Diagnosis value preoperative localization of insulinoma by diffusion-weighted imaging
A pilot study

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Abstract
Insulinoma is the most common functional neuroendocrine tumor that originates from the islet of beta cells. Insulinoma is usually an isolated benign tumor and small in size (<2 cm). Due to the small size of the lesion, it often leads to difficulty in clinical preoperative localization diagnosis. However, we have unexpectedly discovered that the diffusion-weighted-imaging (DWI) adds great value in the preoperative localization diagnosis of insulinoma in non-invasive examination technique.

We verified using operative pathology data and retrospectively analyzed the clinical and imageology findings of 5 cases who reported to have an insulinoma. All the 5 cases underwent DWI examination, among non-contrast enhanced magnetic resonance imaging (MRI) in 1 case, contrast-enhanced MRI in 4 cases.

Five cases of DWI showed a nodular high signal <1.3 cm with pancreatic tail in 3 cases, pancreatic neck, and pancreatic head in 1 case each, respectively. Non-contrast enhanced MRI showed suspicious abnormal signals in the tail of the pancreas were detected in 1 case. MRI enhanced scans presented 2 cases with abnormal enhancement in the arterial phase and 2 cases without abnormal enhancement in arterial phase. Also, 3 cases showed mild persistence enhanced in the portal venous phase and delayed phase. However, 1 case remained normal in the portal venous phase and the delay period.

DWI examination has high clinical value in the localization diagnosis of insulinoma and thus it can be used as a routine examination for preoperative localization diagnosis.

Abbreviations: ADC = apparent diffusion coefficient, CT = computed tomography, DWI = diffusion-weighted imaging, FOV = field of view, MRI = magnetic resonance imaging, NET = neuroendocrine tumor, TE = echo time, TR = repetition time.

Keywords: diagnosis, diffusion-weighted imaging, insulinoma, magnetic resonance imaging, pancreatic neuroendocrine tumors

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1. Introduction

Pancreatic neuroendocrine tumors are divided into functional and non-functional tumors based on clinical manifestations. Non-functional tumors account for 60% to 90%,[1] and 60% of the patients are diagnosed with distant metastasis, 21% have advanced unresectable lesions and poor prognosis.[2] Functional neuroendocrine tumor (NETs) mainly include insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptide tumor, and growth hormone release-inhibiting hormone tumor. Even though the incidence of insulinoma is low it is the most common functional NETs,[3] with benign and malignant tumors accounting for 87% and 13% respectively.[4] Insulinoma is the most common functional NET and originates from the islet of beta cells, accounting for 1% to 2% of all pancreatic tumors.[5] The incidence is 1 to 4 cases per 1 million people in a year.[6] Among them the vast majority are isolated benign tumors with tumor diameter less than 2 cm.[7] The main clinical manifestation of this disease is hypoglycemia due to excessive insulin secretion.[8] Due to the small size of the lesion and the difficulty in preoperative localization diagnosis, conventional magnetic resonance imaging (MRI) is often difficult to display lesions.[9] Diffusion-weighted imaging (DWI) has been widely used in clinic as a non-invasive examination technique for detecting the diffusion ability of water molecules inside and outside living tissue cells.[10] Compared to conventional MRI, DWI improves the sensitivity of lesion detection.[11] We collected clinical and imaging data of 5

pathologically confirmed insulinomas to understand, analyze and improve the diagnostic value of DWI in preoperative localization of insulinoma.

2. Methods

This study was approved by the ethics committee of Gao Xin Hospital Xi'an. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The inclusion criteria were patients who had the classical symptom complex (Whipple triad) at the disease onset and promptly relieved after glucose administration (No. GXYYEC-LW-2019005); histopathological diagnosis of insulinoma after surgical resection; availability of good-quality preoperative MRI and DWI examinations. Exclusion criteria were included: hypoglycemia due to other reasons in clinically and those who cannot accept MRI.

Clinically suspected insulinoma patients (n = 5) underwent an MRI examination. Retrospectively analysis of the MRI and DWI findings were performed based on clinical and pathological diagnostic. The data collection duration of the study was 5 years.

3. Inspection method

Non-contrast enhanced MRI scan, enhanced scan, DWI: used the German Siemens skyra 3.0T superconducting magnetic resonance scanner with 8-channel body coil. The patient was advised to fast 4 to 6 hours before the examination and then non iv contrast MRI scan, enhanced, and DWI examination was carried out on all the 5 patients. Non-iv contrast MRI cross-section T1-weighted images - volumetric interpolated breath-hold sequence scanning parameters: repetition time (TR) 3.9ms, echo time (TE) 1.8ms, layer thickness 3.0 mm, layer spacing 0.6 mm, matrix 195×320, the field of view (FOV) 40×32 cm, reverse angle 9°, NXT 1. Cross-section T2WI-FS: TR3000ms, TE 74ms, layer thickness 6 mm, layer spacing 4.8 mm, matrix 256×216, FOV 40×32 cm, NXT 1. 3D volume acquisition fast spoiler gradient echo sequence (3D-VIBE) enhanced scanning cross-section: TR 3.9ms, TE 1.8ms, reverse angle 9°, layer thickness 3.0 mm, layer spacing: 0.6 mm, FOV42 $\times$ 32 cm, matrix 195×320, NXT1. VIBE coronal scanning parameters: TR: 4.7ms, TE: 1.8ms, reverse angle 9°, layer thickness 3.0 mm, layer spacing: 0.6 mm, FOV 40 x 32 cm, matrix 20 x 32 cm, NXT 1. VIBE delay period scan parameters: TR: 2.5ms, TE: 1.2ms, inversion time: 5ms, reversal angle: 9°, layer thickness 3.0 mm, layer spacing: 0.6 mm, FOV 42 $\times$ 32 cm, matrix 280×192, NXT 1. The scan range is limited to the entire pancreatic region. The contrast agent was gadolinium-diethylene-triaminepenta-acetic acid which was injected at a dose of 0.2 mmol/kg to the cubital vein using a high-pressure syringe at an injection rate of 2.0 mL/s. After 15, 50, 90, and 150 seconds the scan images of early, late, portal, balance, and delayed arteries were obtained. DWI uses a single-shot echo-planar exocrine imaging (EPI) sequence (b value of $0800mm^2/s$): TR 5000ms, TE minimum, layer thickness 6 mm, layer spacing 1.2 mm, FOV 40 x 32 cm, matrix 104 x 128, NXT 2.

4. Result

We retrospectively studied the data collected from 5 cases with insulinoma (3 males and 2 females) aged between 44 and 54 years (median age 47 years). Three patients had fasting hypoglycemia, and their fasting blood glucose, plasma insulin, insulin C-peptide level were about 1.3 to 1.9mmol/L, 8.5 to 18.6 µL U/mL, and 7.8 to 10.9ng/mL, respectively. Two cases had after meal hypoglycemia and reported their fasting blood glucose, postprandial blood glucose, plasma insulin, insulin C-peptide level as 3.6 to 5.48 mmol/L, 1.45 to 1.65 mmol/L, 6.63 to 7.51 µL U/mL, and 2.0 to 3.8 ng/mL, respectively. Among the 5 cases, 4 had reported sweating, palpitations, weakness of the extremities with syncope. Two cases of seizures and 1 case of episodic confusion were reported (Table 1). Three cases were relieved from the hypoglycemic symptom after glucose supplementation given orally or through the veins. However, in 2 cases the symptoms disappeared by consuming sugar.

Five cases of DWI showed nodular high signal, diameter 0.6 to 1.3cm (0.94 ± 0.24), and showed pancreatic tail in 3 cases, pancreatic neck, pancreatic head in 1 case each respectively. A black-and-white inverted image and a pseudo-color image were obtained from 5 DWI images using a post-processing workstation (Figs. 1–5). Non-iv contrast MRI scan showed suspicious abnormal signals in the tail of the pancreas were detected in 1 case. MRI enhanced scan showed abnormal enhancement in the arterial phase in 2 cases and no abnormal enhancement in the arterial phase in 2 cases. Also, 3 cases showed mild persistence enhanced in the portal venous phase and delayed phase. However, 1 case remained normal in the portal venous phase and the delay period. Post-operation, 3 cases complained no complications, but 2 cases had pancreatic fistula which showed improvement after treatment (Table 2). Measurement of postoperative fasting and postprandial blood glucose level remained normal in all 5 cases. There was no occurrence of hypoglycemia symptoms, no recurrence, and no metastatic disease was observed during follow-up from June to January.

Table 1

Demographic and clinical characteristics of patients with insulinoma.

Baseline parameter	Variable patients (n = 5)
Age, Median (IQR) 47 (44–54)	
Gender, n (%)	
Male	3 (60)
Female	2 (40)
Median (IQR)	
Hypoglycemic symptoms, n (%)	
Fasting hypoglycemia	3 (60)
After meal hypoglycemia	2 (40)
Syncopes	4 (80)
Seizures	2 (40)
Confusion	1 (20)
Fasting hypoglycemia	
Glycemia (mmol/L) Mean (SD)	1.3–1.9 (0.24)
Plasma insulin (ng/mL)	8.5–18.6 (4.26)
Serum C peptide (ng/mL)	7.8–10.9 (1.27)
After meal hypoglycemia	
Glycemia (mmol/L) Mean (SD)	1.45–1.65 (0.1)
Plasma insulin (ng/mL)	6.63–7.51 (0.44)
Serum C peptide (ng/mL)	2.0–3.8 (0.9)

Examination and surgical results.

Localization of the tumorn (%)	
Tail	3 (60)
Head	1 (20)
Neck	1 (20)
Diameter of the lesionMean (SD)	0.6–1.3cm (0.94 ± 0.24)
Detection of lesions	
DWI	5
Non-enhanced MRI	1
Enhanced MRI	4
Surgical removal	5
Postoperative complications 3 cases	
Pancreatic fistula 2cases	
Follow-up6 mo∼1 yr	

DWI = diffusion-weighted-imaging, MRI = magnetic resonance imaging, SD = Standard deviation.

5. Discussion

Women are commonly affected by this disease and the age of onset of this disease is usually between 30 and 50 years.[12,13] However, it is reported that at the age of 47 the incidence is more in males when compared to females.[14,15] Whipple triad being the clinical presentation of pancreatic insulinoma is the key to clinical consideration of the disease. The onset of hypoglycemia and the symptoms associated with hypoglycemia (including hypoglycemia, convulsions, mental disorders, etc), rapid relief after eating or supplementing glucose are the main symptoms of the disease.[8,15,16] The blood glucose level of these 5 patients remained significantly lower when compared to normal population. Among the 5 cases, 3 were fasting hypoglycemia, mainly in empty stomach in the early morning, and 2 were postprandial hypoglycemia, mainly in the morning but after lunch. Although most cases show fasting hypoglycemia, studies reveal that about 6% of cases can only exhibit postprandial hypoglycemia, and 21% can be both fasting and postprandial hypoglycemia.[17] The symptoms of this group of patients were immediately relieved after eating or directly supplementing with glucose. Also, their performance was consistent with the Whipple triad.

The size of the lesion is small and hence computed tomography (CT) as well as traditional imaging examination often leads to difficulty in preoperative localization diagnosis.[7,8] Hence, we used DWI and successfully detected 5 clinically suspected insulinomas, which was later confirmed in surgery. DWI is useful in detecting and localizing insulinomas is reported.[11] However, DWI is not used as a routine examination of the upper abdomen in clinical practice. We believe that it may either be due the reason that the clinical application of abdominal MRI is still not as common as CT or the typical case of conventional CT enhancement can be diagnosed and the DWI examination is ignored. In this study, only 1 case of MRI was found to have suspicious lesions on T1WI, and the lesion diameter was >1 cm. The remaining 4 cases had no abnormal findings on both T1WI and T2WI also the lesion diameter was <1 cm. Only 2 cases of MRI routine dual-phase enhanced scan were consistent with typical enhancement of insulinoma but 2 cases showed atypical enhancement, and 1 case showed no abnormal contrast-enhanced. We compared DWI with non iv contrast MRI and MRI enhanced scan to confirm that DWI showed high signal. To be more precise, 4 cases showed significantly high signal and only 1 showed a slightly higher signal. Thus, we believe that DWI has higher sensitivity. The data of the 5 cases analyzed using black-and-white inverted and pseudo-color images for DWI clearly highlights the location of the lesions, especially for lesions with the slightly higher signal on DWI. This method also highlights the contrast between lesions and normal pancreatic tissue.

Preoperative imaging examination of the disease includes both invasive and non-invasive examination.[18] Invasive examinations mainly include selective digital subtraction angiography, endoscopic ultrasound biopsy, percutaneous transhepatic portal vein, and arterial-venous vein blood sampling to determine insulin respectively. There literature in recent years pointing out the use of selective arterial calcium injection test as the new diagnostic criteria for insulinoma localization.[19] But it is not conducive to clinical promotion due to its high cost, complicated operation procedure and huge trauma caused. Non-invasive examinations mainly include abdominal ultrasound, CT, MRI, but these routine examinations have a low detection rate of lesions. Therefore, the use of CT dual-phase enhanced combined perfusion imaging can increase the positive rate of lesion detection, the sensitivity as well as the specificity to 92.7%, 94.65, and 94.7% respectively.[20] Recently, CT angiography has also been considered to have the highest sensitivity (94.4%) and accuracy (90.7%) among all preoperative localization imaging methods.[5] At present, 3T MRI combined with DWI for insulinoma is considered to be more accurate, when compared
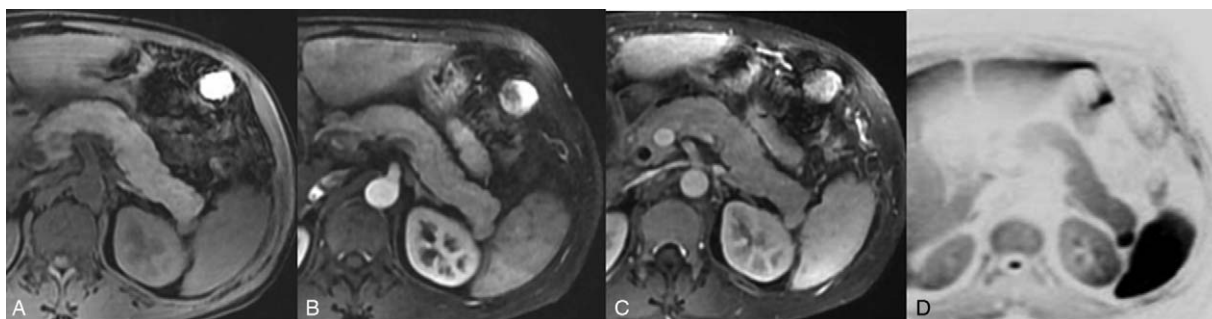

Figure 1. Male, 44 years. a Axial T1-weighted images fat suppression sequence, there is a slightly lower signal nodule can be seen in the tail of the pancreas, b contrast-enhanced magnetic resonance imaging arterial later phase, no significant contrast enhancement in lesions, c contrast-enhanced magnetic resonance imaging portal vein phase, there is a mild enhancement in lesions, d diffusion-weighted imaging black-and-white reversal view showed a nodular low signal in the tail of the pancreas, with a diameter of about 1.3cm.
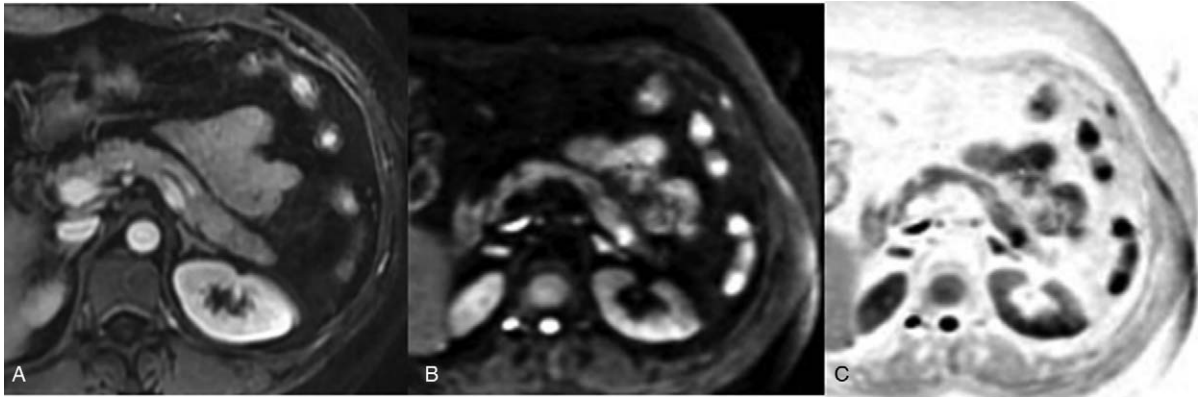
Figure 2. Female, 47 years. a Axial contrast-enhanced magnetic resonance imaging arterial later phase. No abnormal contrast-enhancement in the tail of the pancreas, b axial contrast-enhanced magnetic resonance imaging portal vein phase. No abnormal contrast-enhancement in the tail of the pancreas, c diffusion-weighted imaging showed a nodular high signal in the tail of the pancreas, with a diameter of about 0.8 cm, d diffusion-weighted imaging black-and-white reversal view showed a nodular low signal in the tail of the pancreas.

with the CT dual-phase enhancement, with a sensitivity of 95%.[21] We believe that in non-invasive examinations DWI can effectively avoid X-ray radiation and possible adverse effects of contrast agents, especially for iodine contrast agents, when compared with CT-enhanced scanning or CT perfusion imaging, CT angiography, and MRI. MRI and DWI have certain advantages in avoiding allergic reactions of iodine contrast agents

Abdominal MRI is susceptible to spontaneous breathing and gastrointestinal motility, gas, fluid, ascites, and other factors in the gastrointestinal tract, especially for DWI. Therefore, it is very important to fully water fast before training and also train the patient to breathe. Patients with greater influence on gastrointestinal peristalsis, intramuscular injection of 654-II relaxes smooth muscle. In addition, pancreatic DWI checks the b value and its selection is very important. Our data shows that the selection of b value of $0/800\,mm^2/s$ not only obtains a good tissue image, but the sensitivity of the detection of lesions is also higher. To avoid research bias and confounding factors, clinically, except for hypoglycemia, which caused by other factors, DWI should be compared with the same level of T1WI, T2WI, and MRI enhanced scan to measure the scope of the lesion, and to calculate its standard deviation.

The limitation of our study includes data analysis of retrospective cases and the smaller sample size of the study. Due to the small size of the lesion, it is difficult to measure the apparent diffusion coefficient (ADC) value of the lesions <1 cm. In addition, ADC value is not included in this paper for quantitative analysis as the number of cases in this group is limited. In addition, DWI can only be used as a tool for the localized diagnosis of the disease, and its qualitative diagnosis, which still needs to be combined with non-enhanced MRI and enhanced scan.

In the future, this study can use (reduced field of view, rFOV) technology to achieve high-resolution DWI, which can improve the deformation and artifacts of DWI images. Quantitative analysis of the lesions through ADC values can be used to classify tumors using intravoxel incoherent motion.

In conclusion, DWI is simple to operate, highly repeatable, and has no ionizing radiation. DWI has an advantage in preoperative localization diagnosis of insulinoma. Especially for atypical
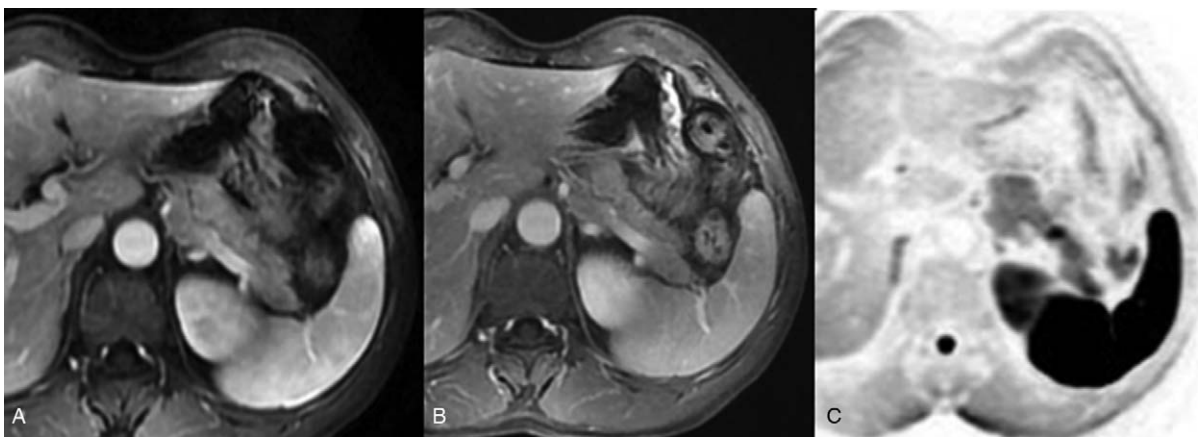

Figure 3. Male, 54 years. a Axial contrast-enhanced magnetic resonance imaging (MRI) arterial early phase, there is a mild enhancement lesions in pancreatic tail, b Axial contrast-enhanced MRI arterial later phase. No abnormal contrast-enhancement in the tail of the pancreas, c axial contrast-enhanced magnetic resonance imaging Portal vein phase. No abnormal contrast-enhancement in the tail of the pancreas, d diffusion-weighted imaging black-and-white reversal view showed a nodular low signal in the tail of the pancreas, with a diameter of about 0.7 cm.
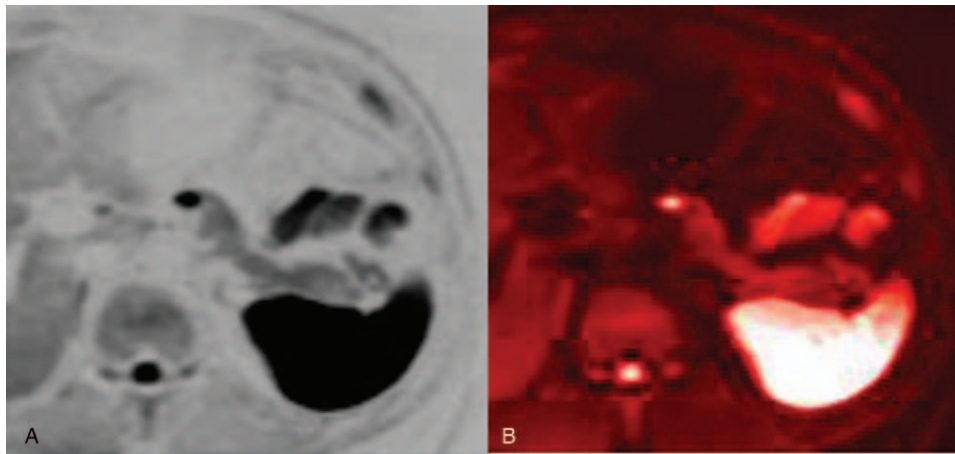
Figure 4. Female, 45 years. a diffusion-weighted imaging (DWI) sees a nodular high signal in the pancreas neck with a diameter of 0.7 cm, b DWI black-and-white reversal view, c DWI pseudo-color map.

Figure 5. Male, 48 years. a Axial contrast-enhanced magnetic resonance imaging arterial early phase, there is a significant enhancement lesions in pancreatic head, b axial contrast-enhanced magnetic resonance imaging arterial delay phase. Mild delayed enhancement of lesions, c diffusion-weighted imaging showed a slightly higher signal in the head of the pancreas, with a diameter of about 0.8 cm, d diffusion-weighted imaging black-and-white reversal view showed a nodular low signal in the head of the pancreas.

tumors of <1 cm, the sensitivity of DWI is higher when compared to the conventional CT and MRI enhancement. Thus, we recommend DWI examination to be used as a routine examination for the diagnosis of preoperative localization of insulinoma.

Acknowledgment

Author contributions

Li-Jun Chen performed most of the investigation, data analysis and wrote the manuscript; Yue-Dong Han provided pathological assistance; Ming Zhang contributed to interpretation of the data and analyses. All of the authors have read and approved the manuscript

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