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ORIGINAL PAPER

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Pituitary volumes in relatives of bipolar patients

High-risk study

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Abstract *Background* Increased, decreased, as well as unchanged pituitary volumes have been reported in bipolar disorders (BD). It is unclear, whether abnormal pituitary volumes increase vulnerability for BD (primary vulnerability marker), or are secondary to burden of illness. To address this question, we performed the first high-risk study of pituitary volumes in affected and unaffected relatives of bipolar subjects. *Method* High-risk participants (age range 15–30 years) were recruited from families multiply affected with BD and included 24 unaffected, 19 affected subjects with first or second degree bipolar I or II relative, matched by age and sex with 31 controls without a personal or family history of psychiatric disorders. Pituitary volumes were measured on 1.5 T 3D anatomical MRI images using standard methods. *Results* We found comparable pituitary volumes among unaffected, affected relatives of bipolar patients and controls. There were no differences in pituitary volumes between male and female subjects nor was there any sex by group interaction. Analyzing 26 participants with bipolar I parent or excluding 5 medicated subjects did not change the results. There were no differences between subjects from families containing bipolar I versus families containing only bipolar II subjects. *Conclusions* The lack of abnormalities in unaffected and also affected subjects early in the course of illness in our study, as well as previous investigations of bipolar and familial unipolar children and adolescents, suggest that pituitary volume abnormalities are unlikely to be a primary risk factor for mood disorders.

Key words bipolar disorders · MRI · pituitary · offspring · high-risk

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Introduction

Abnormalities within hormonal systems regulated by hypothalamus and pituitary have long been recognized as a feature of mood disorders. Aside from functional changes, such as abnormal hormone or regulatory neuropeptide levels [decreased levels of thyroid hormones, increased levels of thyroid stimulating hormone, corticoliberin (CRH), cortisol], abnormal dynamic tests [dexamethasone supression test (DST), CRH stimulation test, combined DST/CRH tests, thyrotropin releasing hormone stimulation test], the hypothalamo pituitary axis abnormalities

likely have morphological correlates, including adrenal hyperplasia [26], visceral lipid deposition [31], decreased hippocampal [29] and abnormal pituitary volumes [1]. Impaired negative feedback of the hypothalamo pituitary adrenal axis resulting in protracted hypercortisolemia following stressors or episodes of mood dysregulation, may underlie changes in hippocampal volumes often seen in depression and cognitive deficits persisting into euthymia in patients with mood disorders [6, 14].

Studies in bipolar patients reported increased [23], decreased [27], as well as unchanged [4] pituitary volumes. This discrepancy may be due to scanning of populations at different stages of illness, since it is unclear, whether pituitary volume changes are secondary to burden of the illness [14] or primary, increasing vulnerability for mood disorders [12]. Interestingly, available indirect evidence could support both of these options. If pituitary volume abnormalities are secondary, they should be present only in patients with longer history of illness. Indeed studies in bipolar patients demonstrated decreased pituitary volumes in middle aged patients [27], but not in affected children at the early stages of the illness [4].

If however pituitary volume abnormalities are primary and causative of episodic hormonal dysregulations or increased vulnerability to developing mood disorders, they should be present already prior to or early in the course of illness. Studies in unipolar depression showed increased pituitary volumes already in first episode [23], pediatric treatment naive patients [20] and early onset unipolar depression patients [19]. Even studies in patients early in the course of illness however cannot completely eliminate confounding effects of illness burden. One of the best ways, how to distinguish between primary and secondary abnormalities is to study unaffected subjects at high risk of developing mood disorders. Investigators have thus suggested a need for studies in unaffected relatives of probands with mood disorders [20].

To investigate, whether pituitary volume abnormalities are a primary risk factor for mood disorders, we assessed pituitary volumes in relatives of bipolar parents, both affected and unaffected with psychiatric disorders. To our knowledge this is the first high-risk study of pituitary volumes in mood disorders.

Methods

Subjects

Families

The high-risk (HR) offspring were recruited from families with multiple members affected with BD according to methods described elsewhere [7]. Briefly, suitable families were identified through adult probands with bipolar I or II disorder, who had participated in genetic studies and had been recruited from outpatient clinics at the Queen Elizabeth II Health Centre in Halifax. Each proband completed a SADS-L interview [8] conducted by two research psychiatrists blind to the identity of the person. Final DSM-IV diagnoses were decided using all available clinical materials in a blind consensus fashion by an independent panel of senior clinical researchers. Similar to previous studies [7, 30], we included subjects with family history of bipolar I disorders in second degree relatives or bipolar II disorders in first or second degree relatives. Bipolar II subjects were similar in their clinical presentation to the bipolar I participants in that they experienced a low prevalence of comorbid conditions and an episodic course of illness. Bipolar II probands differed from bipolar I participants only in severity of mania. Family studies using similarly narrow diagnoses generally found bipolar II to be a part of the same genetic spectrum as bipolar I [10].

High-risk offspring

Depending on their age, the offspring were interviewed by a child/adolescent or adult psychiatrist using KSADS-PL [15] or SADS-L format. Diagnoses were made based on DSM-IV, as well as Research Diagnostic Criteria in a blind consensus review, which included at least two additional research psychiatrists. As part of the high-risk study, offspring are re-assessed annually or at any time symptoms develop. The HR unaffected group was comprised of 24 offspring with no lifetime history of psychiatric disorder. High-risk affected subjects consisted of 19 offspring who met criteria for a lifetime diagnosis of mood disorder or in one case psychosis NOS, which may be considered an antecedent of BD. All HR affected subjects were in remission at the time of scanning, as determined by clinical interview and functioning at school or work. As a measure of psychopathology at the time of scanning, we used 17 items Hamilton depression rating scale (HAMD) and Young mania rating scale (YMRS). Exclusion criteria included: (1) history of closed head injury resulting in loss of consciousness; (2) untreated active medical illness (e.g., diabetes); (3) identified learning disability or diagnosis of Attention Deficit /Hyperactivity Disoder (ADHD); (4) substance-related disorder within the past 6 months; (5) lifetime history of substance dependence; (6) history of neurological disease.

Offspring of well parents (controls)

Controls consisted of 31 healthy offspring of well parents recruited from similar sociodemographic areas as the patients, who were interviewed by a child/adolescent or adult psychiatrist in accordance with KSADS-PL or SADS-L format and deemed to be well upon blind consensus review. The control subjects were selected to closely match HR subjects by age and sex. Exclusion criteria were the same as in the HR groups with the addition of a personal or family history of psychiatric disorders.

Prior to conducting the assessments, all interviewers underwent extensive training consisting of participation in interviews, interviews under supervision, and blind consensus diagnostic reviews.

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Research Ethics Boards of IWK Health Center and Capital District Health Authority, Halifax, Nova Scotia.

MRI methods

MRI acquisition parameters

All MR acquisitions were performed with a 1.5 T General Electric Signa scanner and a standard single-channel head coil. After a

localizer scan, a T1-weighted spoiled gradient recalled (SPGR) scan was acquired with the following parameters: flip angle = 40°, TE = 5 ms, TR = 25 ms, FOV = 24 cm × 18 cm, matrix = 256 × 160 pixels, NEX = 1, no inter-slice gap, 124 images with 1.5 mm slice thickness. Subjects were scanned at approximately the same time of the day to minimize biological variability.

MRI volumetry

Anatomical measurements were conducted using the AFNI software for Linux [5] in a single batch, according to a well-established procedure [23, 27]. Prior to volumetric measurements, all scans were reoriented perpendicular to bicomissural line. We excluded the infundibular stalk and traced around the usually well-defined borders of anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. We included the bright spot, corresponding to the posterior pituitary, which represents hyperintense signals from the neurosecretory vesicles or intracellular lipids in the posterior pituitary cells. We used both coronal and sagittal planes for tracing. Importance of the assessment on the sagittal plane is prominent, as anterior and posterior borders of pituitary gland are best identifiable on this plane, please see Fig. 1. Volume of the pituitary (in mm^3) was calculated by summing volumes for all relevant slices.

The tracings were done blindly to the diagnosis and group assignment of subjects by neuroanatomist (EG), after training with another member of the team (TH). Subsequently all scans were checked for consistency of tracing by a second rater (TH) also blinded to the diagnosis and group assignment of subjects. The inter-rater reliability established by blindly tracing ten scans by two independent raters (EG, TH) was 0.96; the intra-rater reliability for ten randomly selected pituitaries measured twice by the same rater (EG) was 0.98.

Intracranial (ICV), gray (GM) and white (WM) matter volumes, were obtained by automated tissue type segmentation algorithm, using 3dAnhist command in AFNI software [5]. This command uses cut-off values to separate tissue types, cerebro spinal fluid (CSF) and vasculature. The volumes of each tissue type were calculated according to the criteria previously published [11].

Statistical analyses

All statistical analyses were done using the BMDP statistical software. We performed analysis of variance (ANOVA) with pituitary volumes as the dependent variable and status (affected, unaffected, control subjects) and sex as the grouping variables. To compare intracranial and gray matter volumes between affected, unaffected HR subjects and controls, we used one way ANOVA. Categorical demographic variables (sex, handedness) were compared using Pearson X^2 test. To look for association between age, GM, ICV and pituitary volumes, we calculated correlation coefficients. To control for potential confounders, we performed analysis of covariance with variables significantly associated with pituitary volumes as covariates. To compare pituitary volumes in patients with vs. without family history of bipolar disorders with psychotic symptoms and between high-risk and control subjects, we performed t tests. We report nominal, two tailed P values.

We carried out a power analysis for one-way ANOVA with 3 groups and an average of 23 subjects (71/3) in each group. To compare our results to those of previous studies, we calculated Cohen's d effect size (Cohen's $d = M_1 - M_2/s_{pooled}$).

Results

Demographics

Twenty four unaffected familial, 19 affected familial subjects and 31 controls participated in the study. Among familial subjects, 26 had bipolar I parent, 5 had bipolar I second degree relative, 11 had bipolar II parent or sibling and 1 had bipolar II second degree relative. There were no differences in proportion of women, age, laterality, intracranial or gray matter volumes between the groups. For details see Table 1.

Pituitary volumes

The pituitary volumes were comparable among groups ($F = 0.50$, $df = 2$; 68, $P = 0.60$), (see Table 1). There were no differences in pituitary volumes between male and female subjects ($F = 0.04$, $df = 1$; 68, $P = 0.84$) nor was there any sex by group interaction ($F = 0.59$, $df = 2$; 68, $P = 0.56$). Excluding families containing only bipolar II subjects did not change the results. There were no differences between subjects from families containing bipolar I versus families containing only bipolar II subjects.

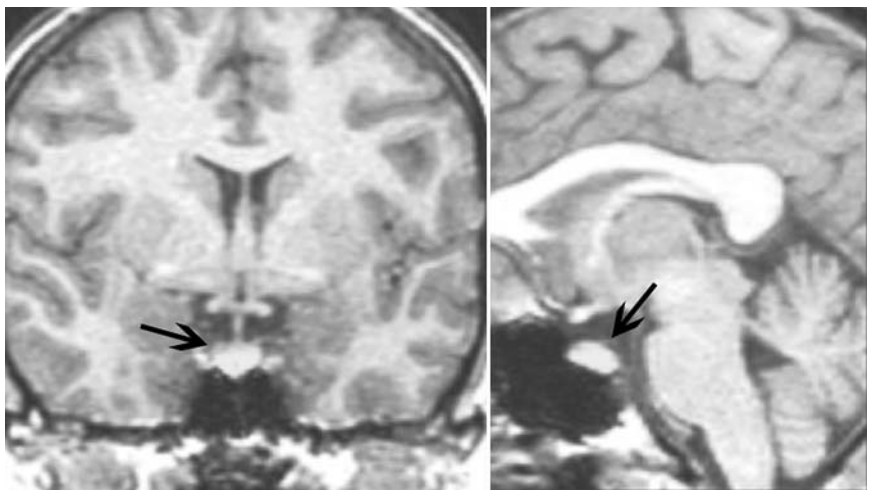

Fig. 1 The pituitary gland in coronal (*left*) and sagital (*right*) plane. Both coronal and sagital slices were used for the tracing of the pituitary

Table 1 Demographics and pituitary volumes for unaffected, affected high-risk participants and controls without personal or family history of mood disorders

	Unaffected HR subjects	Affected HR subjects	Controls	P
N	24	19	31	NA
Sex *N* (%) female	15 (62.5)	14 (73.7)	20 (64.5)	NS
Age—years, mean (SD)	19.8 (3.2)	21.3 (3.5)	20.6 (3.3)	NS
Age range—years	15.0–25.6	15.1–30.4	15.8–30.2	NA
Diagnosis of offspring	NA	10MD, 3BDI, 1BDNOS, 3BDII, 1 dysthymia, 1 psych. NOS	NA	NA
Family history (bipolar second degree relatives, bipolar I parent, bipolar II parent)	5, 13, 6	2, 13, 4	0, 0, 0	NA
Treatment at the time of scanning	NA	2Li, 1AD, 1AP, 1 LA, 14 No treatment	NA	NA
HAMD mean (SD)	0.2 (0.8)	2.6 (2.9)	NA	<0.001
YMRS mean (SD)	0.2 (0.6)	1.4 (3.2)	NA	NS
Illness duration—years, mean (SD)	NA	4.81 (2.9)	NA	NA
Percentage of right handed	70	89	90	NS
ICV mean (SD) cm^3	1451.4 (183.8)	1428.9 (139.74)	1415.5 (126.3)	NS
GM mean (SD) cm^3	876.9 (109.4)	898.7 (174.3)	864.6 (121.9)	NS
Pituitary mean (SD) mm^3	803.1 (181.6)	805.9 (226.7)	763.0 (175.5)	NS

AD antidepressants, *AP* antipsychotics, *BD* bipolar disorder, *HAMD* 17 item Hamilton depression rating scale, *HR* high-risk, *LA* lamotrigine, *Li* lithium, *MD* major depression, *NOS* not otherwise specified, *YMRS* Young mania rating scale

Exploratory analyses

There were no differences between high-risk (unaffected + affected) and control subjects ($t = 0.92$, $df = 72$, $P = 0.36$). There was a significant positive correlation between GM and pituitary volumes ($r = 0.26$, $P = 0.03$) and a trend for positive correlation between intracranial and pituitary volumes ($r = 0.21$, $P = 0.08$). There was no association between pituitary volumes and age ($r = -0.01$, $P = 0.94$), HAMD ($r = -0.07$, $P = 0.67$), YMRS ($r = -0.19$, $P = 0.24$) or duration of illness in affected HR subjects ($r = 0.10$, $P = 0.73$). Covarying for gray matter or excluding the five medicated subjects did not change the results.

There were no differences in pituitary volumes between high-risk subjects with vs. without parent with psychotic symptoms during episodes of mood dysregulation (offspring of parents with psychosis $N = 10$, mean pituitary volume = 791.7, SD = 162.8, offspring of parents without psychosis $N = 32$, mean pituitary volume = 804.7, SD = 214.9, $t = -0.18$, $df = 40$, $P = 0.86$). Furthermore the number of relatives with bipolar disorders with psychotic symptoms did not correlate with pituitary volumes in high-risk subjects ($r = -0.23$, $P = 0.13$).

With 74 subjects in three groups, we have 86% power to detect effect size of 0.5.

Discussion

Our findings extend the previous report [4] of comparable pituitary volumes in bipolar children and adolescence (age range 10–21 years), to both affected and unaffected relatives of bipolar probands between 15 and 30 years of age.

This is the second largest study of pituitary volumes in mood disorders. The largest effect size observed in our study was 0.23 (95% confidence interval = −0.31–0.76, NS). This is much less than effect sizes found in previous positive studies, range of 0.74 [27]–0.86 [20]. Our study was sufficiently powered to detect effect sizes of 0.5 as statistically significant. It is thus unlikely, that this is a false negative study or that we are missing a clinically significant effect.

Our findings contrast with some previous studies. However investigations of pituitary gland volume in BD are inconsistent, with one report of lower [27], one report of larger [23] and one report of unchanged [4] pituitary volumes. Studies in unipolar depression are more consistent, with most, [16, 19, 20, 23], but not all studies [27, 28] reporting increased pituitary volumes. Potential confounders, including symptomatic status, comorbid conditions, and treatment, need to be considered in interpreting the available data. It is of interest, that with exception of a single study which contained preponderance of euthymic subjects (13/23) [27] all other studies reporting pituitary volume abnormalities, were done in patients symptomatic at the time of scanning. On the other hand the only negative study in bipolar patients contained only 2 depressed and 14 euthymic subjects. Cortisol abnormalities are mostly present only during episodes of mood dysregulation. It is thus a question, whether the pituitary volume could also represent a state marker. This hypothesis is supported by association between pituitary volumes and post dexamethasone cortisol levels [1]. On the other hand the only prospective study in patients with seasonal affective disorder did not find fluctuations in pituitary volume with clinical status [28]. Since cortisol abnormalities are rare among patients with seasonal affective disorders [22], this finding may not be generalizable to other subtypes of mood disorders. Therefore the fact that all of our subjects were in remission could have contributed to the lack of pituitary volume abnormalities.

Alternatively abnormal pituitary volumes may be associated with psychosis [23, 24] and increased pituitary volumes have been shown to precede full onset of psychotic disorders [9]. However in our sample family history of bipolar disorders with psychotic symptoms in parents or number of relatives affected with bipolar disorders with psychotic symptoms were not associated with pituitary volumes.

Conditions often comorbid with mood disorders, such as alcohol abuse, have also been associated with abnormal pituitary volumes [2]. Typical as well as atypical antipsychotics have been shown to increase pituitary volumes in retrospective [23], as well as prospective studies [17, 18]. Majority of patients in the single previous study reporting increased pituitary volumes in bipolar subjects, were treated with typical antipsychotics [23]. Low sample size did not allow the authors to control for this confounder. Effects of mood stabilisers on pituitary volumes have not yet been systematically tested. We carefully controlled for all of these confounders, by scanning only subjects without comorbid conditions. Only five patients were medicated, none with typical antipsychotics. Exclusion of these subjects did not change the results.

Our study was designed to investigate whether pituitary volume abnormalities meet criteria for primary vulnerability marker. Lack of abnormalities in unaffected relatives of bipolar patients, as well as comparable pituitary volumes in already affected subjects early in the course of illness relative to healthy controls, does not support this hypothesis. Our findings are congruent with the only study in bipolar children and adolescents [4], and partially with a study in unipolar treatment naïve children and adolescents. Significantly larger pituitary volumes in this study were found only among males without family history of mood disorders, whereas no pituitary volume abnormalities were noted in unipolar patients with family history of mood disorders [20]. Lack of pituitary volume abnormalities is congruent with lack of changes in other brain regions (hippocampus, ventricles, subgenual cingulate) in unaffected relatives of bipolar subjects [13, 21]. Our finding is incongruent with findings of larger pituitary volumes in patients with first episode of affective psychosis mostly treated with typical antipsychotics [23], pediatric treatment naive [20] and early onset unipolar depression patients [19]. Generalizing findings from unipolar to bipolar patients may be problematic, as these two conditions likely have different pathophysiology, which is reflected in contradictory volumetric findings regarding the pituitary [27] and also other brain regions (hippocampus, amygdala, hypothalamus) [3, 25].

This study has following limitations—similar to previous studies, we did not include endocrine measures, used a cross sectional design and available MRI volumetric methods did not allow us to distinguish between anterior and posterior pituitary. Aside from bipolar I subjects, we also included probands with conservatively defined bipolar II disorders. There were no volumetric differences in the pituitary volume between relatives of bipolar I and II subjects, and the exclusion of relatives of bipolar II patients from our sample did not change the results. This is in keeping with another study [27]. We thus feel that clinical heterogeneity did not play a significant role in our data, especially as we also excluded subjects with other psychiatric comorbid conditions including alcohol/substance abuse and ADHD. In some cases more than one subject per family was recruited, which due to presumably lower variance within family might bias towards false positive findings. Since none of the findings were positive, we did not use mixed models to control for this. We used manual tracing. To eliminate subjective bias, all tracings were done blindly. To ensure replicability we used standard methods and tested interrater reliability, which was sufficient (0.96).

Overall pituitary volume abnormalities do not seem to be a consistent hallmark of mood disorders, but rather may be present only in subgroups of patients (psychotic mania, psychotic depression, non-familiar male unipolar patients), or related to clinical symptoms, treatment or comorbidities. The lack of abnormalities in unaffected and also affected subjects early in the course of illness in our study, as well as previous investigations of bipolar and familial unipolar children and adolescents, suggest that pituitary volume abnormalities are unlikely to be a primary risk factor for mood disorders.

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