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Treatment of Pediatric Graves’ Disease with Thyroidectomy

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Title          Treatment of Pediatric Graves' Disease with Thyroidectomy
Department     Nursing
Degree         Master of Science

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Abstract

This paper explores twelve research articles regarding the treatment of pediatric Graves’ disease. There are three main treatment options available for Graves’ disease including antithyroid drugs, radioactive iodine therapy, and thyroidectomy. Minimal information on antithyroid drugs and radioactive iodine therapy is available to help the reader develop a foundation for learning. Pediatric Graves’ disease is the most common form of hyperthyroidism in children, and it poses many different risks to the child’s mental, physical, emotional, and sexual development. There have been limited research studies performed solely on pediatric populations making this topic so important for the future of healthcare. The case report related to this topic of discussion is on a 65-year-old female patient that presents to the clinic with complaints congruent with hyperthyroidism. Knowing that there are many studies evaluating the effectiveness of different treatment options in adult populations, it is important to shift the focus of this paper onto the pediatric population. The focus of this paper is to evaluate the effectiveness of thyroidectomy based on the implications, complications, cure rates, treatment before and after, and impact for future practice.

Keywords: pediatrics, hyperthyroidism, Graves’ disease, and thyroidectomy
Background

Pediatric Graves’ disease is an autoimmune disease resulting from the formation of autoantibodies against the thyroid hormones. With these autoantibodies, the function of the thyroid is altered leading to an increase in production of thyroid hormones. With an increase in the production of Triiodothyronine (T3) and Thyroxine (T4), the body signals the hypothalamus to stop secreting thyroid releasing hormone which then signals the pituitary gland to stop secreting thyroid stimulating hormone. Despite the body’s actions through the negative feedback loop to prevent the release of excess thyroid hormones, the thyroid continues to secrete T3 and T4 due to the autoantibodies resulting in hyperthyroidism and Graves’ disease (LaFranchi, 2018).

Graves’ disease is the most common form of hyperthyroidism in pediatric populations, accounting for roughly 15 percent of cases (LaFranchi, 2018). The peak incidence of this disease occurs during puberty (LaFranchi, 2018). It is more common in females, and there is a strong genetic inheritance of the disease (LaFranchi, 2018). With Graves’ disease, the child may experience tachycardia leading to increase in cardiac workload and increase in oxygen demand, increased cardiac output, atrial fibrillation, weight loss despite the body’s need for increased caloric consumption, exophthalmos, goiter, tremors, hyperreflexia, cognitive dysfunction, weakness, behavior problems, and risk for osteoporosis related to accelerated growth (LaFranchi, 2018). As a result of these clinical manifestations, children suffer from delayed brain development, learning disabilities, poor self-esteem, and negative self-image (LaFranchi, 2018). Knowing this information, it is extremely important to address the disease and treat it promptly (LaFranchi, 2018).
Based on the above-mentioned information, it is concluded that the diagnosis and treatment of Graves’ disease in pediatric populations need to be prompt. With the initiation of prompt treatment, the child can resume normal functioning and lead a normal life. There are treatment options including antithyroid drugs, radioactive iodine therapy, and thyroidectomy (LaFranchi, 2018). There is limited evidence that specifically pertains to the pediatric population. Based on this information, this case report will be focused on the treatment of pediatric patients diagnosed with Graves’ disease with thyroidectomy rather than the adult population despite the case description being on a 65-year-old female.

**Case Documentation**

The patient was a pleasant, 65-year-old Caucasian female that presented to the clinic with complaints of troubles sleeping and being tired throughout the day. Her symptoms started abruptly six weeks ago. The patient cannot identify any changes in her life that would have initiated her symptoms. She reported she can fall asleep okay, but she wakes up after an hour and a half of sleeping. She cannot fall back asleep. This has happened every night for the past six weeks. She has tried limiting her coffee consumption to only one cup of coffee in the morning and having no coffee in the later afternoon or evening. She has also used Tylenol PM with no benefits. She reported feeling anxious with heart palpitations and fluttering. She has lost about 10 pounds unintentionally in the past six weeks. She has noticed that she is unable to eat as much as she used to due to the fatigue. She is having troubles concentrating, and her husband and friends have told her that she is “more irritable than ever before”. She also has “hot flashes” intermittently, which has been happening for several years. She did not report any shortness of breath, chest pain, lightheadedness, dizziness, her heart “skipping” any beats, vision changes,
changes in skin or hair texture, diarrhea, constipation, nausea, vomiting, or weakness. She reported she is extremely frustrated and “just wants to sleep.”

Her past medical history includes benign positional vertigo. She has had only one surgery, which was a thumb amputation. She is currently taking Antivert as needed, a multivitamin daily, and a calcium supplementation daily. She has an allergy to almonds that causes hives. She is up to date on all vaccinations except for the new shingles vaccine due to vaccination shortage. Her maternal grandmother had Alzheimer’s disease, and her mother had heart disease that resulted in a stent placement. Her father had diabetes mellitus type II. The patient is married and has two children delivered vaginally. She does not consume any alcohol. She did smoke cigarettes in college for one year before having children. She swims three times per week. She lives a relatively busy life and feels that her social life is active and healthy. She has never suffered from anxiety or depression in the past.

Patient’s vital signs were all within normal limits except for her heartrate and temperature, which were both elevated at 96 beats per minute and 99.4 degrees Fahrenheit. Her physical examination was negative for cardiac arrythmia, murmur, or bruises; negative for respiratory distress, shortness of breath, or cough; negative for abdominal discomfort, tenderness, or bruises; negative for skin and hair texture abnormalities, no bruising, skin warm and dry; negative for hyperreflexia, weakness, or delayed cognition; negative for visual changes, thyroid enlargement/goiter, or abnormalities in sensation and point discrimination; positive for nervous/anxious mood, tendency to move from idea to idea, and hyperactive.

Possible differential diagnoses for this patient include, but are not limited to, hyperthyroidism, paroxysmal atrial fibrillation, anxiety, malignancy, infection, and hormonal imbalance. Her urinalysis was negative, normal sinus rhythm on EKG, and basic metabolic
panel without abnormal lab values. Her thyroid panel was abnormal with a TSH of 0.13, Free T4 of 2.93, Total T4 of 15.5, and T3 of 0.3. A diagnosis of hyperthyroidism was made after these lab results were reviewed. Treatment for this patient consisted of starting on Levothyroxine daily and Propranolol daily for symptomatic control. She will follow-up in 6 weeks with labs repeated at that time. We will continue to monitor her thyroid closely for enlargement, goiter, and nodules. The patient will be sent for a thyroid ultrasound if these findings are present. In the meantime, patient will be referred to endocrinology for further evaluation. In addition, the patient was also educated on signs and symptoms of the disease, length of treatment required, additional laboratory testing frequently until euthyroid, and when to return to the clinic with worsening of symptoms.

**Literature Review**

For the treatment of pediatric Graves’ disease, there are three treatment options including antithyroid drug therapy, radioactive iodine therapy, and thyroidectomy. Twelve research articles were reviewed, and many studies shared similar findings. Almost all of the information that will be presented was unanimously agreed upon throughout the research. However, it was difficult finding articles that related specifically to the pediatric population, as much of the research has been performed only on adult populations. Most of the guidelines for the pediatric populations are based upon these adult studies. Despite this information, it is extremely important to remember that children are not just small adults.

**Antithyroid Drug Therapy (ATD)**

Many researchers agree that antithyroid drug therapy is the first line treatment for Graves’ disease in pediatric populations (Hanley, Lord, & Bauer, 2016; Leger & Carel, 2013). “These drugs inhibit thyroid hormone synthesis by interfering with the thyroid peroxidase-
mediated iodination of tyrosine residues in thyroglobulin” (Leger & Carel, 2013, p. 51).

Antithyroid drug therapy is usually started with methimazole (MMI) because propylthiouracil (PTU) has shown to have a high rate of liver failure. The Food and Drug Administration (FDA) removed the approval of the use of PTU in pediatrics in 2010 (Breuer, Tuggle, Solomon, & Sosa, 2013b; Hanley et al., 2016; Rivkees, 2014). MMI is to be taken once or twice a day with a dose initiated at around 0.5 to 1.0 milligrams per kilogram (Gordner, 2014; Rivkees, 2014). Once the patient is euthyroid, the medication is decreased (Gordner, 2014; Leger & Carel, 2013). With ATD therapy, there are increased rates of drug failure, decreased remission rates, and high recurrence rates (Breuer et al., 2013b; Elfenbein, Katz, Schneider, Chen, & Sippel, 2016; Gordner, 2014; Hanley et al., 2016; Leger & Carel, 2013; Rivkees, 2014). Only minimal amounts of patients remain in remission, which is considered 12 months without recurrence (Breuer et al., 2013b; Hanley et al., 2016). Rivkees (2014) noted that only 33 percent of children go into remission with ATD, and Leger and Carel (2013) found that less than 30 percent of children go into remission with ATD. Given these statistics, antithyroid drug therapy seems to be less effective in children.

While taking these medications, complete blood counts focusing on the white blood cells and liver function tests are routinely monitored while taking these medications (Hanley et al., 2016; Leger & Carel, 2013; Rivkees, 2014). For the patient to see the benefits of the medications, long term medication treatment is required for roughly two to four years. This lengthy treatment course influences medication compliance leading to reduced compliance rates (Gordner, 2014; Hanley et al., 2016; Leger & Carel, 2013; Rivkees, 2014). The drug failure rate is also influenced by the side effects of the medications including sore throat, pruritis,
agranulocytosis, loss of appetite, and abdominal tenderness (Gordner, 2014; Leger & Carel, 2013; Rivkees, 2014).

Before prescribing antithyroid drug therapy, the prescriber and patient need to formulate a plan of action if drug therapy is not sufficient. If medication is chosen to be trialed first, then radioactive iodine therapy or thyroidectomy should be considered for second line treatment (Gordner, 2014; Hanley et al., 2016; Rivkees, 2014). However, if the patient and prescriber decide that drug therapy is not ideal, has a lengthy course of treatment, and may not result in reaching euthyroid levels, thyroidectomy should be the chosen route of treatment as it is a quick and proven effective treatment option (Gordner, 2014; Leger & Carel, 2013; Rivkees, 2014).

**Radioactive Iodine Therapy (RAI)**

Radioactive iodine therapy is a second line treatment option and should only be used in pediatric populations if ATD fails (Breuer et al., 2013b; Wu et al., 2017). It is a relatively inexpensive procedure, and usually only requires one to two sessions of radioactive therapy (Rivkees, 2014; Wu et al., 2017). RAI becomes expensive due to frequent laboratory testing that is necessary for up to several years after treatment to evaluate if there was a response to RAI (Breuer et al., 2013b; Wu et al., 2017).

It is argued that RAI should not be used in children younger than five (Elfenbein et al., 2016; Gordner, 2014; Rivkees, 2014). However, some researchers say that RAI should not be used in any child less than ten years of age (Breuer et al., 2013b). The rationale for these age limitations is due to the potential carcinogenic and teratogenic risks with radioactive therapy (Gordner, 2014; Rivkees, 2014). Radiation exposure is thought to be related directly to the dose and size of the patient (Breuer et al., 2013b; Rivkees, 2014; Wu et al., 2017). Gordner (2014) and Rivkees (2014) note that treatment with RAI can also lead to the development of thyroid cancer.
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in an unknown amount of children. However, some researchers dispute this and claimed that RAI is safe and that there have been no documented cases of cancer development following treatment with RAI (Breuer et al., 2013b; Elfenbein et al., 2016).

The size of the thyroid gland can also influence treatment with RAI grams (Breuer et al., 2013b; Rivkees, 2014; Wu et al., 2017). Several researchers agree that RAI should not be considered in those patients with thyroid glands larger than 80 grams (Breuer et al., 2013b; Rivkees, 2014; Wu et al., 2017). The failure rate of treatment is only 26 to 37 percent when RAI is used on thyroid glands smaller than 80 grams (Rivkees, 2014; Wu et al., 2017). Given this information, radioactive iodine therapy should be considered for children older than 10 years of age due to the low failure rate.

**Thyroidectomy**

Thyroidectomy, which is the removal of the thyroid gland, is recommended as a definitive treatment option that can be used initially in children where prompt treatment is needed and for those children that are too young (younger than five years of age) to receive RAI (Rivkees, 2014; Wu et al., 2017). A thyroidectomy can also be used as a second line treatment option for cases of Graves’ disease that are resistant to ATD and RAI due to the complexity of treatment courses, drug failure, or adverse drug effects (Rivkees, 2014; Wu et al., 2017). In the past, thyroidectomy was the last treatment option to be considered, but today, researchers conclude that thyroidectomy should be one of the first treatment options discussed and performed (Breuer et al., 2013b; Hanley et al., 2016; Wu et al., 2017). They also reported that recurrence rates of Graves’ disease are significantly less than those treated with ATD and/or RAI (Rivkees, 2014; Wu et al., 2017). Thyroidectomy is recommended for those thyroid glands larger than 80 grams in volume (Breuer et al., 2013b; Hanley et al., 2016; Wu et al., 2017). This
procedure can also be considered for those patients that continue to have symptoms of Graves’ disease that interfere with the patient’s quality of life and daily activities despite reaching a euthyroid state with other treatment modalities (Breuer et al., 2013b; Hanley et al., 2016; Rivkees, 2014).

There is conflicting information regarding whether there should be a complete removal of the thyroid or partial removal of the thyroid. Wu et al. (2017) claimed that a subtotal thyroidectomy should be the choice of action due to the potential of damage to surrounding tissue with the removal of the entire thyroid gland. All other research journals conclude that total thyroidectomy is the preferred method because there is a high likelihood of recurrence of Graves’ disease when thyroid tissue is left behind (Breuer, Solomon, Donovan, Rivkees, & Udelsman, 2013a; Breuer et al., 2013b; Leger & Carel, 2013). The recurrence rate of Graves’ disease following a subtotal/partial thyroidectomy is quite high (Breuer et al., 2013a; Leger & Carel, 2013). This is compared to the recurrence rates of Graves’ disease following a total thyroidectomy which is less than 4 percent (Breuer et al., 2013a; Breuer et al., 2013b). The success rates of total thyroidectomy are 96 to 100 percent effective (Breuer et al., 2013b; Leger & Carel, 2013). Therefore, the benefits of total thyroidectomy outweigh the risks of complications.

Throughout the research, the different complications that can result from a thyroidectomy were congruent from study to study. It is noted that complications from surgery are more common in pediatric patients than adult patients (Breuer et al., 2013a; Breuer et al., 2013b; Bussieres et al., 2019; Cristison-Lagay, 2016). However, Akkari et al. (2014) and Kundel et al. (2014) disputed this information and claimed that the risk of complications is equal among pediatric and adult patients. Of those complications, hypocalcemia and laryngeal nerve injury
were the most common (Breuer et al., 2013b; Bussieres et al., 2019; Elfenbein et al., 2016; Rivkees, 2014; Wu et al., 2017).

Hypocalcemia can be transient or permanent, and it results from damage to the parathyroid glands during surgery (Breuer et al., 2013b; Bussieres et al., 2019; Elfenbein et al., 2016; Wu et al., 2017). The treatment for hypocalcemia includes calcium supplementations until levels return to normal or for life depending on the underlying cause for the low calcium. The risk for hypocalcemia is more significant in those having a total thyroidectomy rather than a partial thyroidectomy, but the rate of permanent hypocalcemia due to permanent hypoparathyroidism is less than 4 percent in all cases despite how much of the thyroid is removed (Breuer et al., 2013b; Cristison-Lagay, 2016; Elfenbein et al., 2016; Kundel et al., 2014).

Laryngeal nerve injury can be transient or permanent (Breuer et al., 2013b; Bussieres et al., 2019; Elfenbein et al., 2016). Transient cases occur more commonly in very young patients at a rate of 22 percent compared to the older pediatric populations at a rate of 11 percent (Cristison-Lagay, 2016). Less than 4 percent of these cases suffered from permanent nerve damage (Bussieres et al., 2019; Cristison-Lagay, 2016; Wu et al., 2017). Presentation of laryngeal nerve injury presents itself as paralysis of the vocal cords leading to changes in voice quality (Breuer et al., 2013b; Elfenbein et al., 2016).

Other less common complications of a thyroidectomy include hemorrhage, infection, and “hungry bone syndrome” (Breuer et al., 2013b; Cristison-Lagay, 2016; Rivkees, 2014). Hemorrhages and infections resulted in less than 1 percent of cases (Kundel et al., 2014; Wu et al., 2017). “Hungry bone syndrome” is an infrequent complication, and it is only documented in one research article (Cristison-Lagay, 2016). This condition results from a rapid correction in the
hyperthyroid state (Cristison-Lagay, 2016). This rapid correction leads to a rapid rate of calcium deposition into the osteoid (Cristison-Lagay, 2016). This bone syndrome can be easily avoided with the improvement in medical treatment and preoperative and postoperative monitoring (Cristison-Lagay, 2016).

The overall goal for the removal of the thyroid is to achieve a permanent state of hypothyroidism (Breuer et al., 2013a; Hanley et al., 2016; Rivkees, 2014). Before surgery is performed, it is discussed with the patients and family that the patients will need thyroid hormone replacement for the rest of their lives (Breuer et al., 2013a; Hanley et al., 2016; Leger & Carel, 2013). Medications are taken daily with minimal laboratory tests compared to the other treatment modalities (Breuer et al., 2013a; Hanley et al., 2016; Leger & Carel, 2013). Also, there is a decreased chance of recurrence meaning the patient will likely not have to endure invasive procedures or complex treatment regimens again in the future making daily thyroid hormone replacement the most appealing option (Breuer et al., 2013a; Hanley et al., 2016; Leger & Carel, 2013; Rivkees, 2014).

There are certain interventions that need to be done preoperatively to reduce the possible complications after a thyroidectomy and improve the outcome of surgery. The patient is prescribed antithyroid drugs prior to surgery to bring the patient closer to a euthyroid state (Breuer et al., 2013a; Breuer et al., 2013b; Rivkees, 2014). The patient is also prescribed iodine drops seven days before surgery. The standard dose of iodine drops are five to ten drops three times a day (Breuer et al., 2013a; Breuer et al., 2013b; Rivkees, 2014). The purpose of the iodine is to inhibit the production and secretion of excess thyroid hormones resulting in a firmer, less vascularized thyroid gland prior to surgery (Breuer et al., 2013b; Rivkees, 2014). Also, to limit the extent of hypocalcemia postoperatively, patients are prescribed 1 microgram of calcitriol to
be taken in two divided doses daily starting three days prior to surgery (Breuer et al., 2013a; Breuer et al., 2013b; Rivkees, 2014). When all these interventions are performed prior to surgery, the rate of any form of complications occurring is decreased by 50 percent, and the length of the surgical procedure and length of postoperative hospital stays are significantly reduced (Breuer et al., 2013a; Breuer et al., 2013b; Hanley et al., 2016; Wu et al., 2017).

Not only is it essential to intervene with medications and supplements prior to surgery, but it is also necessary and beneficial to implement monitoring devices during surgery. Akkari et al. (2014) found that less than one percent of pediatric patients undergoing total thyroidectomy suffered from laryngeal nerve paralysis. This was primarily due to the use of laryngeal nerve monitoring devices during surgery. The monitoring device consisted of the “placement of electrodes in each vocal cord by direct laryngoscopy after intubation, placement of electrodes in the vocal cords through the thyroid cartilage after dissection of its anterior surface, [and] vision monitoring by nasal endoscope introduced through a laryngeal mask” (Akkari et al., 2014, p. 294). The monitoring device enables direct visualization of the laryngeal nerve to prevent damage to it (Akkari et al., 2014). This was the only research article found that discussed intraoperative monitoring devices as complex as this one making this an intervention to be researched more in depth.

It was unanimously agreed throughout the literature that the outcomes of surgery are directly related to the experience of the surgeon in any given hospital (Akkari et al., 2014; Breuer et al., 2013a; Breuer et al., 2013b; Bussieres et al., 2019; Elfenbein et al., 2016; Gordner, 2014). Experience of the surgeon correlates to the number of thyroidectomy cases he/she has performed and his/her expertise with thyroidectomies in pediatric patients (Breuer et al., 2013a; Breuer et al., 2013b; Bussieres et al., 2019; Elfenbein et al., 2016; Gordner, 2014). “Surgeon volume
appears to be the most important and robust predictor of pediatric outcomes after thyroidectomy, and it appears to be independent of the effect of surgeon specialty” (Breuer et al., 2013b, p. 83). Not only does the surgeon’s experience matter, the entire multidisciplinary team’s experience matters regarding pediatric Graves’ disease and pediatric thyroidectomies (Akkari et al., 2014; Breuer et al., 2013b; Elfenbein et al., 2016). This multidisciplinary team includes “paediatric endocrinologists, geneticists, radiologists, otorhinolaryngologists, paediatric anesthetists, pathologists, paediatric oncologists, and nuclear medicine physicians” (Akkari et al., 2014, p. 293). In addition to having an experienced multidisciplinary team consisting of pediatric specialists, the hospital must also be equipped with pediatric operating rooms and tools (Akkari et al., 2014; Breuer et al., 2013b; Bussieres et al., 2019). Despite the need for an experienced surgeon and multidisciplinary team and need for daily medications following a total thyroidectomy, thyroidectomy should still be considered due to its relatively low rate of complications, minimal testing, high success rate, and the ease of continued therapy.

**Learning Points**

- When comparing data on ATD, RAI, and thyroidectomy as treatment options for Graves’ disease, thyroidectomy seems to have the most appealing data. ATD and RAI have high rates of failure, a short period in remission, and complex treatment regimens. With thyroidectomy, the patient will need to take medications for one week prior to the surgical procedure, and the patient will require one pill daily to treat his/her hypothyroidism the rest of his/her life as a result of the thyroidectomy. The patient will need laboratory tests every six to eight weeks postoperatively until thyroid hormones return to euthyroid levels. At that point, the patient may only need to follow up once or
twice a year. Overall, thyroidectomy has fewer medications and less testing required compared to ATD and RAI.

- It is important to note that no treatment option is without risk of complications. Providers, patients, and family members need to discuss each option in detail and find the treatment option that will work the best for that patient. There needs to be constant follow up and revisiting of how the patient feels the treatment is going. If the treatment option needs to be switched, the patient and family members need to know that is okay and acceptable.

- If thyroidectomy is the choice for treatment, referral needs to be placed with the most experienced pediatric surgeon that has operated on a high volume of pediatric thyroids at a facility that is equipped with pediatric specialists and equipment. Thyroidectomy is only as good as the surgeon.

- Very few research studies have been performed solely on pediatric populations diagnosed with Graves’ disease. It would be beneficial to evaluate each of the three treatment options long term to assess the effectiveness of each treatment. Current research is only on the short-term outcomes of treatment. There is a lack of information regarding recurrence and side effects of treatment options 20 to 30 years after therapy.

**Conclusion**

In conclusion, brief descriptions were provided regarding ATD and RAI with a very detailed description of thyroidectomy. With this information, high cure rates, minimal complications, and improved outcomes are reported with thyroidectomy compared to the other two treatment options. These success rates are made through the utilization of experienced surgeons, multidisciplinary teams, preoperative interventions, and total thyroidectomy rather than subtotal thyroidectomy. In all, thyroidectomy should be considered as initial treatment due
to high success rates, less complex treatment regimen, and the quick return to euthyroid levels following total thyroidectomy.
References


