Neuroscience

Acromegaly: Underdiagnosed in Patients with Prolactinoma

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Prolactin secreting adenomas are very common and account for 50-60% of all functional pituitary adenomas. Medical history pertaining to reproductive and sexual function initiates the work up for prolactinoma. At the time of initial assessment other pituitary hormones may be evaluated, including growth hormone (GH). Thereafter, patients are treated medically with dopamine agonist, typically with no further assessment of GH hypersecretion. Review of the literature suggests that up to 4% of patients with an established diagnosis of prolactinoma can develop acromegaly even after many years of the initial evaluation. Acromegaly is a rare disease with mortality rates 2-3 times higher as compared to that of the general population. The interval from onset of symptoms to the diagnosis may range from one year to several decades. Thus, omitting IGF-1 assessment. Acromegaly is a rare disease with mortality rates 2-3 times higher as compared to that of the general population. The interval from onset of symptoms to the diagnosis may range from one year to several decades. Thus, omitting IGF-1 measurements at the initial evaluation of prolactinoma, and/or in the follow up period, can miss mild and subtle cases of acromegaly. Therefore, biochemical evaluation for GH excess should be considered in patients with prolactinoma initially as well as in the remote follow up.

Acromegaly | Prolactinoma | Growth hormone | Pituitary | Insulin like growth factor

Background

Prolactinoma is the most common functional pituitary adenoma [1, 2]. The initial assessment starts by checking the prolactin (Prl) level for evaluation of hypogonadism and/or infertility. Upon presentation, other pituitary hormones, including growth hormone, may also be checked [6, 7] but thereafter no further assessment for co-secretion is routinely recommended. Prolactin producing adenomas are known to co-secrete growth hormone (GH) [3-5]. GH excess can be detected at the initial diagnosis or many years later. Based on available literature approximately 4% of patients with prolactinoma develop acromegaly in the remote follow up period [3, 8]. Acromegaly has an insidious nature. The related co-morbidities such as diabetes, hypertension, and cardiovascular disease are commonly seen in the general population and may not raise a suspicion for GH excess. Untreated acromegaly has a 2-3 times higher mortality rate as compared to the general population. Thus, it is paramount to evaluate patients with prolactinoma periodically for the development of acromegaly. In this paper we present the current recommendations for diagnosing prolactinoma followed by review of GH/Prl co-secretion adenomas.

General approach to diagnosis of prolactinoma:

Pituitary adenomas are very common with an approximate prevalence of 10.6 % based on autopsy series [9]. About 40% of pituitary adenomas are prolactin producing adenomas. The disease comes into clinical consideration frequently due to the nature of its presentation. The common symptoms in women are galactorrhea, amenorrhea and infertility, while in men the symptoms of hypogonadism prevail. The diagnosis is easily established by checking serum prolactin level followed by gadolinium-enhanced head MRI, after ruling out physiologic and pharmacologic causes of hyperprolactinemia [2, 7]. Other hormones like cortisol and GH levels may be assessed initially to rule out co-secretion [2, 6] but the guidelines do not routinely recommend checking them in all patients with prolactin producing adenomas [2, 7].

GH/Prl Co-secreting Adenomas

Prevalence

GH/Prl co-secretion is well recognized. Up to 25% of growth hormone (GH) secreting adenomas co-secrete prolactin [16-18]. In contrary, the frequency of GH secretion in established prolactinoma cases is thought to be rare. In 1977 Kleinberg et al reported that 8 out of 48 prolactinoma patients had biochemical and clinical acromegaly, with a prevalence of 17%. However, this may be under or overestimated, given the technical challenges associated with measuring Prl and GH levels.

Histological Types:

Histologically, three different types of combined GH/Prl pituitary adenomas have been described. The first and most common type of GH/Prl co-secreting adenoma originates from both somatotrophs and lactotrophs. These adenomas have two distinctive cell types on the immunohistochemistry staining for GH and Prl [20]. The second type of combined GH/Prl secreting pituitary lesion is a monomorphous mammosomatotroph adenoma with GH and Prl hormones produced by a single cell. This type accounts for 8 to 10 % of GH-secreting tumors. Clinically, in both types, patients have signs and symptoms of acromegaly with limited manifestation from the hyperprolactinemia [18, 20]. The third and the last type of combined GH/Prl co-secreting adenoma is a primitive acidophilic stem cell adenoma, also with dual hormone secretion by a single cell. It is a very rare subtype and only described in case reports [13, 21, 22], more often in teenagers and younger adults. Clinically, symptoms from hyperprolactinemia are more prevalent in these patients, followed by presentation of acromegaly. The clinical course of acidophilic stem cell adenomas is usually aggressive requiring multiple surgeries and additional treatments.

Pathogenesis

The pathogenesis of mixed GH/Prl pituitary adenomas is not fully understood. It thought to be due to the development of somatotrophs and lactotrophs from a single progenitor cell during embryogenesis, under regulation of ProP1 and Pit1 transcription factors [1, 15]. However, recent literature also suggests that the anterior pituitary has a group of polyclonal cells that are capable to differentiate from one pituitary cell line to another, especially under physiologic demand. This process, termed as “transdifferentiation” is described by Senovilla et al [23].

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Late Development of Acromegaly in Prolactinoma Patients

Number of case reports describe late development of acromegaly in prolactinoma patients with variable presentation [3, 4, 8, 10-14]. The time between initial diagnosis of prolactinoma to development of acromegaly ranged from 2 [3] to 20 years [4, 5]. Some patients were reported to be resistant to dopaminergic treatment [12] while others were well controlled on medical treatment, developing acromegaly after many years [4].

There are two recent studies that examined the incidence of acromegaly in prolactinoma patients [3, 8]. Anderson et al [3] periodically monitored 78 prolactinoma patients from 1996 to 2001 with IGF-1 levels. 3 out of 78 patients with initial normal age and gender IGF-1 levels developed clinical and biochemical acromegaly. The time interval from the initiation of screening until the second diagnosis was 29, 40 and 60 months. Of note, one patient underwent pituitary surgery before the diagnosis of acromegaly and the pathology revealed only Prl levels, especially in GH and nonfunctioning pituitary adenomas, leading to tumor formation [25]. Furthermore, Wang et al showed HMGA1 to be associated with aggressive and invasive pituitary adenomas [26]. Thus, HMGA1 may have a critical role in the growth of these cells. The role of these proteins is unclear in prolactinoma and/or mixed GH/Prl adenomas and further studies are needed to understand the pathogenesis to better formulate the management plan for patients with prolactinomas.

Conclusion

Prolactinoma is the most common secretory pituitary adenoma. Subset of patients do present with GH co-secretion which is detected either at the time of diagnosis or decades later. Acromegaly has an insidious nature and co-morbidities, such as diabetes, and cardiovascular disease, are very common in the general population and may not raise the suspicion for GH excess. As a result the diagnosis is often delayed. Untreated acromegaly has a mortality rates 2-3 times higher as compared to the general population, mostly due to cardiomyopathy and cardiac valve abnormalities [16]. Therefore, based on the literature review, we recommend checking IGF-1 on the initial assessment as well as periodically thereafter. More studies can delineate the optimal interval and the duration of biochemical evaluation in this patient population.


