

Thyroid Autoimmunity

Understanding our immune system

The immune system

The immune system, which has evolved to protect us from foreign proteins such as bacteria and viruses, is complex, comprising antibodies in the blood which are produced by one type of white blood cells called B lymphocytes. These cells mature into plasma cells and various other white blood cells including T lymphocytes, killer cells, suppressor cells and regulating cells, which reside in the lymph nodes and bone marrow. Although serum antibodies are good markers of the autoimmune process - since they can be easily measured in the blood in a variety of antibody tests such as ELISA, it is usually the white blood cells, in particular the T lymphocytes which cause cell and tissue damage. T lymphocytes, including the cytotoxic T lymphocytes, produce a variety of proteins and other soluble peptides which act in a complex manner to lead to cell death.

Autoimmunity

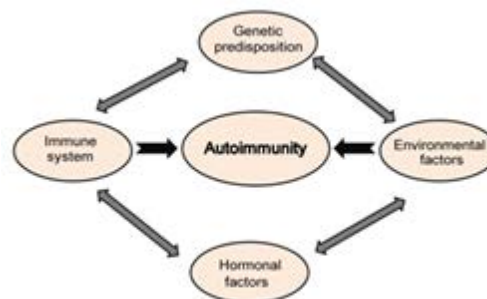
Hashimoto's thyroiditis, which leads to hypothyroidism, and Graves' disease, which leads to hyperthyroidism and the associated eye changes (referred to as 'ophthalmopathy'), are "organ-specific autoimmune disorders" of the thyroid gland. With these disorders, the immune system reacts against the body's own antigens. This leads to a focused destructive reaction within the thyroid gland. In the case of Hashimoto's thyroiditis, it leads to a focused destructive reaction within the thyroid gland. In the case of Graves' disease it leads to stimulation of the thyroid cells due to the production of a unique antibody called TSH-receptor antibody.

Other organ-specific autoimmune disorders include:

- Addison's disease, in which destruction of the adrenal gland leads to deficiency of cortisone
- Type 1 diabetes where antibodies and lymphocytes target those pancreatic islet cells which produce insulin, leading to insulin deficiency, increased blood sugar and the characteristic features of diabetes of youth
- psoriasis
- vitiligo and
- celiac disease

When the immune reactions affect more than one tissue or cell type, this is termed "multi-system autoimmune disease" and these include systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma and Sjogren's Syndrome.

The autoimmune reaction, of which thyroid autoimmunity is a good model, was originally considered to be impossible but in reality, this process is very common. For example, Hashimoto's thyroiditis affects about 8% of all adult women and 1% of men and Graves' disease affects about 1% of adults. There are combinations of these organ-specific autoimmune disorders; for example 25% of patients with type 1 diabetes also have autoimmune thyroid disease and there are well known associations between Addison's disease, hypothyroidism, pernicious anaemia and type 1 diabetes. However, for most patients with autoimmune thyroid disease, their life time chance of developing one or other of these other disorders is very small.



Thyroid autoimmunity is not genetically determined, but the tendency to develop Graves' disease and Hashimoto's thyroiditis (and other autoimmunity conditions) runs in families. The onset of autoimmune disease involves a second factor, such as stress, infection and other environmental factors that trigger the autoimmune reactions in the thyroid gland in predisposed subjects. Despite the central role of genetic predisposition in this process, interplay between genetic and non-genetic factors seems essential for the development of the full-scale autoimmune reaction. The presence of one factor without the other may not be sufficient for the development of full-scale human autoimmunity.

The role of stress

As demonstrated above, the development of autoimmunity in humans is the endpoint of a complex process involving the immune system, hormonal factors and environmental factors in a genetically predisposed individual, hence the term 'mosaic of autoimmunity'. The evidence for stress contributing to the onset and course of autoimmune disease is circumstantial and the mechanisms by which stress affects autoimmune disease remain poorly understood. The best evidence for an effect of stress on the development of an autoimmune disorder is the well-known relationship between the clinical onset of Graves' hyperthyroidism, and its subsequent clinical course, and major stress in the preceding 2-3 months. When patients with Graves' disease are treated for a year with anti-thyroid drugs they become well and go into remission, and may remain well for many years, but sometimes the disease relapses, usually due to major stress. In the case of Hashimoto's thyroiditis, stress is probably important but less readily identified since the disease is slowly progressive and asymptomatic over many years before the development of hypothyroidism. Stress may be the major environmental factor in most patients who develop Graves' hyperthyroidism but there are other factors as well such as smoking, vitamin D deficiency and infections. Although future studies to tease out the role of all of these components will be difficult, they must be carried out and we need to be patient.

Antibodies and Autoimmunity

Hashimoto's thyroiditis

In the case of Hashimoto's thyroiditis, antibodies react against two main proteins, thyroglobulin (TG), a large protein in the thyroid gland which stores thyroid hormones, and thyroid peroxidase (TPO), an enzyme located on the surface of the thyroid follicular cells. The antibodies are reliable clinical markers of the process but thyroid cell and tissue destruction in Hashimoto's thyroiditis is probably due to an effect of cytotoxic T cells, even though this has not been well studied nor convincingly demonstrated. The autoimmune process in Hashimoto's thyroiditis is progressive and extends over many years so that there may be long intervals between the detection of antibodies against TG and TPO and the development of hypothyroidism, which occurs when sufficient numbers of thyroid follicular cells have been destroyed by the inflammatory reaction leading to thyroid

hormone deficiency. Real-time thyroid ultrasonography reveals the characteristic black spaces, scarring and so-called pseudo nodules in patients with end stage disease.

Because of the classical feedback relationship between pituitary thyroid stimulating hormone (TSH) and T4 and T3 produced by the thyroid gland, the pituitary recognises decreasing production of thyroid hormones and produces more TSH to "fire up" the failing thyroid gland. When patients have reached a certain threshold they develop symptoms of hypothyroidism such as tiredness, fatigue, tendency to gain weight / inability to lose weight and puffiness of the face. This process is progressive and the symptoms worsen if left untreated.

Graves' disease

Graves' disease is unique in that the disease is caused by an antibody which stimulates the TSH receptor, a protein on the surface of the thyroid follicular cell which binds TSH. TSH stimulates the thyroid cells to produce thyroid hormones while antibodies against the TSH receptor do the same thing, so they compete with TSH on the cell surface. They bind more intensely than TSH and eventually lead to overstimulation of the thyroid cells which become enlarged and divide and produce more and more thyroxin and T3, leading to the symptoms of hyperthyroidism which include increased heart rate, anxiety, heat intolerance, sweatiness, increase in appetite and weight loss.



Ophthalmopathy

The associated abnormalities in Graves' disease as described by Robert Graves himself include "poppy eyes", or ophthalmopathy, a lumpy thickening of the skin called pretibial myxoedema and inflammation and swelling of the long bones in the hands and arms, and clubbing, called acropachy. These associations occur in patients with more severe disease, so that the great majority of patients with pretibial myxoedema and acropachy will have ophthalmopathy and severe

hyperthyroidism. The immune reactions are different but somehow related to each other. The eye disorder is particularly important because some patients have distressing eye symptoms such as double vision, blurring of vision and cosmetic concerns. The appearance of “poppy eyes” (as seen above and below) are due to 1) upper eyelid retraction which results from the hyperthyroidism itself and 2) inflammation of the eye muscles and surrounding fatty tissues (referred to as ‘true ophthalmopathy’). Intense studies carried out over many years point to a reaction of antibodies against the TSH-receptor, which is also found in the orbital fatty tissue, although the evidence linking the development of the eye disorder with TSH-receptor antibodies is mainly circumstantial. The author has studied the role of antibodies against eye muscle proteins including calsequestrin and flavoprotein, which may be produced only after the eye muscle fibre has been damaged. Recent studies suggest that TSH-receptor antibodies are not found in patients with ophthalmopathy who have normal thyroid function not associated with thyroid dysfunction or thyroid autoimmunity, so-called euthyroid Graves’ disease.



Treatment

Studies carried out over decades addressing the different aspects of the autoimmune reaction are ongoing, but in the case of thyroid autoimmunity, few advances have been made because the treatment is straightforward and not directed towards the immune abnormalities themselves. Other organ-specific autoimmune disorders such as type 1 diabetes, myasthenia gravis and multiple sclerosis are much more problematic and research is necessary to lead to the discovery of specific therapies for these serious and often life-threatening diseases. Although research continues into aspects of the cause of the disease such as the effects of infection and stress, and the relationship between the brain and the immune reaction, treatment is limited to either replacing thyroxin, in hypothyroidism, or

removing, blocking or destroying the thyroid gland, in Graves’ hyperthyroidism.

We do not treat with steroids or immunosuppressive agents because of side effects and, in the long term, it is unlikely that we would ever aim to treat the immune disorder itself unless very specific agents which block the thyroid autoimmune reaction are discovered. In ophthalmopathy, the autoimmune reaction is directed against the eye muscles and the surrounding connective and fatty tissue. This is a complex disorder, somehow linked to the thyroid reaction. In this serious disorder, we do sometimes treat with immunosuppressive drugs or steroids and even radiotherapy and surgery if there is loss of vision. Life-threatening diseases such as multiple sclerosis and type 1 diabetes require more intense and specific therapies with attempts to suppress the immune reaction which is causing tissue damage, whereas in Graves’ disease we use anti-thyroid drugs to block the overproduction of the thyroid hormone and in Hashimoto’s thyroiditis we use thyroxin replacement to compensate for the decreased production of thyroid hormones.

Finally, one might ask – why does treatment of hyperthyroidism with Carbimazole or Propylthiouracil for one year or more lead to long-term remission of the Graves’ disease? Anti-thyroid drugs do have some immunosuppressive role, but there is also a non-specific effect of the hyperthyroidism itself on the immune system which decreases as the hyperthyroidism is reduced with treatment and the patient may remain well for many years. On the other hand, radio-active iodine destroys, and thyroidectomy removes, the thyroid tissue including the proteins which are the target of the antibodies and cytotoxic white blood cells, so the autoimmune reactions cannot continue. Following these procedures, patients become hypothyroid and need to be given full replacement doses of thyroxin which are taken long term.

Sex hormones and autoimmunity

Thyroid autoimmunity, and indeed most other autoimmune disorders except type 1 diabetes, occurs more commonly in women than men. Adding to the complex mix of the factors which lead to the development of autoimmune disease are the androgens and estrogens (or sex hormones). Estrogens in females

somehow favour the development of autoimmunity and androgens may protect, but this is much more complex and involves other factors as well, such as genes on the X chromosome. When thyroid autoimmunity occurs in males, the genetic factor tends to be more evident i.e. there is often a strong family history of thyroid autoimmunity, lupus, rheumatoid arthritis or other autoimmune disorders in their first degree relatives.

Conclusion

Thyroid autoimmunity is common but generally easily managed and we do not need to worry about the underlying cause or role of genetics. We should not have our children checked “for thyroid disease” unless they have symptoms and we must somehow teach them how to deal with major stresses. Good luck with that!

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