Hyperprolactinaemia: when MRI is indicated?

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Abstract:
Design: This prospective study was carried out at the magnetic resonance imaging (MRI) unit at the department of diagnostic imaging of Al-Kadhmiya Teaching Hospital over a period of 26 months.
Objective: To establish a strategy for the use of MRI of the pituitary region in patients with hyperprolactinaemia based on the possibility of finding a pathology in the pituitary region as a cause of hyperprolactinaemia with respect to serum prolactin (PRL) as well as the analysis of serum PRL in relation to the size of adenoma in the pre & post medical treatment evaluation to determine the need for MRI in the follow up in patients with pituitary adenoma.
Subjects & Methods: We selected 69 women recently found to have clinical & biochemical evidence of hyperprolactinaemia with serum PRL exceeding the double the upper normal level of the control. MRI of the pituitary region & serum PRL were assessed at the initial presentation for all patients & after the institution of bromocriptine (BRC) treatment for 28 patients who were shown to have either micro or macroadenomas at the initial MRI. The diameter of the adenoma served as a predictor for its size & was considered for correlation with serum PRL level at the follow up period of 3 , 6 & 12 months of treatment.
Results: At the initial MRI, 27 patients had microadenomas (39.1%), 12 patients had macroadenomas (17.4%), 9 patients had empty sella turcica (13.1%), and 21 patients (30.4%) had no obvious abnormality in the pituitary region The analysis of individual serum PRL level to establish a cut-off point of serum PRL above which all cases were positive for a pathology in the pituitary region on MR imaging, revealed a cut-off value = 84.6 ng/ml. A strong correlation has been found between the size of adenoma and serum PRL level at the initial presentation as well as at the follow up assessment that revealed a parallel reduction in adenoma diameter & serum PRL level.
Conclusion: MRI of the pituitary region is justifiable in women with hyper-prolactinaemia when serum PRL level is approximately two & a half folds of the upper normal level where its likely to reveal an abnormality , but it should not be used routinely for the follow up of patients on treatment as the assessment of serum PRL level will suffice as a predictor of tumor shrinkage unless there is no response to medical treatment or the patient developed new symptoms that suggest increase in the size of the adenoma or involvement of the surrounding structures.
Keywords: hyperprolactinaemia, MRI, pituitary adenoma

Introduction:

Hyperprolactinaemia is the most common disorder of the anterior pituitary, caused by an increased secretion of prolactin (PRL) from the pituitary gland [(1)]. Although the disorder is detected in less than 1% of the general population [(2)], it has been found in up to 25% of women with secondary amenorrhea [(3)] and in up to 5% of men being evaluated for sexual dysfunction [(4)]. Typical presenting features are oligomenorrhea or amenorrhea and/or galactorrhea. Hyperprolactinaemia in men may cause decreased libido, erectile dysfunction [(5)] and rarely gynaecomastia [(4)] . Hyperprolactinemia may lead to bone loss in both men and women due to the inhibitory effect of PRL on sex steroids [(6)]. Hyperprolactinaemia can occur as a consequence of pharmacological alteration in the pathways that control PRL secretion or of physiological or

metabolic effect on PRL production and clearance or due to neoplastic conditions [4]. Common causes of hyperprolactinaemia are listed in table 1.

Prolactinomas are the most common endogenous cause of hyperprolactinaemia and the most common functioning pituitary tumor [1, 8].

The Dopamine agonist, Bromocriptine (BRC), has been the mainstay of medical therapy in prolactin secreting adenomas. It reduces the serum PRL level, inhibits PRL secretion and decreases tumor size in 70-100% of patients. [5].

Evaluation with pituitary imaging is essential even with mild PRL elevation in order not to overlook a non secreting tumor which if left untreated there is risk of continued growth and compression of optic chiasm [8]. The role of MR imaging in the initial evaluation & diagnosis of hyperprolactinaemia is well established, MRI of pituitary region may reveal a prolactinoma, a large mass lesion which cause stalk compression or rarely infiltrative process involving the pituitary region [5].

TABLE 1 – Common causes of hyperproloctinemia[1,7]

- Physiologic: Pregnancy, lactation , stress
- Non Physiologic
  - Prolactin-secreting tumors: Prolactinomas – unihormonal - Tumors secreting multiple hormones
  - Drugs :-Dopamine synthesis inhibitors, depletors, and receptor blockers, methyldopa , reserpine , verapamil , phenothiazines , thiothixenes, and butyrophenones -Others- estrogen, narcotics
  - Hypothalamic lesions-tumor, sarcoid, histiocytosis X, and other infiltrative diseases
  - Pituitary stalk lesions-trauma (stalk section) and compression by tumor or other mass lesions
  - Miscellaneous:-Systemic illnesses (cirrhosis, renal failure)-Primary hypothyroidism -Chest wall and spinal cord lesions- postsurgical, herpes zoster,-burns-Polycystic ovarian disease
- Idiopathic

Although many researches have dealt with the application of MRI in pituitary prolactinomas , to our knowledge non of these have suggested a strategy for the use of MRI in hyperprolactinaemia based on the possibility of finding a pathology in the pituitary region as a cause of hyperprolactinaemia with respect to serum PRL level as well as the analysis of serum PRL in relation to the size of adenoma in the pre & post medical treatment evaluation to determine the need for MRI in the follow up in patients with pituitary adenoma

Patients and Methods:

A prospective study over a period of 26 months carried out at Al-Kadhmiya Teaching Hospital. The subjects of the study composed of 69 women with clinical and biochemical evidence of hyperprolactinaemia. The study subjects were selected after exclusion of drug intake that may contribute to hyperprolactinaemia, any clinical & biochemical evidence of hypothyroidism & exclusion of features of associated renal & hepatic dysfunction. The patients agreed to be part of the study & committed to have the follow up as the necessary in accordance with the study design.

Data collection regarding age, chief complaint and associated symptoms were obtained at the initial presentation. The dose and duration of treatment were recorded after institution of medical therapy with BRC. All those data were obtained in each case and recorded on a special protocol form.

The study included 69 women recently diagnosed of having hyperprolactinaemia with serum PRL level exceeding double the upper normal control value (upper normal level = 35 ng/ml , vidas prolactin) .The mean serum PRL level was 159.9 ng/ml (range 70.6-466 ng/ml). MRI of the pituitary region was performed at the initial presentation for all 69 patients but only 28 patients underwent another MRI after medical treatment with BRC. The findings of the pre & post medical treatment MRI were recorded. The follow up MRI was performed after 3 months, 6 months & 12 months interval

Magnetic resonance imaging was performed at 1.5 T superconductive unit (Gyroscan;Philips). The examination employed T1-weighted TSE coronal and sagittal planes pre & post administration of Gd DTPA (0.1 ml / kg body weight). In this study T2- weighted images were usually not obtained except for cases in which information concerning the presence of hemorrhage was required.

The analysis of MR examination focused on the detection of a focal lesion within the sella turcica or in the parasellar region with assessment of the size, signal intensity & the delineation of the lesion from the surrounding structures. Only the size of the tumor is included & discussed in details as it relates closely to the aim of the study. The size was measured on the coronal and sagittal images by assessing the maximum height, width & AP diameter & the mean diameter, expressed in millimeters, is used to represents the tumor volume based on the criticism that tumors are seldom spherical in shape & thus calculation of the tumor volume using ellipsoid formula could lead to misleading results, in disagreement with previous study [9] & in agreement with other studies [10-12]. We evaluated tumor shrinkage as reduction in the mean diameter compared with baseline by a semi quantitative four point scale as follows : less than 10% as absent , 10-20% as mild , 20-30% as moderate & 30% as remarkable

Statistical Analysis:

In order to define the cut-off point of serum PRL level above which all cases were positive for an abnormality in the pituitary region on MRI, The 95% lower confidence limit was calculated to represent the cut-off value.

The correlation coefficient (r) was calculated to assess the correlation between serum PRL and the diameter of the adenoma.

Results:

The pituitary region had been studied using MRI in 69 women with clinical and biochemical evidence of hyperprolactinaemia. The age of the patients ranged from 17- 50 y (mean age 30.7y).

Out of the 69 patients with hyperprolactinaemia , 27 patients were shown to have microadenoma (39.1%), 12 had macroadenoma (17.4%), 9 had empty sella turcica (13.1%), and in 21 patients (30.4%) no abnormal finding could be identified in the MR examination and were reported as normal MR study

Table (2) shows the distribution of different MR findings in relation to serum PRL with the mean and range of serum PRL indicated for each group in table (3).

Table (2): distribution of different MR finding in relation to serum PRL

	Serum PRL level (ng / ml)					
	70–139	***140–209***	***210–279***	***280–349***	***350–419***	***≥420***
Microadenoma	7	13	6	1	0	0
Macroadenoma	1	3	3	4	0	1
Empty sella	9	0	0	0	0	0
Normal study	21	0	0	0	0	0
Total	38	16	9	5	0	1
Percent (%)	***55.0***	***23.1***	***13.0***	***7.2***	***0***	***1.4***

Table (3): The mean and the range of serum PRL indicated for each group

	PRL mean (ng/ml)	***PRL range(ng/ml)***
Microadenoma	205.1	97.8 –286
Macroadenoma	285.3	75.9 – 466
Empty sella	73.6	71.3 – 76.1
Normal study	75.9	70.6- 74.4

The analysis of individual serum PRL level to establish a cut-off point of serum PRL above which all cases were positive for a pathology in the pituitary region on MR imaging, revealed a cut-off value = 84.6 ng/ml

Microadenomas:

Microadenomas (diameter of 10 mm or less) were identified in 27 patients (39.1%). The mean age was 30.5 y (range 18-38 y), and the mean serum PRL level was 205.1 ng / ml (range 97.8-286 ng / ml). The diameter of the tumor ranged from 4.6 mm to 9.7 mm (mean=7.1 mm). A positive correlation exists between the serum PRL & diameter of microadenoma (0.88).

Follow up MR examinations were performed in 21 patients with microadenoma after institution of BRC treatment at 3 months, 6 months & 12 months interval. The dose of BRC treatment ranged from 2.5-5 mg three times a day.

Macroadenomas:

Macroadenomas (diameter more than 10 mm) were identified in 12 patients (17.4%). The mean age was 36.4 y (range 33- 43 y). The mean serum PRL level was 285.3 ng/ml (range 75.9– 466 ng/ml). The tumor ranged in diameter from 12.3-27.8 mm with an average of 18.2 mm. A positive correlation exists between the serum PRL & diameter of macroadenoma (0.90)

Follow up MRI was performed in 7 patients with macroadenoma after institution of BRC treatment at a dose ranged from 5-7.5 mg three times a day, 6 of the patients had MRI at 3, 6 & 12 months interval & one of them had MRI at 3 & 4 months after BRC as this patient suddenly developed headache & visual disturbance & MRI revealed the development of hemorrhage within the macroadenoma.

Effect of 12 months treatment on serum PRL during BRC treatment :

PRL level lowered progressively in both micro & macroadenoma patients. At 12 months, PRL normalized in 16 patients out of 21 with microadenoma (76.1%) & 3 patient out of 6 with macroadenoma (50%).

Those patients who did not normalize their PRL were shown to have higher mean base line level of serum PRL than those who normalize their serum PRL level (325.8 ng/ml vs. 240.6 ng/ml). Figure 1 & 2 shows the decline of serum PRL in both micro & macroadenomas over the treatment period of 12 months.

Effect of 12 months treatment on tumor shrinkage:

The mean tumors diameters were progressively reduced in all treated cases during the 12 months of treatment by 76% in microadenoma & by 68% in macroadenoma. A remarkable shrinkage in size (> 30%) was achieved in all cases of microadenoma while macroadenomas showed moderate tumor reduction (20% -30%) in all cases (fig.3) but one that showed 12% reduction in diameter (mild shrinkage).

The reduction in serum prolactin correlated positively with a parallel reduction in tumor diameter (0.90 for microadenoma & 0.8 for macroadenoma). Figures 4 & 5 show the shrinkage of tumor diameter in micro & macroadenomas over the treatment period of 12 months.

therapy shows pronounced reduction in the size of the adenoma.

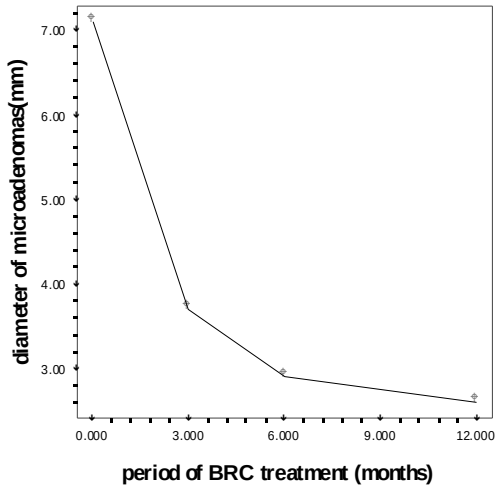

Figure 4: shrinkage of tumor diameter in microadenomas over the treatment period of 12 months

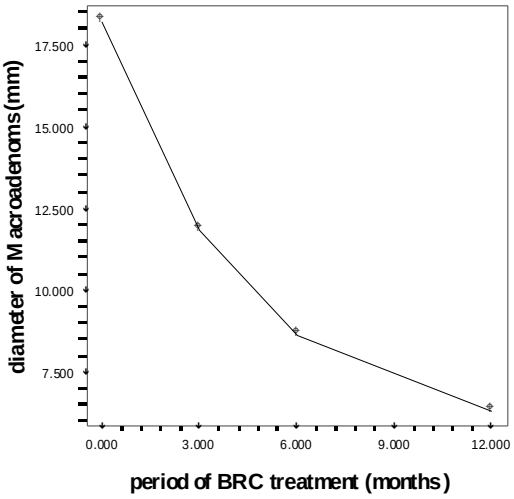

Figure 5: shrinkage of tumor diameter in macroadenomas over the treatment period of 12 months

Discussion:

The role of MRI in the assessment of the pituitary gland in patient with hyperprolactinaemia is well established[13-16,] however to our knowledge non of these articles or more recent articles that dealt with the management of hyperprolactinaemia had suggested a strategy for the use of imaging modalities namely MRI in the diagnosis & follow up of patients after medical treatment. In a recent review, Serri et al [17] stated that MRI is considered whenever elevated serum PRL is found after exclusion of pharmacological, physiological & secondary causes of hyperprolactinaemia, in this way MRI would be considered as an expensive routine examination. We aimed at this study to investigate & follow up patients with double upper normal PRL level by both serial MRI & serial serum PRL assessment over a period of 1 year for each patient in the follow up group. Initially we performed MRI in 69 women with serum PRL level exceeding 70 ng/ml (double upper normal level N= 35 ng/ml) looking for a genuine abnormality in the sellar & para sellar region, We didn't consider the serum PRL level in patients with empty sella turcica in the calculation of the cut off value as empty sella is considered as a normal variant rather than a true pathology [18]. Consequently we determined the serum PRL level of 84.6 ng /ml (approximately two & a half fold the upper normal PRL level) as a cut off value above which all cases were positive for an abnormality in the pituitary region. In a local study [19] who investigated 23 patients with hyperprolactinaemia, a triple upper normal level of PRL was considered as a cut off value. We believe that the limited sample size of that study may attribute to this difference in the cut off value, moreover our result is more acceptable in the clinical practice as different article have mentioned that a non functioning macroadenomas could cause only a mild increase of serum PRL as a result of compression of the pituitary stalk [20, 21] & one may expect to find macroadenoma even when serum PRL level is less than triple upper normal level.

The design of this study was both prospective & longitudinal & involved following up 28 patients who were shown to have micro or macroadenoma after 3, 6 & 12 months following institution of medical therapy with BRC.

A strong correlation (0.88 & 0.90 for microadenoma, & 0.90 & 0.80 for macroadenoma) was found between the level of serum PRL & the size of the adenoma (represented by the mean diameter) at the pre & post treatment assessment. These results concur fully with those of Lundin et al & Gillam et al [16, 22] who found a positive correlation between the tumor size and the PRL level. Rand

et al [14] did not found a similar correlation in a series of 38 hyperprolactinaemic patients with microadenoma but did observe a positive trend

The follow up of patients after BRC treatment revealed a reduction in serum PRL as well as a parallel reduction in tumor diameter, the steeper decline was noted at the 3rd month of treatment followed by a more gradual decline over the next 9 months (fig 1, 2, 4, 5). Our results come in accordance with previous study by Bevan et al , Siek et al & Vanverlaat et al [23-25]who found that the maximum tumor shrinkage took place with the first three months & the reduction then after occur at much slower rate .

A remarkable shrinkage of tumor size was achieved in all cases of microadenomas & moderate shrinkage was achieved in all but one case of macroadenoma regardless to the pre treatment serum PRL. The single macroadenoma that revealed only mild reduction in size (12%) has an initial serum PRL level of 75.9 ng/ml , such a mildly elevated serum PRL with the presence of a macroadenoma suggests that this lesion is more likely to be a non functioning adenoma rather than a macroprolactinoma & this suggestion is further reinforced by the mild reduction of tumor diameter in response to BRC as many studies stated that non functioning adenoma are barely responsive to dopamine agonist & that even if they show tumor shrinkage , it will not be dramatic or remarkable[26-30]

In conclusion as an expensive imaging modality, MRI need only to be performed in patients with hyperprolactinaemia when serum PRL level exceeds two & a half fold the upper limit of the control. In addition , MRI is not justifiable for the follow up of every patient with adenoma who are on medical treatment, as the simple , cheap & minimally invasive assessment of serum PRL will be sufficient taking into knowledge that a reduction in serum PRL is associated with a parallel reduction in the tumor size , however MRI is still indicated when there is failure of response to medical treatment or when the patient develops new symptoms that suggest increase in the size of the tumor or involvement of the surrounding structures.

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