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The clinical characteristics, presentation, and treatment outcomes of prolactinomas at Groote Schuur Hospital

by

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DECLARATION

I, Mohamed Abdalla, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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SUPERVISOR

This study was conducted from March 2019 to March 2020 under the Supervision of Associate Prof JA Dave, Division of Endocrinology, Medicine, University of Cape Town.

As a candidate Supervisor, I have approved this dissertation for submission.

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
CNS	central nervous system
CT	computed tomography
DA	Dopamine agonists
DST	dexamethasone suppression test
FSH	Follicle-stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
IGF-1	Insulin-like growth factor 1
kDa	kilodaltons
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
PRL	Prolactin
PRLR	Prolactin receptor
TRH	Thyrotropin-releasing hormone
TSH	thyroid stimulating hormone
VP	ventriculo-peritoneal

CHAPTER 1:

1Literature review

1.1 Background

The pituitary gland is considered the master gland of the endocrine system as it releases hormones that stimulate and control many important endocrine glands such as the thyroid, adrenal, ovaries and testes (1). It is a small pea-sized gland that weighs about 500 mg. The size is variable and is usually larger in women, especially during pregnancy and lactation. It is connected to the hypothalamus by a stalk and is embedded in a bony structure called the Sella turcica (Turkish saddle) (2). The structures lateral to the pituitary gland are the cavernous sinuses, which contain cranial nerves III (oculomotor), IV (trochlear), VI (abducens), V1 (ophthalmic branch of the trigeminal nerve), and V2 (maxillary branch of the trigeminal nerve) as well as the carotid artery that lies medical to the cranial nerves (3).

The release of pituitary hormones is under the influence of hypothalamic neurohormones which are secreted from the median eminence (a site where axon terminals emanate from the hypothalamus) and that reach the adenohypophysis via a portal venous system (4).

The anterior part of the pituitary gland secretes trophic hormone: growth hormone (GH), prolactin, adrenocorticotrophin (ACTH), thyrotrophin (TSH), and the gonadotrophins (FSH and LH) whilst the posterior part secretes vasopressin and oxytocin (5).

1.2 Pituitary adenoma

The pituitary gland can be affected by many diseases that can influence hormone secretion (hyposecretion or hypersecretion)(see table 1). An adenoma in the pituitary gland is one of the more common causes of pituitary dysfunction.

Pituitary adenomas account for approximately 14% of CNS neoplasms and the prevalence in population is about 17% (6)(7). The non-functional adenomas (adenoma not secreting hormone) are about 36%- 54%, the functional adenomas (adenoma secreting hormone) about 46%- 64% (8)(9).

The exact cause of pituitary adenoma is unknown, and most cases of adenomas are sporadic. The genetic mutations are a rare cause of some pituitary adenomas (multiple endocrine neoplasia type 1 and 4, Carney complex, familial isolated pituitary adenomas) (10).

In one large population-based study from Northern Finland included the adenomas that diagnosed between 1992 and 2007 the incidence rate per 100,00 as follows (11)

- All pituitary adenomas – 4.0
- Lactotroph adenomas – 2.2
- Clinically non-functioning adenomas – 1.0
- Somatotroph adenomas – 0.34
- Corticotroph adenomas – 0.17

Pituitary tumours are classified by size and the cell of origin. Tumour less than 10 mm are classified as microadenomas, and lesions larger than 10 mm are classified as macroadenomas.

1.3 Non-functioning pituitary adenoma

Non-functioning pituitary adenomas are about 43.1% of all adenomas with most of them being classified as gonadotroph adenomas (70-90 %) (9).

Patients usually present to healthcare workers when they develop a hormone disturbance or a neurologic symptom such as impaired vision (bitemporal hemianopsia and diminished visual acuity), nonspecific headache, diplopia, cerebrospinal fluid rhinorrhoea, or rarely pituitary apoplexy (12). Some patients are incidentally found to have a non-functional pituitary adenoma when magnetic resonance imaging (MRI) is done for another reason (13).

At diagnosis, about 60 % of patients have some symptoms of hypopituitarism as a result of compression of the tumour with the gonadotropins the most common hormones affected. Symptoms are usually non-specific (fatigue and lethargy) and not severe enough for the patient to seek medical attention (14).

Patients with neurological symptoms such as a visual field abnormality, usually have transsphenoidal surgery as their initial therapy. The choice of surgical procedure, microscopic or endoscopic, depends upon the neurosurgeon's experience (15). Radiation therapy is indicated if there is significant residual tumour 6-12 months after surgery or if there is significant regrowth of the tumour after surgery (16). It is essential to replace the specific hormone deficiencies and lifetime re-evaluation is needed.

1.4 Cushing's disease

Cushing's syndrome due to an ACTH-secreting pituitary adenoma (Cushing's disease) is 5-6 times more common than other causes of Cushing's syndrome. The incidence of Cushing's disease is about 5 to 25 per million per year and in one population-based study the incidence was much lower (1.2 to 2.4 per million per year) (17).

The clinical features that most implicate the presence of hypercortisolism include proximal muscle weakness, wide purplish striae, bruising with no obvious trauma and thin skin (18).

Establishing the diagnosis of Cushing's syndrome can be complex and includes measurement of late-night salivary cortisol (two measurements) and 24-hour urinary cortisol excretion (two measurements) as well as an, an overnight 1 mg dexamethasone suppression test (DST) (18). Next steps would include measurement of serum ACTH to determine whether the hypercortisolism is ACTH-dependent or ACTH-independent and imaging, a pituitary MRI scan for ACTH-dependent hypercortisolism of an adrenal CT scan for ACTH-independent hypercortisolism. In some cases, a high dose DST and/or inferior petrosal sinus sampling would be required to exclude ectopic production of ACTH.

The goal of treatment for all patients with Cushing's syndrome is to achieve normalization of serum levels of cortisol and subsequent reversal of Cushingoid signs/symptoms and co-morbidities (19).

The best modality for potential cure for Cushing's disease (ACTH-producing pituitary tumour) is transsphenoidal micro-adenectomy when possible, but medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Adrenal enzyme inhibitors are the most used drugs, other drugs that can be used include adrenolytic agents, drugs that target the pituitary, and glucocorticoid-receptor

antagonists. Moreover, if fertility is not desired then pituitary irradiation can be used (20).

1.5 Acromegaly

Acromegaly is the clinical syndrome characterized by excessive secretion of somatotrophin (GH). The incidence of acromegaly is 6-8 per million people annually and the mean age at diagnosis is 40 to 45 years. A Somatotroph adenoma is the commonest cause of acromegaly, it accounts for roughly one-third of all hormone-secreting pituitary adenomas and 75 % of patients have macroadenomas (tumour diameter 10 mm or greater). When GH excess occurs before fusion of the epiphyseal growth plates it causes pituitary gigantism in children and adolescent (21).

About 40% of patients with acromegaly have an activating mutation of the alpha subunit of the guanine nucleotide stimulatory protein (Gs-alpha) gene (22).

Progression of the disease is insidious with many patients only being diagnosed after a mean time of 12 years(23). The most common symptoms are headache (60 %) and visual symptoms (10 %) (24).

Long-term over-secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) results in overgrowth of many tissues, including connective tissue, cartilage, bone, skin, and visceral organs. Almost all patients with acromegaly have acral and soft tissue overgrowth and skin thickening. The characteristic signs are an enlarged jaw (macrognathia) and enlarged swollen hands and feet. Major causes of mortality are cardiovascular abnormalities including hypertension, left ventricular hypertrophy, and cardiomyopathy. Insulin resistance is common among patients with acromegaly, frank diabetes occurs in 10 to 15 % of cases, and impaired glucose tolerance in a further 50 %(25). Other systemic complications include sleep apnoea, metabolic disorders, and colon neoplasia.

The insulin-like growth factor-1 (IGF-1) concentration is high in acromegaly. Anormal serum IGF-1 concentration is robust evidence that the patient does not have acromegaly. Failure to suppress growth hormone during an oral glucose tolerance test

confirms the diagnosis. Once that diagnosis of acromegaly is confirmed a pituitary MRI scan is needed to localize the lesion. A normal MRI scan would require further investigations including measurement of growth hormone-releasing hormone (GHRH) and imaging to identify ectopic growth hormone secretion. Since most tumours causing acromegaly are macroadenomas cure by transsphenoidal surgery is uncommon and medical treatment or radiation treatment are often required (26).

1.6 Hyperprolactinemia

1.6.1 Molecular Forms of prolactin

Human prolactin was first discovered in 1970 by Henry Friesen but was identified 40 years earlier in animals by Oscar Riddle (27).

Prolactin is encoded by one gene on chromosome 6. This gene consists of six exons and 4 introns. The molecular weight of mature biologically active prolactin is 23 kDa and the protein consists of 199 amino acids. Other variants of prolactin include: 'big prolactin' and 'big-big prolactin' (macroprolactin), it has high molecular mass (>150 kDa) and it is complexes of 23 kDa prolactin and IgG autoantibodies, but it has no biological activity. Structurally prolactin similar to growth hormone and placental lactogen (28).

1.6.2 Prolactin Receptor

The prolactin receptor is encoded by the *PRLR* gene on chromosome 5. It consists of about 10 axons and is one of the haematopoietic cytokine receptor superfamily members. It has three extracellular domains, a transmembrane domain and an intracellular signal-transducing domain (29).

1.6.3 Regulation of prolactin secretions

Prolactin is mainly produced from the anterior pituitary (lactotroph cells) but there is also extra pituitary production of prolactin (myometrium,
breast, lymphocytes, leukocytes, and prostate) (30).

The prolactin gene is regulated by transcription factor POU1F1. Thyrotropin-releasing hormone (TRH) enhances the release of prolactin whereas dopamine inhibits prolactin secretion.

In the absence of pregnancy, prolactin is tonically inhibited by dopamine, and the effect of dopamine overcomes the effect of TRH. In pregnancy, the high levels of estrogen stimulate prolactin release directly from the anterior pituitary. Suckling stimulates sensory nerves which carry a signal through the spinal cord to the arcuate nucleus to inhibit dopamine and increase the production of prolactin. An efferent signal from the nipple stimulates supraoptic and paraventricular nuclei to produce oxytocin to eject milk. Prolactin inhibits the release of GnRH causing amenorrhea during lactation (31) (32).

1.6.4 Function of prolactin

The main functions of prolactin in women are stimulation of milk secretion and enhancement of breast tissue growth in the presence of estrogen and progesterone. Prolactin activates the enzymes that are responsible for milk production, however, during pregnancy, lactogenesis is inhibited by the high level of estrogen and progesterone (33).

In men, studies show that prolactin can increase the sensitivity of luteinizing hormone-receptors in testes which results in maintaining the production of sperm (34).

Prolactin may enhance myelin repair in the maternal central nervous system and it may also have a role in regulating maternal behaviour (35).

1.6.5 Causes of hyperprolactinemia

In most laboratories, the upper limit of normal for serum prolactin is approximately 20 ng/mL (20 mcg/L SI units). The measurement of prolactin is not affected by food, so it can be checked at any time of the day.

Hyperprolactinemia may be divided into four types: physiological, functional, analytical, and pathological hyperprolactinemia.

High levels of estrogen during pregnancy can cause a physiological increase in the prolactin level, usually in the range of 35 to 600 ng/mL (35 to 600 mcg/L SI units). During the postpartum period the level decreases gradually and by 6 weeks it returns to the normal value, even if the mother lactating (36).

Other causes of physiological hyperprolactinemia include nipple stimulation during breastfeeding, stress, physical exertion, hypoglycaemia, or sexual intercourse. Prolactin levels in these situations are typically very mild (37).

Dopamine D2 receptor antagonists (antipsychotics) may raise serum prolactin usually into the range of 25 to 100 ng/mL (25 to 100 mcg/L), however, risperidone may increases prolactin concentrations up to 200 ng/mL (200 mcg/L) (38). Several other drugs have been associated with hyperprolactinemia, for example, selective serotonin reuptake inhibitors (39), methyldopa(40) and verapamil (41).

The most important pathological cause of hyperprolactinemia is hypothalamic-pituitary disease (HPD) that interferes with the secretion of dopamine (Stalk-Effect) and Lactotroph adenomas. The usual prolactin level in patients with HPD is not more than 200 ng/mL (200 mcg/L SI units), whereas the prolactin level varies according to the size of lactotroph adenoma, and can vary from mildly elevated up to several thousand fold elevated (42).

Other causes of hyperprolactinemia include hypothyroidism, chest wall injury, use of estrogen, renal failure, macroprolactinemia and idiopathic. Mutations in the prolactin receptor gene can cause familial hyperprolactinemia (see table 2) (43).

1.6.6 Clinical presentation of hyperprolactinemia

The main consequence of hyperprolactinemia is secondary hypogonadism and the effect of hypogonadism on bone. High levels of prolactin cause inhibition of luteinizing hormone (LH), and follicle-stimulating hormone (FSH) secretion, through inhibition of the release of gonadotropin-releasing hormone (GnRH) (see table 3).

Premenopausal women can present with amenorrhea or oligomenorrhea and this may be associated with galactorrhea but galactorrhea is often not present (42). In men, hyperprolactinemia is associated with impaired libido and impotence, infertility (oligospermia and decreased in volume), gynecomastia (rarely galactorrhea), decreased muscle mass and body hair (37).

Prolactin within the normal range has a positive effect on bone formation, whereas a high prolactin level may increase bone resorption and inhibit bone formation. Premenopausal women with amenorrhea and hyperprolactinemia have low bone density compared with women with normal menses with or without hyperprolactinemia. In addition, men with hyperprolactinemia are at risk of metabolic bone disease.

Trabecular bone is affected earlier than cortical bone and the abnormal bone density can be improved when the hyperprolactinemia is corrected (44).

Postmenopausal women with hyperprolactinemia due to a pituitary tumour usually come to clinical attention when the tumour becomes large enough to cause headaches or impaired vision or if it is detected as an incidental finding on magnetic resonance imaging (MRI).

1.6.7 Prolactin Assays

Clinical settings in which prolactin is commonly requested are menstrual irregularities (amenorrhea and oligomenorrhea), infertility, galactorrhoea, sexual dysfunction, gynaecomastia in men, suspected pituitary dysfunction, suspected pituitary mass lesion, before initiation of some antipsychotic medications (baseline) or monitoring of prolactin levels in patients on antipsychotic medications

Prolactin is currently measured by a two-site immunometric or sandwich principle which is more sensitive and specific. It uses two antibodies directed to different epitopes of the analyte: the first antibody (the 'capture' antibody) is immobilized onto a solid support and binds analyte in the sample; a second antibody (labelled antibody) binds to a different epitope on the analyte to form a sandwich complex, with the analyte bound to both the first and second antibodies. Any unbound labelled antibody is washed away before quantification of the generated signal. The dose-response curve generated in an immunometric assay is directly proportional to the analyte concentration (i.e. the signal increases progressively with the analyte concentration). Other molecules like growth hormone and placental lactogen may cross-react with the prolactin assay, however, using two antibodies directed to both prolactin epitopes can prevent the cross-reactive process. Heterophile antibodies can cause a falsely elevated prolactin level, but adding blocking agent can prevent this interference(28) (45).

Macroprolactin is a complex of prolactin and IgG with a mass of more than 150 kilodaltons compared with 23 kDa for monomeric prolactin. Macroprolactin is biologically inactive and is of no clinical consequence [46]. Therefore excluding macroprolactinemia is crucial as it prevents the misinterpretation of results and can prevent unwanted further investigations. The best method to avoid misdiagnosis is to pre-treat the serum before the immunoassay with polyethylene glycol (PEG) to

precipitate macroprolactin(46). High-pressure liquid chromatography is another method that can be used for the separation of monomeric prolactin (47).

1.6.8 Hook effect

The Hook effect should be excluded particularly in presence of a macroadenoma and if the prolactin level is between 20 and 200 ng/mL (20 to 200 mcg/L SI units)
It occurs in the setting of very high serum prolactin e.g., 5000 ng/mL (5000 mcg/L SI units) and is due to the elevated number of analyte molecules that bind to both the capture and detection antibodies, thereby preventing them from forming sandwich immune complexes. The result is an underestimation of the analyte concentration, while the actual analyte concentration is much higher (48).
It can be overcome by serial sample dilution a 1:10, 1:100, or even a 1:1000 dilution, so that the true analyte concentration will fall within the analytical measurements range for the assay (49).

1.7 Prolactinoma

The cause of a prolactinoma is not fully known. The tumour has undergone somatic mutation and the tumour arises from the monoclonal line of lactotroph cells. Pituitary tumour transforming gene *(PTTG*) overexpression and mutation of a receptor of fibroblast growth factor 4 *(FGF4)* seem to play a role in pathogenesis. The tumour is sporadic but may occur as part of familial syndromes, for example isolated familial prolactinoma, tumour and multiple endocrine neoplasia type 1 *(MEN1*) tumour(50). Anatomically, the most common sites involved by a prolactinoma is the lateral part of the anterior pituitary gland (28).
Pituitary adenomas secreting prolactin (prolactinoma) account for approximately 30 to 40 %% of all pituitary adenomas. It is more common in women than in men, especially between the ages of 20 and 40 years (51). However, in men the adenomas are usually larger(52). The prevalence of a prolactinoma is estimated to be 500 cases per million, the incidence is 27 cases per million per year, and 60% of microadenomas prevailing in women. Prolactin-secreting carcinomas are extremely rare (53). In addition, any tumour in or near the hypothalamus or pituitary interfering with the secretion of dopamine can cause hyperprolactinemia and may present as a prolactinoma (54).

The clinical manifestations of hyperprolactinemia in premenopausal women and men are mainly symptoms and signs of hypogonadism (hypogonadotropic hypogonadism). Postmenopausal women are already hypogonadal, so they only seek medical advice when the tumour becomes large enough to cause headaches or impair vision or is detected as an incidental seller mass by magnetic resonance imaging (MRI). Galactorrhoea is rare in this age group because of low estrogen levels.

Prolactinomas are classified as a microprolactinoma (smaller than 10 mm), macroprolactinoma (larger than 10 mm), or a giant prolactinoma (larger than 40 mm). Prolactin levels secreted by lactotroph adenomas are usually correlate with adenoma size. Adenomas <1 cm in diameter are typically associated with serum prolactin values below 200 ng/mL (8.7 nmol/L), those 1 to 2 cm in diameter with values between 200 and 1000 ng/mL (8.7 to 43.48 nmol/L), and those greater than 2 cm in diameter with values above 1000 ng/mL (43.48 nmol/L) and as high as 50,000 ng/mL (2173.91 nmol/L). There are exceptions to these rules, as occasional patients have a large macroadenoma and mild elevation in prolactin levels. In general, prolactin values more than 200 ng/mL usually indicate the presence of a lactotroph adenoma (55).

The factors that lead to modest elevations of prolactin in patients with a macroadenoma are the hook effect, adenomas that are not well differentiated and if adenomas are largely cystic with only small portion producing prolactin.

In all patients with hyperprolactinemia and after excluding other causes a MRI scan of the pituitary should be performed with any degree of hyperprolactinemia to look for a mass lesion in the hypothalamic-pituitary region (55). Other pituitary function should also be assessed, particularly in macroprolactinomas, especially growth hormone (GH) co-secretion should be excluded clinically and biochemically if necessary. Bone densitometry may be required. Patients with a macroadenoma need ophthalmological assessment, and a transthoracic echocardiogram should be considered before the initiation of dopamine agonist (56).

A strong indication to treat a prolactinoma is existing or impending neurologic symptoms due to mass effect (visual disturbances or headache) with the goal being to reduce the size of adenoma. There is a 5% risk of a microadenoma enlarging over four to six years (57). Another indication for treatment is to restore e eugonadism, thereby preventing the adverse effect of hypogonadism on bone (premenopausal

women and men), as well as other symptoms due to hyperprolactinemia, such as galactorrhoea. Treatment options are medical, surgery, and radiotherapy (49).

The first line of treatment is a dopamine agonist drug (DA). These drugs are indicated for patients with hyperprolactinemia of any cause, including lactotroph adenomas (prolactinomas) of all sizes because they decrease serum prolactin concentrations and decrease the size of most lactotroph adenomas in more than 90% of patients(58). Generally, DA have better results in normalising prolactin levels than tumour reduction, and the reduction of size is frequently based on prolactin levels (50).

Cabergoline is the first choice because of its efficacy and favorable side-effect profile compared to bromocriptine(49). Resistance to bromocriptine is about 25 %% and most (80 %%) can achieve normal prolactin concentrations with cabergoline therapy. Resistance to cabergoline is approximately 10 %% (59).

In the first two to three weeks of therapy with a DA the serum prolactin level starts to decrease (60). The decrease in adenoma size can occur within six weeks to six months after initiation of treatment (61) and vision usually begins to improve within days after starting treatment (62). There is a recovery of menses and fertility in women and of testosterone secretion, sperm count, and erectile function in men. The rest of the pituitary function (thyroid and adrenal axis) may also have a return to normal (63).

The common side effects of DAs are nausea, postural hypotension, and mental fogginess, less common side effects include nasal stuffiness, depression, Raynaud phenomenon, alcohol intolerance, and constipation. The side effects can be avoided by titrating the DA gradually, and by giving it with food or at bedtime. Cabergoline and pergolide have been associated with valvular heart disease, also bromocriptine may lead to subclinical valvular fibrosis(64), but most studies showed that the low doses of cabergoline usually used to treat hyperprolactinemia are not associated with excess risk (65). Impulse control disorders (such as hypersexuality and compulsive gambling, shopping, or eating) are one of DAs adverse effects that have recently been described (66).

For a microadenoma, the Endocrine Society clinical guidelines suggest to reduce the dose gradually, as long as the prolactin level remains within the normal range, and if the prolactin levels remains normal for two years while the patient is taking a low dose (e.g., 0.25 mg twice a week) of cabergoline and there is no evidence of an adenoma on MRI for the same period the suggestion is a trial of discontinuation of the drug. The same approach can be applied to a macroadenoma as long as there is no adenoma

detectable by MRI for at least two years, otherwise discontinuation should probably not be considered. Follow up is clinical and by measurement of prolactin after three months and annually thereafter. If the prolactin increases substantially (e.g., to >100 ng/mL), particularly in a patient who had a macroadenoma, a MRI scan should be requested and treatment with a DA should be resumed to normalize the prolactin (67) (49).

Dopamine agonist resistance was defined as a failure to achieve normoprolactinemia or failure to enable a 50% reduction of hyperprolactinemia under maximally tolerated doses of DA (≥ 15 mg of bromocriptine/day, ≥ 2.0 mg of cabergoline 2 times per week) for at least 3-6 months, and the lack of a 30% or more reduction in tumour diameter in the case of a macroprolactinoma(68)(69). Options available for these situations are transsphenoidal surgery or radiotherapy. Other indications for surgery are intolerable side effects of DA, patient preference, and a woman with a macroprolactinoma (e.g., >3 cm) wishes to become pregnant, to attempt to avoid dopamine agonist treatment during pregnancy(70). Overall transsphenoidal surgery normalizes prolactin levels in 80 %% in cystic prolactinomas, and 84.8 %% in microprolactinomas and the recurrence rate is 18.7 %, although only 7.1 % in microadenomas (71).

Because most prolactinomas respond well to DAs, radiation therapy is only usually used after debulking surgery to avoid regrowth of any residual tumour and there is no role to use radiation in patients with microadenomas. The effect of radiation (single dose or multiple fraction) on the aggressive lactotroph adenoma is less well-known compare to other types of pituitary adenomas (72) (73).

The largest study in Africa on prolactinomas is found in the literature as a thesis and has not yet been published and undergone peer review. Beyene *et al* (2021) report on 69 patients with a prolactinoma in Ethiopia (74). The majority of patients were female (76.8%) and the majority (79.7%) were found to have a macroprolactinoma. Surgery for mass effect was only required in 11 patients and 85.5% had a good clinical response to treatment with carbergoline. Three small studies from Cameroon (n=25), Cameroon (n=36 cases) and Ethiopia (n=20 cases) all showed a good response to treatment with carbergoline with few patients requiring surgery (75)(76)(77). A study form Nigeria included 76 patients with infertility secondary to hyperprolactinaemia and found that at the end of 8 weeks of treatment with cabergoline 98.7% had their serum prolactin levels restored to normal (78).

1.7.1 Prolactinomas in pregnancy

During pregnancy there is enlargement of the pituitary gland due to lactotroph hyperplasia (79). Hyperprolactinemia suppresses gonadotropin-releasing hormone (GNRH) through suppression of kisspeptin which causes decreases of luteinizing hormone (LH) pulse amplitude and frequency. Hyperprolactinemia inhibits progesterone production and directly suppresses estrogen secretion from ovaries (80). The short-luteal phase is the earliest evidence of a cycle abnormality caused by hyperprolactinemia in women and most women with hyperprolactinemia become anovulatory with resultant amenorrhea and infertility. Treatment of hyperprolactinemia may restore the normal menstrual cycle and women with a prolactinoma can get pregnant.

During pregnancy in a woman with prolactinoma, two important issues arise, the effect of DAs on fetal development and an increase in adenoma size because of the high levels of estrogen. The risk of enlargement for a microprolactinoma is low, while the risk for a macroprolactinoma is substantially higher. The safety of DAs during pregnancy has not been established and the recommendations are to stop it during pregnancy. Human studies showed that bromocriptine crosses the placenta and cabergoline has been shown to do so in animal studies but no data is available in humans (81).

There is sparse data on the use of bromocriptine and cabergoline during pregnancy, however, available data shows the risk of congenital malformations did not appear to be higher in pregnant women taking a DA than non-exposed pregnancies (82) (83). DAs should be restarted in women with evidence of tumour growth throughout the remainder of the pregnancy, and transsphenoidal surgery may be considered in the second trimester if the condition deteriorates or does not respond to DA.

Adenoma size doesn’t increase during lactation but the prolactin level is usually increased (84) and DAs impair lactation. Breastfeeding is not contraindicated in women with a macroadenoma or microadenoma that is of stable size, but it is contraindicated for patients who have visual field impairment because they should be treated with a DA.

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CHAPTER 2:

2.1 Abstract

Background: Prolactin-secreting tumours(prolactinomas) are the commonest type of pituitary tumour, accounting for approximately 30 to 40 %% of all pituitary adenomas. Although there is ample epidemiologic and clinic data from Industrialized countries there remains sparse data from Africa. Specifically, the clinical presentation, and hormonal deficiencies and treatment outcomes in the South Africa have not been described.

Methods: A retrospective study of all patients with a diagnosis of prolactinoma attending the Endocrine and Pituitary Clinics at Groote Schuur Hospital over a 12-month period, between March 2019-March 2020. Patients folders were reviewed to retrieve the following information: demographic data, clinical presentation, clinical signs, prolactinoma phenotype, hormonal deficiencies, treatment modalities and clinical outcomes.

Results: Over 12-month period 52 patients were included in this study, females 73% (n=38), mean age of all participants was 46.1 ± 14.6 years. A macroprolactinoma was present in 67.3% (n=35) of patients and 32.7% (n=17) of patients had a microprolactinoma. In the macroprolactinoma group: the common presenting symptoms were headache 88.6% (n=33), altered vision 40% (n=14) and, in females, amenorrhea 63.6% (n=14) but a cranial nerve palsy 17.1% (n=6) and apoplexy 5.7% (n=2) were uncommon. In the microprolactinoma group the common presenting symptoms included amenorrhea 75% (n=12), galactorrhoea 70.6% (n=12), headache 64.7% (n=11). On presentation the majority of patients with a macroadenoma had at least one hormonal abnormality with hypogonadism 73.1% (n=19) being most common, followed by hypothyroidism 53.8% (n=14) and hypoadrenalism 30% (n=8). Over 50% of patients with a giant adenoma had panhypopituitarism with hypogonadism in 100%, hypothyroidism in 77.8% (n=7) and hypoadrenalism in 66.7% (n=6). Hormonal deficiencies in the microadenoma group on presentation included hypogonadism 64.7% (n=11), hypothyroidism 35.3 (n=6) and one patient had hypoadrenalism. All patients received medical treatment, however, in the macroadenoma group 4 patients required surgical debulking of the tumour, 3 patients

required a ventriculo-peritoneal (VP) shunt for hydrocephalus and 2 patients required radiation.

After a median follow-up of 46.5 months, the median prolactin level decreased from 322.5 ug/l (94.0-4282.0) at presentation to 17.5 ug/l (8.6-82.5) at follow-up. In parallel there was a reduction of 12.2 ±9.7 mm in tumour size after a mean of 59.8 ±53.3 months.

There was resolution of hypogonadism in 56.4% (n=22), of hypothyroidism in 2.7% (n=2) and hypoadrenalism only resolved in 1 patient.

Conclusions: Most patients with a prolactinoma are symptomatic and have at least one hormone deficiency on presentation. With medical management most patients experienced a reduction in prolactin levels and tumour size. This was associated with the resolution of hypogonadism in the majority, however, hypothyroidism and hypoadrenalism are unlikely to resolve despite a reduction in tumour size.

Keywords

Hyperprolactinemia; hypogonadism; Prolactin; Prolactinoma

2.2 Introduction

Prolactin-secreting tumours (prolactinomas) are the commonest type of pituitary tumour, is associated with significant hormonal disturbances and may cause neurological complications. The burden and management of prolactinoma in Africa have not been well documented. Although there is ample epidemiologic and clinic data from Industrialized countries there remains sparse data from Africa. Specifically, the clinical presentation, and hormonal deficiencies and treatment outcomes in the South Africa have not been described. This is first description of patients with a prolactinoma being managed in sub-Saharan Africa. The current study is expected to increase awareness of management and outcome of this disease.

2.3 Aims & Objectives

Aim

The aim of this study was to assess all patients with a prolactinoma attending the Pituitary and General Endocrine Clinics at Groote Schuur Hospital. These findings will confirm the effectiveness of the current treatment strategy and may inform changes to management for future patients managed for a prolactinoma at Groote Schuur Hospital.

Objective 1: To describe the spectrum of prolactinomas.

Objective 2: To describe the phenotype and the clinical presentation of a patients diagnosed with a prolactinoma.

Objective 3: To describe the treatment of patients diagnosed with a prolactinoma and their response to management.

2.4 Methods

2.4.1 Study design:

Retrospective folder review

2.4.2 Setting:

Pituitary and General Endocrine Clinics at Groote Schuur Hospital (GSH). GSH is a tertiary hospital in Cape Town, SA.

2.4.3 Study population:

All patients between March 2019- March 2020 attending the Pituitary and General endocrine Clinics at Groote Schuur Hospital with a diagnosis of a prolactinoma.

2.4.4 Procedures:

Patient's folder was reviewed and the following information was obtained:

1. Patients Characteristics
    a) Age
    b) Gender
    c) Ethnicity
2. Clinical presentation
    a) Headache
    b) Visual field defect
    c) Apoplexy
    d) Cranial nerve palsy
    e) Amenorrhea
    f) Galactorrhoea
    g) Incidental finding
3. Tumour type
    Prolactinoma
4. MRI at presentation and most recent MRI
    a) Diagnosis
    b) Size of tumour
5. Outcome
    a) Hypothyroidism
    b) Hypoadrenalism
    c) Hypogonadism

d) Prolactin level

6. Management

a) Medical
b) Surgical
c) Radiotherapy

2.4.5 Data safety, analysis, and monitoring:

The data were collected by clinicians working in the Pituitary and General endocrine Clinics at GSH and processed in an excel spreadsheet. All patient data was anonymized identification number. No personal/identifying details will be utilized in the analysis and subsequent publications. The patient's data will be confidential and will be accessible to researchers only. This data will be updated regularly as new information is collected.

2.4.6 Statistical analysis

The data were analysed using Stata 16.1 and descriptive statistics were performed. We described the baseline characteristics of the study cohort and grouped them by according to the size of macroadenoma (giant, macro- and micro-adenoma). We also described the change in tumour size, and hormonal status of the participants during the study period. Proportions and percentages for each variable were calculated and presented in tables and figures. No comparative statistical analysis was performed owing to low sample size and inadequate power.

2.4.7 Ethical aspects:

Ethics approval was obtained from the UCT - Faculty of Health Sciences Human Research Ethics Committee (REC-210208-007). Also, application for renewal of ethical approval was requested, see appendix 2. In addition, GSH research committee gave permission to review the relevant folders on the premises. Since it is a retrospective study and data were retrieved from patients' folders, individual patient consent was not required.

Before the study commenced and data was collected, research ethics approval for

the project was received from the Faculty of Health Sciences Human Research Committee. Approval number Ref no: 170/2019.

(Ethics approval for the study – see Appendix 2)

The most important ethical consideration in this study was patient confidentiality. The data was collected through a folder review. The retrospective information was confidentially collected by a review of the information already present within the patients' folders. The patients' clinic visits and routine laboratory investigations were not altered and the study followed the best clinical practice guidelines. As this was a retrospective folder review, informed consent was waived. Patient confidentiality was maintained by storing all of the information from the patients' folders, under the unique folder number in the registry. This registry was only accessible via a unique coded password, known only to the investigators. The data was stored on a password locked computer. This was in keeping with the declaration of Helsinki 2013.

2.5 Results

Between 15 March 2019 and 30 March 2020, 52 patients with prolactinomas were identified and included in this study. A 1-year period was selected as most patients with a prolactinoma are seen in our clinic each year. The median age at diagnosis was 36.5 years (29.0-46.0) and the majority of patients were female, 73.1% (n=38) (Table 4). The most common presenting symptoms were headache [80.8% (n=15), amenorrhea in females [68.4% (n=26), galactorrhoea [42.3% (n=22) and a visual field defect [38.5% (n=20)].

Clinical presentation by size category of tumour

A macroprolactinoma was present in 67.3% (n=35) of patients with a median age at diagnosis of 36.0 years (27.0-49.0), whereas 32.7% (n=17) of patients had a microprolactinoma with a median age at diagnosis of 38.0 years (30.0-44.0) (Table 4). Patients with a macroprolactinoma were more likely to be female [62.9% (n=22)] and were more likely to present with a headache [88.6% (n=31)], a visual field defect [51.4% (n=18)], altered vision [40.0% (n=14)] and galactorrhoea 28.6% (n=10). Patients with a microprolactinoma were also more likely to be female [94.1% (n=16)] and to present with galactorrhea [70.6% (n=12) and/or headache [64.7% (n=11)].

Amenorrhea was present in 36.8% (n=14) of females with a macroprolactinoma and in 31.6% (n=12) of females with a microprolactinoma. Cranial nerve palsies 17.1% (n=6) and pituitary apoplexy (n=2) were uncommon in both groups. In the subset of patients with a giant adenoma, the majority of patients were male [55.6% (n=5)] with a median age of 34.0 years (28.0-38.0) (Table 5). The most common symptoms on presentation were headache [100% (n=9)] and altered vision 44.4% (n=4).

Clinical presentation by sex

The majority of males were diagnosed with a macroprolactinoma [57.1% (n=8)] or a giant prolactinoma [35.7% (n=5)] whereas 42.1% (n=16) of females presented with a microprolactinoma, 47.4% (n=18) presented with a macroprolactinoma and 10.5% (n=4) presented with a giant prolactinoma (Table 6). Males were more likely than females to present with a visual field defect [64.3% (n=9) vs 28.9% (n=28.9%, p=0.020] and a cranial nerve palsy [28.6% (n=4) vs 5.3% (n=2), p=0.020] whereas females were more likely to present with apoplexy [5.3% (n=2) vs 0.0% (n=0), p=0.009]. There was no significant difference between females and males for altered vision (p=0.18), headache (p=0.18) or galactorrhea (p=0.064)

Tumour size and hormonal abnormalities at diagnosis

The mean tumour size of a microprolactinoma was 6.1 ± 2.3 mm (n=12, five microadenomas reported as “evidence of microadenoma and bulky pituitary” without an actual tumour size provided), a macroprolactinoma was 21.4 ± 8.8 mm (n=25) and of a giant prolactinoma was 51.6 ± 6.4 mm (n=9) (Table 7). At diagnosis, males had larger tumours than females [34.3 ± 17.7 mm vs 18.5 ± 14.5 mm, p=0.003) (Table 8). Median serum prolactin levels in patients with a microprolactinoma, macroprolactinoma or a giant prolactinoma were 97.0 ug/l (72.0-142.0), 434.5 ug/l (133.0-282.0) and 10 986.0 ug/l (6278.0-14051.0), respectively (Table 7). Males had higher serum prolactin levels than females [299.7 ug/l (412.0-4671.0) vs 145.5 ug/l (73.0-726.0), p=0.013) (Table 8). The majority of patients had at least one hormonal abnormality with hypogonadism 73.1% (n=19) being most common, followed by hypothyroidism 53.8% (n=14) and hypoadrenalism 30% (n=8).

Hypogonadism was present in 64.7% (n=11) with a microprolactinoma, 73.1 % (n=11) with a macroprolactinoma and in 100% (n=9) with a giant prolactinoma (Figure 1 A).

Hypothyroidism was present in 35.3% (n=6) with a microprolactinoma, 53.8 % (n=14) with a macroprolactinoma and in 77.8 % (n=7) with a giant prolactinoma (Figure 2 A). Hypoadrenalism was present in 5.9% (n=1) with a microprolactinoma, 30.8 % (n=8) with a macroprolactinoma and in 66.7% (n=6) with a giant prolactinoma (Figure 3 A). Males were more likely than females to have hypoadrenalism [71.4% (n=10) vs 13.2% (n=5), p<0.001], however, there was no significant difference between males and females having hypogonadism or hypothyroidism at diagnosis (Table 8)

Treatment of patients with a prolactinoma

All patients were treated medically [cabergoline 88.46% (n=46) and bromocriptine 11.54% (n=6)], however, 4 patients with a macroadenoma required surgical debulking of the tumour (3 trans-sphenoidal, 1 craniotomy), 3 patients with a giant adenoma required a ventriculo-peritoneal (VP) shunt for hydrocephalus and 2 patients required radiation (1 with a giant adenoma, 1 with a macroadenoma after surgical debulking of the tumour).

Serum prolactin level and tumour size after treatment

After a median follow-up of 46.5 months there was significant reduction in the serum prolactin level. In the macroadenoma group the median prolactin level decreased from 434.5 ug/l (133.0-4282.0) at presentation to 13.2 ug/l (8.2-27.0) at follow-up, whilst in the giant adenoma group the median prolactin level decreased from 10986.0 ug/l (6278.0-14051.0) at presentation to 411.0 ug/l (15.0-1073.0) at follow-up. In the microadenoma group the median prolactin level decreased from 97.0 ug/l (72.0-142.0) at presentation to 19.0 ug/l (7.0-80.0) at follow-up. There was no significant difference in prolactin levels between males and females after treatment (p=0.27) (Table 8).

In parallel with the reduction in prolactin level there was a reduction in tumour size. In the giant adenoma group, after a mean of 30.5 ± 23.6 months, there was a 19.5 ± 11.8 mm reduction in size, in the macroadenoma group, after a mean of 74.8 ± 62.2 months, there was a 11.2 ± 7.8 mm reduction in size and in the microadenoma group, after a mean of 52.6 ± 33.5 months, there was a 4.0 ± 3.4 mm reduction in size. There was a greater reduction in tumour size in the males when compared to the females [-18.6 ± 12.6 mm vs -9.1 ± 6.3 mm, p=0.009] (Table 7). Only 5 patients with a microadenoma had a follow-up MRI scan, and in 3 of these patients no residual tumour was visible.

However, 18 patients with a macroadenoma had a repeat MRI scan and in 3 of these patients there was a normal pituitary gland and in 4 of these patients there was an empty Sella (Table 7). Only 1 patient with a microadenoma had an increase (of 1 mm) in size of their tumour and 2 patients with a macroadenoma their tumour size remained the same size despite a decrease in their serum prolactin level (Table 7).

Hormonal abnormalities after treatment

In the giant adenoma group, 1 patient developed new hypothyroidism after treatment that included a VP shunt, in 2 patients hypogonadism resolved, 1 patient developed new onset hypoadrenalism and in 1 patient the hypoadrenalism resolved. In the macroadenoma group, 2 patients developed new hypothyroidism after treatment, in 1 patient the hypothyroidism resolved and in 8 patients hypogonadism resolved. In the microadenoma group, in 3 patients the hypothyroidism resolved, in 12 patients the hypogonadism resolved and in 1 patient the hypoadrenalism resolved. Hypogonadism was present in 0.0% (n=17) with a microprolactinoma, 38.5 % (n=10) with a macroprolactinoma and in 77.8% (n=7) with a giant prolactinoma (Figure 1 B). Hypothyroidism was present in 23.5% (n=4) with a microprolactinoma, 50.0% (n=13) with a macroprolactinoma and in 88.9% (n=8) with a giant prolactinoma (Figure 2 B). Hypoadrenalism was present in 5.9% (n=1) with a microprolactinoma, 26.9% (n=7) with a macroprolactinoma and in 66.7% (n=6) with a giant prolactinoma (Figure 3 A). Males were more likely than females to have hypogonadism [78.6% (n=11) vs 15.8% (n=6), p<0.001], hypothyroidism [71.4% (n=10) vs 13.2% (n=5), p=0.011] and hypoadrenalism [64.3% (n=9) vs 13.2% (n=5), p<0.001]. Over a mean time of 46.5 months the prolactin level reduced from 2997.0 (412.0-4671.0) ug/l at presentation in males to 12.6 (4.0-27.0) ug/l and from 145.5 (73.0-726.0) ug/l to 19.5 ug/l (10.2-85.0) in females. After a mean time of 59.8 ± 53.3 months of follow up, MRI showed a mean reduction in tumour size of 18.6 ±12.6 mm in males and 9.1 ± 6.3 mm in females (Table 2).

2.6 Discussion

This study is one of the largest studies from Africa and the 1st study from South Africa to describe a cohort of patients diagnosed with a prolactinoma. The main aim of this

study was to describe the presentation and clinical outcomes of patients attending the Endocrine Clinic with a diagnosis of a prolactinoma. The results of this study were similar to Beyene *et al* (2021) in that the majority of the patients were female (Abdalla 73.1% vs Beyene 76.8%), the majority had a macroprolactinoma (Abdalla 67.2% vs Beyene 79.7%), surgery was required in few (Abdalla 13.5% vs Beyene 11.6%) and the majority had a good clinical response to dopamine agonists (Abdalla 90.3% vs Beyene 85.5%). The preponderance of females in this study is consistent with the literature. The reason for the predominance of females in studies is attributed to the nature of the disease presentation, usually resulting in women seeking medical attention for infertility and/or a menstrual disturbance. The absence of these symptoms may underdiagnose early disease in males and may also result in them presenting later in the course of their disease only when they develop symptoms of mass effect. Indeed, in this study we have found that males were more likely to have a macroprolactinoma and a giant prolactinoma with only one male patient having a microprolactinoma. In addition, males were more likely to present with symptoms of mass effects such as headache and visual disturbances. According to the 2017 World Health Organization classification of pituitary adenomas, the more aggressive and resistant densely granulated prolactinomas are likely to be found in males (1). Also, multiple studies have also shown that the prevalence of macroprolactinomas is more common in males compared to females (2) (3) (4).

Interestingly, we found patients with a microprolactinoma were more likely to present with galactorrhea in comparison with patients in the macroprolactinoma and giant prolactinoma groups, despite the prolactin level in the latter groups being significantly higher. This is difficult to explain. Some macroprolactinomas may have higher levels of macroprolactin rather than monomeric prolactin, however, in our institution, macroprolactinemia is often excluded when an elevated prolactin level is identified. Aisaka *et al* (2018) demonstrated that the presence of macroprolactin was a significant factor in reducing the onset of galactorrhea (5).

Notably, headache was the most common symptom among all groups and more common in patients with a macroprolactinoma. The high prevalence of headache in patients with a microprolactinoma is surprising given the small size of most microprolactinomas, considered unlikely to cause any significant mass effect. A few reports have found that patients with a microprolactinoma may present with severe headaches, whereas the patients with macroprolactinoma may not have headaches

and may present with visual symptoms and/or hormonal deficiencies. The functionality and biochemical activity of a microprolactinoma may explain the mechanism of headache in patients having small size tumours. Also, the alterations in the dopamine–prolactin axis may play a role in the pathogenesis of headaches, this hypothesis is supported by the fact that usually, patients with prolactinomas respond well and the intensity of the headache improves after commencement of treatment with a dopamine agonist and before regression of adenoma size (6) (7) (8).

Apoplexy was rare in this cohort with only two patients presenting with apoplexy from the macroadenoma and giant adenoma groups. In a large retrospective clinic population study, including 368 patients with a prolactinoma, the overall prevalence of pituitary hemorrhage in patients with a prolactinoma was 6.8% and was significantly higher in patients with macroadenomas 20.3% versus 3.1% in patients with a microadenoma (9) (10) (11).

Interestingly, one patient with a giant prolactinoma presented with epistaxis. In this patient the prolactin level was very high, and an MRI of the pituitary gland showed a large suprasellar lesion extending into the nasopharynx. The patient responded well to treatment with cabergoline and the tumour regressed in the size without requiring surgical intervention. Epistaxis is a rare presenting symptom in patients with a pituitary adenoma. It has been attributed to infrasellar extension of the tumour into the nasopharynx or rupture of an internal carotid artery aneurysm embedded within a large prolactinoma or an ectopic pituitary adenoma (12) (13) (14).

Medical management with a dopamine agonist is the primary treatment of a prolactinoma. All patients in this study received medical treatment with only a few requiring some form of surgical intervention. or radiotherapy. The main indications for surgery were neurological deficit including visual loss, apoplexy, or resistance to medical treatment (cystic prolactinoma). No patient developed dopamine agonist intolerance. The outcome of hormonal status, tumour size, and improvement of vision were better in patients who received medical treatment versus those who received medical and underwent surgery (15).

All patients experienced a decrease in prolactin level on medical treatment and, in parallel with this, most patients experienced a reduction in tumour size. In most patients the prolactin level is thought to be an accurate predictor of tumour size (16). Only 2 patients in our cohort experienced a marginal increase in tumour size despite a reduction in the serum level of prolactin (17).

Hypogonadism and hypothyroidism resolved on treatment to various degrees in all patients, however, hypoadrenalism did not resolve significantly after treatment in any patient. In addition, hormone deficiencies in patients with a giant prolactinoma were least likely to resolve on treatment. Male patients were more likely to present with a hormonal deficiency, most likely explained by the larger size of their tumours on presentation. All patients who received radiotherapy developed panhypopituitarism. A reduction in the level of prolactin and the reduction in tumour size achieved after treatment with a dopamine agonist often results in the improvement of various hormone deficiencies.

In a prospective study that assessed the gender response to cabergoline, after 5 years of treatment menses had resumed in 82% of women and libido had improved in 57% of men. Studies have also shown that hypogonadotropic hypogonadism was successfully treated in 90% of the patients who were treated with Cabergoline and in 70–80% when treated with bromocriptine (18) (19).

A systematic review and meta-analysis that included 736 men treated medically mostly with cabergoline no difference in the success rate in treating hyperprolactinemia due to microprolactinoma or macroprolactinoma(20). Another study included 51 patients followed for 24 months treated with cabergoline describe the same conclusion (21). In contrast, a macroprolactinoma may cause permanent damage to pituitary cells due to mechanical destruction, a surgical procedure, or radiation and hypogonadism may become irreversible (18) (22).

In this cohort there were four adolescent patients, age 17-18 years at presentation, three females and one male, two of them had a giant prolactinoma, one had a macroprolactinoma and one had a microprolactinoma. The patient who presented with a microprolactinoma had no hormonal deficiency on presentation as well as after treatment, whereas the patient with macroprolactinoma had only hypothyroidism at the time of the diagnosis and the pituitary function became normal during the period of the follow-up. The giant macroadenoma patients, one of them presented with panhypopituitarism which persisted after treatment, the other patient presented with hypogonadism and hypothyroidism and developed panhypopituitarism during follow-up. All were treated medically with a dopamine agonist. On follow-up, periods the MRI normalize in two patients (the microprolactinoma and the macroprolactinoma patients) as well as the prolactin level. A prolactinoma is rare in adolescents but has a significant

impact on growth and development. Similar to adults, the first-line treatment is a dopamine agonist and the indications of surgical intervention and radiation therapy are also the same, but the long-term prognosis and consequence of the disease is not well known (23) (24).

This study has few limitations. The main limitation is that it is a cross-sectional study so only associations can be shown, and causation cannot be implied.

The strengths of this study reside in it being the first description of patients with a prolactinoma being managed in sub-Saharan Africa. It represents real-world local clinical data that can now be used to design long-term prospective studies to better guide investigation and management of these patients. The median length of follow-up of 5 years allows for adequate comment on treatment success with respect to serum prolactin levels, reduction in tumour size and resolution of hormonal deficiencies.

2.7 Conclusion

Prolactinomas were more common among young females, particularly a microprolactinoma. It is most commonly associated with a headache, sexual dysfunction and a hormone deficiency. With medical management most patients experienced a reduction in prolactin levels and a reduction in tumour size. This was associated with the resolution of hypogonadism in the majority, however, hypothyroidism and hypoadrenalism are unlikely to resolve in the majority irrespective of tumour size.

Future research might include increasing the number of cases and assessing factors that predict remission on medical treatment so that medical treatment can be withdrawn timeously thereby decreasing the costs associated with long-term management of these patients.

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Table 1: Functional pituitary Adenomas

Pituitary cell type	Hormone	Disease
Lactotroph	Prolactin	Prolactinoma
Somatotroph	Growth Hormone	Acromegaly
Corticotroph	Adrenocorticotropin	Cushing Disease
Gonadotroph	Follicle-stimulating Hormone	inappropriate FSH over-secretion (Gonadal hyperstimulation)
Thyrotroph	Thyroid Stimulating Hormone	TSH-secreting Tumor

Table 2: Causes of hyperprolactinemia

Physiologic	Pharmacologic	Pathologic
Lactation & pregnancy	Antipsychotics, first generation	Prolactinoma
Stress	Antipsychotic, second generation	Hypophysial stalk lesion (stalk effect)
Exercise	Antidepressants, cyclic	Hypothyroidism
Sleep	Antidepressants SSRI	Chronic renal failure
Seizures	Antihypertensives Methyldopa Verapamil	Sever liver failure

Table 3: Clinical presentation of prolactinoma

Neurological symptoms	Hormonal deficiency
Headache	Hypogonadism (amenorrhea, erectile dysfunction, loss of libido, infertility)
Visual field defect	Growth hormone deficiency
Loss of vision	Hypothyroidism
Pituitary apoplexy	Hypercortisolism
Cerebrospinal fluid rhinorrhea	Galactorrhea

Table 4: Baseline characteristics and presentation of patients with a prolactinoma by size of the prolactinoma

Variable	Total	Macroprolactinoma	Microprolactinoma
	N=52	N=35	N=17
Age at diagnosis	36.5 (29.0-46.0)	36.0 (27.0-49.0)	38.0 (30.0-44.0)
Female sex	38 (73.1%)	22 (62.9%)	16 (94.1%)
Apoplexy	2 (3.8%)	2 (5.7%)	0 (0.0%)
Altered Vision	15 (28.8%)	14 (40.0%)	1 (5.9%)
Headache	42 (80.8%)	31 (88.6%)	11 (64.7%)
Field defect	20 (38.5%)	18 (51.4%)	2 (11.8%)
CN palsy	6 (11.5%)	6 (17.1%)	0 (0.0%)
Galactorrhea	22 (42.3%)	10 (28.6%)	12 (70.6%)
Amenorrhea*	26 (68.4%)	14 (36.8%)	12 (31.6%)

* only females included so n=38

Table 5: Clinical presentations, and managements at diagnosis and after treatment in the various categories of prolactinomas

	Total	Giant Adenoma	Macroadenoma	Microadenoma
	N=52	N=9	N=26	N=17
Age at diagnosis	36.5 (29.0-46.0)	34.0 (28.0-38.0)	38.5 (27.0-52.0)	38.0 (30.0-44.0)
Female sex	38 (73.1%)	4 (44.4%)	18 (69.2%)	16 (94.1%)
Apoplexy	2 (3.8%)	1 (11.1%)	1 (3.8%)	0 (0.0%)
Altered Vision	15 (28.8%)	4 (44.4%)	10 (38.5%)	1 (5.9%)
Visual field defect	20.8 (38.5%)	8 (88.9%)	10 (38.5%)	2 (11.8%)
Headache	42 (80.8%)	9 (100.0%)	22 (84.6%)	11 (64.7%)
CN palsy	6 (11.5%)	3 (33.3%)	3 (11.5%)	0 (0.0%)
Galactorrhea	22 (42.3%)	2 (22.2%)	8 (30.8%)	12 (70.6%)
Amenorrhea*	26 (68.4%)	2 (50.0%)	12 (66.7%)	12 (75.0%)

Table 6: Clinical presentation by sex

	Total	Female	Male	p-value
	N=52	N=38	N=14	
Diagnosis				
Age	36.5 (29.0-46.0)	36.0 (27.0-44.0)	37.0 (31.0-59.0)	0.39
Classification				
Giant Prolactinoma	9 (17.3%)	4 (10.5%)	5 (35.7%)	0.021
Macroprolactinoma	26 (50.0%)	18 (47.4%)	8 (57.1%)	
Microprolactinoma	17 (32.7%)	16 (42.1%)	1 (7.1%)	
Apoplexy	2 (3.8%)	2 (5.3%)	0 (0.0%)	0.009
Altered Vision	15 (28.8%)	9 (23.7%)	6 (42.9%)	0.18
Headache	42 (80.8%)	31 (81.6%)	11 (78.6%)	0.18
Field defect	20 (38.5%)	11 (28.9%)	9 (64.3%)	0.020
CN palsy	6 (11.5%)	2 (5.3%)	4 (28.6%)	0.020
Galactorrhea	22 (42.3%)	19 (50.0%)	3 (21.4%)	0.064

Table 7: Serum prolactin level and tumor size at diagnosis and after treatment by size category of the prolactinoma

	Total	Giant Adenoma	Macroadenoma	Microadenoma
Prolactin level (ug/L)	N=52	N=9	N=26	N=17
At diagnosis	322.5 (94.0-4282.0)	10986.0 (6278.0-14051.0)	434.5 (133.0-282.0)	97.0 (72.0-142.0)
After treatment	17.5 (8.6-82.5)	411.0 (15.0-1073.0)	13.2 (8.2-27.0)	19.0 (7.0-80.0)
Tumour size				
At diagnosis	N=46	N=9	N=25	N=12
Tumour size	23.39(17.0)	51.6(6.4)	21.4(8.8)	6.1(2.3)
After treatment	N=31	N=8	N=18	N=5
Tumour size change (mm)	-12.2(9.7)	-19.5(11.8)	-11.2(7.8)	-4.0(3.4)
Change in size*				
Decreased	28 (90.3%)	8 (100%)	16 (88.9%)	4 (80%)
Increased	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
Not changed	2 (6.5%)	0 (0.0%)	2 (11.1%)	0 (0.0%)
Follow up (months)	59.8 (53.3)	30.5 (23.6)	74.8 (62.2)	52.6 (33.5)
Size classification				
Empty Sella	4 (12.9%)	0 (0.0%)	4 (22.2%)	0 (0.0%)
Macroadenoma	18 (58.1%)	8 (100.0%)	9 (50.0%)	1 (20.0%)
Microadenoma	3 (9.7%)	0 (0.0%)	2 (11.1%)	1 (20.0%)
Normal pituitary	6 (19.4%)	0 (0.0%)	3 (16.7%)	3 (60.0%)

Table 8: Tumour size, prolactin levels and hormone abnormalities at diagnosis and after treatment by sex

	Total	Female	Male	p-value
	N=52	N=38	N=14	
Diagnosis				
Tumour size (mm)	23.3 (17.0)	18.5 (14.5)	34.3 (17.7)	0.003
Hypothyroidism	27 (51.9%)	18 (47.4%)	9 (64.3%)	0.28
Hypogonadism	39 (75.0%)	26 (68.4%)	13 (92.9%)	0.071
Hypoadrenalism	15 (28.8%)	5 (13.2%)	10 (71.4%)	<0.001
Prolactin	322.5 (94.0-4282.0)	145.5 (73.0-726.0)	2997.0 (412.0-4671.0)	0.013
Follow-up				
Tumour Size Change	-12.2 (9.7)	-9.1 (6.3)	-18.6 (12.6)	0.009
Hypothyroidism	25 (48.1%)	15 (39.5%)	10 (71.4%)	0.041
Hypogonadism	17 (32.7%)	6 (15.8%)	11 (78.6%)	<0.001
Hypoadrenalism	14 (26.9%)	5 (13.2%)	9 (64.3%)	<0.001
Prolactin level	17.5 (8.6-82.5)	19.5 (10.2-85.0)	12.6 (4.0-27.0)	0.27

Figures:

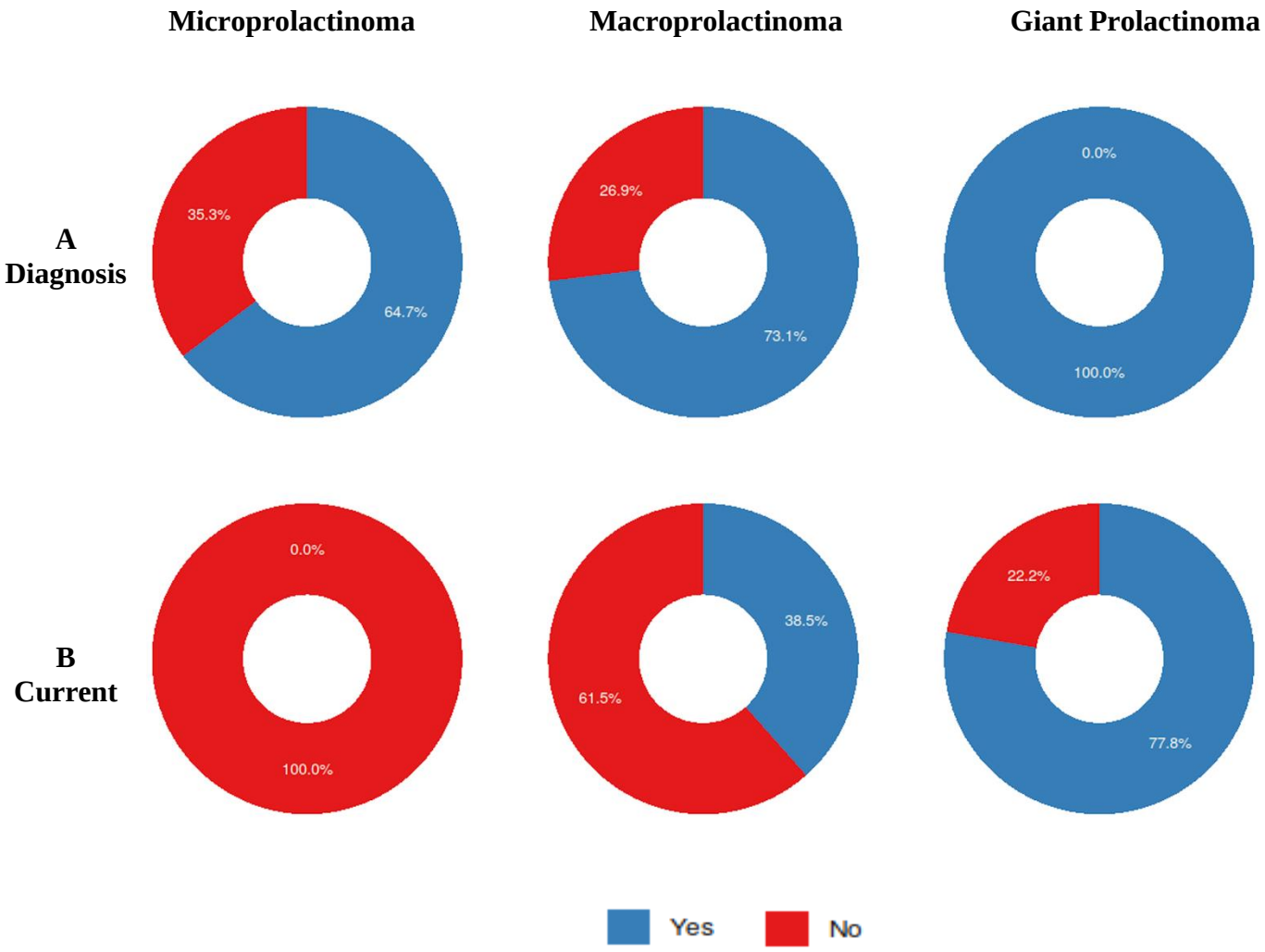

***Figure 1**: prevalence of hypogonadism at diagnosis and after treatment in various categories of prolactinomas*

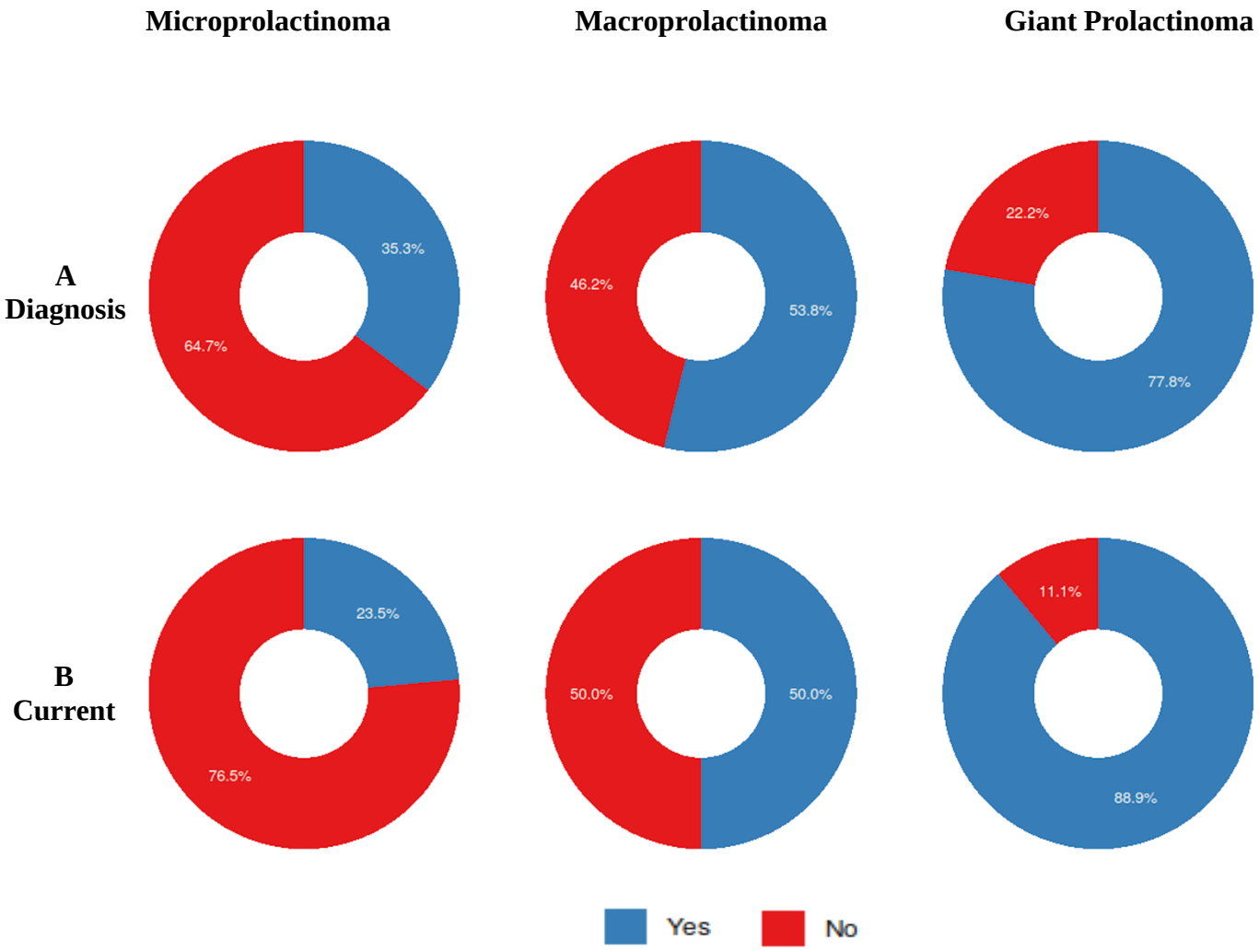

Figure 2: prevalence of hypothyroidism at diagnosis and after treatment in various categories of prolactinomas

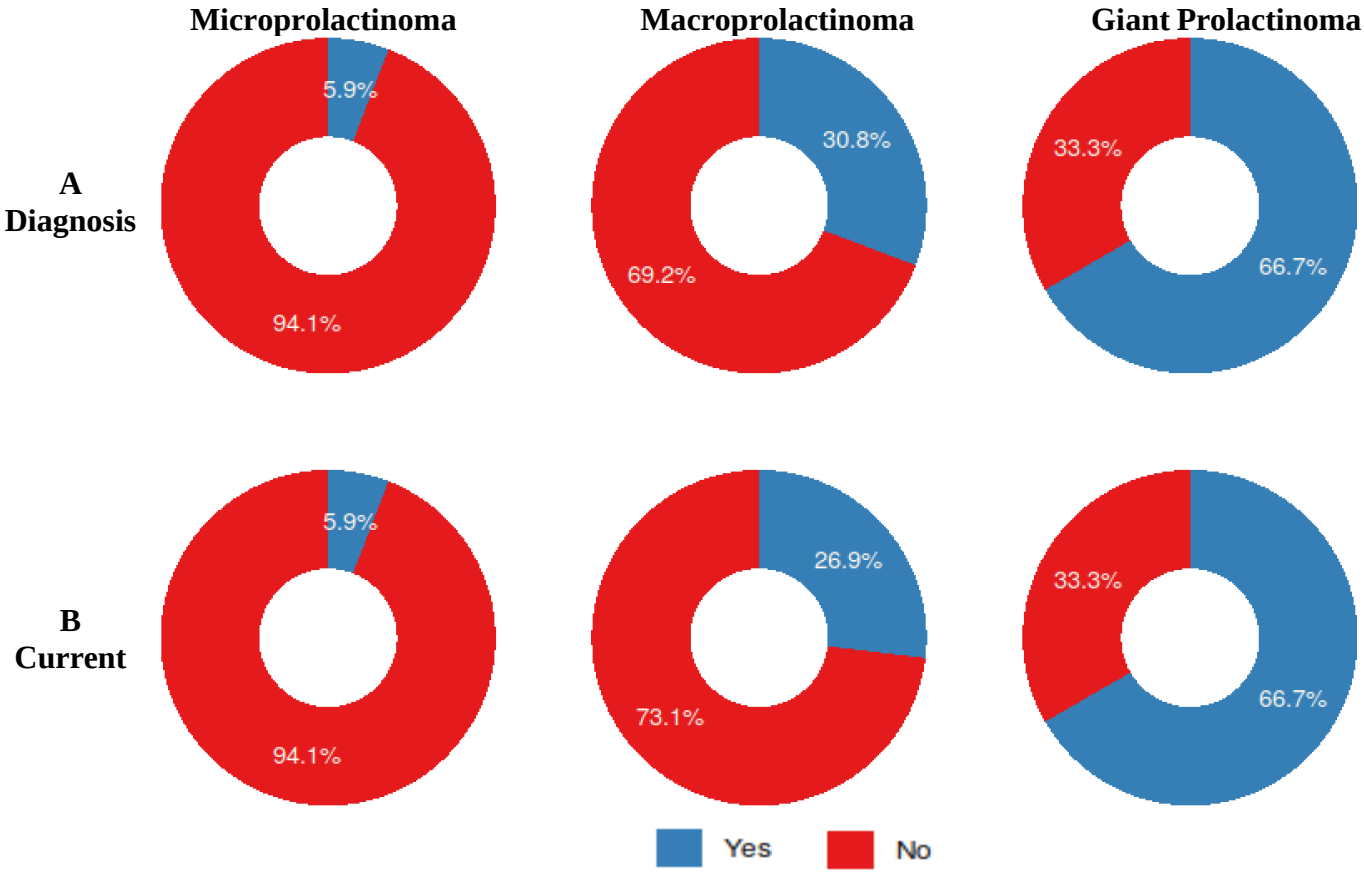

Figure 3: Prevalence of hypoadrenalism at diagnosis and after treatment in various categories of prolactinomas

Appendices

Data capture sheet

Patient sticker

Age at presentation …… Current age……

Clinical presentation

Apoplexy Y / N Incidental finding Y / N Altered vision Y / N

Symptoms

Headache Y / N
Visual field defect Y / N
Cranial nerve palsy Y / N
Galactorrhea Y / N
Incidental finding Y / N
Amenorrhea Y / N

Diagnosis

Prolactinoma

MRI	**Presentation**	**Last**
Date		
Diagnosis		
Size		

Blood tests (please indicate whether normal, high or low)

	Hypothyroidism	Hypogonadism	Hypoadrenalism	Prolactin level
At diagnosis	Y / N	Y / N	Y / N	
Last follow up	Y / N	Y / N	Y / N	

Management of primary diagnosis

1. Medical Y / N Type _____
2. Surgery Y / N Procedure _____
3. Radiotherapy Y / N Procedure _____

Outcome

Improvement in vision Y / N / NA Cure Y / N / NA

Ethics approval

UNIVERSITY OF CAPE TOWN
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15 March 2019

HREC REF: 170/2019

A/Prof J Dave
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Dear A/Prof Dave

PROJECT TITLE: PREVALENCE, CLINICAL MANIFESTATIONS, TREATMENT OUTCOMES AND COMPLICATIONS OF PITUITARY DISEASE IN PATIENTS PRESENTING TO THE PITUITARY AND ENDOCRINE CLINICS AT GROOTE SCHUUR HOSPITAL. (MASTERS CANDIDATE: DR M ABDALLA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Mohamed Abdalla will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.