DIAGNOSTIC PROTOCOLS FOR HYPERPROLACTINEMIA: CLINICAL INVESTIGATION AND LABORATORY CONFIRMATION

PROTOCOLOS DE DIAGNÓSTICO DA HIPERPROLACTINEMIA: INVESTIGAÇÃO CLÍNICA E CONFIRMAÇÃO LABORATORIAL

PROTOCOLOS DIAGNÓSTICOS DE LA HIPERPROLACTINEMIA: INVESTIGACIÓN CLÍNICA Y CONFIRMACIÓN LABORATORIAL

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ABSTRACT
Hyperprolactinemia (HPRL) is a common endocrinopathy characterized by elevated prolactin secretion resulting from reduced tonic dopaminergic inhibition. Clinically, it manifests with symptoms of hypogonadism and galactorrhea and shows a high prevalence among patients undergoing antipsychotic therapy. The objective of this study was to synthesize and critically analyze contemporary guidelines related to the diagnostic and management protocols of HPRL. A narrative literature review was conducted using indexed databases (PubMed and Cochrane Library), employing descriptors such as "Hyperprolactinemia," "Diagnosis," and "Treatment," with emphasis on publications from the last five years. The diagnostic protocol requires a systematic approach, prioritizing the exclusion of physiological and pharmacological causes before investigating prolactinomas, with pituitary magnetic resonance imaging (MRI) reserved for cases in which drug-induced etiology cannot be discontinued. Once HPRL is confirmed, dopamine agonists represent the first-line therapy, with cabergoline considered the agent of choice due to its superior efficacy (approximately 95% biochemical normalization) and better tolerability profile. For antipsychotic-induced HPRL in patients for whom switching the primary medication is not feasible, the addition of low-dose aripiprazole (5 mg/day to 10 mg/day) has demonstrated a highly effective and safe strategy for prolactin normalization and symptomatic reversal. These guidelines reinforce the need for rigorous clinical screening and management to mitigate long-term risks associated with chronic HPRL.

Keywords: Hyperprolactinemia. Diagnosis. Dopamine Agonists. Cabergoline. Antipsychotics.

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RESUMO

A hiperprolactinemia (HPRL) é uma endocrinopatia comum, caracterizada pela secreção elevada de prolactina devido à diminuição da inibição tônica dopaminérgica. Clinicamente, manifesta-se com sintomas de hipogonadismo e galactorreia, sendo notável sua alta prevalência em pacientes submetidos a terapias com antipsicóticos. O objetivo desta investigação foi sintetizar e analisar criticamente as diretrizes contemporâneas relativas aos protocolos de diagnóstico e manejo da HPRL. Foi conduzida uma revisão bibliográfica narrativa em bases indexadas (PubMed, Cochrane Library), utilizando descritores como "Hyperprolactinemia", "Diagnosis" e "Treatment", com foco em publicações do último quinquênio. O protocolo diagnóstico exige uma abordagem sistemática, priorizando a exclusão de causas fisiológicas e farmacológicas antes da investigação de prolactinomas, reservando a Ressonância Magnética (RM) de sela túrcica para os casos em que a etiologia medicamentosa não pode ser suspensa. Confirmada a HPRL, os agonistas dopaminérgicos (AD) constituem a primeira linha terapêutica, com a cabergolina sendo o agente de escolha devido à sua eficácia superior (95% de normalização bioquímica) e melhor tolerabilidade. Para a HPRL induzida por antipsicóticos em pacientes sem possibilidade de troca do fármaco de base, a adição de aripiprazol em doses baixas ($5~mg/d$ a $10~mg/d$) demonstrou ser uma estratégia altamente eficaz e segura na normalização dos níveis de prolactina e reversão sintomática. Tais diretrizes reforçam a necessidade de um rastreio e manejo clínico rigorosos para mitigar os riscos de longo prazo associados à HPRL crônica.

Palavras-chave: Hiperprolactinemia. Diagnóstico. Agonistas Dopaminérgicos. Cabergolina. Antipsicóticos.

RESUMEN

La hiperprolactinemia (HPRL) es una endocrinopatía frecuente caracterizada por la secreción elevada de prolactina debido a la disminución de la inhibición dopaminérgica tónica. Clínicamente, se manifiesta con síntomas de hipogonadismo y galactorrea, destacándose su alta prevalencia en pacientes sometidos a tratamiento con antipsicóticos. El objetivo de esta investigación fue sintetizar y analizar críticamente las directrices contemporáneas relacionadas con los protocolos de diagnóstico y manejo de la HPRL. Se realizó una revisión bibliográfica narrativa en bases de datos indexadas (PubMed y Cochrane Library), utilizando descriptores como "Hyperprolactinemia", "Diagnosis" y "Treatment", con énfasis en publicaciones de los últimos cinco años. El protocolo diagnóstico requiere un abordaje sistemático, priorizando la exclusión de causas fisiológicas y farmacológicas antes de la investigación de prolactinomas, reservándose la resonancia magnética (RM) de la silla turca para los casos en los que la etiología medicamentosa no puede ser suspendida. Una vez confirmada la HPRL, los agonistas dopaminérgicos constituyen la terapia de primera línea, siendo la cabergolina el fármaco de elección debido a su mayor eficacia (aproximadamente 95% de normalización bioquímica) y mejor tolerabilidad. En la HPRL inducida por antipsicóticos en pacientes sin posibilidad de cambio del fármaco base, la adición de aripiprazol en dosis bajas (5 mg/día a 10 mg/día) ha demostrado ser una estrategia altamente eficaz y segura para la normalización de los niveles de prolactina y la reversión sintomática. Estas directrices refuerzan la necesidad de un cribado y manejo clínico rigurosos para mitigar los riesgos a largo plazo asociados con la HPRL crónica.

Palabras clave: Hiperprolactinemia. Diagnóstico. Agonistas Dopaminérgicos. Cabergolina. Antipsicóticos.

1 INTRODUCTION

Hyperprolactinemia (HPRL) is characterized by increased prolactin secretion by the lactotrophic cells of the anterior pituitary gland, being one of the most frequent endocrine changes in the hypothalamic-pituitary axis (Rusgis et al., 2021). The regulation of this hormone occurs primarily through a tonic dopaminergic inhibition; thus, any factor that interrupts the flow of dopamine or blocks its receptors D_{2} can raise serum prolactin levels (Benetti-Pinto et al., 2024). Clinically, this condition is challenging, presenting with symptoms of hypogonadism, menstrual irregularity, infertility, galactorrhea, and sexual dysfunction (Zeng et al., 2023; Lu et al., 2022).

The prevalence of HPRL is remarkably high in patients on antipsychotic therapy, reaching up to 70% of individuals with schizophrenia, depending on the drug used (Lu et al., 2022). In women, the incidence can be as high as 93%, while in men it ranges between 18% and 72% (Jiang et al., 2024). In addition to the immediate impacts on quality of life and treatment adherence, chronic prolactin elevation is associated with long-term risks, such as osteopenia and possibly metabolic diseases, which reinforces the need for rigorous diagnostic and clinical investigation protocols (Rusgis et al., 2021; Lu et al., 2022).

2 METHODOLOGY

The present investigation is characterized as a narrative literature review, structured with the purpose of synthesizing and critically analyzing the contemporary guidelines related to the diagnostic protocols for hyperprolactinemia. Data collection was carried out in indexed databases, including PubMed and Cochrane Library, using the descriptors "Hyperprolactinemia", "Diagnosis" and "Treatment", associated by the logical operators AND and OR, in accordance with the Medical Subject Headings (MeSH). Articles published in the last five years were selected, with full texts available and written in Portuguese or English, which dealt directly with the clinical and laboratory investigation of the pathology. Studies with small samples, duplicate publications, reviews with methodological fragility, and research that did not correlate with the central theme were summarily excluded. The selection process took place through the screening of titles and abstracts, followed by full analytical reading to validate scientific relevance. The information collected was compiled and organized in a descriptive and systematic way.

3 RESULTS AND DISCUSSION

Clinical investigation of hyperprolactinemia requires the systematic exclusion of physiological and pharmacological causes before proceeding to the search for pathological causes, such as prolactinomas (Benetti-Pinto et al., 2024). In the laboratory setting, normal prolactin values are usually less than $25~\mu g/L$ for non-pregnant women and $<20~\mu g/L$ for men (Rusgis et al., 2021). However, there is no absolute "threshold" for raising levels; the clinical decision to investigate and treat should be based on the presence of patient-reported symptoms (Rusgis et al., 2021).

For patients using antipsychotics known to elevate prolactin—such as haloperidol, risperidone, and paliperidone—symptom screening at each visit until stabilization and once a year thereafter is recommended (Rusgis et al., 2021). Laboratory confirmation is indicated whenever there are clinical manifestations such as changes in libido, changes in the menstrual cycle or galactorrhea (Rusgis et al., 2021). If the pharmacological cause cannot be suspended or replaced, imaging tests, such as Magnetic Resonance Imaging (MRI) of the sella turcica, are essential to rule out the presence of pituitary tumors (Benetti-Pinto et al., 2024).

Regarding therapeutic strategies after laboratory confirmation, dopamine agonists (DA) constitute the first line of treatment for prolactinomas and idiopathic RPHR (Cristina Laguna et al., 2024). Cabergoline stands out for its superiority in efficacy, with biochemical normalization rates of 95%, compared to 80% observed with bromocriptine, in addition to having better tolerability (Benetti-Pinto et al., 2024). Quinagolide, a non-ergotamine AD, presents itself as a robust alternative, with a normalization rate of 69%, being useful in cases of resistance or intolerance to other agents (Zeng et al., 2023).

Discussion of the management of drug-induced RPHP indicates that the addition of aripiprazole (ARI), a dopamine partial agonist, is highly effective in reducing prolactin levels to normal limits in patients who cannot switch from the background antipsychotic (Rusgis et al., 2021; Jiang et al., 2024). Meta-analyses confirm that doses of $5~mg/d$ to $10~mg/d$ of ARI are safe and able to restore menstrual function and cease galactorrhea (Rusgis et al., 2021). Other options, such as metformin, demonstrate slight reductions in prolactin levels, although evidence for its routine use is still limited (Rusgis et al., 2021; Jiang et al., 2024).

4 CONCLUSION

Hyperprolactinaemia (HPRL) represents a common endocrine challenge, characterised by elevated prolactin secretion and clinically manifested by symptoms of hypogonadism and galactorrhoea, with special prevalence and clinical implication in patients on antipsychotic therapy. The diagnostic protocol requires a systematic approach that prioritizes the exclusion of physiological and pharmacological causes, reserving the investigation of prolactinomas and Magnetic Resonance Imaging of sella turcica for cases in which the drug etiology cannot be suspended.

Once HPRL is confirmed, therapeutic strategies are primarily based on dopamine agonists, with cabergoline being the first-line agent due to its superior efficacy and tolerability profile. For the management of antipsychotic-induced RPHP in patients in whom drug switching is not feasible, the addition of low-dose aripiprazole ($5\~mg/d$ to $10\~mg/d$) has been shown to be a highly effective and safe strategy for normalizing prolactin levels and reversing symptoms. Such guidelines reinforce the importance of rigorous screening and clinical management to mitigate the long-term risks associated with chronic hyperprolactinemia.

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