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Magnetic Resonance Imaging Of Pituitary Gland Volumetry In First Episode Of Psychopathology And Follow Up After Three Months

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INTRODUCTON

There has been growing interest in studying neuroanatomical basis of various psychiatric disorders, in the face of scant validated data available. The introduction of brain imaging technology revolutionized the study of psychiatric illness and continues to advance understanding of the biological abnormalities that underpin psychiatric disorders. Aside from ruling out organic brain pathology, neuroimaging modalities do not yet have a major role in the diagnosis of psychiatric disorders. [1]

Magnetic Resonance Imaging (MRI) has become a standard initial imaging modality in all psychiatric patients, due to better delineation of brain parenchyma and intracranial structures. Many MRI studies have been undertaken focusing on differences in grey matter volume, cortical thickness, curvature surface area and white matter volume and ventricular volume measurements, in mental disorders. However, there are only few studies quoting Pituitary volume changes in psychiatric conditions. [1]

People who are in the acute phase of a psychiatric disorder, with florid symptoms, newly hospitalized or unmedicated, show Hypothalamic-Pituitary-Adrenal (HPA) axis hyperactivity, but the central mechanisms underlying this neuroendocrine abnormality are unclear. [2]

To investigate whether HPA axis activation in psychosis is also associated with Pituitary volume changes, measurements of the Pituitary glands by MRI in patients experiencing their first episode of psychopathology is most suitable, when they are most likely to show HPA axis abnormalities.

AIMS AND OBJECTIVES:

- To study the Pituitary volume in first episode of psychopathology using MRI and comparing the age and gender matched controls.
- Follow up MRI scan of psychiatric patients, to review Pituitary volume after 3 months or more and correlate with the final psychiatric diagnosis.

MATERIALS AND METHODS

SOURCE OF DATA:

A prospective observational study of 50 patients with symptoms of psychiatric illness for the first time and presenting within one month of onset of illness, referred to the department of Radiodiagnosis, MVJ Medial College and Research Hospital, Hoskote and 50 age & gender matched healthy controls. The controls were from among those who had undergone MRI brain scan for general health checkup. The study period was two years starting from July 2022 to June 2024.

METHOD OF COLLECTING DATA:

MRI was performed using a 1.5 Tesla MR scanner and routine imaging sequences were done.

The cases and the controls were briefed about the nature of the study and its importance. Clinical data including the date and pattern of onset of presenting illness was collected from the patients presenting with first episode of psychopathology.

Inclusion criteria:

Study population:

Patients presenting with symptoms of psychiatric illness for the first time and reporting within one month of onset of symptoms.

Control:

1) Healthy individuals who had undergone general health checkup.
2) Age and gender matched with cases.

Exclusion criteria:

a) Cases of any known structural neurological disease.
b) Patients who had metallic implants, pacemakers, hearing aids, insulin and medication pumps.
c) Controls volunteers with first degree (blood relation) relative known to be suffering from psychiatric illness.
d) Patients already on antipsychotic medication.

STUDY DESIGN: Hospital based prospective observational study.

EQUIPMENT AND PROTOCOL:

The imaging was done using a SIEMENS MAGNETOM ESSENZA 1.5 TESLA MRI machine and routine sequences were obtained.

SIEMENS MAGNETOM ESSENZA1.5 TESLA MRI MACHINE

STATISTICAL ANALYSIS:

- The results of the descriptive analysis were presented in numbers and percentages. The statistical software SPSS 15.0 was used for analysis of the data and Microsoft word and excel was used to generate graphs and tables.
- Original data are presented as means and standard deviations.
- Initially, test of homogeneity of linear regressions between Pituitary volumes of cases (initial) and controls, with age as the covariant variable, was done.
- Analysis of Covariance (ANCOVA) was done to compare the significance of differences between Pituitary Volumes in Control and Cases at initial MRI and again between Pituitary volumes in cases at initial MRI and review MRI and review MRI, i.e. after three months.

RESULTS:

Table 1: Gender Profile

Variables	Category	Case		Control		Total	
		n	%	n	%	n	%
Gender	Male	28	56	28	56	56	56
	Female	22	44	22	44	44	44

The cases were classified based on their ages, into various class intervals, from 11-20 years to 71-80 years. Maximum number of cases were of the age group 21 to 30 years (No=16) and 31 to 40 years (N=14). The youngest among the cases was a 15 years old male and the oldest an 80 years old male.

Table 2: Age distribution of cases.

Age in years	No. of males	No. of females	Total	Percentage
11 - 20	2	3	5	10
21 - 30	12	4	16	32
31 - 40	8	6	14	28
41 - 50	1	6	7	14
51 - 60	1	3	4	8
61 - 70	2	0	2	4
71 - 80	2	0	2	4
Total	28	22	50	100

Figure 1: Age and Gender distribution of cases.

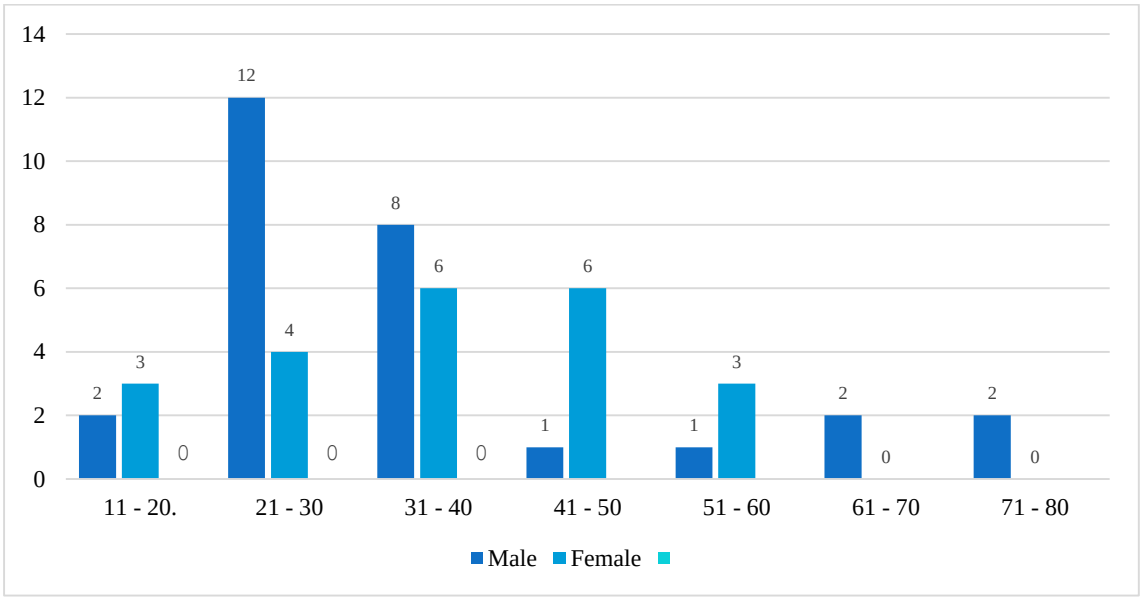
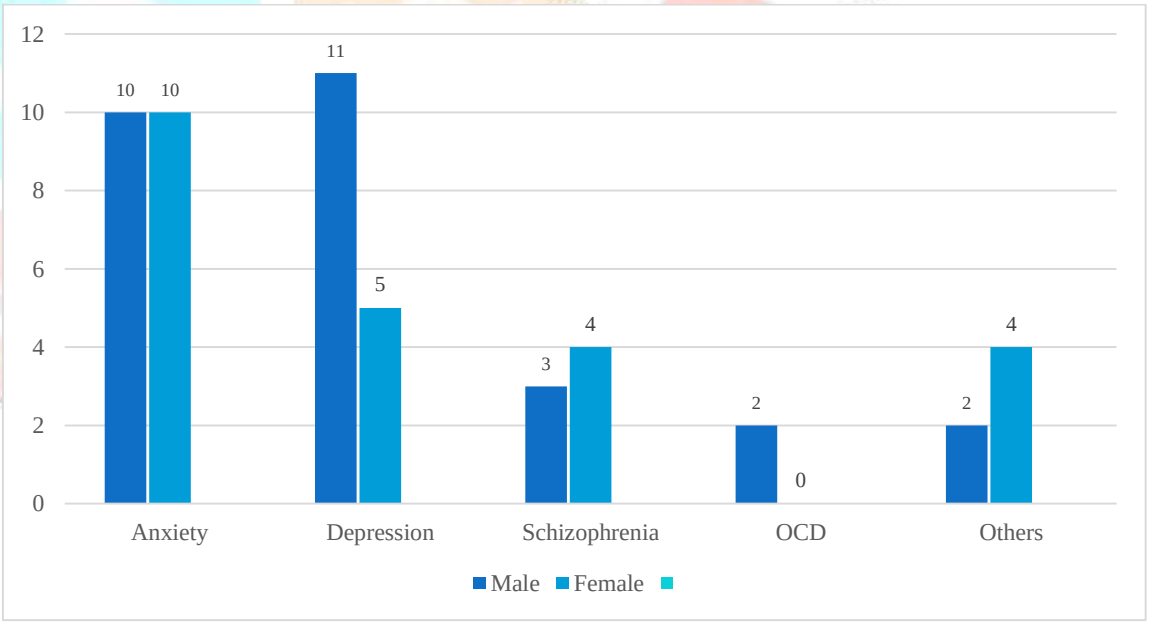


Figure 2: Psychiatric diagnosis profile.



A significant number of cases fell into the category of anxiety and depressive psychosis.

There were 20 cases diagnosed as depressive psychosis. Other groups included schizophrenia, obsessive compulsive disorder, somatoform disorder and personality disorders.

MRI findings:

1. Pituitary volume.

A test of homogeneity of linear regressions between Pituitary volumes of cases(initial) and controls with age as the covariant variable showed significant correlation of slopes (F – 0.53, P=0.468). Similar strong correlation was observed between slopes of initial and review Pituitary volumes of cases (F = 0.005, P = 0.94).

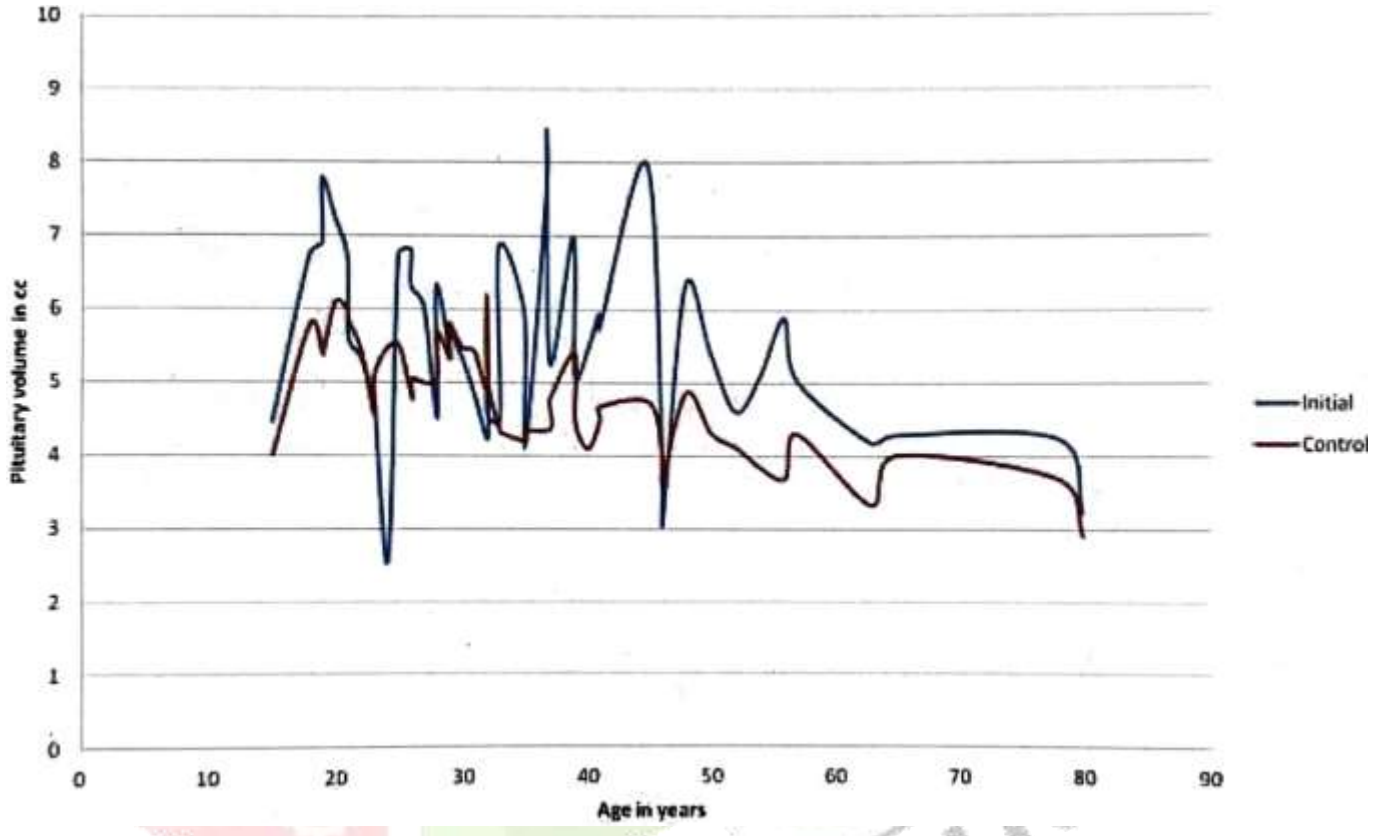


Figure 3: Comparison of Pituitary volume between cases (initial) and controls.

There is significant difference in pituitary volume between the controls and cases at initial MRI (ANCOVA, F=15.56 ; P=0.0002). The mean pituitary volume of control group was 4.78 ml. Mean Pituitary volume of cases at initial MRI was 5.52 ml. Pituitary volumes in cases at initial MRI were 15.36% (0.73 ml) higher than controls.

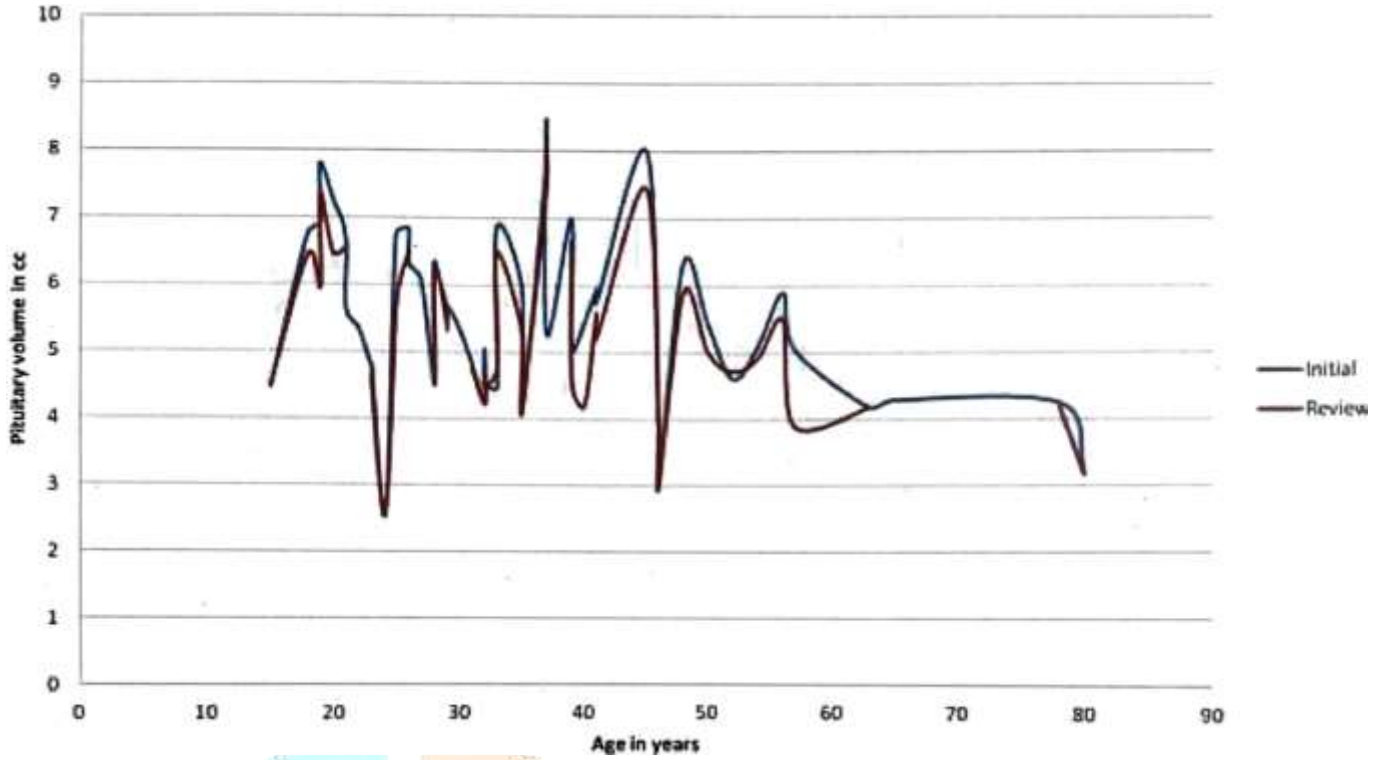


Figure 4: Comparison of Pituitary volume between initial and review of MRI cases after 3 months.

There is no significant difference in Pituitary volume between the initial and review Pituitary volumes of cases (ANCOVA, 1.30; P=0.257). The difference between Pituitary volumes of cases at initial MRI and review MRI was 5.51% (0.3 ml), volumes at initial MRI being higher.

Table 3: ANCOVA analysis – Comparison of Total Pituitary volumes between cases and controls.

Total Pituitary volume		
Comparison	**F value (ANCOVA)**	**P value**
Initial & Control	**15.56**	**0.0002**
Initial & Review	**1.30**	**0.2577**

Table 4: Mean Pituitary gland volumes on MRI.

	Mean Pituitary Volume	Standard Deviation
Cases at initial MRI	**5.52 ml**	**1.29 ml**
Cases at review MRI	**5.23 ml**	**1.24 ml**
Controls	**4.78 ml**	**0.76 ml**

Although examination of the individual data showed an overlap between the groups, the presence of group differences was suggested by the fact that 37 of the 50 patients in the first-episode group (74%) had Pituitary volumes that were larger than the mean of the control group, whereas 28 of the 53 cases at review (65%), had Pituitary volume that were larger than the mean of the control group.

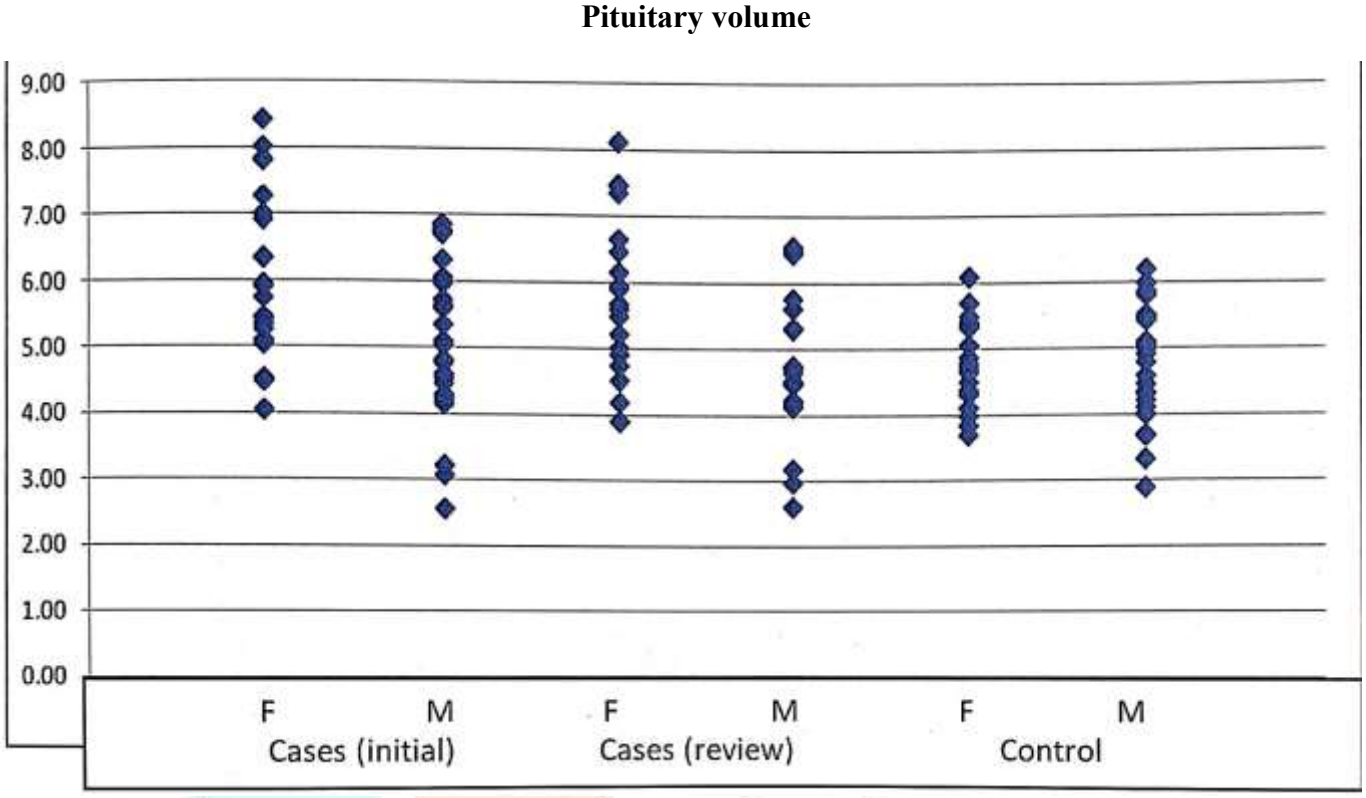


Figure 5: Comparison between Pituitary volumes of cases (initial and at review) and controls (F-Females, M-Males). From the above scatter diagram, female cases showed significantly higher Pituitary volumes than controls as compared to their male counterparts.

Table 5: ANCOVA: Comparison of anterior Pituitary gland volumes between cases and controls.

Anterior Pituitary volume		
Comparison	**F value (ANCOVA)**	**P value**
Initial & Control	**14.01**	**0.0003**
Initial & Review	**0.87**	**0.3542**

Table 6: ANCOVA: Comparison of posterior Pituitary gland volumes between cases and controls.

Posterior Pituitary volume		
Comparison	**F value (ANCOVA)**	**P value**
Initial & Control	**0.30**	**0.588**
Initial & Review	**0.83**	**0.3638**

On further analysis it was found that the difference in the volumes of the posterior pituitary gland between cases and controls was insignificant (ANCOVA, F=0.3, P=0.588). The cases had significantly higher anterior Pituitary volume than controls (ANCOVA, F=14.01, P=0.0003).

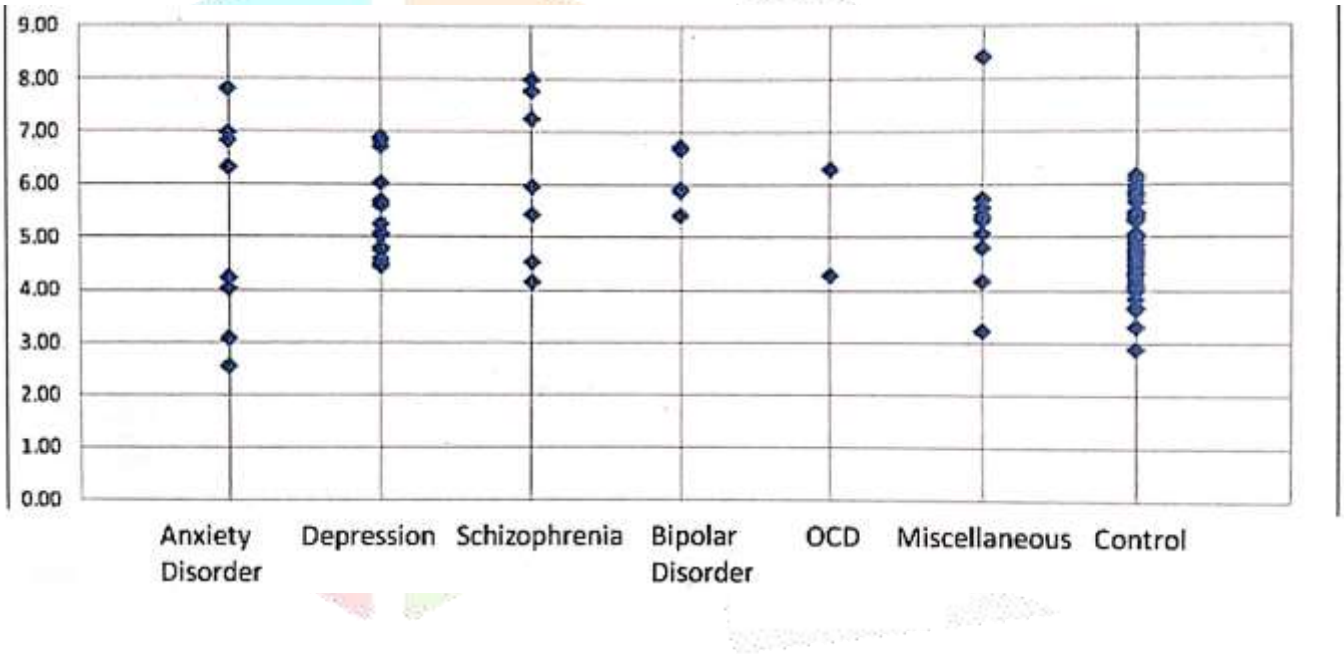


Figure 6: Comparison of the Pituitary volumes between various psychiatric conditions with controls.

On analysis of Pituitary volume in broad categories of psychiatric diagnostic profile, it was noted that, there was a wide range of pituitary volumes exhibited by most of the groups, and the control group showed a much narrow range of dispersion of pituitary volumes.

Other findings:

None of the cases or controls enrolled in the study showed any abnormality in the MRI scans of the brains.

MRI scans of all the cases and controls showed that the Pituitary stalks were central in location on coronal reformatted images. None of the cases showed deviated Pituitary stalks.

Figure 7: A T1 Weighted coronal image of Pituitary at the level of stalk of Pituitary gland showing the midline stalk (solid black arrow). All cases and controls enrolled in the study had midline Pituitary stalk.

Loss of follow up.

43 cases of 50 cases underwent review MRI after 3 months of initial scan. 7 cases enrolled in the study underwent MRI at initial presentation and did not undergo review MRI scan. Hence, these cases were only included in initial comparison with controls and not included in comparing Pituitary volumes between initial and review MRIs of cases.

REPRESENTATIVE CASES

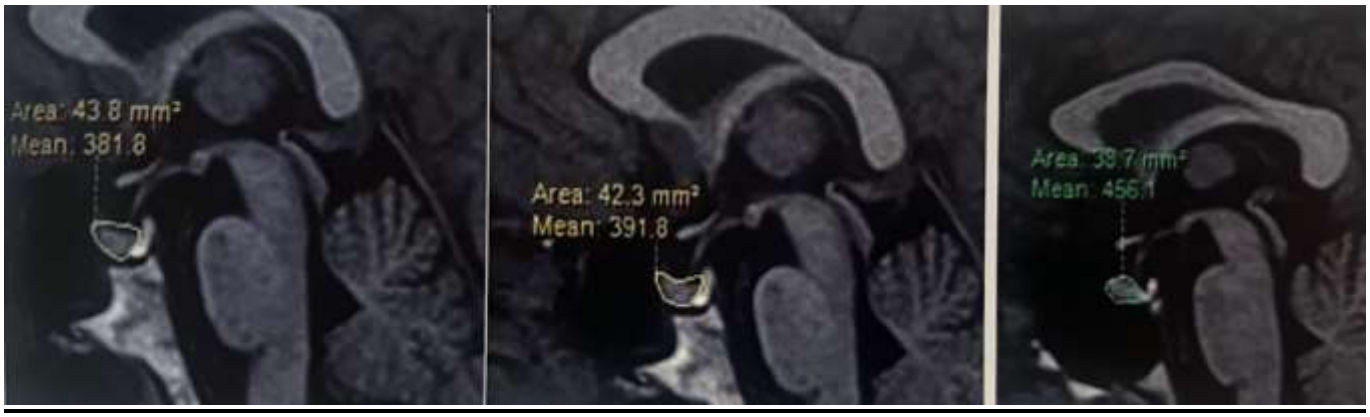


Figure 8: A 32 year old male with history of martial discord, underwent MRI within 3 weeks of onset of severe Depression.

a) Mid sagittal image of the T1 weighted MPR sequence, at 3 weeks of onset. Patient was put on anti-depressants for 3 months.
b) Mid sagittal image of T1 MPR sequence at four and half months of onset.
c) Mid sagittal image of T1Weighted sequence in 31 year old male control.

There is significant difference in the size of the pituitary gland between the patient (both at initial MRI and at review MRI and control. However, there is no significant difference between the initial and review MRI scans of the case.

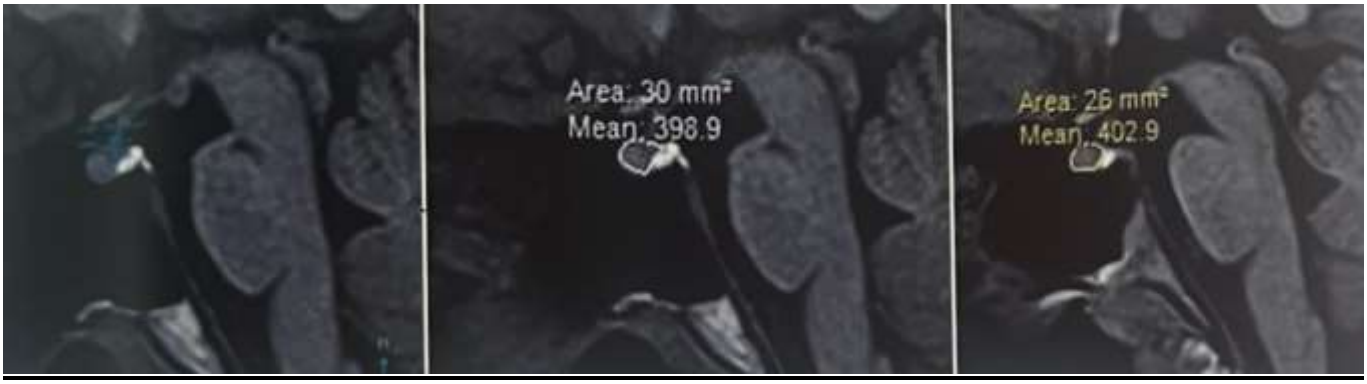


Figure 9: A 26 year old male underwent MRI within 2 weeks of sucidal attempt.

a) Mid sagittal image of T1 Weighted MPR sequence at initial MRI.

b) Mid sagittal image of T1 MPR sequence at three and half month of onset.

c) Mid sagittal image of T1 Weighted sequence in a 26 year old healthy male control.

There is significant difference in the size of the anterior Pituitary gland between the patient (both at initial MRI and review MRI) and control. Also noted was the significant Posterior pituitary bright spot as compared to the control.

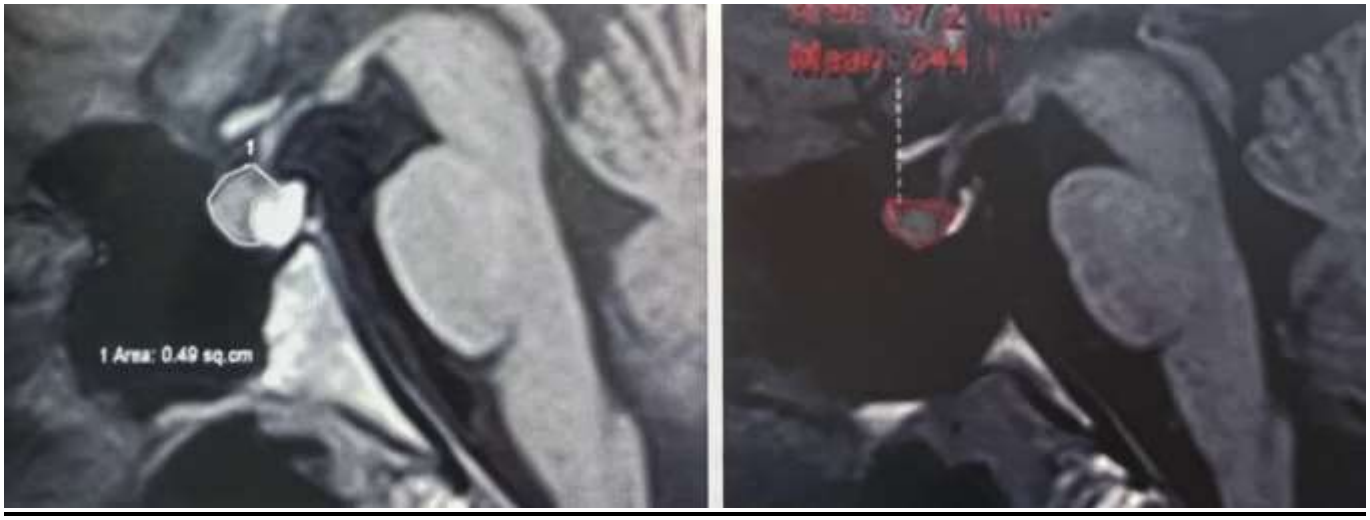


Figure 10: A 19 year old female with history of depression, underwent MRI of the Brain.

a) Mid sagittal image of the T1 Weighted MPR sequence.

b) Mid sagittal image of T1 MPR sequence in a 19 year old female control.

There is significant difference in the size of the pituitary gland between the patient and control. This is one of the case showing significant difference in the posterior Pituitary gland size also.

DISCUSSION

The Pituitary gland regulates HPA axis activity probably by secreting adrenocorticotropic hormone, which in turn stimulates the Adrenal gland to produce cortisol.

In this study, patients with first episode of psychopathology had larger Pituitary volumes than healthy volunteers. This difference was significant irrespective of age at presentation or psychiatric condition. This finding is in concordance to many studies done previously.

In a study done by Pariante CM et al,[3]17 of the 24 patients in the first episode group (71 %) had Pituitary volumes that were larger than the mean of the control group by an average of 10% and women had larger Pituitary volumes than men in the group. In the present 37 of 50 patients (74%) of first episode of psychopathology showed larger Pituitary volumes by an average of 15.4% of mean of the control group. Also, in the whole sample, women had largest pituitaries than men.

11 of the 16 (69%) patients in the present study, with depression had higher Pituitary volumes then controls. K Rama Krishna et al, [4] found that depressed patients had larger Pituitary glands volumes than age and sex matched controls. The study also found that there was significant difference in the anterior Pituitary

sizes only, which is in concordance with the present study. No significant correlation of posterior Pituitary volumes were found in either if there studies.

Roberto B Sassi et al, [5] had found decreased Pituitary volume in patients with bipolar disorder. In contrast to this, present study revealed higher volumes in 4 out of 5 (80%) patients with bipolar disorder.

MacMaster FP et al, [6] studied Pituitary gland volume on MR, in adolescent and young adult bipolar and unipolar depression and concluded that Pituitary glands are enlarged in adolescents with mood disorders compared to controls. They also found that healthy young females have larger Pituitary glands than males, but such a difference was not evident in individuals with unipolar depression or bipolar disorders. In the present study the healthy female controls had higher Pituitary volumes than their male counterparts.

Murad Atmaca et al, [7] found smaller Pituitary volume on MRI, in a group of patients with Obsessive compulsive disorder. They also showed that men with OCD and control men had smaller Pituitary volume compared to women with OCD and control women, respectively. Both the patients, in the study with OCD had larger Pituitary glands than their control.

Mechanism leading to increased Pituitary volume.

It is suggested that the increased Pituitary volume in patients with first episode psychopathology is due to actitation of the HPA axis. Sachar et al [8], examines the HPA axis in people with first episode of psychosis and have found hyperactivity of this hormonal system. Krishnan et al [4], and Axelson et al [9], described both HPA axis hyperactivity and increased Pituitary volume in patients with severe major depression. Pariante & Miller in 2001 [10] and again Pariante in 2003 [11] especially at the level of the Pituitary (glucocorticoids resistance).

Muneura et al [12], found that increased size and number of corticotrophs and increased Pituitary volume are also present in people with lack of negative inhibitory feedback by circulating glucocorticoid hormones due to Addison's disease.

Therefore, glucocorticoid resistance is a common correlate of stress induced HPA axis activation n in animals and humans [13], the findings of this study could be explained by an activation of the stress response.

Such activation could be due to the distress caused by the first psychotic experience, to an increased biological susceptibility to daily life stress or to an increased level of independence stressors leading to the psychotic episode or to all these causes [8,14,15]. Reassuringly, there is no evidence that HPA axis hyperactivity causes damage to the brain in people with mental disorders [16]. Hormonal levels were not measured in this study. So, the proposed relationship between Pituitary hyperplasia and hyperactivity of the HPA axis remains speculative.

Pituitary gland volume and chronic Psychiatric illness.

The finding of significant increase in Pituitary volume in all types of psychiatric conditions, is in contradiction to many studies done previously. The contradiction may be related to duration of illness at MRI scan. All patients in the study had MRI done within one month of onset of clinical symptoms.

Some studies done on patients with long standing mental illness have showed the Pituitary gland volumes to be low in comparison to normal healthy controls.

Doraiswamy et al [17], showed reduced Pituitary volumes in patients with an eating disorder.

Pariante et al [3], found that patients with Chronic Schizophrenia had smaller Pituitary volumes as compared to healthy controls. 51 patients enrolled with chronic Schizophrenia had history of illness for more than 5 years. 35 of these 51 patients (69%) had smaller Pituitary volumes that were smaller than the median of the control group. In the present study, only 7 patients enrolled were suspected to have Schizophrenia and even the review MRI scan of these cases were done within 4 to 5 months from the onset of clinical symptoms. All of them were found to have higher Pituitary volume as compared to the age and gender matched healthy controls.

Therefore, it is possible that initially in all psychiatric disorders within first few months of onset of illness there is increased Pituitary volume likely due to HPA axis overactivity and as the duration of illness increases there can be rebound hypoplasia of the Pituitary gland. Sassi et al [5], have suggested chronic activation of the HPA axis might decrease Pituitary volume by reducing (through negative feedback) the function of cells producing other Pituitary hormones.

Limitation of the study:

As already stated, hormonal levels were not measured in these samples. Future studies on this topic should include hormone measurements. Without measurements of hormonal levels, our proposed relationship between Pituitary hormones remains speculative.

Finally, we cannot exclude that Pituitary hyperplasia in first episode psychosis is due to increased function of Pituitary cells secreting hormones other than Adrenocorticotropic hormone, such as growth hormone and Prolactin levels of these hormones are also elevated by stress. Furthermore, the patients in our first episode group were receiving antipsychotic drugs at review MR, which can induce proliferation of Prolactin secreting cells in animals [15].

Clinical Implications:

1. The first episode of a psychotic disorder is associated with enlargement of the Pituitary. One possible interpretation of this findings is that indicates activation of the hormonal stress response, and especially of the Hypothalamic – Pituitary – Adrenal axis.

2. Prospective studies will clarify whether measurements of the stress response can be used to predict the development of psychosis.

SUMMARY:

This study was conducted to find pituitary volumes of patients presenting with first episodes of psychopathology.

50 patients of first episode of psychopathology, underwent MRI brain at initial presentation and 43 of them after 3 months. MRI images of the brain were obtained from which volume of the pituitary gland was calculated.

In comparison with age and gender matched controls, the cases had statistically significant higher Pituitary volume. Anterior Pituitary gland showed significant difference, and no such significant correlation

was seen with the posterior Pituitary gland. There was no significant change seen in the Pituitary volumes of the cases in MRI at initial presentation and review MRI after 3 months.

The significant larger Pituitary volume may be attributed to HPA axis on these cases.

CONCLUSION:

Pituitary volumes are significantly higher in patients presenting with psychopathology for the first in comparison with healthy individuals of same age and gender. MRI is the modality of choice to assess Pituitary volumes. Healthy females have higher Pituitary volumes than their male counterparts.

The Pituitary volumes are relatively higher in most psychiatric illness at onset, irrespective of the specific diagnosis. HPA axis overactivity has been postulated to be the cause of larger Pituitary glands in such patients. Further studies are required to ascertain the biochemical and hormonal changes in these patients and to predict the risk of developing psychiatric manifestations based on these stress response measurements.

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