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CASO CLÍNICO/CASE REPORT

First Psychotic Episode: Panhypopituitarism and Psychosis in a Female Patient
Primeiro Episódio Psicótico: Pan-hipopituitarismo e Psicose numa Doente do Sexo Feminino

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ABSTRACT
Endocrine and psychiatric disorders frequently overlap, and neuropsychiatric symptoms can be the primary manifestation of an underlying endocrinopathy. This case report describes a 69-year-old Caucasian female admitted to a psychiatry department with severe persecutory and mystical delusions, auditory-verbal and visual hallucinations, and alopecia. Further investigation revealed a psychotic disorder attributed to panhypopituitarism, secondary to poor adherence to hormone replacement therapy following a pituitary resection in 1990. Following treatment optimization, the patient showed remarkable clinical improvement and was discharged after 31 days. This case highlights that while psychosis is a rare presentation of panhypopituitarism, it is crucial to rule out treatable organic etiologies in patients presenting with acute psychiatric features, preventing diagnostic delays and ensuring appropriate targeted therapy.

Keywords: Hypopituitarism; Psychotic Disorders

RESUMO
As perturbações endócrinas e psiquiátricas sobrepõem-se frequentemente, podendo os sintomas neuropsiquiátricos constituir a manifestação primária de uma endocrinopatia subjacente. Este relato de caso descreve uma doente caucasiana de 69 anos, com um quadro de delírios persecutórios e místicos, alucinações auditivo-verbais e visuais exuberantes e alopécia. A investigação revelou uma perturbação psicótica atribuída a pan-hipopituitarismo, secundária a má adesão terapêutica de substituição hormonal subsequente a resseção hipofisária em 1990. Após a otimização terapêutica, a doente apresentou uma melhoria clínica notável, tendo alta após 31 dias. Este caso realça que, embora a psicose seja uma apresentação rara do pan-hipopituitarismo, é crucial excluir etiologias orgânicas tratáveis perante quadros psiquiátricos agudos, prevenindo atrasos diagnósticos e garantindo uma terapêutica dirigida eficaz.

Palavras-chave: Hipopituitarismo; Perturbações Psicóticas

INTRODUCTION
Endocrine and psychiatric disorders share several common features; in some cases, a 'psychiatric disease' may in fact be the presentation of an underlying endocrine disorder, as is the case with hypopituitarism. Pituitary insufficiency is a challenging diagnosis, as it may manifest as a collection of non-specific symptoms.[1] Psychiatric manifestations have been described in patients with hypopituitarism of different aetiologies.[2] The most common symptoms in adults include dehydration, hypotension, nausea, vomiting, delirium, unexplained hypoglycemia, azotemia, and ionic and hydroelectrolytic disturbances.[3] Although psychosis is

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a rare presentation of this disease,[1] it is an important symptom that should prompt clinicians to rule out an underlying, treatable organic cause. Neuropsychiatric manifestations have also been reported in cases of panhypopituitarism; psychosis with extensive cognitive changes appears to occur more rarely but is associated with more severe panhypopituitarism.[4]

CASE REPORT

The authors describe a 69-year-old Caucasian female patient, single and childless, autonomous in activities of daily living, with 3 years of schooling.

The patient was referred to the emergency department due to behavioral changes and incoherent, delusional speech, which people close to her had noticed for several months. Her main symptoms also included persecutory and mystical delusions, auditory-verbal and visual hallucinations, and alopecia.

The patient appeared oriented and cooperative, with preserved attention, euthymic mood, and preserved affective reactivity. Spontaneous speech was globally logical and cohesive. She presented extremely exuberant hallucinatory activity, primarily auditory (well-defined second-person voices, insulting and threatening her) and visual (identifying a black man following her and describing in detail a machine hidden in her ceiling with the intent to kill her). Furthermore, she described seeing people whom she knew had passed away and told the medical team that they intended to make her pray for them, have masses said in their honor, or punish her for not praying enough. The patient also reported total insomnia for four nights and showed partial insight into her morbid condition. Her clinical condition did not fluctuate throughout the day, apart from brief moments of spatial disorientation. Given the unusual nature of a first psychotic episode at her age, she was admitted to inpatient psychiatry unit in January 2024, where further investigation was carried out.

There was no personal or family history of psychiatric disorders, and no history of substance abuse. No drug allergies were documented. She had been living alone for approximately one year. Regarding her past medical history, she had been diagnosed with obesity in 2023, and with dyslipidemia, osteoporosis, and an osteoarticular disease in 2007. She also had iatrogenic panhypopituitarism with central diabetes insipidus since 1990, secondary to surgery for a Rathke's cleft cyst. She had irregular endocrinology follow-up, her last appointment having been in 2008. Since then, she had reportedly been prescribed desmopressin 0.1 mg/mL, hydrocortisone 20 mg, levothyroxine 0.025 mg, alendronic acid 70 mg weekly, simvastatin 20 mg, meloxicam 15 mg, and pantoprazole 20 mg, but had failed to comply with the prescribed therapy. She admitted taking irregular doses of medication, especially hydrocortisone and levothyroxine, over the past year.

Premorbid personality could not be characterized: the patient had no descendants and no available next of kin, and no informant with long-standing knowledge of her could be identified, so that no reliable collateral history was obtainable.

Further work-up revealed hyponatremia of 133 mEq/L, acute kidney injury (AKI) KDIGO stage 1, and hypoglycemia of 65 mg/dL. Urine toxicology was negative. The patient was treated with fluid therapy to improve the AKI and normalize the glycemic profile; however, hyponatremia worsened to 124 mEq/L four days after treatment initiation, and to 120 mEq/L over the following two days. The internal medicine team was consulted, and transfer to the internal medicine department was recommended. Further etiological work-up revealed positive syphilis serology, and a lumbar puncture (LP) was performed, which excluded neurosyphilis; no records of prior syphilis treatment were found in her clinical file. Endocrine study results were as follows: ACTH 1.9 ng/L [normal range (NR): 10–60 ng/L][5]; cortisol (8 a.m.) 71.5 nmol/L [NR: 171–536][5]; TSH 1.53 mIU/L [NR: 0.27–4.2],[5] within the normal range; and low free thyroxine (fT4) 6.9 pmol/L [NR: 8.24–21],[5] consistent with central hypothyroidism. Swabs for RSV, SARS-CoV-2, and influenza A/B were negative. Neurological examination was unremarkable. Magnetic resonance imaging (MRI) showed an encephaloclastic lesion adjacent to the frontal horn of the right lateral ventricle, causing ex-vacuo dilation of this structure extending to the head of the ipsilateral caudate nucleus, with no other changes in signal or morphology of the brain parenchyma.

The final diagnosis was a psychotic disorder secondary to an endocrinopathy resulting from pituitary resection for a Rathke's cleft cyst.

She was treated with hormone replacement, fluids, and electrolyte correction, in addition to antipsychotic therapy (paliperidone 3 mg once daily). Corticosteroid therapy, levothyroxine, and desmopressin were reintroduced, with normalization of sodium and fT4 levels. As there was no record of previous syphilis treatment, benzathine penicillin G 2.4 MIU weekly for 3 weeks was administered, with the regimen completed during hospitalization.

Formal cognitive screening was precluded during the acute phase by the intensity of the hallucinatory activity. Once this had been resolved, a bedside examination with the Mini-Mental State Examination was within the normal range for her level of schooling.

The patient was discharged 31 days after admission, with remarkable clinical progress, good insight, and preserved cognition. There was a favorable course, with resolution of psychotic symptoms.

Longitudinal follow-up was, however, incomplete. The patient ceased attending psychiatric consultations at the end of 2024 and moved to a foster family in another region, so that no further specialty psychiatric assessment has been performed and contact with public health services has remained scarce. She has maintained endocrinology follow-up in the private sector, with adherence to hormone replacement therapy; nevertheless, she remains on paliperidone 3 mg once daily. Information obtained at the most recent phone contact indicates that she has remained free of psychotic symptoms since discharge.

DISCUSSION

The exact mechanism by which psychosis occurs in individuals with hypopituitarism remains unclear.[6] The possible mechanisms include a combination of hypothyroidism, hypoglycaemia, and hypocortisolism, resulting in complex metabolic and electrolyte changes in the central nervous system, as suggested by Kate *et al*.[2] In a cross-sectional study with a control group, Bülow *et al* showed that hypopituitary women had a higher incidence of mental disorders than controls, with significantly more symptoms of anxiety, depression, obsession-compulsion, hostility-irritability, phobic symptoms, and psychotic symptoms.[7]

In this case, untreated syphilis and hyponatremia are unlikely to be contributing factors for the psychotic symptoms. Neurosyphilis was excluded, as VDRL, TPHA, TPPA, and TP were negative on LP. Hyponatremia was only mild on admission and became marked during hospitalization, whereas the psychotic symptoms had been present for months, arguing against a causal role; its worsening under fluid therapy, in a patient with central diabetes insipidus and untreated secondary adrenal insufficiency, also suggests a dilutional component. The long-standing course was not compatible with delirium or acute confusional syndrome; furthermore, the patient's psychotic symptoms persisted despite antipsychotic treatment until shortly before discharge. Leigh and Kramer reported that patients with severe or long-standing untreated adrenal insufficiency present psychiatric symptoms, including psychosis, in 20 to 40 percent of cases,[8] which may persist for several months.[9] Dissanayake *et al* previously described two cases of psychosis that persisted for years despite treatment with hormone replacement and phenothiazines.[10] Significant, multifactorial, euvolemic hyponatremia may have contributed to the spatial disorientation. As previously described by Reus, confusion and true delusions can also occur; in general, replacement therapy improves some dimensions but not others, with chronic fatigue, lack of initiative, and memory impairment being the most resistant to treatment.[11] Adults with growth hormone deficiency may also have other associated conditions, such as dyslipidemia and decreased bone mineral density (BMD),[3] as observed in this patient. Symptoms related to deficient gonadotropin secretion, such as amenorrhea, loss of libido, and infertility, were more difficult to assess in this single, post-menopausal woman. Alopecia was most likely a sign of thyroid hormone deficiency, and the changes found on MRI were most likely sequelae of the 1990 surgery.

In summary, this patient had iatrogenic hypopituitarism and, due to poor treatment adherence, presented with psychotic symptoms that remitted only after the endocrinopathy was treated; an underlying endocrine pathology was therefore considered the most probable diagnostic hypothesis.

This case illustrates the need to exclude organic pathology in patients with a first psychotic episode before establishing a psychiatric diagnosis, as complete remission of symptoms may be achieved if the underlying condition is correctly treated.

Two caveats temper this causal attribution. First, hormone replacement, fluid therapy and electrolyte correction were administered concomitantly with an antipsychotic (paliperidone 3 mg once daily); a single-case design cannot disentangle the contribution of each, and a therapeutic effect of paliperidone cannot be excluded. The temporal pattern - psychotic symptoms persisting under antipsychotic treatment until shortly before discharge, with remission coinciding with biochemical and hydroelectrolytic stabilization - favors the endocrine hypothesis, but is suggestive rather than conclusive. Second, a first psychotic episode at 69 years of age is itself atypical and widens the differential diagnosis: very-late-onset schizophrenia-like psychosis, as defined by Howard *et al* for onset after 60 years,[12] delusional disorder, psychotic depression and the psychotic prodrome of a neurodegenerative process - notably dementia with Lewy bodies, in which well-formed visual hallucinations are a core feature - remain competing hypotheses. Arguing against dementia, however, she had remained autonomous and living independently alone, with no parkinsonian signs, no cognitive fluctuation and no reported REM sleep behavior disorder. DSM-5-TR requires the disturbance to be the direct pathophysiological consequence of the medical condition[13] (panhypopituitarism); here that evidence is strong but not definitive.

The longitudinal data available is consistent with, but does not confirm, this attribution. Approximately 31 months after discharge, the patient remains asymptomatic with maintained hormone replacement, a course arguing against an untreated primary psychotic or neurodegenerative process, which would be expected to progress. She has, however, remained on paliperidone throughout, so the confounding described above persists: sustained remission under continued antipsychotic treatment cannot discriminate between the competing hypotheses. A supervised taper and discontinuation of paliperidone, with hormone replacement maintained, would be the decisive test, but could not be undertaken, as psychiatric follow-up was interrupted at the end of 2024; serial neuropsychological reassessment was likewise not possible. The diagnosis should therefore be regarded as probable rather than established, and cases of this kind warrant structured symptomatic and cognitive reassessment, with a planned trial of antipsychotic withdrawal once endocrine stability has been sustained.

LIMITATIONS

As the patient had been living in relative isolation over the past year, the authors had difficulty obtaining precise additional information from family members and neighbours. Therefore, the 'duration of untreated psychosis' (DUP) could not be clearly established. Although an endocrine etiology is the most likely cause, other causes cannot be completely excluded. The same absence of informants also precluded any characterization of premorbid personality. No formal neuropsychological assessment was undertaken: cognitive evaluation was limited to bedside examination, whose interpretation is further constrained by three

years of schooling, and no pre-treatment cognitive baseline is available. The concomitant administration of hormone replacement and of an antipsychotic precludes any firm inference about the relative contribution of each to the improvement. Finally, psychiatric follow-up was interrupted at the end of 2024, when the patient relocated; subsequent longitudinal information is indirect, and no supervised trial of antipsychotic discontinuation could be carried out. The attribution proposed here should accordingly be regarded as probable rather than definitively established.

CONCLUSION

As demonstrated in the literature and in several previous studies, clinicians must remain aware that psychiatric symptoms may be the first manifestation of an endocrine condition such as panhypopituitarism. Therefore, a first psychotic episode in an elderly woman should raise suspicion of an underlying medical condition. Such cases justify prolonged follow-up and structured cognitive reassessment, and, once endocrine stability is achieved, a supervised trial of antipsychotic withdrawal.

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Ambos os autores deram contributos substanciais para a conceção, redação e revisão crítica do manuscrito, aprovaram a versão final e concordam em assumir a responsabilidade pelo seu conteúdo.

CONTRIBUTORSHIP STATEMENT

Both authors made substantial contributions to the conception, drafting, and critical revision of the manuscript, approved the final version, and agree to be accountable for its content.

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