

Mood Disorders Associated With Pituitary Adenoma

Authors: Michael A Magoha¹, Faisal Nageyle²

¹Department of Surgery, University of Nairobi.

²Faculty of Health Sciences, University of Nairobi.

Corresponding author: Faisal Mohamed Nageyle. Email: faisalnageyle@gmail.com

Summary

Pituitary adenomas have been found to exhibit associations with various mood disorders, including depression, mania, and anxiety disorders. Additionally, these adenomas have been observed to manifest other psychiatric symptoms, such as psychosis, eating disorders, apathy, and suicidal ideation. A comprehensive literature review was conducted, employing diverse search engines including PubMed, Cochrane, and Google Scholar. The search terms utilised encompassed "pituitary adenomas," "mood disorders," "Hypothalamo-pituitary axis," "hypopituitarism," "acromegaly," "depression," "mania," and "psychosis." The publications that were chosen consisted of case reports and relevant research articles. There is a high prevalence of comorbidity between pituitary adenomas and depressive and anxiety disorders. The manifestation of these symptoms can be attributed to the endocrine dysfunction associated with pituitary adenomas, as well as the physical impact and infiltration of the tumours into the brain. Furthermore, it has been noted that apathy syndrome and chronic fatigue syndrome may be mistakenly diagnosed as depression among individuals within this specific patient demographic. Mood disorders can impact the process of diagnosing and treating pituitary adenomas. Diseases of this nature can potentially impact patients' daily functioning and their ability to engage in social activities. These individuals require suitable medical intervention to enhance their prognosis.

Introduction

The Diagnostic and Statistical Manual classifies mood disorders that develop due to medical or physical conditions under "Mood disorders due to a general medical condition." Organic mood disorders can develop secondary to numerous intracranial pathologies that may be degenerative, neoplastic, infective or inflammatory (1).

Up to 42% of brain tumours are associated with mood symptoms, while 50 to 78% of patients present with a form of psychiatric illness (2). Primary brain tumours are ten

times more likely to occur in psychiatric patients; it is estimated that 1 in 1000 psychiatric patients have a brain tumour, which is 20 times greater than the general population; however, it is not clear whether the tumours are the cause of their mental illness (3–5). 18% of patients develop psychiatric symptoms as the only indication of a brain tumour(5). Imaging studies show structural changes in the frontal lobe, medial temporal lobe and striatum of patients with mood disorders; significant changes have also been found in these regions in patients

with secondary mood disorders. the pathophysiology of mood disorders reflects dysfunction of the cortico-limbic and cortico-striatal networks(1).

Pituitary adenomas constitute 15% of all intracranial tumours, with autopsy data indicating a prevalence ranging from 11-25%; a recent meta-analysis reports an overall prevalence of 16.7% in the general population. 22% of the adenomas are incidentally diagnosed, and 14% are

diagnosed post-mortem. The annual incidence of primary adenomas is estimated to be between 2 and 9 per 100,000 individuals (6). The incidence of pituitary adenomas is higher in the elderly, with autopsy analysis showing that more than 30% of people 50-60 years of age harbour clinically undetected tumours; conversely, the occurrence of this medical condition is infrequent among children, only 3.5-8% of cases are found in patients under 20 years (7)

Methods

A comprehensive literature review was conducted, employing diverse search engines including PubMed, Cochrane, and Google Scholar. The search terms utilised encompassed "pituitary adenomas," "mood

disorders," "Hypothalamo-pituitary axis," "hypopituitarism," "acromegaly," "depression," "mania," and "psychosis." The publications that were chosen consisted of case reports and relevant research articles.

Results

1. Depression

Depression is a prevalent psychiatric symptom in patients with brain tumours, studies show that the prevalence of depression in this population ranges from 44% to 80% (5,8,9). A systematic review of published cases on pituitary lesions found that depression is a symptom in 71% of cases. It is also noteworthy that depression can precede other symptoms of pituitary dysfunction by an average of 11 years. In 51% of cases, depression appears before other symptoms, such as sexual dysfunction, amenorrhea, visual disturbances, and abnormal hair growth. In only 15% of cases, depression develops after these symptoms. Interestingly, 46% of cases of depression in patients with pituitary lesions are consistent with atypical depression, while 20% show melancholic features. Overall, the evidence suggests that depression is a common and significant complication of brain tumours and A

pituitary lesions. It is important to be aware of this association so that depression can be identified and treated early, leading to improved patient outcomes (9).

Abnormal endocrine functioning of the pituitary plays a significant role in the development of depression; depressed patients have larger pituitaries than the rest of the population, and approximately 10% of people develop an affective disorder as a result of endocrine dysfunction in their lifetime; the primary cause of these disorders is the dysfunction of the Hypothalamo-pituitary axis caused in part by pituitary lesions such as adenomas (5,8,10). Functional adenomas of the pituitary commonly associated with depression include those that secrete ACTH, growth hormone, prolactin and TSH (11–13).

significant proportion of individuals diagnosed with Cushing's syndrome (85%-100%)

experience psychological disturbances, including but not limited to anxiety, emotional

instability, depression, sleep disturbances, psychosis, and elevated mood. 50-63% of patients diagnosed with Cushing's syndrome meet the criteria for mood disorders. Depression is present in approximately 25% of patients during the prodromal phase of the disease. Notably, the incidence, type, and treatment response of mood disorders is not associated with the underlying cause of Cushing's syndrome (6,14–16). The psychiatric symptoms can result from hormonal and biochemical alterations and physiological deformities (17). Chronic atypical depression is common in patients with a hypoactive HPA axis, characterised by low levels of ACTH and cortisol in serum and urine; this state of hypopituitarism has been observed in patients with expansive non-functional pituitary macro-adenomas(9,11,18).

Thyrotropin-producing pituitary adenomas are comparatively rare (3%) and are an uncommon aetiology of hyperthyroidism(19). Hyperthyroidism is commonly associated with various manifestations of mood disorders, including anxiety, insomnia, irritability, quick-temperedness, occasional ideas of reference, paranoia, psychomotor agitation, mood lability, and deterioration of cognitive function. Many meet the diagnostic criteria for major depressive disorder, organic affective disorder or generalised anxiety disorder as outlined in the DSM-5 (12).

The prevalence of depression and anxiety disorders among individuals with thyrotoxicosis ranges from 31-69% and 33-61%, respectively; they can also present with psychotic disorders and rapid cycling bipolar disorder. It is hypothesised that these disorders may be attributed to an imbalance in serotonin levels and β adrenergic dysfunction in the central nervous system.(20). However, The causal relationship between TSH-producing adenomas and mood disorders remains unclear, and depression may develop as a result of thyroid dysfunction or treatment for conditions such as hyperthyroidism; furthermore, there is a low prevalence of

thyroid disease in patients with existing depression (12).

Patients with Growth hormone-producing adenomas have a higher prevalence of affective disorders than those with chronic somatic disorders and healthy controls. The neurophysiological integrity of the prefrontal and temporal cortices is affected by excessive growth hormone (GH) and insulin-like growth factor (IGF), leading to reduced cognitive performance in patients with acromegaly. In India, individuals with acromegaly exhibit a psychological morbidity rate of 35%, primarily characterised by depression, while in Spain, the rate is 62.5%. In Germany, these patients exhibit a higher incidence of anxiety and greater levels of neuroticism and harm avoidance than individuals without the condition. This pattern of behaviour is similar to that observed in patients with non-functioning pituitary adenomas (11,21).

The current hypothesis posits that an overabundance of GH and IGF leads to significant growth of white and grey matter within the limited confines of the skull. This growth ultimately results in a reduction of the necessary space required for proper cerebrospinal fluid flow. Consequently, the resulting hydrocephalus and mass effect may exert pressure on vital structures such as the cortico-striatal-thalamic tracts and the hypothalamic-pituitary tract. Previous research has elucidated the adverse neuropsychological consequences of acromegaly by establishing a correlation between the neurovascular comorbidities commonly observed in individuals with acromegaly, including hypertension, endothelial dysfunction, dyslipidaemia, and heightened oxidative stress.(11,21).

Other psychiatric disorders associated with acromegaly are mostly characterised by a lack of initiative and spontaneity, auditory and visual hallucinations and delusions. These patients also suffer from personality changes leading to impaired self-esteem, body image distortion, disruption in interpersonal relations, social withdrawal and reduced impulsivity,

loss of initiative, spontaneity and marked lability in mood, especially with anxiety and depression (22)

The exact incidence of depression in pituitary adenomas and other brain tumours is unclear as existing studies on the condition are not specific to different tumours and their

2. Apathy

A study published in 2019 showed that 22% of patients with pituitary dysfunction suffer from apathy (9). Apathy is linked to a functional disconnect between the frontal lobe and para-limbic areas and is characterised by a lack of motivation diminished goal-directed behaviour (lack of effort or reliance on others to structure activity), diminished goal-directed cognition, and diminished emotion (unchanging affect, or lack of emotional responsiveness to positive or negative events) (5,8).

Apathy is one of the most critical neuropsychiatric symptoms of pituitary adenomas, especially prolactinomas, being one of the "four As" (apathy, asexuality, adiposity, and "aches" or headaches) that characterise the condition; it is also a symptom of various mental health disorders, frontal lobe syndromes, and neurodegenerative disorders such as Alzheimer's and Parkinson's, apathy distinguishes the four symptoms in pituitary adenomas from a similar symptom cluster present in functional affective disorders (24). Studies show that patients diagnosed with prolactinoma demonstrate a heightened incidence of depressive symptoms compared to those with normal prolactin levels (13). However, the precise mechanism through which elevated prolactin levels bring about changes in mood and behaviour remains unclear (25).

Cohen et al. argue that apathy is often misdiagnosed as depression, patients with pituitary adenomas are often complacent rather than dysphoric, and therefore, these patients do not meet the diagnostic criteria for

respective locations. Depression may present itself at different phases of brain tumour advancement, exhibiting itself in many forms, such as dysphoric mood, feelings of helplessness and worthlessness, guilt, diminished self-esteem, difficulties with concentration, and thoughts of suicide (9).

depression or organic affective syndrome. As a result of apathy, these patients are less likely to complain about their condition or seek care and may develop a tolerance to other symptoms such as headaches, obesity, and sexual dysfunction (24). This argument was supported by a study in 2005 that showed that Pituitary adenoma patients more often present with apathy syndrome than depression; they present with diminished emotional responsiveness to goal-oriented events and decreased emotional distress; this is especially significant when patients are unresponsive to traditional antidepressants, patients with apathy are responsive to stimulants such as methylphenidate, with patients reporting improved task-oriented function, multitasking, improved arousal and attention (13).

In a study on 16 patients diagnosed with prolactinomas, 63% were diagnosed with apathy, this symptom persisted following hormone replacement therapy; the symptoms also did not correlate with the serum prolactin levels, it suggested that the symptoms i.e. apathy, adiposity, asexuality and headache ensued from hypothalamic derangement that may have caused the adenoma in the first place or a mixture of defects consequent to hypothalamic dysfunction, pituitary suppression, hyper-production of pituitary hormones or altered receptor sensitivity(24).

It is suggested that patients suffering from disorders of the pituitary have a neurobiological illness with dysfunction in the cerebral hemispheres and the diencephalons that manifest as apathy and chronic fatigue, it is also proposed that the syndromes of

chronic fatigue and major depression may share similar underlying pathologies, patients with depression who respond to antidepressants may suffer residual fatigue, however, the inverse is not common(13).

Apathy is also present in patients with hypopituitarism resulting from primary pituitary

3. Bipolar Disorder

Rapid cycling Bipolar disorder and psychosis is associated with TSH-producing adenomas(20), patients presenting with thyrotoxicosis may appear to have similar symptoms to mania, and studies associating bipolar disorder with hyperthyroidism are rare, in a study of 31 patients, ¼ had elevated free and total t4 levels upon admission, this finding may not be significant as similar elevations are often found in acutely admitted psychiatric patients(12). Approximately 15% of patients with brain tumours exhibit manic symptoms,

4. Psychosis

Brain tumours have the potential to induce psychotic manifestations that bear resemblance to those observed in individuals with schizophrenia, however, this is a relatively infrequent phenomenon (29). Studies estimate that psychosis occurs in approximately 22% of cases. This symptom is commonly associated with tumours located in the pituitary gland, pineal gland, posterior regions of the brain, cerebral cortex, and temporal lobes. Notably, a meta-analysis published in 2010 showed that while there is typically no direct correlation between the symptoms of brain tumours and their location, there is a potential association between pituitary tumours and psychosis (5,8).

Psychosis can also present in patients who develop functioning pituitary adenomas; this condition has been observed in a patient with a macro-prolactinoma who had presented with acute onset psychosis; the condition

diseases such as adenomas or as a side effect of therapy modalities such as external beam radiotherapy and surgery, other psychiatric symptoms of this condition include weakness, fatigue, anhedonia, mood disturbances, psychosis and delirium(26,27).

with the majority of these tumours (81%) being situated in the frontal temporal or subcortical limbic structure. A significant proportion of these tumours (75%) are located in the right hemisphere, with only 6% confined to the left hemisphere and 6% bilateral. The remaining 13% affect midline structures. The prevailing theory is that manic symptoms result from the mass effect of tumours on the limbic and subcortical structures. Additionally, these tumours can exacerbate pre-existing bipolar disorders (8,28).

improved 48 hours after induction of intravenous fluids and hydrocortisone; this shows that the hyperprolactinemia is unlikely to be a significant cause of psychosis(30).

Psychosis can present secondary to hypopituitarism, however, the cause is not clear, it could be due to hormonal deficiency as it also presents with other endocrine deficiencies such as Addison's and hypothyroidism. The combination of hypothyroidism, hypoglycaemia and hypocortisolism resulting in complex metabolic and electrolyte dysregulation in the central nervous system may be the cause of the psychosis, this condition may be refractory to traditional antipsychotics, however, patients recover shortly after hormonal replacement therapy(30).

5. Anxiety disorder

In contrast to the general population, patients with pituitary adenomas exhibit a distinctive pattern of elevated anxiety-related features that is brought on by the lesion or hormonal dysregulation(11). This symptom is present in 22% of reported pituitary conditions, along with depression, high levels of anxiety is present in patients with hormonal excess due to ACTH and TSH-producing adenomas; furthermore, patients with prolactinomas have a higher prevalence of anxiety than the general population (9,13,20).

Patients with brain tumours exhibit a significantly higher incidence of generalised anxiety disorder, with up to a 60% greater prevalence. Anxiety symptoms frequently

co-occur with depressive symptoms, which may be attributed to heightened apprehension regarding the diagnosis and impact of the tumour. It is plausible that these disorders share common etiological factors and symptomatology. The prevalence of these symptoms is higher among female patients than their male counterparts. The manifestation of generalised anxiety disorder in patients with brain tumours is influenced by factors such as gender, level of education and tumour grade (31).

There is a paucity of research regarding anxiety and pituitary adenomas. However, it is clearly one of the commonly diagnosed mood disorders in these patients, along with depression, mood instability and apathy (13).

6. Eating Disorders

Eating disorders, such as bulimia and anorexia nervosa, are seldom linked with focal brain lesions; there are clinical accounts of eating disorders occurring in individuals with a history of prenatal problems and head injury(32). The majority (75%) of these disorders are related to hypothalamic lesions (2), pituitary adenomas presenting with anorexia are relatively rare; the few related

cases have been linked to pituitary insufficiency (33). Anorexia is a common early symptom of brain tumours; however, the diagnosis of these tumours is more often missed due to the attempt to explain the symptoms of anorexia and behavioural change in patients as a psychiatric disorder rather than an organic cause (34).

7. Mood disorders caused by management for pituitary adenoma

Radiotherapy for pituitary adenomas and other brain tumours have been associated with increased neuropsychological morbidity in recovering patients(21), cognitive dysfunction has been identified as a delayed adverse outcome of whole or large field brain radiation, this may occur with low radiation doses in adults (20 Gy) and children (24 Gy), symptoms include cognitive slowing, poor attention and concentration, difficulty

multitasking, decreased short and long-term memory, decreased IQ in children, changes in energy and mood, particularly fatigue, anxiety and depression(35), patients treated with External beam radiotherapy often develop hypopituitarism, anterograde memory impairment (27).

A study comparing the quality of life and mood outcomes of patients who underwent

different methods of management i.e. surgical (trans-sphenoidal or trans-frontal) or medical and healthy subjects showed that the patients who had been treated reported mild mood disturbance, poorer social adjustment and higher levels of emotional distress, the patients who had undergone the trans-frontal procedure did not rate themselves as different from the comparison group, however, further assessment revealed that they were distinct from the comparison group, this was related to a lack of insight following frontal lobe surgery. Patients undergoing radiotherapy have been shown to have lower quality of life scores, they perform poorer than comparison groups in speech, executive functioning verbal and visual memory(13)

The administration of dopamine agonist agents, such as Carbegoline, for the treatment of prolactinomas can result in the manifestation of adverse effects such as depression, hypersexuality, gambling, and impulse control disorders(36), carbegoline is also associated with the dysregulation of fronto-striato-thalamic circuits, which can result in the occurrence of psychosis as a rare side effect, similarly bromocriptine has been found to exacerbate psychosis (27) , while The aetiology of psychosis in patients with prolactinoma remains uncertain, as it is unclear whether the drug or the mass effect of the tumour is responsible for this effect. In cases where dopaminergic agents induce this side effect, alternative treatments such as surgery and radiotherapy should be considered. Additionally, clozapine can serve as a viable alternative agent for patients

8. Suicide and pituitary adenomas

Research indicates that suicide and suicidal behaviours have a neurobiological foundation. Specifically, depression-related suicides are linked to decreased activity of the dopaminergic system. Additionally, dysfunction of the HPA and serotonin system may also play a role. Further evidence suggests a correlation between suicidality in depression and heightened production of TSH

experiencing cabergoline-induced psychosis (37).

The administration of antipsychotics and neuroleptics warrants careful consideration due to the potential for adverse effects, they potentially exacerbate hormonal dysfunction by increasing the size of prolactinomas. This effect is attributed to the antagonism of dopamine, which results in hyperprolactinemia. A study examining patients treated with olanzapine, ziprasidone, risperidone, aripiprazole, haloperidol, and quetiapine identified 77 cases of pituitary adenomas associated with these drugs. Additional studies have reported eight patients who developed prolactinomas as a result of antipsychotic and neuroleptic use. While the direct causality between these drugs and the development of adenomas remains unclear, these findings underscore the challenges of managing patients with pre-existing psychosis and prolactinomas (25,26).

This phenomenon is a well-documented side effect of both typical and atypical antipsychotics. In psychiatric patients receiving antipsychotic treatment, elevated serum prolactin levels have been observed in a significant proportion of cases, with approximately 71% of patients affected. Furthermore, nearly 37% of these patients exhibit serum prolactin levels exceeding twice the normal range. (22). Misdiagnosis of prolactinoma may occur due to this phenomenon.

(38), since pituitary adenomas may have all these effects, they can increase the risk of suicide (23).

A study aimed at determining the prevalence of pituitary adenoma in Polish suicide victims discovered a high prevalence of pituitary macro adenomas among suicide victims, with a recorded incidence of 47.7% (32 cases) compared to a control group of non-suicidal

individuals, which had an incidence of 18.3% (15 cases). Notably, all of the adenomas discovered were macro adenomas discovered post-mortem. The study aimed to find out whether the presence of a pituitary adenoma in a patient affects their risk of suicide or suicidal behaviours. The study's findings imply that mental diseases such as depression, mania, and other mood disorders may increase the chance of suicide. Despite this, the study found no detectable variations in hormone levels between the two groups (38).

Discussion

Mood symptoms can be an early indicator of a brain tumour, they indicate an evolving tumour that is disrupting the normal chemistry and physiology of the brain, although they do not provide a localising sign of a tumour, sudden onset psychiatric symptoms or exacerbated and atypical symptoms of a previously controlled psychiatric condition should be scrutinised by physicians (2), the presence of psychiatric symptoms is dependent on many factors including familial history of psychiatric disorders, the location of the tumour and the impact of the physiological impact of the tumour on the patient in terms of pain, discomfort, disability and physical deformity that can result from some of these tumours.

The mood symptoms of pituitary adenomas have not received adequate attention in research studies, which have primarily focused on the somatic manifestations of endocrinopathies and tumours. Mood disorders have a significant impact on the diagnosis of the tumours; in cases where patients present with psychiatric symptoms that precede physical symptoms, the patient may receive psychiatric treatment; this may lead clinicians to treat such patients as psychiatric cases while ignoring other physical symptoms; the mood symptoms symptoms

Additional allusions to suicide in correlation with pituitary adenomas are discoverable in case studies. Waiter et al. documented a case of a patient who experienced pan-hypopituitarism following surgery for pituitary adenoma. The patient exhibited symptoms of personality change, mood disorder, apathy, and intermittent suicidal thoughts(13).

can also mask the symptoms of pituitary adenomas.

The manifestation of certain symptoms, such as apathy and depression, can potentially impact the health-seeking behaviours of patients. In the case of individuals with pituitary adenomas, the neuropsychiatric effects of the tumours may result in a heightened propensity to disregard and endure their symptoms. This, in turn, can prolong the duration of the disease, ultimately affecting the outcome. Patients may only seek medical attention for their symptoms during the advanced stages of the disease, which could result in permanent neuropsychiatric and physical changes or a longer recovery period. The duration between symptom onset and treatment initiation may also influence the management approach, thereby increasing the likelihood of complications and treatment costs.

The diagnosis of pituitary adenomas can be complicated by challenges in obtaining precise medical histories and information from patients with mood disorders. Symptoms such as psychosis, delusions, and paranoia can impede patients' ability to provide accurate information to their healthcare providers, who may already be influenced by their psychiatric

condition. Consequently, mood disorders may be misdiagnosed, and patients may be prescribed medications that provide only temporary relief. Pituitary adenomas are slow-growing benign tumours, symptoms such as behavioural changes have a slow onset and progress over time as do the physical symptoms, this implies that patients may develop certain behavioural changes over long periods of time sometimes spanning decades, these behaviours become part of their personalities and are considered normal by them and those around them, thus masking the existence of the tumour.

Pituitary adenomas have a significant impact on the physical functioning of patients which may cause mental distress, the general state of poor health, fluctuations in weight as seen in ACTH and thyrotropin-producing adenomas, changes in physical appearance as in GH-producing adenomas, sexual and reproductive dysfunction as in prolactinomas and other comorbid conditions may induce mood disorders such as depression or act as perpetuating factors for other pre-existing mental disorders such as bipolar disorder.

Patients with mood disorders caused by tumours often present to psychiatric care providers and receive treatment. However, their symptoms do not resolve with therapy, and as the tumour grows, they develop physical symptoms and are referred for neurological care and imaging. At this point, the tumour is detected and treated with chemotherapy, surgical resection, or hormone replacement therapy. These treatments are highly effective in resolving the psychiatric manifestations of these tumours, likely due to their ability to reduce oedema, intracranial pressure, hydrocephalus, and hormonal

derangements, all of which can contribute to psychiatric symptoms. In some cases, pharmacological therapy may be necessary to treat psychiatric symptoms that persist after tumour removal.

It is clear that in most cases of mood disorders related to pituitary lesions and the resultant endocrine dysfunction usually remit after some time and often without psychiatric treatment, this is seen in cases of ACTH and TSH-producing adenomas, although patients require some therapy to come to terms with the more chronic symptoms of their condition as seen in acromegaly, there is a marked improvement in psychiatric condition of these patients after surgical removal of the lesion and return of hormone levels to normal.

The occurrence of mood disorders in patients with pituitary adenomas indicates the importance of a multidisciplinary approach in treatment, which necessitates the presence of endocrinologists, neurosurgeons, neurologists, psychiatrists, and many other auxiliary medical personnel and social workers to provide effective management and support to these patients and ensure good outcomes and quality of life.

Conclusion: Mood disorders significantly influence the diagnosis and treatment of patients with Pituitary adenomas diagnosis and treatment are influenced by mood disorder. Such disorders may also have an impact on patients' daily functioning and social involvement. To enhance their prognosis, these individuals require adequate medical and psychological therapy.

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