Epidemiology and Pathophysiology of Benign Thyroid Diseases

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Epidemiology and pathophysiology of benign thyroid diseases are presented as a basis for the understanding of rational diagnosis and therapy. The discussion is focused mainly on those benign thyroid diseases which are most relevant in nuclear medicine, i.e. benign nodular and diffuse goiter as well as the various types of hyperthyroidism.

Epidemiology

Goiter: In iodine-deficient areas, goiter prevalence may be as high as 80%. After correction of iodine deficiency, prevalence decreases slowly over a generation’s time to but not below a few per cent. In iodine-sufficient areas, cross-sectional studies showed a decline in frequency of diffuse goiter and, in contrast, an increase of thyroid nodules and thyroid antibodies with age. For prevalence of diffuse goiter, the ratio of women to men is at least 4:1.

Hyperthyroidism: In iodine-sufficient areas, Graves’ disease is the most frequent cause of hyperthyroidism and accounts for about 70% of the cases. Its prevalence may be as high as 1%. In areas with actual or recent iodine deficiency, Plummer’s disease is more frequent due to a much higher prevalence of nodular goiter. Prevalence and incidence of thyrotoxicosis is higher in females than in males by a factor of 5 to 10.

Pathophysiology

Goiter: The basic process in goiter formation is the generation of new follicular cells, which are used either to form new follicles or to enlarge the size of the follicles. The driving force behind goiter growth is the intrinsically abnormal growth potential of a small fraction of thyroid cells, the same way as in other benign tumors. Genetic, endogenous and environmental factors may act on this basic process and thereby accelerate goiter growth. TSH is the most important stimulating factor of thyroid growth and function. A number of growth-stimulating factors such as EGF, IGF-I, FGF-1 and FGF-2 as well as growth-inhibiting factors such as transforming growth factor-β and activin A play a role, too. Iodine is an important modulator of thyroid growth and function acting by direct (autoregulatory) and indirect (TSH) mechanisms.

Nearly all long-standing goiters and even most normal thyroids become nodular with time. In most cases, no morphologic, functional, or biochemical characteristic clearly distinguishes these nodules from extranodular tissue. Thyroidal nodule formation can be explained by three mechanisms: The presence of thyrocyte subpopulations and their tendency to remain clustered cause uneven proliferation within the thyroid gland and lead to focal hyperplasia or nodular transformation over the years. Another mechanism is somatic mutation conferring a heritable growth advantage to a single cell and finally resulting in the formation of a clonal tumor, for example a toxic adenoma caused by an activating TSH-receptor mutation. A third mechanism is the nodular growth pattern caused by the network of fibrous strands resulting from the scarring necrosis and hemorrhage that occur in most growing goiters.

Hyperthyroidism: The overall hormone production by any nodular goitre depends on the number of new follicles and on their functional activity. In Plummer’s disease, thyrotoxicosis develops only slowly over years or decades, contrary to the rapid appearance of Graves’ disease, which is caused by an autoimmune reaction to the thyroid leading to the production of stimulating autoantibodies to the TSH receptor. So called toxic adenoma is in many cases caused by activating TSH receptor mutations. Due to their pathophysiological characteristics, Plummer’s disease and toxic adenoma are slowly but steadily progressing, whereas Graves’ disease leads to a single episode of hyperthyroidism in the minority of cases and in majority either to prolonged continuous episodes of hyperthyroidism or to a relapsing and remitting course undulating over a long time.