CCTC Clinical Chemistry Trainee Council | AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

www.traineecouncil.org

TITLE: Hypothyroidism

PRESENTER: Zahra Shajani-Yi

Slide 1:

Hello, my name is Zahra Shajani Yi and I am a second year clinical chemistry fellow at Dartmouth-Hitchcock Medical Center. Welcome to this Pearl of Laboratory Medicine on hypothyroidism.

Slide 2:

Hypothyroidism is defined as a deficiency of thyroid action and secretion and affects 1-5% of the population. It is more prevalent in women and the risk of developing hypothyroidism increases with age. Diagnosis of hypothyroidism is based primarily upon laboratory testing due to the lack of specificity of the clinical symptoms.

Slide 3:

Hypothyroidism causes a generalized slowing of metabolic processes leading to fatigue, lethargy, weight gain and intolerance to the cold. Hypo-metabolism also leads to a reduction in cardiac output resulting in decreased exercise capacity and dyspnea while exercising. Other symptoms include muscle weakness, hair loss and hoarseness. Hypothyroidism also has implications for reproduction and can cause menstrual abnormalities and infertility. In children, untreated hypothyroidism can lead to delayed puberty, mental delay and growth failure.

Slide 4:

Some of the clinical signs of hypothyroidism include bradycardia, goiter, hypotension and puffy eyes. Skin changes include coolness, dry skin, mild jaundice and non-pitting edema. In more severe cases myopathy can develop, there is delayed bone age in children and even congestive

heart failure and coma. Hypothyroidism has a heterogeneous presentation and different patients will present with different clinical symptoms and signs. These symptoms are non-specific and highlight the importance of laboratory testing to make a definitive diagnosis.

Slide 5:

Synthesis and secretion of thyroid hormones is controlled by a negative feedback system that involves the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin releasing hormone or TRH which subsequently signals the anterior pituitary to release thyroid stimulating hormone, or TSH. TSH in turn stimulates the thyroid to produce primarily T4, and a smaller concentration of T3. In other hypothalamic-pituitary-target organ axes, the hypothalamus is the major site of negative hormone feedback; however, in the HPT axis, the major site of negative feedback is the anterior pituitary. This continuous negative feedback mechanism between the thyroid gland and the pituitary keeps free T4 concentrations within the physiologically appropriate range and prevents uncontrolled production of T4 and T3. High free T4 concentrations suppress TSH production from the pituitary and low TSH concentrations result in decreased production of T4 and T3 by the thyroid.

Slide 6:

In primary hypothyroidism the thyroid gland cannot synthesize and release the appropriate concentrations of T4 and T3. In order to compensate for these low concentrations, the feedback mechanism described in the previous slides causes an increase in secretion of TSH and to a lesser extent TRH.

Slide 7:

Unlike primary hypothyroidism, central hypothyroidism is not due to thyroid dysfunction. It is caused by insufficient stimulation of the thyroid gland by TSH. This leads to inappropriately low levels of thyroid hormone. As the levels of T4 secretion fall, TSH secretion does not suitably increase. In order to make a diagnosis, measurement of free T4 in serum and clinical symptoms of hypothyroidism must be used. Central hypothyroidism can be further divided into two categories. In secondary hypothyroidism the pituitary is the source of dysfunction. Isolated pituitary TSH deficiency is rare and most patients with TSH deficiency also have deficiencies in other pituitary hormones.

Slide 8:

In tertiary hypothyroidism, hypothalamic disease or a disorder of the hypothalamic-pituitary portal system leads to TRH deficiency, causing a reduction in TSH release and subsequently a decline in T4 and T3 synthesis.

Slide 9:

Subclinical hypothyroidism is defined as a persistent elevation of TSH in the setting of normal free T4 values. It is very common and affects 3-8% of the population. Patients with subclinical hypothyroidism are at risk for developing overt hypothyroidism, with 2-4% of subjects with subclinical hypothyroidism going on to develop primary hypothyroidism each year.

Slide 10:

This disorder is very common and increases with age. The risk for developing overt hypothyroidism increases with TSH concentration and the presence of anti-thyroid peroxidase antibodies. Patients with TSH values above 10mIU/L are treated with thyroid hormone replacement in an effort to reduce TSH values to within the reference interval. Patients with ovulatory dysfunction or infertility who are attempting pregnancy are also advised for T4 replacement if TSH concentrations are above the first-trimester-specific normal reference range even if free T4 values are in the normal range. For patients with TSH values above the reference interval but below 10 mIU/L, treatment remains controversial.

Slide 11:

Primary hypothyroidism is characterized by a high serum thyroid-stimulating hormone (TSH) concentration and a low serum free thyroxine (T4) concentration. Central hypothyroidism is characterized by a low serum T4 concentration and a serum TSH concentration that is not appropriately elevated. Subclinical hypothyroidism is defined as having high TSH values but normal thyroid hormone levels and patients with subclinical hypothyroidism are at risk for developing primary hypothyroidism. You may sometimes see primary hypothyroidism divided into two subclasses: subclinical and overt. Primary hypothyroidism is far more common the secondary or tertiary hypothyroidism and accounts for 95% of hypothyroidism cases.

Slide 12:

The causes of primary hypothyroidism can be divided into two categories. The first are endogenous disorders: these develop within the patient. Autoimmune thyroid disease is the most common cause of primary hypothyroidism in the developed world. Hashimoto's thyroiditis and postpartum thyroiditis are two of the main causes of Autoimmune thyroid disease. Congenital hypothyroidism is one of the most common congenital endocrine disorders and leads to intellectual disability if left untreated. Consumptive hypothyroidism is a very rare form of hypothyroidism that has been found in patients with certain types of ectopic tumors that produce type 3 deiodinase which degrades thyroid hormones. Exogenous disorders are conditions that originate outside of the patient and the most common cause in the world is iodine deficiency. Iodine excess, certain medications, surgical removal of the thyroid gland and radiation therapy can also cause primary hypothyroidism. Viral and bacterial thyroiditis is a rare cause of primary hypothyroidism. Over the next few slides we will be discussing the more common causes of primary hypothyroidism.

Slide 13:

Hashimoto's thyroiditis leads to the destruction of the thyroid follicular cells and is also referred to as chronic autoimmune thyroiditis. Lymphocytes and plasma cells infiltrate the thyroid gland and cause the gland to enlarge. >90% of patients have auto-antibodies to thyroid peroxidase or TPO or thyroglobulin or Tg. Interestingly Hashimoto thyroiditis may initially present as transient hyperthyroidism as the destruction of the thyroid follicular cells leads to a sudden release of thyroid hormone. This phenomenon is known as Hashitoxicosis.

Slide 14:

Postpartum thyroiditis is a variant of autoimmune hypothyroidism and is a consequence of a decline in immunosuppression after delivery. It can present as transient hypothyroidism, transient hyperthyroidism or hyperthyroidism followed by a period of hypothyroidism. Most women recover and are euthyroid within one year postpartum. Unfortunately, some women never recover from the initial hypothyroid phase and have permanent hypothyroidism or goiter. Postpartum thyroiditis affects about 5% of all pregnancies and nearly 10% of pregnancies in women who have type 1 diabetes. Women with TPO antibodies are at an increased risk for developing postpartum thyroiditis.

Slide 15:

The incidence of congenital hypothyroidism ranges from 1 in 2000 to 1 in 4000. The major cause of congenital hypothyroidism is abnormal development of the thyroid gland or thyroid dysgenesis. Other causes of congenital hypothyroidism include inborn errors of thyroid hormone biosynthesis or dyshormonogensis and hypothalmic or pituitary abnormalities. Untreated, congenital hypothyroidism leads to intellectual disability and earlier intervention improves clinical outcomes. At birth, less then 5% of infants with congenital hypothyroidism have clinical symptoms of hypothyroidism as maternal T4 can cross the placenta, which highlights the need for newborn screening. Dried blood spot screening for congenital hypothyroidism can either begin by measuring T4 concentration with follow up testing of TSH if the T4 concentration is below a certain predetermined cutoff. This test will miss cases of subclinical hypothyroidism. Some newborn screening programs employ an initial TSH assay with follow up confirmatory testing for patients with elevated TSH concentrations. These screening programs will miss the rare cares of congenital central hypothyroidism.

Slide 16:

Iodine deficiency is the most common cause of hypothyroidism in non-developed countries and the most common cause of goiter. It can cause maternal hypothyroidism which is harmful for the fetus. During the first half of pregnancy the fetus is dependent on the mother for its supply of thyroid hormone. Paradoxically, iodine excess can also cause hypothyroidism. This is known as the Wolff–Chaikoff effect. Organification of iodide, the synthesis of thyroid hormones inside the thyroid follicle and the release of these hormones into the bloodstream are all inhibited. The Wolff–Chaikoff effect is an auto-regulatory mechanism that prevents the thyroid from synthesizing large quantities of thyroid hormone in the presence of excess iodide. Patients with a normal thyroid gland will recover from this inhibitory effect after approximately 10 days but patients with underlying thyroid disease can develop permanent hypothyroidism.

Slide 17:

Central hypothyroidism is much less common than primary hypothyroidism. Isolated pituitary TSH deficiency is rare and most patients with TSH deficiency also have deficiencies in other pituitary hormones. This is known as panhypopituitarism. Some of the causes of central hypothyroidism are tumors, trauma, post-surgical and post-infection damage that interfere with TSH or TRH secretion, or subarachnoid hemorrhage. Central hypothyroidism should be suspected when there is a mass present in the pituitary, known hypothalamic or pituitary disease or when other endocrine hormonal deficiencies are present. There are a few very rare hereditary disorders that can also cause hypopituitarism and TSH deficiencies.

Slide 18:

The goal of therapy is to have patients return to a euthyroid state, a normalization of TSH secretion and elimination of clinical symptoms. Unless the cause of the hypothyroidism is transient, treatment is life-long oral administration of synthetic T4 also known as levothyroxine. After identification of the proper maintenance dose, the patient should be examined and serum TSH measured once yearly, or more often if there is an abnormal result or a change in the patient's status. If the patient gains or loses weight or becomes pregnant the maintenance dose may need to be adjusted. Successful treatment reverses all the symptoms and signs of hypothyroidism. The overall prognosis is excellent with little to no increase in mortality among patients who are properly treated.

Slide 19:

In summary, hypothyroidism is a deficiency in thyroid hormone secretion and action. It can be caused by deficiencies of the thyroid gland, pituitary gland, hypothalamus or hypothalamus-portal system. The clinical signs and symptoms of hypothyroidism can be non-specific and vary between patients making laboratory testing of TSH, free T4 and the presence of thyroid auto-antibodies essential in establishing a diagnosis and in monitoring treatment.

Slide 20: References

Slide 21: Disclosures

Slide 22: Thank You from www.TraineeCouncil.org

Thank you for participating in this Clinical Chemistry Trainee Pearl of Laboratory Medicine.