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Nuclear Medicine Imaging and Therapy: Gender Biases in Disease

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Gender-based medicine is medical research and care conducted with conscious consideration of the sex and gender differences of subjects and patients. This issue of Seminars is focused on diseases for which nuclear medicine is part of routine management and for which the diseases have sex- or gender-based differences that affect incidence or pathophysiology and that thus have differences that can potentially affect the results of the relevant nuclear medicine studies. In this first article, we discuss neurologic diseases, certain gastrointestinal conditions, and thyroid conditions. The discussion is in the context of those sex- or gender-based aspects of these diseases that should be considered in the performance, interpretation, and reporting of the relevant nuclear medicine studies. Cardiovascular diseases, gynecologic diseases, bone conditions such as osteoporosis, pediatric occurrences of some diseases, human immunodeficiency virus–related conditions, and the radiation dose considerations of nuclear medicine studies are discussed in the other articles in this issue.
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Introduction

Sex-based differences in disease are those related to biological and physiological factors (chromosomes, gonads, and hormones), whereas gender-based differences are those related to sociocultural, behavioral, and psychological factors. In gender-based medicine (also known as gender-biased medicine), issues such as how sex- and gender-based differences affect the natural history of a disease and the prognosis, treatment response, and outcome in management of a disease are considered. Nuclear medicine should be practiced as gender-based medicine, particularly in the management of certain diseases and when a practitioner seeks to apply personalized interventions, targeted therapies, and individualized preventions.

Thyroid Disease

Thyroid disease, including hypothyroidism, hyperthyroidism, and thyroid cancer, is, in general, 3-5 times more common in women than in men. The natural history, severity, and response to therapy of thyroid conditions differ between the sexes. The role of nuclear medicine for thyrotoxicosis and thyroid cancer includes diagnostic imaging and thyroid uptake in benign conditions using sodium iodide-123 (^{123}I) and technetium 99m (^{99m}Tc)-pertechnetate. ^{131}I is used for imaging and therapy of patients with thyroid cancer after surgical thyroidectomy. At times, imaging may also include SPECT/CT with the aforementioned isotopes or PET/CT with ^{18}F-FDG.[1]

Hypothyroidism and Goiter

In iodine-depleted regions of the world, goiter is endemic. In regions where iodine deficiency is not an issue, the prevalence of spontaneous hypothyroidism is 1%-2%.[2] Subclinical hypothyroidism is more common in elderly women and 10 times more common in women than in men. The greatest prevalence of goiter is in premenopausal women, and the ratio of women to men is at least 4:1.[3] Further, it has been observed that women have a significantly higher prevalence of palpable goiter than men do.[4]

Imaging with ^{123}I and ^{99m}Tc-pertechnetate is sometimes performed using a pinhole collimator on the scintillation camera. This imaging is performed with the objective of enlarging small regions of the thyroid gland in patients with goiter and thyroid nodules. If thyroid nodules are palpated or if there is a goiter, thyroid scintigraphy is used to characterize nodules as hypofunctioning, hyperfunctioning, or normal.

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Cold or hypofunctioning nodules are found to be malignant in 5%-35% of cases. They are often correlated with ultrasound images for biopsy.[1]

Thyroid scintigraphy is useful for evaluation of other disorders such as thyroid dysgenesis, including ectopic thyroid tissue. Such disorders are more frequent in childhood and are discussed in more detail in the article on pediatrics in this issue. Lingual thyroid is more prevalent in young adult women (4-7 times more frequent in women than in men). Planar and SPECT/CT are useful tools to evaluate lingual thyroid and other types of thyroid dysgenesis, particularly SPECT/CT, if it is determined that both anatomical and functional data would be useful.[5]

Hyperthyroidism and Graves Disease

Gender-Focused Epidemiology in Graves Disease

Parry, Graves,[6] and von Basedow[7] (in the mid-1800s) made the earliest descriptions of patients with thyrotoxicosis. Their descriptions of such disease were exclusively in women.[8]

Graves disease is seen in 0.5%-1% of the population, with a female-to-male preponderance of 5:1 to 10:1.[2,9,10] It presents most commonly in the fourth decade of life. The strongest known risk factor is a family history of disease, seen in approximately 50% of patients.[9,10] Autoimmune processes, including Graves disease, are in general more common in women.[11,12] The fact that the phenomenon of autoimmune processes is more common in women has been postulated to be related to sexual dimorphism in the immune response and the influence of sex hormones.[13]

The etiology of Graves disease is multifactorial, encompassing genetic and environmental factors. In addition to female disease preponderance, it is well accepted that part of the genetic component of the inheritance pattern involves human leukocyte antigen genes, which encode for immune response–related proteins. The genes associated with the development of Graves disease are being studied. One of the most relevant is cytotoxic T-lymphocyte antigen 4. This is a negative regulatory molecule of the immune system that inhibits T-cell responses. It has been associated with many other autoimmune diseases.[9,10] Research is also underway in the area of X chromosome inactivation as one of the factors influencing the female preponderance of Graves disease.[10,14]

Toxic multinodular goiter or autonomously functioning thyroid adenomas are also predominately seen in the female population; however, available data regarding gender prevalence are lacking.[3]

Thyroid-associated ophthalmopathy is the most common extrathyroidal manifestation of Graves disease. It occurs in 3%-5% of patients with Graves disease. It has been described as more frequent in female patients, with a rate of 16 per 100,000 per year for women, as opposed to 2.9 cases per 100,000 per year for men. Severe graves ophthalmopathy is more frequent in male patients older than 60 years and in male or female patients who smoke cigarettes.[8,15]

Nuclear Medicine Imaging in Graves Disease

Imaging with ^{123}I and ^{99m}Tc-pertechnetate using a pinhole collimator on the scintillation camera has been used in the workup of hyperthyroidism and Graves disease. If ^{123}I is used, a study protocol generally provides iodine uptake values at 4-6 and 24 hours, (normal uptake is 10%-30% at 24 hours and less than 16% at 4 hours).[16] ^{123}I is preferred over ^{99m}Tc-pertechnetate because ^{123}I is trapped and organified within the gland vs only trapping with ^{99m}Tc-pertechnetate. The uptake measurement is an important component for the differential diagnosis of hyperthyroidism. If the uptake at 24 hours is high, Graves disease is more likely than toxic nodular goiter. If the uptake is significantly low, subacute, postpartum thyroiditis or amiodarone toxicity should be considered. The pattern of iodine distribution and the size estimate of the gland are important for patient management.[1,17]

Radioiodine Therapy Considerations in Graves Disease

Permanent therapy with ^{131}I is a valuable noninvasive approach and an alternative to thyroid surgery or antithyroid medications. Calculation of appropriate doses for such therapies (there are several algorithms in use to accomplish this) requires appropriate information from thyroid uptake and thyroid imaging studies. Radiation safety precautions focus mainly on avoiding unnecessary exposures to family members and the public, particularly on limiting exposures to young children and pregnant women to levels <5 mSv (0.5 rem).[18] In general, higher and faster cure rates for Graves disease are seen with orally administered doses of 15 mCi or more. Toxic multinodular goiter is usually treated with higher doses of 25-30 mCi.[19] Women have a higher cure rate for Graves disease with radioactive iodine than men do.[4]

The only significant side effect of using ^{131}I for permanent thyroid gland destruction is the gland destruction, which requires that a patient take thyroid hormone replacement for the rest of her or his life. Surgery is an alternative; it has the risk of hypoparathyroidism, recurrent laryngeal nerve injury that may result in vocal cord paresis or paralysis, bleeding, and anesthesia-related risks.[20,21] Antithyroid medications have the risks of aplastic anemias and frequent recurrence of the disease if stopped.[22,23]

Thyroid Cancer

Gender-Focused Epidemiology in Thyroid Cancer

The incidence of thyroid cancer has increased in the last 30 years. The estimates for 2014 from the American Cancer Society are 62,980 new cases of thyroid cancer (47,790 in women and 15,190 in men). Although the death rate due to thyroid cancer is and has been low for many years, it is estimated that there will be approximately 1890 deaths due to thyroid cancer (1060 women and 830 men) in 2014.[24] Although this malignancy is more prevalent in women, men have a higher rate of poor prognosis.[25] The causes for the well-known gender bias in thyroid cancer incidence remain unclear. Several mechanisms have been postulated as possible contributing factors. Androgen receptor and testosterone levels have been suggested as possible mechanisms, although such mechanisms are not well understood.[26] Animal studies suggest that estradiol may influence the increase in size and function of the thyroid gland.[27,28]