ORIGINAL RESEARCH PAPER

Physiology

KEY WORDS: : Pituitary gland, Magnetic Resonance Imaging, Size, Height.

PHYSIOLOGICAL CHANGES IN PITUITARY MORPHOLOGY IN LONGITUDINAL ASSOCIATION WITH AGE AND GENDER: AN IMAGING EVALUATION.

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ABSTRACT

Pituitary gland being centre of all the endocrinal activity in the body is responsible for regulating the internal endocrinal milieu. This pea-sized gland situated at the base of the brain is protected by a bony enclosure called sella turcica. Before the advent of cross-sectional imaging, the sella used to be evaluated by radiographs. As Magnetic Resonance Imaging (MRI) is now fast becoming established as the modality of choice for evaluating the pituitary gland, it is therefore imperative to re-visit this area and evaluate the normal patterns of this gland to help identify the departures with confidence. With this objective in mind, the present study has been undertaken to evaluate the normal dimensions of pituitary gland in a cross-section of people across different age-groups and genders.

Introduction

Pituitary gland has very aptly been referred to as the 'master gland', owing to its supreme control of other endocrine stations in the body. In terms of morphology, the pituitary gland exhibits dynamic changes in size and shape at different stages of human growth and development. Such changes also show wide gender based variations in adolescence, at different stages of menstrual cycle, climacterium and pregnancy (1-3).

With the widespread use of Magnetic Resonance Imaging (MRI) in evaluating brain and skull base, multiplanar images of the pituitary gland become readily available, even when such evaluations are not particularly focussed on the sellar and para-sellar regions. Difficulties arise when incidental physiological variations in the shape or size of the pituitary exhibit apparent departure from the normal (4). Such situations become challenging and warrant revisiting this issue with a primary objective of establishing reliable data which would help in differentiating physiological changes in pituitary morphology from small microadenomas. While some studies on the subject stand published, no such data is available on populations inhabiting the sub-himalayan belt of northern India, particularly the Kashmir valley. Therefore, this study was undertaken with intent of establishing sound data for this population sub-group, that would act as a future guide while evaluating physiological changes in pituitary and reliably differentiating them for micro-adenomas.

Materials and Methods

This study included 279 consecutive patients who were referred to the department of Radiodiagnosis & Imaging at the Sher-i-Kashmir Institute of Medical Sciences, Kashmir, India for undergoing MRI of the brain for reasons other than suspected sellar or para-sellar pathology. The patient ages ranged from 11 to 79 years and included 156 males and 123 females.

Only those patients were included in this study, who had an essentially normal MRI of the brain with no evidence of any pituitary or para-sellar pathology. Furthermore, other defined inclusion criteria were absence of any clinical or laboratory evidence of a hypothalamo-pituitary disorder and no previous history of sellar or para-sellar surgery. The criteria for excluding certain patient groups from the study were: patients who were pregnant or breast feeding; those on hormonal or steroid treatment; patients on medications known to affect pituitary size such as phenothiazines, reserpine and sulpiride; patients with a pituitary height of less than 3 mm (empty sella); and patients aged 10 years and below.

Images were obtained on a super-conductor 1.5 Tesla MRI machine using dedicated head coils. After preliminary examination of all the images in different planes, the mid-sagittal T1- weighted slice was selected to make the necessary MR based measuring analysis for purposes of this study. For overwhelming majority of the patients the imaging parameters for T1- weighted sagittal images were: repetition time of 450; echo time 10; matrix 256 x 205; FOV 250 mm and section thickness of 7 mm.

Using Syngo-based imaging software, the pituitary height was measured on a work-station as shown in the Figure 1. The measurements were taken from the upper-most to the lower-most limit of the gland keeping the infundibular stalk and the sellar floor outside the limits of the measuring callipers.

The subjects were classified into 7 groups on basis of age, with each group representing a time scale of one decade from second to the eighth. Furthermore, each of these groups was sub-divided into two components based on gender. We used parametric t test and ANOVA for statistical analysis and all results were discussed at 5% level of significance ($p < 0.05$).

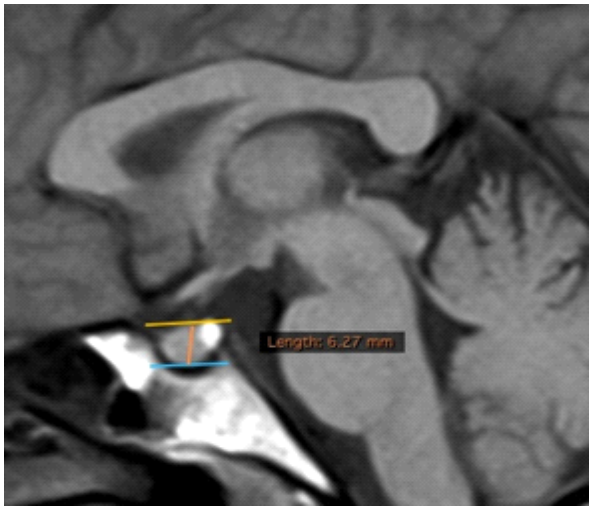

Fig1: T1-weighted mid-sagittal image of pituitary gland. Vertical line shows height of gland.

Results

The present study revealed a mean pituitary height of 5.0 mm irrespective of age and gender (Table 1). The combined mean

pituitary height in both genders reached a peak of 5.9 mm in the 21-30 decadal age group, followed by decreasing trend in the next two decades (5.5. and 5.0 mm) which was briefly interrupted by a minor peak in the 51-60 age group (5.1 mm) before continuing decline further on.

Table 1: Combined data of both genders depicting pituitary height mean (mm) with 95% Confidence Interval using ANOVA test.

Age Group	No	Mean	Std. Dev	Std. Error	95% C.I. for Mean		Min.	Max.
					Lower Bound	Upper Bound		
11-20	7	5.500	1.6000	0.6047	4.020	6.980	3.5	7.5
21-30	25	5.984	1.5453	0.3091	5.346	6.622	3.5	8.5
31-40	22	5.591	1.4162	0.3019	4.963	6.219	3.2	8.5
41-50	33	5.036	1.2520	0.2179	4.592	5.480	2.6	7.8
51-60	55	5.122	1.2104	0.1632	4.795	5.449	2.6	7.3
61-70	79	4.862	1.0706	0.1205	4.622	5.102	2.8	7.2
71-80	57	4.586	1.0343	0.1370	4.312	4.860	2.6	6.7
Total	278	5.052	1.2580	0.0755	4.904	5.201	2.6	8.5

The mean pituitary height in males was 4.9 mm, it stood at 5.2 mm in females without regard to age (Tables 2 & 3). Amongst males the average pituitary height reached a peak of 5.8 mm in the age group of 21-30 years and recorded a gradual decrease in the succeeding decades except for a second peak in the 61 to 70 age group summing up to an average of 4.8 mm (Fig.2). The maximum pituitary height recorded in males was 8.5 mm; the index patient falling in the decadal age group of 31-40 years.

Table 2: Mean pituitary height (mm) in Male subjects during different decades of age with statistical significance test (Student's t-test)

Age Group	Number	Range	Mean	Std. Deviation	P-Value
11-20	5	3.90	5.3600	1.54693	0.001
21-30	15	4.90	5.8000	1.53157	0.000
31-40	14	5.30	5.5286	1.46573	0.000
41-50	19	3.80	4.9895	1.11350	0.000
51-60	28	4.20	4.7857	1.14721	0.000
61-70	44	4.00	4.8000	0.90013	0.000
71-80	31	4.10	4.4839	1.07458	0.000
Total	156	5.90	4.9372	1.19818	0.000

Table 3: Mean pituitary height (mm) in Female subjects during different decades of age with statistical significance test (Student's t-test)

Age Group	Number	Range	Mean	Std. Deviation	P-Value
11-20	2	3.30	5.8500	2.33345	0.175
21-30	11	4.80	6.3000	1.52905	0.000
31-40	8	4.70	5.7000	1.41623	0.000
41-50	14	5.20	5.1000	1.46077	0.000
51-60	27	4.70	5.4704	1.19512	0.000
61-70	35	4.30	4.9400	1.26240	0.000
71-80	26	3.50	4.7077	0.99113	0.000
Total	123	5.90	5.2114	1.32258	0.000

In females, the average pituitary height also peaked in the age group of 21-30 years and stood at 6.3 mm (Fig.3). This was followed by a gradual decrease over the next two decades, before recording a second average peak of 5.4 mm between 51-60 years and again showing a downward trend thence on. The female population group also recorded a maximal pituitary height of 8.5 mm, with the index patient falling in the decadal age group of 21-30 years.

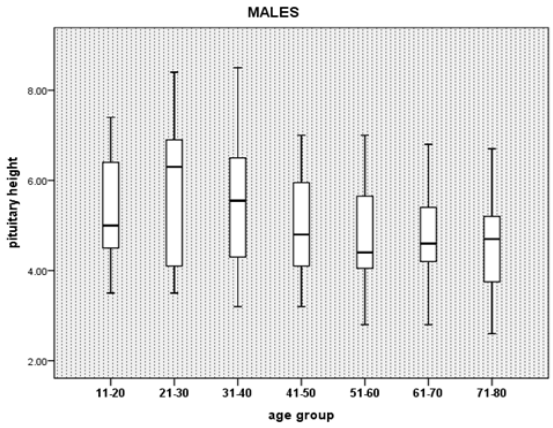

Fig.2: Box plot showing pituitary gland height in mm (vertical axis) in Male subjects by decadal age group in years (horizontal axis). The horizontal lines indicate the average pituitary height in each decadal age group. Boxes indicate 25th to 75th percentile.

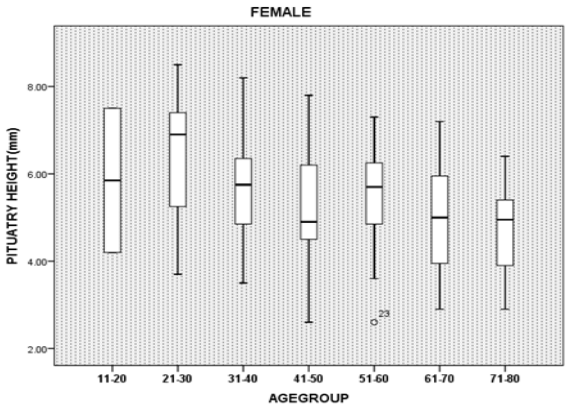

Fig.3: Box plot showing pituitary gland height in mm (vertical axis) in Female subjects by decadal age group in years (horizontal axis). The horizontal lines indicate the median (average pituitary height) in each decadal age group. Boxes indicate 25th to 75th percentile.

On an average, the mean height of pituitary gland in the female population group stood higher than the corresponding male population group in each decade. In both genders, the average pituitary height peaked in the decadal age groups of 21-30 years before exhibiting a downward trend. In males, the height decreased in the age-groups of 31-40, 41-50 and 51-60 years, before recording a minor peak between 61-70 years. In females, the average pituitary height decreased in the age groups of 31-40 and 41-50 years, before recording a second peak between 51-60 years. However, in both genders the average pituitary height again showed a continued downward trend after the second peak.

We excluded certain patient groups from the study, including patients with an empty sella, which for purposes of this study was defined as a T2-hyperintense cerebrospinal fluid filled sella with a small, flattened pituitary gland having a height less than 3 mm.

Discussion

On MRI, pituitary gland has characteristic appearances on both T1- and T2- weighing. While the anterior pituitary is isointense on both T1- and T2- weighted images, the posterior pituitary presents a high T1- signal, what has been aptly described as the 'posterior pituitary bright spot". On T2- weighing the neurohypophysis presents a hypointense signal.

In general, the pituitary gland in females is larger in height than their age-related male counterparts. In our study, the average recorded mean pituitary height across both the genders was 5 mm; standing at 5.2 mm and 4.9 mm in females and males respectively. The female predominance in pituitary height reflects the stark gender based differences (5). During development, brain shows a phenomenon of gender based dimorphism (6), best characterised by differing volumes of limbic system and the pituitary gland. In males, the amygdala develops at a faster scale, explained by its abundance of androgen receptors (7,8). Contrarily, the hippocampus develops at a faster scale in females, presumably due to abundance in estrogen receptors (7,9). Similarly, the pituitary gland is also known to show gender related developmental dimorphism. This interesting phenomenon was initially reported on CT studies, despite the modality lacking an adequate temporal resolution. On evaluating coronal CT images of 251 subjects, Peyster and colleagues reported significantly larger pituitary height in females than males (5). These findings were later confirmed using MRI (10).

On a time scale, the pituitary gland undergoes dynamic changes in morphology. Our study confirms the interesting phenomenon of double crescendo in pituitary height, observed during life span of the subjects; initial sharp peak occurring during puberty followed by a post-middle age gentle transient peak. We found the average peak pituitary height reached a crescendo in the age group of 21-30 years standing at 6.3 mm and 5.8 mm in females and males respectively. This pubertal peak was followed by a downward trend only to be interrupted by a second minor peak in the 51-60 year age group with average pituitary height standing at 5.4 mm and 4.8 mm in females and males respectively. Similar phenomenon has been observed in other studies (1,2,5,11,12). Despite two peaks, the general trend of post-pubertal age-related decline in pituitary height was also observed, which is in conformity with other studies (4,10,13). This demographic and gender based dynamicity of pituitary height is best explained on basis of the endocrinology of puberty and ageing. The onset of puberty is heralded by a surge in the Gonadotropic hormones, which include the luteinizing hormone and the follicle-stimulating hormone; this is reflected by concomitant increase in height of the pituitary gland (14). Thereafter, the basal serum concentrations of gonadotrops start declining. However; this trend is shortly interrupted in the fifth and sixth decades, when concentration of gonadotrops records a momentary increase owing to negative feedback emanating from decline in the levels of circulating gonadotrops (14). It is thus logical to assume that changes in pituitary height reflected across age and gender are intimately related to the changing endocrine milieu.

While axial scanning cannot be reliably used for determining height of an object, we preferred using sagittal sections over coronal images for evaluating the pituitary height. Thick-section mid sagittal images have an advantage of presenting a holistic picture of the pituitary gland including the infundibulum and the optic chiasm above. The pituitary gland has unique shape with a concave upper border that gently slopes upwards towards the edges, resembling a boat. Our study evaluated pituitary dimensions using sagittal section images with slice thickness ranging between 8 to 10 mm; using thicker slice images for measurements may exhibit only the lateral higher margins. We believe, our measurement methodology for assessing pituitary height reflects an average dimension of gland height.

Our study took into account the pituitary height, despite this gland being a three dimensional structure having other parameters like length, width and volume. This raises doubts regarding reliability of this measurement protocol; however, upon searching the literature, it comes to fore that dynamic physiological changes in pituitary size are exhibited by alterations in the gland height rather than length or width (4,12,14). This reiterates our belief that using mid-sagittal MRI image for determining pituitary height is the easiest and the most reliable method for determining the pituitary size.

Imaging of the pituitary gland is now consistently being undertaken by MRI. Even under physiological conditions, the pituitary gland shows wide variations in size, especially in response to the operative hormonal milieu in the body. This study has attempted to revisit this arena, with a firm belief that establishing measurement limits across age and gender would help in confidently interpreting pituitary measurements and differentiating physiological hypertrophy from other affections.

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