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CRITICAL TOPICS IN THE CLINICAL AND THERAPEUTIC APPROACH TO INSULINOMA: A COMPREHENSIVE REVIEW TO IMPROVE CARE AND MANAGEMENT

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Abstract: Objective: The purpose of this literature review article is to analyze the challenges related to insulinoma, providing relevant insights into the clinical approach to these patients. Methodology: An integrative review was carried out using the PubMed database. The initial search resulted in 191 articles, of which, after applying inclusion and exclusion criteria, 12 were selected to compose the present work. Results: Studies indicate that insulinoma is a pancreatic neuroendocrine tumor associated with hypoglycemia. Endoscopic ultrasound has emerged as the most effective diagnostic method for its detection, with emphasis on its integration into the preoperative routine due to its high diagnostic value. Radical surgical resection stands out as the main treatment option, highlighting the importance of precisely identifying the location of the insulinoma before surgical intervention, aiming to increase the success rate and reduce the risk of complications. Final Considerations: This study highlights the persistence of challenges in the management of these patients, resulting both from the absence of neurogenic and neuroglycopenic symptoms and the lack of early screening for insulinomas.
Keywords: Insulinoma; Diagnosis; Hypoglycemia.

INTRODUCTION

Insulinoma is a functional variant of a neuroendocrine tumor that affects the beta cells of the pancreas, responsible for producing insulin. It is estimated that its annual incidence is approximately 1 in 250,000 people, with no notable distinction by age group, although there is a slight predominance in females (PATEL S.M. et al., 2020). It is essential to highlight that, within this context, around 90% of insulinomas appear as single lesions, generally benign and small (< 2 cm), which can be located in different regions of the

pancreas (MARX M. et al., 2022; YUAN T. et al., 2021). However, between 5% and 10% of these tumors may be associated with Type I Multiple Endocrine Neoplasia, a condition that is related to less favorable prognoses (CRINÒ S.F. et al., 2023).

Most people affected by insulinoma manifest symptoms resulting from insulin hypersecretion, such as autonomic symptoms, including sweating, tremors, palpitations, sensation of heat, and neuroglycopenic symptoms involving headache, drowsiness, difficulty speaking, inability to concentrate, amnesia, mental confusion, decreased level of consciousness, seizures and neurological deficits. This results in plasma glucose concentrations below 3.0 mmol/L (YUAN T. et al., 2021). The diagnosis of this condition is, in essence, based on clinical and biochemical criteria. In situations where the patient does not experience spontaneous episodes of hypoglycemia, a 72-hour prolonged fasting test may be considered. Additionally, most insulinomas can be visualized using imaging tests. When diagnostic uncertainty persists, the single photon emission computed tomography technique may be useful, as it distinguishes splenic tissue from pancreatic tissue (PATEL S.M. et al., 2020).

Conventional treatment of insulinoma involves surgical resection of the affected pancreatic tissue, an effective intervention, but associated with a significant rate of adverse events (AEs) (CRINÒ S.F. et al., 2023). As such, minimally invasive surgical approaches such as laparoscopic enucleation have gained prominence. This approach has advantages, such as preserving the endocrine and exocrine function of the pancreas, in addition to reducing the length of hospital stay (NAPLES R. et al., 2022). However, even these minimally invasive techniques are not free from relevant AEs (CRINÒ S.F. et al., 2023).

Given the scenario of invasive procedures, there has been a growing interest in exploring less invasive therapeutic interventions. In this context, ultrasound-guided radiofrequency ablation (EUS-RFA) has emerged as an effective therapeutic strategy. This technique promotes necrosis of the majority of neuroendocrine tumor cells and demonstrates remarkable clinical results, with an acceptable safety profile (NAPLES R. et al., 2022). EUS-RFA, previously reserved for patients with unfavorable clinical conditions, now presents itself as an initial treatment alternative for patients with insulinoma, with the potential to avoid excessive surgical procedures (CRINÒ S.F. et al., 2023; NAPLES R. et al, 2022).

Furthermore, for patients who are not candidates for surgical interventions, especially those with metastatic disease, medical treatment, which includes the use of diazoxide and long-acting somatostatin analogues, may be an option. However, an important challenge, especially for this group of patients, is glucose monitoring to assess the effectiveness of therapy and identify severe hypoglycemia episodes in time. In this context, continuous glucose monitoring (CGM) emerges as a useful tool, as it allows the continuous assessment of glycemic fluctuations and minimizes the discomforts associated with spot glucose monitoring (YUAN T. et al., 2021).

Therefore, the central objective of this literature review article is to explore and summarize the main challenges associated with the clinical and therapeutic approach to insulinoma, focusing on the areas of diagnosis, treatment and monitoring. This study aims to provide valuable information to improve the care and management of patients with insulinoma, with an emphasis on early detection, effective therapeutic strategies and continuous monitoring, aiming to optimize the clinical results and quality of life of these

affected individuals.

METHODOLOGY

This study represents a bibliographic review based on the criteria of the PVO strategy, which comprises the analysis of the Population or Research Problem, Variables and Outcomes. This methodology was applied to answer the following research question: "What are the challenges faced in the clinical and therapeutic approach to insulinoma, especially with regard to early diagnosis, effective treatment and continuous monitoring, and how can we overcome them?" Under the PVO strategy, the population of interest for this research consists of patients with insulinoma, emphasizing early detection, the effectiveness of therapeutic interventions and continuous monitoring, with the aim of optimizing clinical outcomes and quality of life for affected individuals. The literature search was conducted in the PubMed Central (PMC) database and involved a combination of descriptors, including "Insulinoma [MeSH]" and "Diagnosis [MeSH]", using the Boolean operator "AND". This initial search resulted in the identification of 191 articles, which were subsequently subjected to selection criteria.

The inclusion criteria adopted comprised articles written in English, Portuguese and Spanish and published between 2018 and 2023; articles that addressed topics relevant to this research, including case-control studies, observational studies, multicenter retrospective studies, systematic reviews, meta-analyses, case reports and experimental studies; available in full. On the other hand, the exclusion criteria covered articles that did not directly address the central research question and that did not meet the other inclusion criteria. After rigorous application of these criteria, a total of 12 articles were selected from the PubMed database to compose the present study, offering a valuable contribution to understanding the challenges related to insulinoma, especially with regard to early diagnosis, effective treatment and continuous monitoring.

DISCUSSION

CHALLENGES IN DIAGNOSING INSULINOMA

Malignant insulinoma, a rare form of pancreatic neuroendocrine tumor (panNET), constitutes approximately 10% of insulinoma cases. Veltroni A. et al. (2020) highlights that its clinical presentation is characterized by a severe hyperinsulinemic hypoglycemia syndrome, often associated with locoregional and/or distant metastases. The diagnosis is based on inadequate levels of insulin, proinsulin and C-peptide during episodes of hypoglycemia, whether spontaneous or triggered by fasting tests. The average age at diagnosis (48 years), the average size of the tumor (41±31 mm), and the presence of liver (41.9%) and lymph node metastases (19.4%). Furthermore, it shows that hyperglycemic syndrome can appear late in originally non-functioning cases, negatively impacting the prognosis.

In a comparative analysis, Liu et. al (2022) discuss that, in the context of Multiple Endocrine Neoplasia type 1 (MEN1), insulinomas represent 10% to 30% of pancreatic tumors. The precise preoperative localization of these tumors is challenging and is essential to ensure surgical success. The lack of consensus guidelines on the most accurate methods for screening and detection is evident, highlighting the need for additional research in this area.

Both studies converge on the importance of accurate diagnosis of insulinoma, with Veltroni A. et al. (2020) emphasizes the effectiveness of surgery (67.7%) and highlights peptide receptor radionuclide therapy (PRRT)

as an approach with effective control of the syndrome in 93% of patients. Liu et. al (2022) introduce the role of functional imaging, such as 68Ga-exendin-4 PET/CT, and highlight the elevated expression of glucagon-like peptide 1 (GLP-1) receptors in benign insulinomas, offering a sensitive method of detection.

The approach to malignant insulinoma is multidisciplinary, involving precise diagnostic methods and therapies adapted to individual characteristics. Progress in functional imaging, as demonstrated by Liu et. al (2022), offers new perspectives, while Veltroni A. et al. (2020) reinforces the importance of surgery and PRRT. The lack of clear guidelines highlights the need for future research to optimize the detection and treatment of these rare tumors.

Beek, D.J et al (2020) introduces insulinoma as a rare pancreatic neuroendocrine tumor (pNET), responsible for producing insulin and triggering symptomatic hypoglycemia. Surgical resection is currently the only curative treatment, with approximately 4–8% of cases associated with multiple endocrine neoplasia type 1 (MEN1). The challenge lies in the location of the tumor, especially in patients with MEN1, who often present with multiple pNETs.

Sugawa T., et al. (2018) highlights the complexity of diagnosing insulinoma, especially due to the lack of neurogenic and neuroglycopenic symptoms, leading to a lack of awareness of hypoglycemia on the part of the patient. Early detection is crucial, as late diagnosis can result in serious complications, including coma and death.

Beek, D.J et al (2020) propose advances in preoperative localization, such as endoscopic ultrasound (EUS) and PET/CT with Ga-DOTA-exendin-4, as promising tools to overcome challenges in deciding the ideal surgical procedure. The study includes 96 patients undergoing resection for MEN1-related insulinoma, with a 10-year hypoglycemia-free survival rate of 91%. Enucleation is recommended for solitary cases, while distal pancreatectomy combined with enucleation is considered favorable for patients with multiple insulinomas.

Sugawa T., et al. (2018) presents a clinical case of insulinoma diagnosed late, highlighting the importance of Flash Glucose Monitoring (FGM) in detecting and preventing severe hypoglycemia while the patient was awaiting surgery. MGF, with its factory calibration, is highlighted as a valuable tool for managing these cases.

Both studies converge on the importance of precise location of the insulinoma to guide the surgical approach. Beek, D. J. et al (2020) provides robust clinical data demonstrating higher cure rates than previously reported, while Sugawa T., et al. (2018) highlights the effectiveness of FGM in preventing severe hypoglycemia. The surgical approach to insulinoma, especially in patients with MEN1, continues to evolve with advances in preoperative localization. The combination of techniques such as EUS and PET/CT offers a promising perspective. The incorporation of technologies such as FGM also proves valuable for preoperative management and prevention of complications. Continued research in this area is essential to optimize the clinical and surgical approach to insulinoma.

LABORATORY AND IMAGING DIAGNOSTIC METHODS

The diagnostic approach to insulinoma presents significant challenges, highlighting the need for effective methods for early detection and precise localization. Yang Y.A. et al. (2021) point out that the incidence of this tumor is relatively low, with the majority of cases being benign and solitary. Surgical excision is the main curative strategy, emphasizing the importance of an accurate

diagnosis.

Preoperative detection is crucial for therapeutic success. Various imaging tests, such as magnetic resonance imaging, computed tomography and ultrasound, are used to identify the affected pancreatic region. Invasive methods, such as angiography and selective arterial calcium stimulation testing, are reserved for specific cases, such as failed previous surgeries (MARX M. et al., 2022).

Endoscopic ultrasound stands out with high specificity (80%) and sensitivity (93%) in accurately identifying insulinoma. In contrast, for malignant insulinomas, magnetic resonance tomography, computed axial tomography, GLP-1 receptor scintigraphy and angiography are more sensitive, highlighting the importance of adapting the methods according to the nature of the tumor (MARX M. et al, 2022).

Comparative analysis of preoperative localization methods reveals considerable variations in diagnostic sensitivity. GLP-1 receptor scintigraphy stands out for its highest detection rate (100%) (MARX M. et al., 2022). However, its limited accessibility can be a practical barrier.

Given the lack of defined preoperative location, challenging or doubtful cases must be referred to specialized centers that have experience in both the biochemical diagnosis of autonomous insulin secretion and qualified surgeons for the accurate detection of insulinomas. This collaborative approach may be crucial for optimizing clinical outcomes and improving insulinoma management in complex situations.

The preoperative phase plays a crucial role in the effective diagnosis and treatment of insulinoma. Wise D. et al. (2023) observe that the vast majority of cases are diagnosed at this stage, enabling conventional tumor resection and preservation of the pancreatic parenchyma. Endoscopic ultrasound, when performed by specialists, has emerged as the most effective method for preoperative detection of insulinoma. However, Wise D. et al. (2023) also point out limitations in their own study, highlighting the monocentric, retrospective and strictly descriptive origin, which suggests the need to consider these limitations when interpreting the results.

An alternative approach is offered by Torimoto K. et al. (2019), who, in an observational case-control study, identified significantly lower levels of glycated hemoglobin (HbA1c) and glycated albumin (AG) in patients with insulinoma. This finding suggests the potential usefulness of these markers in diagnosing and differentiating between benign and malignant insulinomas.

Another diagnostic perspective is presented by Antwi K. et al. (2020), highlighting the effectiveness of PET/CT and SPECT/CT in mapping the glucagon-like peptide 1 receptor in the pancreas. Although it is considered effective in detecting benign insulinomas, the authors recognize the lack of evaluation of other markers and the exclusion of malignant insulinomas, suggesting caution in interpreting the results. Wang H. et al. (2018), in a systematic review and meta-analysis, corroborate the effectiveness of endoscopic ultrasound, endorsing its inclusion in the preoperative routine due to its high diagnostic value.

When comparing the diagnostic methods discussed, endoscopic ultrasound stands out as the most effective, as evidenced by Wang H. et al. (2018). However, the diversity of approaches suggests the importance of a comprehensive assessment, adapting the methods to the specific profile of each patient and considering the limitations inherent to each technique.

FINAL CONSIDERATIONS

Multiple challenges permeate the clinical approach to patients with insulinoma, aggravated by the lack of neurogenic and neuroglycopenic symptoms, resulting in a lack of awareness of hypoglycemia by the patient himself. However, numerous investigations have been conducted to improve diagnostic criteria, therapeutic options and monitoring of individuals with this pathological condition. Conducting this study allowed us to verify that, despite advances in research, there is still a significant lack of guidelines that offer precise guidance for the screening and early detection of insulinomas. Therefore, it is imperative to develop projects that thoroughly explore the approach options for insulinomas, taking into consideration, the individual characteristics and limitations of each patient, with the aim of speeding up interventions and, therefore, optimizing therapeutic results.

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