Mini Review

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Neuropsychiatric manifestations of Cushing's syndrome: a mini-review

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Abstract

Cushing's syndrome is an endocrine disorder that is challenging to the managing physician due to its diverse presentations. The underlying endocrine abnormality is the exposures of various organs to excess glucocorticoids for a prolonged period. This makes the disease to present with various symptoms and signs in different organ systems. However, despite prominent neuropsychiatric features present in Cushing's syndrome, the published works on these features are relatively scanty. This mini-review aims to give an overview of the various neuropsychiatric disorders in Cushing's syndrome.

The effects of excess steroids on the neuronal cells and supporting glial cells in the brain are the underling pathophysiologic mechanisms by which Cushing's syndrome manifest with neuropsychiatric disorders. Brain atrophy due to excitotoxicity and impaired neurogenesis are some of the reported mechanisms. Functional neuroimaging have supported these mechanisms.

Mood disorders are the most common psychiatric manifestation of Cushing's syndrome. Patients may present with varying severity of depressive illness. Some even have suicidal ideation and attempts. Manic episodes have also been reported. Cognitive disorders, characterized by impairment in various domains of cognition such as attention, memory, visuospatial orientation, judgment and verbal fluency have been reported in the literature. Psychotic disorders are rare but their presentation may precede the diagnosis of Cushing's syndrome and they may not respond to the usual antipsychotic medications. Accurate diagnosis and treatment of Cushing's syndrome is usually associated with resolution of the psychotic symptoms. Generalized anxiety disorder and panic disorders have also been scantily reported in Cushing's syndrome. In rare instances, some of these neuropsychiatric features persist even after resolution of the endocrine disease.

Keywords: Cushing's syndrome; Neuropsychiatric manifestations; adrenocorticotropic hormone.

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Background

Cushing's syndromereferstoaconstellation ofsigns and symptoms that are due to exposure of body tissues to excess glucocorticoids which are steroidal hormones. If the steroids are administered by any route, it is termed exogenous Cushing's syndrome. If the excess steroids are produced from the adrenal glands, it is called endogenous Cushing's syndrome. Cushing's syndrome can also be categorized based on the amount of adrenocorticotropic hormone (ACTH) in the circulation. If it is due to excess secretion of adrenocorticotropic hormone (ACTH), it is described as ACTH-dependent Cushing's syndrome whereas when ACTH secretion is suppressed, it is termed ACTH-independent Cushing's syndrome. [1] Among the endogenous Cushing's syndrome, ACTH-dependent causes are 4 times as common as ACTH-independent causes [2.3]. ACTH-dependent Cushing's syndrome that is due to excess production from adenomas of the corticotrophs of the pituitary gland is called Cushing's disease. Cushing disease's is the commonest cause of Cushingsyndrome.

The mechanisms of neuropsychiatric disorders in Cushing syndrome

The main stress hormone is glucocorticoids. The intranuclear receptors of glucocorticoids are widely distributed in the brain

neurons and especially in the hippocampus [4]. This can explain the various structural and functional changes seen in the brain of a patient with Cushing's syndrome. Among the structural changes, the most prominent is generalized brain atrophy [5]. Excess glucocorticoids causes disordered glucose metabolism in the brain neurons and this leads to overactivitity of neurotoxic excitatory amino acid neurotransmitters such as glutamate. The overall effect of this neurotoxicity is brain atrophy, most profound in the hippocampal areas bilaterally.

Moreover, there are some neurotrophic factors that enhance long term potentiation and neurocognition. Excess glucocorticoids in the brain reduces the quantity, quality and neurophysiologic actions of these factors which can affect learning and memory [6]. This suppression of neurogenesis is most prominent in the prefrontal cortex and the dentate gyrus and it has been reported to be the underlying pathophysiologic mechanism of depression commonly seen in patients with Cushing's syndrome [7].

Mood disorders

The most common psychiatric disorder in Cushing's syndrome is major depressive disorder and it is said to be present in more than half of the population of patients with Cushing's syndrome [1]. The risk factors that have been associated with depression in patients with excess glucocorticoids include age, female gender and the levels of glucocorticoids metabolites in the urine. Some cases of depression are so severe that suicidal attempts have been reported in them [8] Some of the documented symptoms in them include sad mood, episodes of unprovoked crying, feelings of hopelessness, fatigue, loss of appetite, reduced libido, sleep disturbance and anhedonia.[8] Manic episodes have also been described in the literature [1].

Cognitive disorders

Disorders of cognition have also been documented in more than half of the population with endogenous Cushing's syndrome [8]. Memory impairment including forgetting names of people, location of things, important dates and even their own past medical history have all been reported in patients with Cushing's syndrome. The ability to concentrate is affected also. They find it difficult to focus their minds on conversations and even when reading or watching television. Other cognitive features present in them include difficulty with comprehension, affectation of reasoning and judgment, impaired verbal controls and reduced visuospatial abilities.

Psychotic disorders

Psychotic disorders are not commonly reported in Cushing's syndrome [9]. Sometimes, the psychotic presentation precedes the diagnosis of Cushing's syndrome and the presentation may not be typical of well characterized psychotic disorders. Some patients were diagnosed with Cushing's syndrome after postmortem examination. Interestingly, those that are diagnosed on time usually have resolution of their psychotic disorders following the successful treatment of Cushing's syndrome. In other reported cases, diagnosis of Cushing's syndrome precede the onset of psychotic symptoms. Therefore, it is important for the Endocrinologists to be able to identify the concomitant psychotic symptoms in Cushing's syndrome and more importantly, the Psychiatrists should be able to recognize the phenotype of Cushing's syndrome in patients with typical or atypical psychotic illness and screen the patient appropriately or seek Endocrine consultation.

The psychotic symptoms hardly resolve with the use of antipsychotic drugs only, hence the need to treat the underlying Cushing's syndrome as soon as possible. Mifepristone, at appropriate doses can however be used during acute psychotic presentation of patients with Cushing's syndrome [10].

Anxiety disorders

The literature on the anxiety disorders in Cushing's syndrome is rather scanty. Various anxiety disorders have been described but the most common ones are generalized anxiety disorders and panic disorders [9]. Even the reported anxiety disorders vary in their severity of symptomatology. It has been documented that the severity of symptoms correlate with the ACTH level. The higher the ACTH, the more severe the symptoms. Therefore, patients with ACTH-dependent Cushing's syndrome are more likely to manifest severe symptoms of anxiety compared with patients with ACTH-independent Cushing's syndrome.

Neuropsychiatric disorder after disease remission

Interestingly, with normalization of cortisol following adequate treatment associated with resolution of the clinical features, some clinical complications of Cushing's syndrome have been found to be persistent. Some of these persistent complications include metabolic syndrome, increased cardiovascular risk and some neuropsychiatric manifestations. It has been documented that the resolution of depression, anxiety disorders, psychosis and some neurocognitive disorders does not correlate with normalization of cortisol levels [11]. In fact, some domains of cognition such as attention, visuospatial orientation, verbal fluency and working memory have been reported to show permanent impairment despite complete resolution of Cushing's syndrome [12]. Functional imaging modalities of the brain such as proton magnetic resonance spectroscopy have demonstrated dysfunction of the neuronal and glial cells, even after resolution of other symptoms of Cushing's syndrome and normalization of the cortisol levels [13].

Conclusion

Cushing's syndrome is an endocrine disorder due to the chronic exposure of tissues to excess glucocorticoids. It has myriads of symptoms and signs but the neuropsychiatric manifestations have often been overlooked. This review has given an overview of the common neuropsychiatric features reported in patients with Cushing's syndrome. There are several reports on the deleterious effects of steroids on the neuronal and glial cells of the brain and this is believed to be the underlying mechanisms of neuropsychiatric disorders in Cushing's syndrome.

Mood disorders are the most common psychiatric manifestations of Cushing's syndrome. These patients may also present with impairment in various domains of neurocognition. Psychotic disorders are rarely reported among patients with Cushing's

syndrome but when they are present they may not respond to the common antipsychotic medications. Anxiety disorders are scantily reported in Cushing's syndrome but some authors have documented generalized anxiety disorder and panic disorders in the psychopathology of Cushing's syndrome.

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