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Peer Review

Review of: "Two Cases of Non-Surgical Hypoparathyroidism That Were Diagnosed with Delay"

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Strength of Clinical Detailing

The authors present two well-documented clinical cases of non-surgical hypoparathyroidism with distinct etiologies. The meticulous timeline of symptoms, laboratory findings, and treatment interventions in both cases—particularly the complex and protracted diagnostic odyssey of patient A—adds significant depth and clarity to the discussion. This clinical granularity enhances the article's educational value for practitioners, especially in endocrinology, neurology, and internal medicine.

Highlighting Diagnostic Challenges

A major strength lies in the article's illumination of the diagnostic delays common in Ns-HypoPT, especially when surgery is not part of the patient's history. The misattribution of symptoms to psychiatric or neurological disorders, as seen in both cases, underlines a key clinical pitfall. The authors might strengthen this discussion by offering diagnostic algorithms or practical screening strategies to mitigate such delays.

Integration of Genetic Findings

The inclusion of advanced genetic analyses (e.g., a 2,211-gene panel) in patient A's workup provides compelling evidence of the genetic heterogeneity in Ns-HypoPT. The identification of pathogenic variants in TBX1, LZTR1, and CLCN1 reinforces the growing recognition of overlapping syndromic and neurological features in patients with hypoparathyroidism. However, the article could benefit from a more structured explanation of how each gene contributes to the phenotypic complexity.

Therapeutic Implications and Vitamin D Formulation

The article powerfully demonstrates the inadequacy of non-hydroxylated vitamin D (ergocalciferol) in treating Ns-HypoPT. The authors appropriately stress the clinical benefit of using calcitriol (1,25(OH)2D3),

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which corrected calcium levels and reduced seizure frequency. A quantitative comparison of treatment outcomes (e.g., symptom resolution timelines or seizure frequency) before and after calcitriol initiation could enhance the argument further.

Underexplored Genetic Pathophysiology

While the article alludes to LZTR1-related schwannomatosis and autoimmune interactions between DGS and Graves' disease, these remain superficially explored. A more detailed pathophysiological discussion would benefit readers, especially regarding how these gene variants disrupt parathyroid, immune, or neuromuscular pathways. Are these independent disorders coincidentally present, or is there a shared pathogenic axis?

Case Comparisons and Contrasts

The comparison between the two patients is informative but could be better structured. A side-by-side tabular summary of key clinical features, biochemical values, genetic findings, and treatment responses would significantly improve the clarity of contrasts and commonalities between cases. Was there a reason genetic testing was not extended further in patient B despite the unclear etiology?

Unclear Role of Comorbidities and Environmental Factors

The mention of potential environmental exposures (e.g., patient A's father's Chernobyl involvement) is intriguing but speculative. Similarly, the impact of repeated COVID-19 infections on patient A's immune status is not elaborated. Could these comorbid or environmental factors have epigenetic or immune-modulating effects relevant to the pathogenesis or progression of hypoparathyroidism?

Diagnostic Gaps in Patient B

Although patient B responded well to calcitriol, the underlying etiology remains unexplained. The authors mention sarcoidosis as a possibility, yet diagnostic confirmation is pending. Would it be appropriate to consider whole-exome sequencing or autoimmune panels to rule out other rare syndromes? How might long-term management be tailored without a definitive diagnosis?

Educational Potential and Practice Guidelines

The paper raises an important educational issue: the risk of misdiagnosing epilepsy in patients with underlying hypocalcemia. The authors might consider referencing relevant clinical practice guidelines or proposing a flowchart for evaluating seizure-like symptoms when hypocalcemia is suspected. Should screening for serum calcium and PTH be standard in adult-onset "epilepsy" without a clear etiology?

Conclusion and Call for Broader Genetic Screening

The authors' conclusion rightly emphasizes the value of timely diagnosis and appropriate vitamin D formulation. However, they could broaden the call to action by suggesting more widespread access to genetic testing in similar clinical scenarios, particularly in countries like Ukraine where diagnostic resources may be constrained. How might such genetic testing be incorporated into routine practice for endocrine or neurological clinics?

Declarations

Potential competing interests: No potential competing interests to declare.