Case Report

Isolated Neuropsychiatric Features with Non-functioning Pituitary Adenoma: Association or Coincidence?

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Non-functioning pituitary macroadenomas are often detected after a long latency period, with symptoms due to compression of adjacent structures (headache, visual field abnormality) and hyposcretion of pituitary hormones. Irrespective of endocrinological disturbances, these patients sometimes demonstrate mood abnormalities, cognitive deterioration, and psychotic symptoms, in such cases usually other symptoms prevail in the clinical picture. Only rare anecdotal case reports are available in which isolated neuropsychiatric or cognitive symptoms were the presenting features of pituitary adenomas. We report a 17-year-old boy with non-functioning pituitary macroadenoma, who presented with depressive symptoms for 6 months, along with predominantly mood-congruent psychotic features and anterograde memory impairment. On subsequent evaluation, he was found to have subclinical abnormalities in visual field testing. His endocrinological and other ancillary investigations were normal. He partially responded to multiple antidepressants and is currently being planned for surgical intervention. Hence, clinicians need to perform neuroimaging in cases with depressive symptoms, when the course is atypical, unsatisfactory response to multiple antidepressants, prominent psychotic/memory-related symptoms to rule out secondary causes. In such cases, pituitary adenomas should also be considered as one of the clinical differentials.

Keywords: Macroadenoma, mood changes, neuropsychiatric symptoms, pituitary

INTRODUCTION

Non-functioning pituitary adenomas are relatively rare with a prevalence of around 70–90 cases per million people and constitute around 15% of all pituitary adenomas.[1] Almost exclusively these are benign; do not produce symptoms due to excessive hormone secretion.[2] Rather they cause symptoms due to compression of nearby structures leading to headache and visual symptoms.[3] Up to 15% of cases are detected incidentally in neuroimaging.[4] Personality changes, mood disorders, and psychotic features have also been explained with both hormonally active and non-functioning pituitary adenomas, but visual or endocrinal symptoms have predominated the clinical picture in these cases.[3] Isolated neuropsychiatric features as a presentation of non-functioning pituitary adenoma are rare and only anecdotal case reports are available in the existing literature.

CASE PRESENTATION

A 17-year-old previously healthy boy with normal cognition and average scholastic performance was brought with complaints of depressed mood for the last 6 months. He had apathy, poor appetite, and sleep, decreased interaction with caregivers, anhedonia, occasional suicidal ideations, and low motivation and energy, even for activities of daily living. He also demonstrated interpersonal rejection sensitivity, poor...
self-esteem, crying spells, hopelessness, and occasional self-harming behavior. He also had substantial memory impairment and although he remembers the details of past events but unable to register new information and used to forget even simple instructions given a few minutes back. He also had a low-grade chronic headache for the last 3 months of nonspecific nature and showed some psychotic behaviors, including talking to self and the walls, hallucinations, and delusions. There was no history of seizure, movement disorder, or profound encephalopathy. There was no family history of depression or other psychiatric illness. Physical examination was grossly normal. Mini-mental status examination showed a score of 22 (mild cognitive impairment). The full-scale intelligence quotient in Malin’s Intelligence Scale for Indian Children (MISIC) was 81 (below-average intelligence). The boy was also found to have mildly impaired attention and executive function, which could have confounded the previous two results. Behavior Rating Inventory of Executive Function (BRIEF)-adult version showed an elevated global executive composite T score of 68. Beck’s depression inventory score was 21 (suggestive of moderate depression) and the brief psychiatric rating scale score was 31 suggestive of mild psychotic symptoms. Memory functioning questionnaires and working memory rating scale scores were also suggestive of mild impairment.

He was already tried on olanzapine, fluoxetine, amitriptyline in improper doses and duration before presenting to our center and no relief in symptoms. Magnetic resonance imaging (MRI) of the brain revealed benign macroadenoma of the pituitary measuring 11.3 × 12.1 mm size [Figure 1]. On subsequent evaluation, he also had bitemporal visual field restriction, which was not clinically perceived previously, but all endocrinological investigations including thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, cortisol, and other hormonal assays were within normal limits. Morning serum cortisol and adrenocorticotropic hormone (ACTH) levels were in the lower normal range. The cerebrospinal fluid (CSF) examination was within normal limits, including workup for autoimmune encephalitis and neurometabolic diseases. Electrolyte imbalances and diabetes insipidus were also ruled out in the boy. Given subclinical visual symptoms, persistent headache, and psychiatric symptoms, he is currently being planned for partial transsphenoidal hypophysectomy. Meanwhile, over 3 months after optimizing the antidepressants (escitalopram), he had partial resolution of psychiatric symptoms.

Figure 1: Magnetic resonance imaging of the brain. T2-weighted axial (A) and coronal (B) and T1-weighted coronal sections showing macroadenoma of pituitary measuring 11.3 × 12.1 mm size (arrow). Post-contrast sagittal sequences (D and E) showed moderate contrast enhancement.
**DISCUSSION**

Neuropsychiatric symptoms have been described as an early manifestation of a pituitary tumor in few cases. This has been attributed to the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Increased levels of serum ACTH and cortisol have been documented in patients with depressive disorder. However, the relationship between cortisol/ACTH levels and depression is more complex. While patients with severe mood disorders more often demonstrate hyperactive HPA axis, corticotropin-releasing hormone (CRH) hypersecretion, increased ACTH secretion, elevated serum, urine, and CSF levels of cortisol and exaggerated cortisol response to ACTH secretion, a downregulated HPA axis, and CRH deficiency align with chronic atypical depression.\(^5\)–\(^7\) This appears to be the more reasonable explanation for neuropsychiatric symptoms in our case, as the ACTH and cortisol levels in serum were in the lower normal range. Hyposcretion of pituitary hormones has been well documented in expansile non-functioning pituitary macroadenomas.\(^8\)

Cardoso et al.\(^8\) described a case of benign non-functioning pituitary adenoma presenting with longstanding chronic atypical depression in a 52-year-old male, who did not respond to any hormone replacement and required transphenoidal hypophysectomy. Antidepressants administered concurrently provide reasonable evidence that the affective and other neuropsychiatric symptoms were not idiopathic and most probably due to pituitary adenomas. Even a literature review by Cardoso et al.\(^8\) has demonstrated more than 10 cases with prominent neuropsychiatric symptoms, associated with panhypopituitarism, pituitary adenoma, Sheehan syndrome, and even after surgical removal of pituitary adenoma. In this review, around 51% of cases had prominent mood and psychotic symptoms before other classical symptoms of the pituitary lesion. But these symptoms were nonspecific so that clinicians rarely suspect pituitary pathology in every case of depression. In our case, atypical age of onset, no definite stressors, prominent psychotic symptoms, and absence of sustained response to antidepressants prompted us to perform a neuroimaging, as predominantly frontal and sometimes temporal lobe neoplasms are known to present with isolated neuropsychiatric features.\(^8\)

Cohen et al.\(^9\) described 16 male patients with prolactin-secreting pituitary adenomas with a characteristic tetrad (4A) of neuropsychiatric symptoms: apathy, adiposity, asexuality, and headache, which persisted even after adequate hormone replacement therapy and did not correlate with serum prolactin levels. They proposed these symptoms ensued from the hypothalamic derangement that might have caused these adenomas in the first place, or, more likely, there was a mixture of defects consequent to hypothalamic disturbance, suppression of normal pituitary function, pituitary hormone overproduction, and altered receptor sensitivity.

Guinan et al.\(^10\) demonstrated neurocognitive deficits, especially impaired anterograde memory in patients with pituitary adenomas, irrespective of their hormone secretory status, and modality of treatment received (transfrontal or transsphenoidal surgery, radiotherapy, or bromocriptine). Moreover, Pereira et al.\(^11\) have shown increased psychopathology and poor QOL in survivors of patients with both functioning and non-functioning pituitary adenomas. They have suggested multifactorial pathophysiology for the same, like persistent effects of hormone excess affecting behavior and personality and intrinsic imperfections of surgical or endocrine replacement therapy.

In our case, although surgical intervention targeted for resection of pituitary adenoma is yet to be performed, yet we consider the presence of pituitary macroadenoma to have some association with psychiatric symptoms, because of temporal correlation of symptoms and also the presence of headache and subclinical visual symptoms. As such childhood atypical depression occurring concurrently with headache and memory impairment points more toward an organic etiology and previous literature also supports the role of pituitary adenoma in accusation of depressive and other neuropsychiatric symptoms. Endocrinal, autoimmune, and other reversible causes had been ruled out in our case. Sood et al. have previously described a case of pituitary adenoma, who even after surgery developed multiple psychiatric problems, as she was left with a residual tumor. So, it seems more likely that the presence of neuropsychiatric features in our case with non-functioning pituitary adenoma is an association in all probability, rather than a mere coincidence. However, there is still a possibility that the cause and effect relationship, in this case, is only conjectural.\(^12\) Complete reversal of symptoms could have been possible in our case with surgical resection as shown in a case by Muraleedharan et al., who also had atypical depression as a presenting symptom of pituitary adenoma.\(^13\)

**CONCLUSION**

Pituitary tumors have an impact on personality, cognition, mood, and behavior of patients, irrespective of hormone secretion status, and medical/surgical
treatment. Hence, neuroimaging should be considered in any patient with atypical neuropsychiatric symptoms, not responding to pharmacological interventions as expected. Pituitary adenomas if detected in such cases in neuroimaging should be considered as pathological rather than incidental.

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**Conflict of interest**
The authors declare that they have no conflict of interest.

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