogenicity and increased

thyroid blood flow can also be found in GD patients [15]. Our study utilized neck US as part of the routine examination. The sonographic features of diffuse thyroid gland enlargement with heterogeneous echogenicity and increased vascularity were found.

Treatment modalities for pediatric GD can be divided into three categories: medical therapy, radioactive iodine, and surgery. Most pediatric endocrinologists recommend antithyroid drugs (ATDs) as first-line treatment for hyperthyroidism in children and adolescents. Methimazole is preferred over propylthiouracil due to its lower side effect profile [3, 16]. Beta-blockers such as propranolol are used primarily for adrenergic symptoms in pediatric GD until euthyroidism is accomplished [17]. All patients in this study received initial medication therapy through methimazole administration. However, only four out of five patients received propranolol as adjunctive therapy.

American Thyroid Association (ATA) guidelines recommend administering potassium iodide and achieving euthyroid status prior to surgery [18]. In our study, only one patient received lugol therapy preoperatively.

Total thyroidectomy provides a timely and permanent cure for hyperthyroidism but is most often considered second-line treatment after medical therapy [3, 19]. Four patients underwent total thyroidectomy as surgical therapy. However, one patient underwent total thyroidectomy and lymphadenectomy simultaneously. Lymphadenectomy was performed because enlarged lymph nodes were found during surgery. After total thyroidectomy, all patients had no more complaints of GD clinical manifestations.

Patients with GD who undergo total thyroidectomy are more likely to suffer from complications of hypocalcemia than those undergoing thyroidectomy for other indications. The cause of postoperative hypocalcemia is probably multifactorial, but the main factor is parathyroid insufficiency due to damage to the functional parathyroid parenchyma. The decrease of parathyroid hormone (PTH) levels in the blood as a result of trauma, vascular resection, or accidental removal of the parathyroid gland. This can lead to temporary hypocalcemia if the parathyroid function is restored [20, 21]. Two studies suggest that postoperative PTH testing may help identify patients at risk for hypocalcemia [22]. Three out of five patients in this study had postoperative hypocalcemia. But none of the patients had the symptoms of hypocalcemia. The patients were given calcium supplementation with a median duration of 1.5 months. So it can be determined that the hypocalcemia in these patients is transient.

Recurrent laryngeal nerve (RLN) injury is the most common complication of thyroid and parathyroid surgery. In children, the rates of transient and definite lesions after thyroidectomy are 0–28% and 0-9.9%, respectively. The incidence of RLN injuries continues to decrease as children age [23]. Thyroid surgery in the pediatric is generally more difficult than in the adult population. The narrow space in the neck, along with the delicate anatomy and thin RLN, can hinder nerve identification and preservation [24]. All patients in this study experienced the postoperative complication of hoarseness. Four out of five patients had voice improvement within 1 month. In contrast, only one patient experienced complaints of hoarseness for 8 months, so this patient requires regular control to the medical rehabilitation clinic.

Conclusions

Graves' Disease is the most common cause of hyperthyroidism in the pediatric population and mostly affects older female children. Suspicion of GD is appropriate in the presence of an enlarged thyroid gland, elevated FT3 and FT4 serum levels, and undetectable TSH levels. GD treatment methods in pediatrics are divided into three categories: medical therapy, radioactive iodine, and surgery. A total thyroidectomy aims to remove all overactive thyroid tissue, the preferred definitive treatment option for GD patients. Hypocalcemia is the most common complication after total thyroidectomy in pediatric GD patients, while transient RLN injury is the second most commonly reported.

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Data Availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethical Approval This case series was conducted in accordance with the Health Research Ethics Committee Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital-compliant manner.

Conflict of Interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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