SHORT COMMUNICATION

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Diagnostic Power of Bilateral Inferior Petrosal Sinus Sampling with Desmopressin in Paediatric Cushing's Disease

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What is already known on this topic?

Bilateral inferior petrosal sinus sampling (BIPSS) with corticotropin releasing hormone (CRH) stimulation is an accurate test to diagnose Cushing's disease (CD). However, the use of desmopressin has been suggested as an alternative to CRH.

What this study adds?

To the best of our knowledge, this is the first review of this topic. BIPSS with desmopressin stimulation is accurate for the diagnosis of pediatric CD, but the accuracy of lateralizing the lesion is probably not suitable for pediatric clinical practice.

Abstract

Objective: The aim of this study was to evaluate the diagnostic accuracy of bilateral inferior petrosal sinus sampling (BIPSS) with desmopressin for pediatric Cushing's disease (CD).

Methods: We reviewed studies performed in children that evaluated the accuracy of BIPSS with desmopressin.

Results: All included studies were case series of children with adrenocorticotropin hormone (ACTH)-dependent Cushing's syndrome. The overall accuracy of BIPSS before stimulation was 84.1% (37/44), and after stimulation it was 92.3% (36/39). The overall lateralizing accuracy of BIPSS was 50.0%.

Conclusion: Considering that available evidence is limited, it appears that BIPSS with desmopressin stimulation is accurate for the diagnosis of pediatric CD, but its lateralizing accuracy is probably not suitable for pediatric clinical practice.

Keywords: Petrosal sinus sampling, deamino arginine vasopressin, child, pituitary ACTH hypersecretion, systematic review

Introduction

Cushing's syndrome (CS) occurs from prolonged exposure to high levels of cortisol and can be exogenous or endogenous (1). Endogenous CS has an annual incidence of approximately 0.7 to 3 cases per million people (1,2) and can be of two types: adrenocorticotropin hormone (ACTH)-dependent (pituitary tumor or ectopic ACTH syndrome) or ACTH-independent (autonomous adrenal overproduction of cortisol) (1). Overall, among patients with endogenous CS, 70% have a pituitary adenoma (3). ACTH-secreting pituitary adenoma is called Cushing's disease (CD) (1).

There are non-invasive tests to diagnose CD, such as ACTH measurement in the morning, the corticotropin releasing hormone (CRH) stimulation test, and the suppression test with high dose dexamethasone. (1). However, non-invasive tests are less accurate than bilateral inferior petrosal sinus sampling (BIPSS) (1). In a previous study, BIPSS correctly identified 139 out of 140 children with CD (4). Moreover, BIPSS is more accurate than images to locate a microadenoma, which it achieves by demonstrating the lateralization of ACTH secretion (2). It has been reported that the lateralization of ACTH in BIPSS correctly identifies the location of the adenoma in 70% of cases (4).

BIPSS consists of the placement of femoral catheters that reach the right and left inferior petrosal sinuses (5). After this, blood samples are obtained for measurement of ACTH from both petrosal sinuses and from a peripheral pathway before and after the administration of human CRH (5).

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However, the use of stimulation with desmopressin (DDAVP) has been suggested as an alternative to CRH (1).

A synthesis of the evidence on the performance of BIPSS with desmopressin stimulation in children is lacking. For this reason, the aim of this study was to evaluate the diagnostic accuracy of BIPSS with desmopressin for pediatric CD.

Methods

Population and Study Selection

The original protocol was registered in the PROSPERO database (6). We included studies performed in children (≤18 years) with CS (based on clinical features and/or laboratory results) that evaluated the accuracy of any of the following parameters: inferior petrosal sinus to peripheral ACTH ratio before stimulation with desmopressin; inferior petrosal sinus to peripheral ACTH ratio after stimulation with desmopressin at any time point or interpetrosal sinus gradient of one of the two sides to the contralateral side. The target condition was CD. The reference standard was histopathology. Within the inclusion criteria, those studies with the following study designs were considered: cross-sectional, case-control and cohort. In studies where only a subgroup of participants was eligible, these were included only if data specific to that subgroup could be extracted. The search was conducted up to February 14, 2021. There were no restrictions on language or publication date. We searched in the following electronic databases: PubMed, Embase, Scopus, and Web of Science. We also conducted a hand-search of reference lists of all included articles and relevant review articles to identify potentially eligible studies.

We used the following search strategies:

PubMed: (cushing*[tiab] OR "cushing syndrome"[mesh] OR "cushing syndrome"[ot]) AND ("petrosal sinus sampling"[mesh] OR "petrosal sinus"[tiab] OR "petrosal sinus sampling"[ot] OR BIPSS[tiab]) AND (child[mesh] OR child*[tiab] OR child[ot] OR paediatric*[tiab] OR pediatrics[mesh] OR pediatric*[tiab] OR pediatrics[ot] OR adolescent[mesh] OR adolescen*[tiab] OR adolescent[ot] OR youth*[tiab] OR teen*[tiab])

Embase: cushing* AND ('petrosal sinus'/exp OR 'petrosal sinus' OR bipss) AND (child* OR paediatric* OR pediatric* OR adolescen* OR youth* OR teen*)

Scopus: TITLE-ABS-KEY ((cushing*) AND ("petrosal sinus" OR BIPSS) AND (child* OR paediatric* OR pediatric* OR adolescen* OR youth* OR teen*))

Web of Science: TS = ((cushing*) AND ("petrosal sinus" OR BIPSS) AND (child* OR paediatric* OR pediatric* OR adolescen* OR youth* OR teen*))

We downloaded all articles from the electronic search to EndNote X8 and duplicate records were removed. All unique articles were uploaded to Rayyan (https://rayyan.qcri.org/) for the study selection process. Titles and abstracts were independently screened by two review authors to identify relevant studies. Likewise, two review authors independently examined the full text of selected studies and registered reasons for exclusion. Any disagreement on title/abstract and full-text selection was resolved by consensus.

Data Extraction and Statistical Analysis

The information from each selected study was independently extracted by two review authors using a standardized data extraction form in an Excel spreadsheet that was previously piloted. Any disagreement was resolved by consensus. The following data was extracted: first author name, publication year, country, study design, sample size, population, age, sex, comorbidities, index tests, gold standard, adverse events, and the concordance rate of the three index tests. We calculated baseline inferior petrosal sinus to peripheral ACTH ratio, stimulated inferior petrosal sinus to peripheral ACTH ratio at any time point and interpetrosal sinus gradient of one of the two sides to the contralateral side as measures of accuracy. Data from selected studies were not suitable for performing further data synthesis techniques. As the included studies were only case series, no risk of bias assessment was performed.

Ethical approval was not required for this systematic review, as this study did not directly or indirectly involve human participants. Data were extracted from publicly available published literature.

Results

We selected four studies published from 2007 to 2020 (7,8,9,10). Two of them were performed in Brazil (7,9) and the rest were conducted in China (8) and Argentina (10). All studies were case series of children with ACTH-dependent CS (7,8,9,10). None of the studies showed information about comorbidities (7,8,9,10). In two studies there was no information about adverse events available (8,10), one of them reported no complications (7) and the other described hematomas of the groin at the site of venous puncture in some patients, and two major complications even with the use of heparin infusion during the procedure: peripheral venous thrombosis in one patient with a previous thromboembolic event, and right petrosal sinus thrombosis

in another patient with severe hypercortisolism who finally died from sepsis and multiple-organ failure syndrome (9). More information about the selected studies can be found in Table 1.

The overall accuracy of BIPSS before stimulation was 84.1 % (37/44), and after stimulation it was 92.3 % (36/39) (7,8,9,10). The overall lateralizing accuracy of BIPSS was 50.0 % (19/38) (7,8,10). Cavalcante et al. (7) used stimulation with desmopressin and reported a concordance of 60 % (9/15). However, they did not provide complete data to assess accuracy before and after stimulation separately. In contrast, two studies performed BIPSS with desmopressin stimulation and reported an overall accuracy of 6/16 (8) and 4/7 (10). Furthermore, the same studies reported a joint accuracy of 39.1 % (9/23) and 38.9 % (7/18) before and after stimulation, respectively (8,10).

Discussion

The overall accuracy of BIPSS before stimulation was good (84.1 %) (7,8,9,10), which is consistent with this test being considered the gold standard to differentiate pituitary from ectopic CS (1). Moreover, after stimulation accuracy was higher and more suitable for clinical practice (92.3 %) (7,8,9,10). Furthermore, this good performance was consistent with a recent study conducted in children using CRH stimulation that showed an unstimulated accuracy of 75 % (9/12) and a stimulated accuracy of 83.3 % (10/12) (5). Therefore, BIPSS with desmopressin stimulation in pediatric CD has a good diagnostic performance and is clinically more useful than when not using stimulation.

The overall lateralizing accuracy of BIPSS in the studies reviewed (50 %) (7,8,10) was not optimal for clinical practice. This is in accordance with some authors who state that the capacity of BIPSS to localize intra-pituitary tumors is limited, regardless of the stimulus used (1). Recent studies of BIPSS with CRH stimulation performed in children showed a lateralizing accuracy of 58.3 % (7/12) (5) and 69 % (9/13) (11). However, it was not specified whether the accuracy was calculated before or after stimulation. Other studies performed in pediatric and adult CD patients, with and without stimulation by CRH or desmopressin, also describe lateralization accuracy but they do not show separate information for children and do not detail the precision of BIPSS before and after the stimulus separately (12,13,14,15). Feng et al. (13) reported a concordance of 72.5 % (37/51) in patients who had CD and whose lateralization by BIPSS and surgery were either left or right. Wind et al. (15) reported a concordance of 68.9 % (273/396) in patients with pathologic confirmation of CD who underwent BIPSS and had a lateral adenoma. Pereira et al. (14) reported a lateralization accuracy of 63 % (17/27) in patients who had confirmation of CD (immunohistochemistry to ACTH or biochemical cure

Table 1. Detailed information on the studies selected for this review

First author and year of publication	Sample size	Population	Age (years)	Sex	Index tests	Gold standard	Accuracy		
							bIP/P	sIP/P	IPg
Cavalcante et al. (7), 2020	19 (15 had CD and were submitted to BIPSS before surgery).	Patients with ACS submitted to BIPSS.	9-19	9 F and 9 M	bIPS/P > 2 sIPS/P > 3 IPSg > 1.4	Surgical and pathologic findings, postsurgical remission, Nelson's syndrome after bilateral adrenalectomy or an absence of EAS in the follow-up.	14/15	15/15	9/15 *
Chen et al. (8), 2019	16	Patients with CD submitted to BIPSS.	9.8-18.7	10 F and 6 M (5 F and 6 M for those who received DDAVP)	bIPS/P > 2 sIPS/P > 3 IPSg > 1.4	Surgical and pathologic findings or eucortisolism after surgery or irradiation.	11/16	10/11	6/16 (basal: 5/16; stimulated: 3/11)
Gil et al. (10), 2019	7	Patients with CD submitted to BIPSS.	8 - 13	4 F and 3 M.	bIPS/P≥2 sIPS/P≥3 IPSg≥1.4	Surgical and pathologic findings or clinical outcome.	7/7	6/7	4/7 (basal and stimulated)
Machado et al. (9), 2007	6 (5 had CD and 1 had EAS)	Patients with ACS submitted to BIPSS.	14 - 17	4 F and 2 M	bIPS/P≥2 sIPS/P≥3 IPSg≥1.4	Pathologic findings or postsurgical remission	5/6	5/6	NA

*Incomplete data to evaluate concordance before and after stimulation separately.
F: females, M: males, ACTH: adrenocorticotropin hormone, bIP/P: baseline inferior petrosal sinus to peripheral ACTH ratio, sIP/P: stimulated inferior petrosal sinus to peripheral ACTH ratio at any time point, IPg: interpetrosal sinus gradient of one of the two sides to the contralateral side, ACS: ACTH dependent CS, EAS: ectopic ACTH syndrome, NA: information not available

criteria after surgery) and a BIPSS suggestive of CD. Deipolyi et al. (12) reported a lateralization accuracy of 47.8% (87/182) in patients with pathologic confirmation of CD. Of note, there was considerable variability in the lateralizing accuracy reported in individual studies, ranging from 38.9% to 100% (7,8,10,16,17). Therefore, there is also a need for more evidence concerning this topic.

Among the reasons reported as potential causes of false negatives are incorrect cannulation of the inferior petrosal sinuses due to anatomical variants or the performance of the procedure during a phase of eucortisolism (1).

Of the patients included in this review, only two had major complications (peripheral venous thrombosis and right petrosal sinus thrombosis) (9). This coincides with some authors who report that there is a low incidence of complications in experienced centers. However, when complications do occur they can be severe, such as deep vein thrombosis, petrosal sinus thrombosis, and hemorrhage (1).

Study Limitations

An important limitation of this review is the limited number of published studies and hence small amount of evidence available. This probably affects the interpretation of the data on the lateralizing accuracy of BIPSS to a greater degree than the diagnostic accuracy of the test.

Conclusion

In conclusion, considering that available evidence is limited, we suggest that BIPSS with desmopressin stimulation is accurate for the diagnosis of pediatric CD, but its lateralizing accuracy is probably not suitable for pediatric clinical practice. Also, there is not enough evidence to confirm the safety of this test in children.

Ethics

Ethics Committee Approval and Informed Consent: Ethical approval was not required for this systematic review, as this study did not directly or indirectly involve human participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Manuel André Virú-Loza, Concept: Manuel André Virú-Loza, Andrea Venegas Quispe, Design: Manuel André Virú-Loza, Andrea Venegas Quispe, Data Collection or Processing: Manuel André Virú-Loza, Andrea Venegas Quispe, Analysis or Interpretation: Manuel André Virú-Loza, Andrea Venegas Quispe, Literature Search: Manuel André Virú-Loza, Andrea Venegas Quispe, Writing: Manuel André Virú-Loza, Andrea Venegas Quispe.

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