Original Article

Preoperative Localization Of Insulinoma In Nineveh

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Abstract

Background:
Localization of insulinoma, a very rare tumor, is mandatory for surgical removal of the tumor.
Objective: This study aims to investigate pre-operative imaging techniques for insulinoma localization in Nineveh.
Materials and Methods:
This is a retrospective study that revised seventeen years' reports of eighteen cases of insulinoma. After clinical and biochemical diagnosis of hyperinsulinemia, all of the patients subjected to ultrasonography of the abdomen, computerized tomography and magnetic resonance imaging and. Later on, surgical exploration and intraoperative ultrasonography of the pancreas were done. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of magnetic resonance imaging, computed tomography of the pancreas and abdominal ultrasonography, were statistically analyzed, considering the intraoperative ultrasonography as the gold standard.
Results:
The average age was 35.6 years old. The ratio for men/women was 1:5. On surgical exploration using intraoperative ultrasonography, all of the patients proved to have pancreatic insulinoma. Magnetic resonance imaging localized only four out of the eighteen cases of insulinoma. It had a high positive predictor value and a low negative predictor value, low sensitivity, low specificity, low positive, but high negative likelihood ratios, all indicating a low validity. The ultrasonography of the abdomen and computerized tomography of the pancreas completely failed to achieve any localization in any patient.
Conclusion:
In Nineveh, preoperative localization of insulinoma is of low validity. Intraoperative ultrasonography should be the mainstay after confirming the diagnosis hyperinsulinemia.

Keywords: Hypoglycemia. Insulinoma, Localization, Sensitivity, Specificity.

INTRODUCTION

Insulinoma, the most frequent endocrine tumor in the pancreas, is extremely rare, with an annual incidence varying from 1 to 10 cases per million (Service et al.,1991; Tamburrano et al.,1999). Insulinoma is often small; 90% have a diameter of less than two centimeters (Mittendorf et al., 2005). Computed tomography (CT) of the pancreas, abdominal ultrasonography (AUS) and magnetic resonance imaging (MRI) are the most popular preoperative imaging modalities for anatomical localization of tumors. In different studies, MRI sensitivity in diagnosing insulinoma was 40-90%,(Noone et al.,2005 and Anaye et al.,2009) whereas the sensitivity of AUS and CT of pancreas were 15% and 64%, respectively (King et al.,1994; and Lim et al.,2008). Angiography and transhepatic venography are more sensitive, but they are invasive, costly, difficult to achieve and at high risk for complications(Rösch et al.,1994; Kuzin et al.,1998 and Göemes et al.,2020). There is significant progress in the diagnosis of insulinoma, so there is a significant reduction in patients needing an exploratory laparotomy (Placzkowski et al.,2009). Intraoperative ultrasonography (IOUS), is an important technique for operative diagnosis and guidance of surgical treatment of pancreatic lesions (Sun et al.,2010) .

This study is designed to calculate sensitivity, specificity, positive prediction (PPV), negative predictive values (NPV), positive likelihood ratio (PPR), and negative likelihood ratios (NLR) of AUS, CT and MRI to assess their validity as preoperative localizing measures of insulinoma in Nineveh Governorate of Iraq, considering IOUS findings as a gold standard. No studies tackled these issues together in details yet.

PATIENTS AND METHODS

This is a retrospective study that reviewed 17 years' medical records of 18 consecutive patients who had surgery for insulinomas, since January 2001 through June 2018, by a single surgeon in Nineveh Hospitals. The review included patients' characteristics data, clinical

presentation, biochemical measures; fasting plasma glucose (FPG) levels, fasting serum C-peptide and fasting serum insulin levels, localization modalities, intraoperative findings and type of surgeries.

In the studied reports, the preliminary diagnosis of insulinoma was based on Whipple's triad (Chung et al.,2008). The case for endogenous hyperinsulinism was confirmed when plasma glucose level was lower than 40 mg/dl together with a coexisting increase of serum insulin (>150 pmol/l) and C-peptide (>0.6 ng/ml) (Vezzosi et al.,2007). Localization of insulinoma by imaging measures was done when hyperinsulinemic hypoglycemia was biochemically confirmed. The noninvasive imaging tests included AUS, CT of the pancreas and MRI. If the AUS did not locate the lesion, the patients were subjected to a CT scan or MRI or both. All of the patients, were then subjected to surgical pancreatic exploration and IOUS after having their full written and oral consent. During the surgery, the pancreases were keenly palpated to localize the insulinoma. The insulinoma sizes that were detected ranged between two mm -to- two cm. The larger insulinomas that approached about two cm could be manually palpated, however, IOUS was undertaken in all the cases.

To have an acoustic window to conduct the IOUS, one liter of normal saline was introduced into the lesser sac instead of the conventional sterilized gel. A sterilized ophthalmic probe, rather than the specified IOUS probe, was then used by the sonologist to scan the pancreas starting from the head of pancreas down to the tail. When the mass is detected, a spinal needle tip, under the IOUS guide, was passed by the surgeon to the center of the mass and the pancreatic tissue around the tip of the needle was then excised to enucleate the tumor. The indicator of successful excision was the immediate rise of random blood glucose level within 15-30 min after excision. Unfortunately intraoperative frozen section biopsy measures was unavailable to histologically prove the full excision.

Statistical Analysis

Sensitivity, specificity, PPV (true positives/ true positives + false positives), and NPV (true negative/ true negative + false negative), and PLR (true positive/false positive) and NLR (false negative/true negative) of the MRI were calculated using standard formulas (Celentano et al., 2019) and using intraoperative findings as the gold standard. Fischer's exact test for binomial discrete variables done and $p<0.05$ was determined to be statistically significant. Data were analyzed using Microsoft Excel 2010 for statistical analysis.

Ethical Approval:

Approval of the study was obtained from Scientific Ethical Committee, Medical College, University of Nineveh. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

The patients' mean age was 35.5 years (±SD 11.4 years) and the ratio for men to women was 1:5. The mean FPG was 38.9 mg/dl (±SD 5.1 mg/dl). The mean serum insulin level was 258.9 pmol /l (±SD 58.9pmol/l), and the mean C peptide level was 8.5 ng/ml (±SD 2. 4 ng/ml) [Table 1].

The insulinomas of the patients (n. 14) that couldn't be diagnosed by MRI, could only be detected by IOUS during laparotomy.

Table 1: Patients' characteristics and biochemical results.

Gender	Age (Years)	FPG level (mg/dl)	Fasting serum insulin (pmol/l)	Fasting C- peptide levels (ng/ml)
Female	43	30	264	10
Male	38	44	227	7
Female	23	39	370	11.1
Female	44	40	186	3.9
Female	29	33	290	9
Female	62	35	250	5
Male	32	42	233	7.8
Female	47	32	256	11
Female	31	38	380	10.3
Female	40	41	194	4.9
Female	25	36	285	7
Female	52	32	255	6
Female	35	40	210	10
Female	39	50	195	8.5
Female	25	45	225	11

Female	20	39	350	10.5
Female	35	40	190	8
Male	20	45	300	11.5
Mean & SD		38.9(5.1)	258.9(58.9)	8.5(2.4)

AUS and CT scan of the pancreas that were performed in all of the patients, failed to achieve any localization in any patient. MRI of the pancreas that was done to all the patients, could localize only four lesions out of the 18 one subjected to it [Table 2 and 3].

Table 2: (2x2 table) in patients with insulinoma, using MRI for preoperative localization.

Diagnostic criteria (MRI)	**Gold Standard**		**Total**
	Present	**Absent**	
Positive	4	1	5
Negative	12	1	13
Total	16	2	18

Table 3: Sensitivity, specificity, PPV, NPV, PLR, NLR of MRI.

Sensitivity*	**Specificity**	**PPV**	**NPV**	**PLR**	**NLR**
25%	50%	80%	8%	0.5	1.5

*****The Fisher exact test statistic value is 0.4902. The result is not significant at $p < 0.05$

DISCUSSION

Depending on the firm clinical and biochemical diagnosis of hyperinsulinemiam, all of the patients, were operated upon to explore the pancreas for insulinomas. Only four patients out of the 18, were having preoperative localization of the tumors. This split stems from the fact that preoperative imaging studies have a low sensitivity for diagnosing insulinomas (Hashimoto et al., 1999). In addition to that is the possible under-skilled conduct of the consulted sonologists or radiologists.

The age trend and sex preponderance (1 male:5 females) at presentation were similar to that reported elsewhere (Skillern et al.,1953; Hashimoto et al., 1999; Berends et al.,2000; Machado et al.,2001; Hirshberg et al.,2002; Plöckinger et al.,2002; Iihara and Obara, 2002; Jyotsna et al.,2006 and Cemeroglu et al.,2016). Average serum levels of insulin and C peptide in this study were in agreement with other reports (Guettier et al.,2009). The sensitivity and PPV of MRI for diagnosing insulinoma were 25% and 50%, respectively. This low sensitivity of MRI in detecting insulinoma may be due to the small dimensions of the tumors, the fat phenotype of the chronically hypoglycemic patients, or the imprecise MRI technologists.

The PPV allows estimation of how likely a disease of interest is present if the test is positive. In this research the PPV of MRI was 80%, indicating that MRI succeeded in picking up insulinoma in the imaged subjects although that was in only four out of 18 cases.

Concerning the likelihood ratio, the higher the PLR than 1, the stronger the association between the positive test result and the true presence of the disease of interest. Meanwhile the lower the value of the NLR, the stronger the association between the negative test result and not having the disease of interest. The PLR of MRI in this study was 0.5, while the NLR was 1.5. Both of these values indicate a low validity of MRI.

Abdominal ultrasonography and CT scan of the pancreas were performed in all of the patients but failed to achieve localization of the insulinoma in any patient. This, may also be due to technical problems or poor experience of the examiners.

Surgical excision is the treatment of choice for insulinomas, so accurate localization of the tumor before or during surgery is mandatory. In a worldwide survey of 22 centers, it was found that surgical exploration alone is able to detect the tumors in 95% of patients at the first operation (Rothmund et al., 1990). This study confirmed that an operative manual palpation of the pancreas and IOUS scanning of the pancreas are very helpful to identify these lesions readily. These finding are in agreement with the claim of surgeons that preoperative localization of this tumors is not necessary (Hashimoto et al., 1999; Wong et al., 2007; Ravi and Britton, 2007; Kalafat 2007and Shin et al., 2009).

CONCLUSION

In conclusion, Although MRI has a high positive predictive value, it has a low negative predictive value, low sensitivity, low specificity, low positive likelihood ratio and high negative likelihood ratio, all of them means low validity. The AUS and CT scan of the pancreas completely failed to achieve any localization in Nineveh insulinoma patients. This may be applicable to cities that are socio-economically analogous.

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Footnotes

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Conflict of Interest: there is no conflict.

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