International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 26-12-2018; Accepted: 30-01-2019
www.medicalsciencejournal.com
Volume 5; Issue 2; February 2019; Page No. 142-145

Clinical assessment of endocrine gland neoplasms excluding thyroid in patients from Bihar region

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Abstract
Tumours of endocrine glands, although rare in the context of the overall burden of oncological disease, have provided important insights into the mechanisms of sporadic and familial tumour formation, with an overt incidence of 0.6–1.5 per 100 000 per year. Other malignant endocrine tumours, including adrenocortical carcinoma, carcinoid and other neuroendocrine tumours are extremely rare, with incidence figures of less than 0.5 in 100000 per year. Hence the present study was planned to evaluate the endocrine gland neoplasms excluding thyroid.
The present study was planned in the Department of Pathology, Patna Medical College and Hospital, Patna from Aug 2018 to Dec 2018. Total 50 cases of the endocrine neoplasm were enrolled in the present study. Specimens received were analysed and the occurrence of each subtypes were tabulated and its % ages were calculated and compared with other studies. Similarly, demographic variables like age and sex of the patient and the clinical presentations of these tumours were also tabulated and compared with other studies.
The data generated from the present study concludes that thyroid lesions predominantly affecting females during 3rd and 4th decades of life and commonly present as neck swelling. Multinodular goiter was the commonest non-neoplastic lesion followed by colloid goiter. Follicular adenoma was the most common benign neoplasm found while papillary carcinoma was the only and most common malignant tumor. Newly classified borderline category having NIFTP, is indolent malignant tumor with excellent prognosis.

Keywords: Endocrine gland neoplasms, Histopathological types, Bihar region, etc

Introduction
Endocrine glands are glands of the endocrine system that secrete their products, hormones, directly into the blood rather than through a duct. The major glands of the endocrine system include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, parathyroid gland, hypothalamus and adrenal glands. The hypothalamus and pituitary gland are neuroendocrine organs.
The pituitary gland hangs from the base of the brain by the pituitary stalk, and is enclosed by bone. It consists of a hormone-producing glandular portion the anterior pituitary and a neural portion the posterior pituitary, which is an extension of the hypothalamus. The hypothalamus regulates the hormonal output of the anterior pituitary and creates two hormones that it exports to the posterior pituitary for storage and later release. Four of the six anterior pituitary hormones are tropic hormones that regulate the function of other endocrine organs. Most anterior pituitary hormones exhibit a diurnal rhythm of release, which is subject to modification by stimuli influencing the hypothalamus.
Somatotropic hormone or growth hormone (GH) is an anabolic hormone that stimulates growth of all body tissues especially skeletal muscle and bone. It may act directly, or indirectly via insulin-like growth factors (IGFs). GH mobilizes fats, stimulates protein synthesis, and inhibits glucose uptake and metabolism. Secretion is regulated by growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHIH), or somatostatin. Hypersecretion causes gigantism in children and acromegaly in adults; hyposecretion in children causes pituitary dwarfism. Thyroid-stimulating hormone (TSH) promotes normal development and activity of the thyroid gland. Thyrotropin-releasing hormone (TRH) stimulates its release; negative feedback of thyroid hormone inhibits it.
Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to release corticosteroids. ACTH release is triggered by corticotropin-releasing hormone (CRH) and inhibited by rising glucocorticoid levels. The gonadotropins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH) regulate the functions of the gonads in both sexes. FSH stimulates sex cell production; LH stimulates gonadal hormone production. Gonadotropin levels rise in response to gonadotropin-releasing hormone (GnRH). Negative feedback of gonadal hormones inhibits gonadotropin release. The thyroid gland is located at the front of the neck, in front of the thyroid cartilage, and is shaped like a butterfly, with two wings connected by a central isthmus. Thyroid tissue consists of follicles with stored protein called colloid, containing thyroglobulin, a precursor to other thyroid hormones, which are manufactured within the colloid.

- The thyroid hormones increase the rate of cellular metabolism, and include thyroxine (T4) and triiodothyronine (T3). Secretion is stimulated by the hormone TSH, secreted by the anterior pituitary. When thyroid levels are high, there is negative feedback that decreases the amount of TSH secreted. Most T4 is converted to T3 (a more active form) in the target tissues. Calcitonin, produced by the parafollicular cells of the thyroid gland in response to rising blood calcium levels, depresses blood calcium levels by inhibiting bone matrix resorption and enhancing calcium deposit in bones. Excessive secretion cause hyperthyroidism

and deficiency cause hypothyroidism.

The parathyroid glands, of which there are 4-6, are found on the back of the thyroid glands, and secrete parathyroid hormone (PTH) [1]. which causes an increase in blood calcium levels by targeting bone, the intestine, and the kidneys. PTH is the antagonist of calcitonin. PTH release is triggered by falling blood calcium levels and is inhibited by rising blood calcium levels. The adrenal glands are located above the kidneys in humans and in front of the kidneys in other animals. The adrenal glands produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol [2]. It controls the behaviour during crisis and emotional situations. It stimulates the heart and its conducting tissues and metabolic processes.

The pancreas, located in the abdomen, below and behind the stomach, is both an exocrine and an endocrine gland. The alpha and beta cells are the endocrine cells in the pancreatic islets that release insulin and glucagon and smaller amounts of other hormones into the blood. Insulin and glucagon influence blood sugar levels. Glucagon is released when blood glucose level is low, and stimulates the liver to release glucose into the blood. Insulin increases the rate of glucose uptake and metabolism by most body cells. Somatostatin is released by delta cells and acts as an inhibitor of GH, insulin and glucagon.

Local chemical messengers, not generally considered part of the endocrine system, include autocrines, which act on the cells that secrete them, and paracrines, which act on a different cell type nearby. The ability of a target cell to respond to a hormone depends on the presence of receptors, within the cell or on its plasma membrane, to which the hormone can bind. Hormone receptors are dynamic structures. Changes in number and sensitivity of hormone receptors may occur in response to high or low levels of stimulating hormones. Blood levels of hormones reflect a balance between secretion and degradation/excretion. The liver and kidneys are the major organs that degrade hormones; breakdown products are excreted in urine and feces. Hormone half-life and duration of activity are limited and vary from hormone to hormone. Interaction of hormones at target cells Permissiveness is the situation in which a hormone cannot exert its full effects without the presence of another hormone. Synergism occurs when two or more hormones produce the same effects in a target cell and their results are amplified. Antagonism occurs when a hormone opposes or reverses the effect of another hormone.

Diseases of the endocrine glands are common [4]. including conditions such as diabetes mellitus, thyroid disease, and obesity. Endocrine disease is characterized by irregulated hormone release (a productive pituitary adenoma), inappropriate response to signaling (hypothyroidism), lack of a gland (diabetes mellitus type 1, diminished erythropoiesis in chronic renal failure), or structural enlargement in a critical site such as the thyroid (toxic multinodular goitre). Hypofunction of endocrine glands can occur as a result of loss of reserve, hyposecretion, agenesis, atrophy, or active destruction. Hyperfunction can occur as a result of hypersecretion, loss of suppression, hyperplastic or neoplastic change, or hyperstimulation.

Endocrinopathies are classified as primary, secondary, or tertiary. Primary endocrine disease inhibits the action of downstream glands. Secondary endocrine disease is indicative of a problem with the pituitary gland. Tertiary endocrine disease is associated with dysfunction of the hypothalamus and its releasing hormones. As the thyroid, and hormones have been implicated in signaling distant tissues to proliferate, for example, the estrogen receptor has been shown to be involved in certain breast cancers. Endocrine, paracrine, and autocrine signaling have all been implicated in proliferation, one of the required steps of oncogenesis [5].

Other common diseases that result from endocrine dysfunction include Addison's disease, Cushing's disease and Grave's disease. Cushing's disease and Addison's disease are pathologies involving the dysfunction of the adrenal gland. Dysfunction in the adrenal gland could be due to primary or secondary factors and can result in hypercortisolism or hypocortisolism. Cushing's disease is characterized by the hypersecretion of the adrenocorticotropic hormone (ACTH) due to a pituitary adenoma that ultimately causes endogenous hypercortisolism by stimulating the adrenal glands [6]. Some clinical signs of Cushing's disease include obesity, moon face, and Hirsutism [7]. Addison's disease is an endocrine disease that results from hypocortisolism caused by adrenal gland insufficiency. Adrenal insufficiency is significant because it is correlated with decreased ability to maintain blood pressure and blood sugar, a defect that can prove to be fatal [8].

Graves' disease involves the hyperactivity of the thyroid gland which produces the T3 and T4 hormones [7]. Graves' disease effects range from excess sweating, fatigue, heat intolerance and high blood pressure to swelling of the eyes that causes redness, puffiness and in rare cases reduced or double vision. Graves' disease is the most common cause of hyperthyroidism; hyposecretion causes cretinism in infants and myxoedema in adults. Hyperparathyroidism results in hypercalcaemia and its effects and in extreme bone wasting. Hypoparathyroidism leads to hypocalcaemia, evidenced by tetany seizure and respiratory paralysis. Hyposecretion of insulin results in diabetes mellitus; cardinal signs are polyuria, polydipsia, and polyphagia.

Tumours of endocrine glands, although rare in the context of the overall burden of oncological disease, have provided important insights into the mechanisms of sporadic and familial tumour formation, with an overt incidence of 0.6–1.5 per 100 000 per year [10]. Other malignant endocrine tumours, including adrenocortical carcinoma, carcinoid and other neuroendocrine tumours are extremely rare, with incidence figures of less than 0.5 in 100000 per year [9]. Hence the present study was planned to evaluate the endocrine gland neoplasms excluding thyroid.

Methodology

The present study was planned in the Department of Pathology, Patna Medical College and Hospital, Patna from Aug 2018 to Dec 2018. Total 50 cases of the endocrine neoplasm were enrolled in the present study. Specimens received were analysed and the occurrence of each subtypes were tabulated and its % ages were calculated and compared with other studies. Similarly, demographic variables like age and sex of the patient and the clinical presentations of these tumours were also tabulated and compared with other studies.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Patients presenting with thyroid enlargement, who underwent any type of thyroid operation (i.e. lobectomy, subtotal thyroidectomy, near total thyroidectomy or total thyroidectomy) included in the present study.

Exclusion Criteria: Other Endocrine organs and neuroendocrine tumours were exempted from this study.

Results and Discussion

Endocrine glands are present in different parts of the body and are responsible for the secretion of various hormones. The glands of endocrine are commonly referred to as the endocrine system. The endocrine system consists of adrenal glands, hypothalamus, ovaries, pancreas, parathyroid, pineal gland, pituitary gland, testes, thymus and thyroid. The hormones secreted by the endocrine glands are essential in maintaining the balance of the healthy body functions. Endocrine neoplasm refers to the unusual growth of the endocrine glands which are tumors and cancer. The tumors are generally classified depending on the part of the body that is affected, the cell type, and the endocrine gland that is involved. There are several types of endocrine tumors which affect different glands and some of them are adrenal gland tumor, parathyroid tumor, pancreatic cancer, pituitary gland tumor and thyroid cancer [11].

Endocrine and neuroendocrine tumors are relatively uncommon, but they represent an important group of potentially treatable cancers. The frequency of endocrine tumors in our study is 29%, which because of a lack of information regarding the overall incidence of endocrine tumors cannot be compared to those of other geographical areas; our frequency is one of a unicentric study and could be different from other cohort or national studies. Tumours of endocrine glands are rare in the context of the overall burden of neoplastic diseases. Endocrine cancer is a rare malignancy worldwide (1.5% in males and 3.5% in females) [12]. The most commonly affected endocrine organ is the thyroid gland representing 80-92% of all endocrine malignancies [13].

Table 1: Clinical symptoms in cases with thyroid lesions

Clinical symptoms	No. of cases
Males	19
Females	31
Neck swelling	50
Lymphadenopathy	1
Dysphagia	1
Dyspnoea	1
Hoarsness of vioce	1

Table 4: Site of thyroid gland involvement

Site	No. of cases
Right side swelling	25
Left side swelling	18
Bilateral / diffuse swelling	7

Table 6: Gender wise histopathological distribution of thyroid lesions

Lesion		Total
Non neoplastic		
Multinodular goiter		22
Colloid goiter		8
Hashimoto's thyroiditis		3
Thyroglossal cyst		2
Total		35
Neoplastic		
Follicular adenoma		8
Hurthle cell adenoma		1
Papillary Carcinoma	Classical-PTC	2
	Infiltrative FV-PTC	1
	Invasive EFV-PTC	2
	NIFTP	1
Total		15

Thyroid diseases are of great importance as most are amenable to medical or surgical treatment. From a clinical stand point, the possibility of a tumor is of major concern in patients who present with thyroid nodules. Fortunately, majority of solitary nodules of thyroid proved to be either benign adenomas or localized non-neoplastic conditions. Carcinomas of thyroids, by contrast, are uncommon, accounting for less than 1% of solitary nodules. Ultimately, histologic study of surgically resected thyroid tissue provides the most definitive information about the nature of nodules.

They were mainly classified into adenomas and carcinomas according to WHO classification. Pituitary adenomas are found to be more common when compared to pituitary carcinomas. In the present study, the % ages of adenomas were 100% when compared to carcinomas, as no cases were obtained. This study was found to be correlating with the studies of Villwock *et al*., who noted that pituitary tumours constitute 10-15% of all diagnosed intracranial tumours, 90% of which are adenomas [14]. The study done by Minouk J *et al*., found 97.7% cases to be adenomatous neoplasms [15]. In Cho HJ *et al*., study Pituitary adenomas accounted for 83.4% from all the surgically resected pituitary lesions studied [16].

According to latest WHO (2017) classification of thyroid tumors a borderline group of encapsulated follicular patterned thyroid tumors is added recently, which is placed between benign and malignant groups. This includes 1) Follicular tumor of uncertain malignant potential (FT-MP), 2) Well differentiated thyroid tumor of uncertain malignant potential (WDT-MP), 3) NIFTP. 13 NIFTP is indolent and slowly growing tumor having excellent prognosis. The diagnostic criteria of NIFTP are encapsulation or clear demarcation from the adjacent thyroid tissue, follicular growth pattern with <1% papillae, no psammoma bodies, <30% solid/trabecular/insular growth pattern with nuclear alterations of papillary carcinoma. There are no vascular or capsular invasion (after thorough examination of the tumor interface with the surrounding tissues), no tumor necrosis,

no high mitotic activity (i.e., <3 mitoses per 10 high-power fields [×400]) [17].

In recent years, the frequency of follicular variant papillary thyroid carcinoma (FVPTC) has been shown to increase. According to latest classification the four basic morphologic features used to diagnose differentiated thyroid carcinoma-that is papillary growth pattern, follicular growth pattern, presence of a tumor capsule (with or without invasion, of the capsule itself or of vessels), PTC-type nuclei-nuclei identifies following diagnostic categories. 1) Classic PTC, 2) Follicular predominant classic PTC, 3) infiltrative follicular variant PTC, 4) encapsulated follicular variant papillary carcinoma (EFV-PTC) when invasion is present, 5) Non Invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) when there is no invasion. Follicular neoplasm (FTC, when invasion is present; FTA, when there is no invasion) [18]. Follicular variant of papillary carcinoma composed entirely or almost entirely of follicles. Infiltrative follicular variant papillary carcinoma is characterized by infiltrative growth margins with neoplastic cells pervading the thyroid parenchyma with irregular strands and nests composed of neoplastic follicles.

In the present study majority of the patients presented with fatigue, weakness, sweating, epigastric pain, diarrhoea and diabetes mellitus. This was found to be correlating with the study of Simona Gronzinsky-Glasberg, where he stated that based on their secretory hormonal properties and related clinical picture, pancreatic neuroendocrine tumours are divided as functional(rare) and non-functional (>70%) [19]. According to the study done by B Eriksson *et al*., the most frequent presenting features were dyspepsia and epigastric pain, which was found to be correlating with the present study [20]. Similarly, the present study also correlates with the study done by Pattou F *et al* [21]. According to the study done by Pannala Rabout 25% of patients with pancreatic cancer have diabetes mellitus at diagnosis, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels) [22].

Conclusion

The data generated from the present study concludes that thyroid lesions predominantly affecting females during 3rd and 4th decades of life and commonly present as neck swelling. Multinodular goiter was the commonest non-neoplastic lesion followed by colloid goiter. Follicular adenoma was the most common benign neoplasm found while papillary carcinoma was the only and most common malignant tumor. Newly classified borderline category having NIFTP, is indolent malignant tumor with excellent prognosis.

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