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**Case report,**

# Neutropenia Associated with Methimazole Therapy in A 4.7-Year Girl with Graves' disease.

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## Introduction:

We present a case of neutropenia complicating methimazole therapy for Graves' disease in a 4.7-year child. The decreasing neutrophil count encountered 8 months of starting therapy, associated with losing the maintained euthyroid state, presented with the typical manifestations of neutropenia and improved rapidly after a 24 hour discontinuation of therapy followed by changing its frequency with the same dose.

## Case report:

A 4.7-year girl presented with the clinical picture of hyperthyroidism one year ago. At that time, she reported symptoms in the form of colicky abdominal pain, increased bowl motions, excessive sweating, sleep disturbances, bone pains and increased appetite. She had a family history of thyroid disorders in her aunt and grandmother. She was doing well before this presentation with smooth perinatal period, appropriate developmental milestones. By examination, she had mild bilateral eye protrusion; her heart rate was 130/min, otherwise vitally stable. Her height was 2.5 SDS, weight was 0.9 SDS, BMI was -1 SDS and bone age was 4 years. She had a smooth, moderate in size and non-tender goitre. She had one café au lait patch in her trunk. Her thyroid function at that time was: TSH: 0.01 uiu/ml, FT3: >20 pg. /ml, FT4: 3.3 ng/dl. She had high levels of anti-thyroglobulin and tissue peroxidase immunoglobulins. Her haemoglobin level was 11.3 gm/dl. Thyroid ultrasound showed heterogeneous echogenicity of the gland with increased vascularity, bone x ray showed no abnormality. Ionized ca was normal, gonadotrophins showed prepubertal level and she had normal morning cortisol level. Her basal ANC level and liver enzymes were within normal ranges. Medications in the form of methimazole (carbimazole) 0.8mg/kg/d divided every 8 hrs and propranolol 10 mg was started. Methimazole was increased to 1 Mg/kg/d after 2 months that controlled her symptoms of diarrhoea, sweating, sleep disturbance and bone pains. Her heart rate was stabilized on 90 beat/ min. Her condition was settled for about 8 months, she gained 1.5 kg body weight over this period.

Then she presented with an attack of bilateral parotitis associated with high grade fever and increasing eye protrusion and cervical lymphadenopathy. The attack responded rapidly to antibiotics, ophthalmological consultation was done, orbital CT revealed no retroorbital collections and artificial tears were added. At that time liver enzymes were normal, total leukocyte count (TLC) was 4400 cell/ul and absolute neutrophil count (ANC) was 413 cell/ul. Her CRP was 12 mg/l. Over the next month, another 2 attacks of high-grade fever, red eyes, pharyngitis and one oral ulcer with 2 weeks apart. Her TLC was 3500/ ul, ANC was 430/ ul. And hemoglobin was 12.7gm/dl. At that time, her thyroid function tests showed to be uncontrolled; her heart rate was 130 b/min. We needed to increase methimazole dose twice during these two months period. We stopped methimazole for just one day, ANC raised to be 900/ul with TLC 3500/ul. The day after, the patient was advised to take the whole dose of methimazole once in the morning instead of dividing it. Two days later, ANC was 1200 cell/ul, and further 4 days, it reached 3300/ul with TLC 7100/ul.

**Table (1): Blood cell counts during the period of neutropenia:**

| | 8\10\2019 | 9\10\2019 | 12\10\2019 | 16\10\2019 |
|---|---|---|---|---|
| **Haemoglobin (gm\dl)** | 12.7 | 13.3 | 11.6 | 13.8 |
| **Platelets ($\times10^3$\ul)** | 301 | 235 | 203 | 439 |
| **White cell count (WBC) ($\times10^3$\ul)** | 3.5 | 3.5 | 4.48 | 7.1 |
| **Absolute neutrophil count (ANC) (cell\ul)** | 413 | 900 | 1200 | 3300 |

## Discussion:

This is a case of Graves' disease in a 4.7-year child complicated by neutropenia after about 8 months of methimazole therapy. According to the American Academy of Pediatrics (AAP), Graves' disease is the most frequent cause of hyperthyroidism in children being charged for about 96% of cases (1). For diagnosis, thyroid function tests in the form of thyrotropin, free triiodothyronine and free thyroxine levels confirm hyperthyroidism. Thyroid stimulating antibodies confirm the immune process implicated in Graves ' disease, and radionuclide scan may be used to differentiate graves' disease from other causes of hyperthyroidism like subacute thyroiditis. Treatment options include antithyroid medications that are still the first line of therapy, radioactive iodine that is not preferred in young ages and surgery in case of failure of medical treatment(1). Methimazole is considered a first line anti thyroid medication with a dose ranging from 0.1 to 1 mg/d with a maximum dose of 30 mg/d. It inhibits thyroid hormone synthesis via blocking thyroid peroxidase, and consequently the iodination of the tyrosine residues in the thyroglobulin essential for the production of thyroxine and triiodothyronine(2). Minor adverse effects including skin rash, myalgia, nausea, arthralgia and abnormal taste sensation can occur. In about 2% of cases major adverse reactions to methimazole include agranulocytosis, hepatitis, liver failure and vasculitis with a lupus-like syndrome. These can occur usually within the first 6 months of therapy but can develop later(3).

In one study in adults, severe drug induced neutropenia was estimated to be about 0.35% (4).

To our knowledge, the cut-off point of severe neutropenia associated with antithyroid therapy is not defined, however in adults it is usually to be defined as ANC<500 cell/ ul associated with clinical manifestations like fever, sore throat and oral ulcers(5). Our case had bilateral parotitis, fever, sore throat and one oral ulcer associated with decreasing neutropenic count and reached an ANC nadir level of 431 cell/ ul. A number of mechanisms were proposed for explaining neutropenia in these circumstances, of these, autoimmunity, hapten mediated autoantibodies and toxic effect of the medication on bone marrow(6). We suggest that the mechanism involved in our case was a toxic effect on bone marrow as an improvement in all blood elements was observed following our intervention, as shown in table (1). As regard the timing of neutropenia occurrence, it is very variable in the documented literature ranging from few days to many years after starting the therapy(6, 7), in our case it occurred 8 months after initiation of methimazole therapy.It is highly recommended that methimazole should be discontinued when agranulocytosis ensues and radioactive iodine or surgery should be considered. Copper (8) suggested the cut-off point to discontinue the medication is <1000/ul while just closely monitor if the ANC between 1000 and 1500/ul. The time suggested for the recovery of neutrophil count was 10 days by some authors (9). In one case report the neutrophil count of a neonate treated for hyperthyroidism reached a nadir of about 800/ul after 20 days of therapy and started to recover within 10 days of a weaning protocol decreasing 20% of the dose every 2-3 days without discontinuation for being still in the hyperthyroid state, giving the medication in a 3 divided doses(5). Our patient had deterioration in the control of her euthyroid state coincident with the neutropenia and its manifestations. It was not feasible to stop the drug completely, so it was just a 24 hour of stoppage of methimazole when the count rose from 431 to 900/ul, then we started giving the whole dose once in the morning, two days later the count reached 1200/ul, further 4 days an improvement in all blood elements was noticed with neutrophil count 3300/ul. Based on this observation we suggest that toxic suppression of

bone marrow is the implicated mechanism of neutropenia associated with methimazole. We suggest also that changing the timing of giving the dose may have a favourable effect on bone marrow suppression.

## Conclusions:

A decreasing neutrophil count can complicate methimazole therapy for Graves' disease in children. This can occur at any time during the therapy manifesting by fever, oral ulcers, sore throat, congested eyes or parotitis. This presentation can be associated with the derangement in thyroid function control. Regular monitoring and early recognition of neutrophil count disturbance can be lifesaving. Either discontinuation of therapy if feasible, gradual weaning from the medication or changing the frequency of its administration are adopted solutions.

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