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Research Article

Morning Serum Cortisol and ACTH Levels in Cushing's Syndrome: Correlation with Neuropsychiatric Manifestations

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Abstract Cushing's syndrome, characterized by chronic hypercortisolemia, produces multisystem complications extending far beyond metabolic disruption. Among these, neuropsychiatric manifestations—ranging from depression, anxiety, cognitive impairment, and emotional lability—are frequently underdiagnosed despite their substantial effect on functionality and quality of life. The present cross-sectional study aimed to evaluate the relationship between morning serum cortisol and adrenocorticotropic hormone (ACTH) levels with neuropsychiatric symptom severity in patients with confirmed Cushing's syndrome in a tertiary care setting in Pakistan.

Eighty-six adult patients with biochemically confirmed Cushing's syndrome were assessed. Morning fasting cortisol and plasma ACTH were measured using chemiluminescent immunoassay. Neuropsychiatric evaluation was conducted using the Hospital Anxiety and Depression Scale (HADS) and the Mini-Mental State Examination (MMSE). Statistical analysis revealed a strong positive correlation between cortisol levels and HADS depression scores ($r = 0.62$, $p < 0.001$), and a negative correlation with MMSE cognitive scores ($r = –0.48$, $p = 0.002$). ACTH showed moderate correlation with anxiety ($r = 0.44$, $p = 0.004$).

The results suggest that cortisol hypersecretion directly influences emotional and cognitive regulation, potentially through hippocampal glucocorticoid receptor downregulation and altered

amygdalar reactivity. These findings underscore the importance of integrating psychiatric screening into endocrine evaluations of Cushing's syndrome.

Keywords: cortisol, ACTH, Cushing's syndrome, neuropsychiatric manifestations

Introduction: Cushing's syndrome is a rare but clinically significant endocrine disorder resulting from prolonged exposure to elevated glucocorticoid levels, either of endogenous or exogenous origin. Despite its relatively low incidence, its systemic repercussions are profound, affecting metabolic, cardiovascular, musculoskeletal, and neuropsychiatric domains. Over the past decade, the neuropsychiatric dimension of Cushing's syndrome has gained renewed attention as clinicians have recognized that psychological dysfunction often persists even after biochemical remission. The neurobehavioral burden of this condition includes mood disorders, anxiety, irritability, cognitive impairment, insomnia, and in severe cases, psychosis.[1-4]

Chronic cortisol excess affects nearly every component of brain function. Neuroimaging studies after 2022 have confirmed structural changes, including hippocampal atrophy, reduced amygdala connectivity, and prefrontal cortical thinning, correlating with symptom severity. Cortisol's prolonged elevation disrupts neuroplasticity, enhances excitotoxicity through glutamatergic overstimulation, and suppresses neurotrophic signaling, culminating in measurable cognitive decline and mood dysregulation. ACTH, as a central pituitary regulator, not only reflects hypothalamic–pituitary–adrenal (HPA) axis activation but also serves as a neuropeptide with direct behavioral effects.[5-8]

The psychiatric profile of Cushing's syndrome overlaps with major depressive and anxiety disorders, often leading to misdiagnosis or delayed endocrine evaluation. Depression prevalence among active Cushing's patients ranges between 50–80%, with anxiety and cognitive impairment equally common. Studies from 2023 and 2024 emphasize that psychiatric symptoms often precede overt physical signs such as centripetal obesity or striae, suggesting early neuroendocrine dysregulation. Moreover, patients with higher morning cortisol levels tend to demonstrate blunted affect, apathy, and executive dysfunction on psychometric testing.[9-12]

Despite these insights, limited data are available from South Asia, where diagnostic delays and under-recognition of psychiatric comorbidity are frequent. The neuropsychiatric consequences of

cortisol excess in this population may differ due to sociocultural factors, healthcare access disparities, and baseline psychological resilience. Understanding the neuroendocrine–behavioral interface in Cushing's syndrome can aid in earlier identification and tailored management.

Therefore, this study was designed to assess the correlation between morning serum cortisol and ACTH concentrations with neuropsychiatric symptom severity, using standardized psychiatric scales. It explores whether neuroendocrine parameters correspond proportionally to depressive, anxious, and cognitive manifestations, thereby establishing an integrated model for multidisciplinary patient evaluation.

Methodology: A cross-sectional analytical study was conducted at the Endocrinology and Psychiatry departments of Fatima Memorial College for Medicine and Dentistry, Lahore Jinnah Hospital, Lahore, from February to September 2024. Using Epi Info 7.2, the sample size was calculated considering an expected prevalence of neuropsychiatric symptoms of 70% among patients with Cushing's syndrome, a 95% confidence interval, and 10% allowable error, resulting in a minimum of 80 participants. A total of 86 adult patients aged 18–65 years with confirmed endogenous Cushing's syndrome were included. Diagnosis was based on elevated 8 a.m. serum cortisol (>25 μg/dL), non-suppressible dexamethasone suppression test, and elevated or normal ACTH levels depending on etiology.

Exclusion criteria comprised exogenous steroid use, concurrent major psychiatric disorders unrelated to endocrinopathy, chronic neurological diseases, substance abuse, or severe hepatic or renal dysfunction. All participants provided verbal informed consent, and the institutional review board approved the protocol.

Morning fasting blood samples were collected between 08:00–09:00 hours for serum cortisol and plasma ACTH analysis via chemiluminescent immunoassay. Neuropsychiatric evaluation was performed on the same day by a psychiatrist blinded to biochemical data. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression (score range 0–21 for each subscale), and Mini-Mental State Examination (MMSE) for cognitive performance (maximum score 30). Sociodemographic and clinical data, including age, sex, duration of symptoms, and body mass index (BMI), were also recorded.

Data were analyzed using SPSS version 26. Quantitative variables were presented as mean ± SD. Pearson's correlation assessed relationships between hormonal levels and psychiatric scores. Independent t-tests compared cortisol and ACTH across severity categories of depression and anxiety (HADS ≥11 indicating clinical caseness). A p-value <0.05 was considered statistically significant.

Results

Table 1: Demographic and Clinical Characteristics (n = 86)

Variable	Mean ± SD or n (%)
Age (years)	41.7 ± 10.3
Female / Male	58 (67.4%) / 28 (32.6%)
BMI (kg/m²)	31.2 ± 5.6
Duration of symptoms (months)	18.9 ± 7.4
Morning cortisol (µg/dL)	29.8 ± 6.2
Plasma ACTH (pg/mL)	58.7 ± 20.5
Elevated HADS depression (≥11)	52 (60.4%)
Elevated HADS anxiety (≥11)	48 (55.8%)

The majority were middle-aged females with elevated cortisol and ACTH levels, consistent with active hypercortisolism and prevalent psychiatric symptoms.

Table 2: Comparison of Hormonal Levels by Psychiatric Symptom Severity

Parameter	HADS <11 (n = 34)	HADS ≥11 (n = 52)	p-Value
Cortisol (µg/dL)	25.9 ± 4.1	32.1 ± 5.8	<0.001
ACTH (pg/mL)	49.6 ± 17.9	64.2 ± 19.3	0.003
MMSE score	27.4 ± 1.8	24.6 ± 2.2	<0.001

Significantly higher cortisol and ACTH levels were observed among participants with clinically significant anxiety or depression, alongside reduced cognitive scores.

Table 3: Correlation Between Hormonal and Neuropsychiatric Variables

Variable Pair	Correlation (r)	p-Value
Cortisol – HADS depression	0.62	<0.001
Cortisol – HADS anxiety	0.54	<0.001
ACTH – HADS anxiety	0.44	0.004
Cortisol – MMSE	–0.48	0.002
ACTH – MMSE	–0.36	0.012

Cortisol demonstrated the strongest positive correlation with depressive symptoms and inverse correlation with cognitive function, suggesting neurotoxic effects of chronic hypercortisolism.

Discussion: This study revealed significant correlations between elevated morning cortisol and ACTH levels with neuropsychiatric manifestations in patients with Cushing's syndrome. The strong association between cortisol and depressive symptomatology underscores glucocorticoids' central role in modulating mood regulation. Chronic cortisol exposure disrupts serotonergic transmission and hippocampal neurogenesis, mechanisms that mirror those seen in major depressive disorder. The statistically robust findings ($r = 0.62$, $p < 0.001$) support the hypothesis that depression in Cushing's syndrome arises directly from biochemical dysregulation rather than reactive psychological distress.[13-16]

Cognitive impairment, as reflected by lower MMSE scores, correlated inversely with cortisol and ACTH, indicating that neurocognitive deficits stem from structural and functional hippocampal compromise. Studies since 2023 have confirmed that prolonged glucocorticoid exposure reduces dendritic complexity in the hippocampus, impairs declarative memory, and accelerates gray matter loss in the prefrontal cortex. These alterations are reversible to varying degrees following cortisol normalization, emphasizing early detection and intervention.[17-18]

The moderate positive correlation between ACTH and anxiety suggests a distinct neuroendocrine dimension. ACTH acts on melanocortin receptors in limbic circuits, influencing arousal and stress reactivity. Elevated ACTH may thus potentiate anxiety independently of cortisol. Such differentiation highlights the multidirectional complexity of the HPA axis in shaping emotional states.[19]

The prevalence of anxiety and depression (over 50%) in this cohort underscores the high psychiatric morbidity associated with Cushing's syndrome. Importantly, psychiatric symptoms often persisted even among partially treated individuals, reinforcing the need for active liaison psychiatry in endocrine practice. The HADS proved a sensitive instrument for detecting subclinical distress in this endocrine population.[20]

These findings align with emerging post-2022 literature advocating neuropsychiatric screening in endocrine disorders. Elevated morning cortisol serves not only as a diagnostic marker but also as a predictor of psychiatric burden. Routine application of standardized psychiatric scales such as HADS and MMSE in endocrinology clinics could facilitate early intervention.

The study's cross-sectional design limits causal inference, yet the robust correlations and biochemical confirmation strengthen its validity. Further longitudinal studies using MRI-based volumetric assessment and extended neurocognitive batteries could deepen understanding of reversibility patterns after curative therapy.

In resource-limited regions such as Pakistan, where psychiatric evaluation in endocrinology is often overlooked, the findings support establishing collaborative care models. Integrating endocrinologists, psychiatrists, and psychologists in multidisciplinary teams could significantly improve holistic outcomes

Conclusion: Elevated morning cortisol and ACTH levels were strongly associated with depression, anxiety, and cognitive decline in patients with Cushing's syndrome. These findings emphasize the bidirectional neuroendocrine–psychiatric relationship and the need for integrated mental health screening within endocrine management protocols. Early identification and intervention could improve both psychiatric and metabolic recovery.

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