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The Use of Iodine as First Line Therapy in Graves' Disease Complicated with Neutropenia at First Presentation in a Paediatric Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SMN, AG and HH wrote the first draft of the manuscript. Author SMN managed the literature searches. All authors read and approved the final manuscript.

Case Report

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ABSTRACT

Aims: Graves' disease is a common cause of hyperthyroidism in the paediatric population. An association between neutropenia and untreated Graves' disease has been described although the aetiology is unknown.
Presentation of Case: A 13 year old boy presented with a 3 month history of weight loss, insomnia, fatigue, palpitations and anxiety. On examination, he had tachycardia of 140 beats/minute, sweating, tremors and brisk deep tendon reflexes. The clinical and laboratory results were consistent with Graves' hyperthyroidism. He was treated with Lugol`s iodine and Propanolol in view of his low neutropenia count at diagnosis.
Discussion: Thionamide drugs remain the initial treatment of choice in children and adolescents presenting with Graves' disease, however adverse effects such as agranulocytosis remains a concern.
Conclusion: In cases where anti-thyroid thionamides are contraindicated due to the risk of side effects such as agranulocytosis or neutropenia, Lugol's iodine may be an alternative temporary form of first line therapy.

Keywords: Hyperthyroidism; neutropenia; paediatric; lugol's iodine.

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1. INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism in the paediatric age group [1]. This potentially life threatening condition often encounters many complications during its initial phase and subsequent management. Children and adolescents with Graves' disease can be treated with antithyroid thionamide drugs, radioactive iodine, or thyroidectomy [2]. The choice of therapy is determined by an individual consideration of the risks and benefits of the three treatment modalities. The choices for initial treatment of patients with Graves' disease differ in various countries, and many physicians prefer to administer thionamide drugs as the first choice of treatment for thyrotoxic children and adolescents [3].

Prior to the 1940s, iodine had been successfully used to treat goitre before thionamide drugs were available [4,5]. Iodine in the form of Lugol's solution (iodine 5% potassium iodide 15%) was also used to treat exopthalmic goitre and used in the preparation prior to thyroidectomy [6,7].

We report a case of Graves' disease complicated by neutropenia at first presentation in a 13 year old boy. We describe the successful use of Lugol's iodine as a temporary first line treatment for treating the thyroid crisis.

2. PRESENTATION OF CASE

A 13 year old boy presented with a 3 month history of weight loss, insomnia, fatigue, palpitations and anxiety. On examination, he had tachycardia of 140 beats/minute, sweating, tremors and brisk deep tendon reflexes. Both lobes were palpable, smooth in consistency and diffusely enlarged, measuring 6x7 cm. There was no extension of the thyroid gland retrosternally. There was no exophthalmos, extraocular muscle weakness or lid lag. His blood pressure was noted to be 135/75 and there were no other systemic signs of autoimmune disorders. In his past medical history, he had a prior 2-year history of orthostatic proteinuria of unknown aetiology and was under the care of nephrologists. There was no family history of autoimmune or hearing problems.

Blood investigations revealed a thyroid stimulating hormone (TSH) that was undetectable (reference range 0.5-5 iU/L), free thyroxine (FT4) of 32.9pmol/L (reference range 10-24 pmil/L), TSH receptor antibodies (TRAb) were 85 U/L (reference range < 15.0 U/L), haemoglobin 11.5 g/L (reference range 11.5-13.5 g/L), total WBC 3.3 $x10^9$/L (reference range 5.0-17.0 $x10^9$/L), a neutrophil count of <1.5 $x10^9$/L (reference l range 1.5-8.5 $x10^9$/L), and a platelet count of 137 $x10^9$/L (reference range 140-440 $x10^9$/L). TRAb was measured by an in-house enzyme-linked immunosorbent assay. Tests of thyroid peroxidase antibodies, and thyroglobulin antibodies were negative. There was no previous documented neutropenia. His anti-nuclear antibody (ANA) and antineutrophil cytoplasmic antibody **(**ANCA) antibodies were negative and other autoimmune diseases were excluded.

The clinical and laboratory results were consistent with Graves' hyperthyroidism. He was commenced on propanolol and Lugol's iodine at 0.2mls three times a day. He showed rapid clinical improvement with a normal neutrophil count after 16 days on treatment. He was then commenced on Carbimazole and propanolol, for a further 14 days and subsequently started on a "Block and replace" regimen where thyroid hormone production is suppressed by instituting a higher dose of anti-thyroid drug treatment with additional levothyroxine treatment. He showed rapid clinical improvement with a normal neutrophil count after 16

days on treatment. He later underwent total thyroidectomy after 6 months on thionamides and levothyroxine with no complications during that period due to patient choice. He is now stable on lifelong levothyroxine replacement therapy with normalised thyroid function measured serially.

3. DISCUSSION

Disorders of granulopoiesis in untreated Graves' disease have been described in the literature [8,9]. The incidence of neutropenia in hyperthyroid patients has been reported to be between 5 to 18% [9]. The aetiology of neutropenia is not known and treatment of neutropenic Graves' patients with thionamide drugs have resulted in normalisation of the neutrophil count [9]. While antithyroid thionamide drugs remain the initial treatment of choice in children and adolescents with Graves' disease, adverse effects related to thionamide drugs and their dose regimen have been widely reported, and agranulocytosis is thought to be the most severe side effect of antithyroid drugs. Thionamide-induced antineutrophil cytoplasmic antibody (ANCA)-related vasculitis and nephritis has also been reported in the literature [10]. In cases of confirmed agranulocytosis, thionamides must be stopped and often complete resolution of granulocytes occurs after 7 to 14 days. Granulocyte-colony-stimulating factor may be used to shorten the recovery period. Re-challenge of the same drug or an alternative thionamide is not recommended because the risk of recurrence of agranulocytosis outweighs the benefits of therapy. In these circumstances, the alternative treatment is surgery of radioactive iodine [2].

Lugol's iodine has been used to prepare thyrotoxic patients undergoing thyroidectomy [7]. Lugol's iodine mode of action by a reduction in the rate of blood flow, thyroid vascularity and friability of the toxic thyroid gland resulting in reduced thyroid hormone production [11]. Iodine in supraphysiologic doses also acts to decrease the synthesis of new thyroid hormone (the Wolff–Chaikoff effect) and to decrease the release of preformed hormone from the thyroid. The Wolff–Chaikoff effect can be seen within 24 hours of iodine administration and is maximal at approximately 10 days of treatment [5]. Patients with normal thyroid reserve can escape from the Wolff–Chaikoff effect and resume thyroid hormone production. Hyperthyroid subjects, however, have abnormalities in iodine regulation and may use the excess iodine as a substrate for even more thyroid hormone production, resulting in worsening hyperthyroidism. As a result, iodine is generally not given in the absence of pretreatment with antithyroid drugs to prevent an iodine-induced thyrotoxicosis (the Jod–Basedow effect) [8].

Our index case was treated with Lugol`s iodine for short period of time in view of his low neutropenia count at diagnosis. It was felt that starting our patient on thionamides may risk exacerbating the neutropenia and therefore the treatment was perceived to be contraindicated at that time. He subsequently received carbimazole when his neutrophils counts returned to normal. Six months after the diagnosis he had a total thyroidectomy due to patient choice and he had no post operative metabolic complications.

The authors do not believe that the presence of neutropenia was an absolute contraindication for use of thionamides but the risk of agranulocytosis due to thionamides is well described and there is a real and absolute risk of inducing further neutropenia by thionamides, even if the risk was considerably low. It was however, also recognised that hyperthyroidism may worsen if thyroid escape from the Wolff-Chaikoff effect occur due to the use of iodine in the initial treatment and this was done with absolute caution.

This report highlights the use of Lugol's iodine in hyperthyroidism in a paediatric patient presenting with neutropenia. Although worsening of thyrotoxicosis with iodine as primary therapy could be deemed as unethical or untenable, there is strong evidence in the past, prior to the introduction of thionamides (pre 1940s) that suggests that the primary use of iodine in hyperthyroidism is safe and acceptable.

4. CONCLUSION

In cases where anti-thyroid thionamides are contraindicated due to the risk of side effects such as agranulocytosis or neutropenia, Lugol's iodine may be an alternative temporary form of first line therapy. Lugol's iodine leads to an initial reduction in organification and hormone synthesis and may be used with caution, in an acute short term treatment of thyrotoxicosis complicated by neutropenia.

CONSENT

All authors declare that 'written informed consent was obtained from the patient/guardian for publication of this case report.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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