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An unusual case of hypoglycaemia in paediatric; Insulinoma of pancreatic head.
Surgery: Eneucleation of Neuroendocrine Tumour (NET) of the Pancreatic head.

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I. Introduction

Insulinoma is one of the most frequent functioning neuroendocrine tumours (NET) of the pancreas[1,2,3]. Although in general NET tumour is relatively uncommon, insulinomas usually affect adult female patients. Insulinomas are usually benign and rarely present in paediatric age group. The correlation between insulin secretion and pancreatic tumour was first discovered by Wilder et al and the first surgical treatment of single functional cell adenoma was achieved by Graham in 1929.[4]

II. Case Report

A 12 years old boy presented with repeated symptoms of hypoglycaemia. He experienced symptoms of low blood sugar that was more apparent after meal. He started to have this symptom in March 2023. He was rushed multiple times to the Hospital when he presented with reduced consciousness and fitting episodes. Prior to the onset of his first symptoms, his family members denied any similar episodes occurred in the past. He is otherwise a healthy and active young boy.

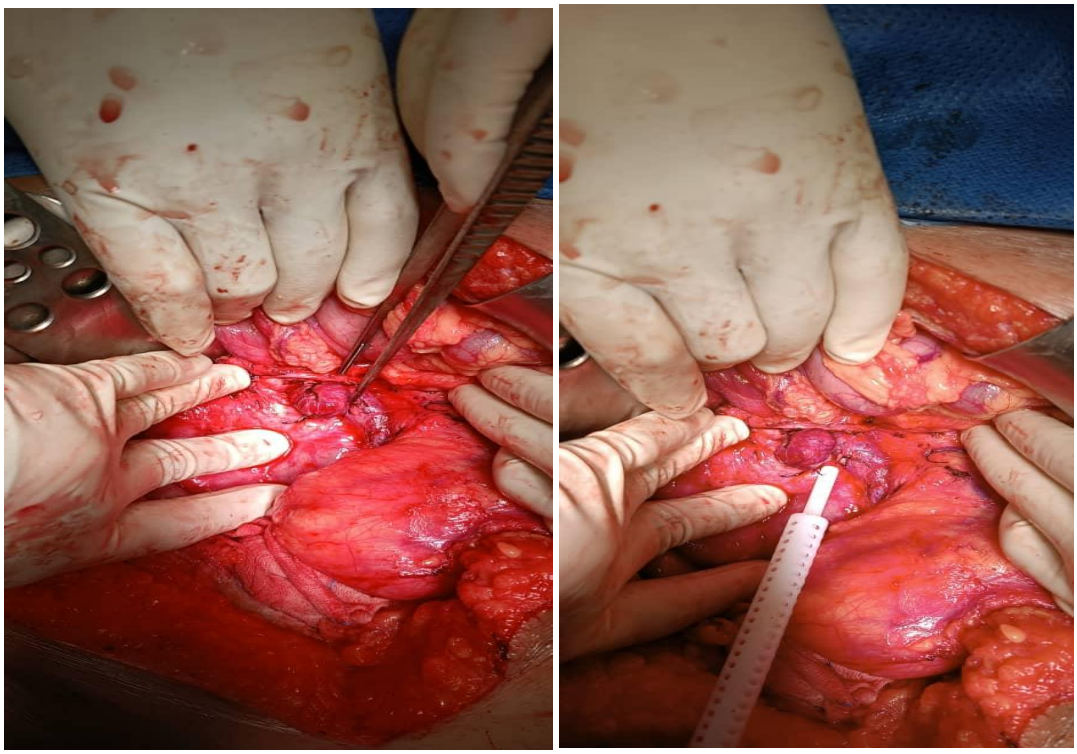
The patient underwent mixed meal test and supervised fasting test in order to trigger and evaluate his glucose level. The test results showed that he had post prandial hypoglycaemia which occurred 3 hours post-meal. During his supervised fasting test, his random blood sugar level was low, 1.7mmol/l. Both his serum insulin level and C-peptide level was high was high 364.8 pmol/l with 4726 pmol/l respectively. Both serum and urine ketone level were not raised. Pituitary hormonal assays were taken but the result was unremarkable. Based on these results he was suspected to have Insulinoma of the pancreas.

A Contrast Enhanced Computer Topographic (CECT) Pancreatic protocol performed for pancreatic lesions. CECT revealed a hypervascular lesion 1.9 x 2.0 x 2.9 cm (APxWxCC) over the head of pancreas in favour of Insulinoma. Patient was started with T. Diazoxide 100mg three times a day and was educated in self-capillary blood sugar (CBS) monitoring. After the initiation of the drug, his CBS level was near normal, ranging between 3.2 to 9.6mmol/l. Patient did not suffer from new episode of hypoglycaemia attack after starting Diazoxide. His serum insulin level dropped to 286.8 pmol/l and C-peptide level reduced to 1459 pmol/l.

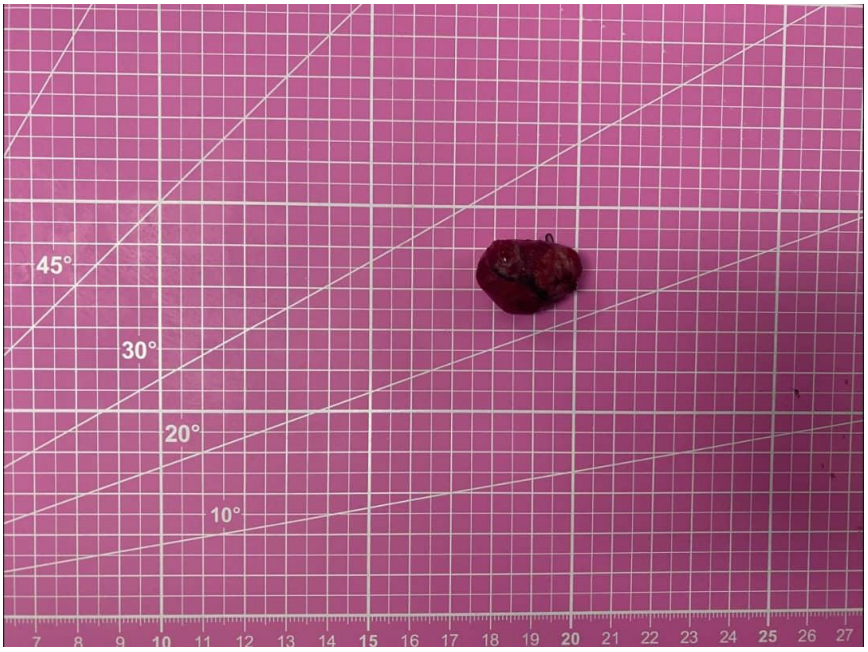
Patient was planned for elective surgery for removal of the NET tumour. Upper midline incision was done. Intraoperatively it was found out that there was a lesion 1cm x 1cm at the pancreatic head abutting the Superior Mesentery Vein (SMV). The measured lesion was assessed with Intraoperative Ultrasound which demonstrated no communication to the pancreatic duct. The pancreatic duct was not dilated on ultrasound assessment. The lesion was also described as soft and well encapsulated. The surgery was continued with enucleation of the lesion. After surgery, patient was well. He had no hypoglycaemic episodes in ward, his drain and serum amylase level were 90 u/L and 50 u/L respectively during post operative day 3. He was discharged after post operative day 4.

Histopathology examination (HPE) of the tumour confirmed the diagnosis of Insulinoma. It showed a lesion that was well encapsulated with benign features. Immunohistochemistry of the lesion revealed strong and diffuse positive for Chromogranin and CD56, Beta Catenin and CK7 was negative and Ki-67 showed proliferation index. Final interpretation of the tumour was well differentiated NET WHO 1.

Follow up 2 months post-surgery, patient showed signs of recovery. He no longer has any hypoglycaemic episodes at home and is active at school activities. His random CBS home monitoring ranges 5-8 mmol/l. He is scheduled for another follow up in the next 3 months.



Insulinoma at the head of pancreas, not involving pancreatic duct.



Well encapsulated insulinoma, 2cm x 1cm.

III. Discussion

Insulinomas are tumours that usually originate from the B-cell of pancreas. They are usually benign and affect female patients more than male with a ratio of 4:1[1,2]. The incidence of insulinoma is around 1 to 4 per million per year[3,5,7]. The range of age at presentation range from as early as 5 years old to 76 years old with the median age of 45 years old [5,6,7]. Insulinoma in its sporadic form is usually solitary which counts for 90% of all the

cases. However, its familial form is usually related to MEN 1 and the lesions tend to be multiple[3,7]. Multiple Endocrine Neoplasia 1 disease involves adenoma of the parathyroid, pituitary and pancreatic gland. [1,2,3,4] This case report described a 12 years old boy presented with hypoglycaemic symptoms with isolated tumour of the head of pancreas.

Patients with insulinoma usually present with multiple episodes of recurrent hypoglycaemia. This is accompanied by sympathoadrenal symptoms such as diaphoresis, palpitations and tremulousness. The classical Whipple's Triad can be demonstrated in patients with insulinoma. Whipple's Triad is described as symptoms of hypoglycaemia due to voluntary fasting or strenuous activity and immediate relieved after glucose administration.[1,2,3,4,5] The common cause of hypoglycaemia especially in patients with pre-existing diabetes mellitus is usually exogenous insulin administration. Excessive endogenous insulin secretion caused by insulinoma is usually overlook causing the delay in diagnosis[1,2,6,7]. In this case, it was uncommon for a patient of paediatric age to be having frequent hypoglycaemic attack. Classical Whipple's Triad can be demonstrated which prompt the attending physician to rule out Insulinoma.

Symptoms of Insulinoma can be divided to 2 categories which are neuro-glycopenic and sympatho-adrenal. Neuro-glycopenic symptoms are the effects of hypoglycaemia towards the central nervous system. Symptoms that may occur are loss of consciousness, fatigability, confusion, motor deficits and seizures. The sympatho-adrenal symptoms are caused by the body autonomic response towards hypoglycaemia such as tremor, palpitations, hunger and diaphoresis.[2,3,7]

Diagnosis of Insulinoma can be ascertained by doing supervised fasting test which typically takes around 72H. Patients will have symptoms of hypoglycaemia and raised serum insulin level, C-peptide protein as well as serum cortisol [insulin (≥6 pmol/mL) and C-peptide (≥0.2 nmol/L)] during provoked fasting period.[1,2,3,4,5, 13] It is important to determine the presence of Ketonemia in patients with suspected Insulinoma. There are various causes of raised ketones especially during hypoglycaemic attack. However, ketonemia will not occur in fatty acid metabolism disorder and in hypoglycaemic hyperinsulinemias. The absences of ketonemia may direct the diagnosis of congenital hyperinsulinemias or insulinoma[9]. This patient demonstrated raised serum insulin and C-peptide during provoked fasting state at low capillary blood sugar level with absence of ketonemia.

Imaging is essential to detect insulinoma. Combination of imaging techniques may help to localize the lesion as the tumour can be small <2cm in 84% of the cases[10]. Some insulinoma may be multiple as well. Imaging technique should be ordered once diagnosis is established biochemically[7]. Contrast Enhanced Computer Topographic (CECT) scan has proven to be have 92-94% sensitivity in detecting insulinoma. It usually appears as a hypervascularised structure. Magnetic Resonance Imaging (MRI) has its benefits in detecting smaller and multiple insulinoma. It has been shown to be superior than CT in recent studies but CT scan is the most preferred imaging technique due to its availability. [7,10,11,12] Localization of tumour is important because excision of tumour remain the definite treatment of insulinoma. Endoscopic Ultrasound (EUS) and Positron Emitting Tomography (PET) scan are two imaging techniques that are capable in localizing pancreatic lesions. EUS helps to improve localization of pancreatic tumor by 8-10%[10]. Combination of EUS and CT scan would help to increase sensitivity by 100%[7]. PET scan such as 68Ga-DOTATATE PET/CT, have shown sufficiently high sensitivity for identifying most insulinomas, and are considered by some adjunct imaging studies when the previous imaging findings were negative[1,2, 10,12]. Recent studies showed that 68Ga-DOTA-Exendin-4 PET/CT has better results, with a sensitivity of nearly 85% and a specificity of 100%. (Exendin is a synthetic glucagon-like peptide-1, which is expressed in cases of insulinoma) [1,2,10] This patient was confirmed biochemically to have insulinoma. Contrast Enhanced Computer Topography (CECT) of the abdomen was able to localized a single lesion at the head of the pancreas. Hence, no further imaging was requested.

Treatment of Insulinoma is surgical resection of the tumour. However, symptoms aggravated from the tumour can be controlled pharmacologically. The most common drug used to reduce insulin secretion is Diazoxide. It works by blocking sulfonylurea receptor 1 on pancreatic beta B cells, which increases the permeability to potassium ions. This will then increase hyperpolarization in B-cells hence blocking the calcium dependent insulin secretions. Other drugs such as octreotide (somatostatin analog), verapamil and phenytoin can be used with variable efficacy. This patient was started on T. Diazoxide 100mg three times a day. He was also taught on how to monitor his capillary blood sugar (CBS) at home and keep a diary of his CBS so that his medication can be catered to his needs.

Surgical treatment depends on the location (head, neck, body or tail of pancreas and types of Insulinoma (singular or multiple). Since most Insulinoma is benign in 90% of the cases, complete excision of the tumour would be adequate[6,7,10,11,12]. Enucleation of Insulinoma is the most preferred choice for small and single Insulinoma that is not involving the pancreatic duct (2-3mm away from the pancreatic duct). Intraoperative Ultrasound (IOUS) assessment may help to identify and characterised the lesion especially those that are multiple. Multiple pancreatic lesions; with lymph nodes involvement or lesions that are big causing compression and involving pancreatic or biliary system may warrant a proper resection. Resections options can be distal pancreatectomy (with or without splenectomy), Whipple's procedure or mid pancreatectomy depending on the site of the lesion[7,10,11,12]. For this patient, enucleation of the tumour was done because of the characteristic of the

tumour. The tumour is singular located at the head of pancreas, no local infiltration, size assess intraoperatively was 1cm in diameter, well encapsulated, IOUS showed no duct involvement and lesion was excised fully. There was no need for further resection of the pancreas.

Current studies mentioned complications such as anastomotic leak, pancreatic fistula, prolong hospital stay and mortality are more apparent in surgical resections (Distal pancreatectomy or Whipple's procedure). In patients with confirmed MEN 1 syndrome, resection is advised because insulinoma lesions tend to be multiple in MEN 1 and risk of malignancies is increased[11]. Nevertheless, complications are relatively low since most studies were done in high volume centres[7,10,11,12].

Surgery can be done by means of midline laparotomy or laparoscopy surgery. The advancement in technology has seen the advent of laparoscopic ultrasonography that may help to assess pancreatic lesions. Even so, laparoscopic surgery may be complicated for pancreatic tumours that are difficult to access. Selection of patients are important before mode of surgery is selected[7,10]. A Dutch trial comparing open and laparoscopic pancreaticoduodenectomy was called off prematurely due to higher mortality rate in the laparoscopic arm[10]. Open surgery technique was done for this patient. Upper midline incision was made in view of the patient's small body habitus and was adequate to gain straight forward access of the tumour location.

The usage of Radio Frequency Ablation (RFA) may serve as an alternative for treatment of Insulinoma. Nonetheless, there are not may centres that practice this technique and the clinical success rate is 83-100%. Further studies need to be considered to assess this technique[10]. This may be an option for unresectable pancreatic lesions or patients that are not fit for surgery. The usage of radio embolization and chemotherapy are not well established. The benefits and efficacy of these techniques need further research[2].

To determine the type of tumour, several immunohistochemistry studies can be applied. The most common ones would be Chromogranin A and synaptophysin which both will appear positive[3,5,9]. Ki-67 index is used to assess tumour grade[3,5,9]. Most patients with complete resection tend to have 100% cure rate. Symptoms of hypoglycaemia disappears almost immediately after surgery. Malignant insulinomas are rare. Recurrence rate is low around 3%, these patients are usually with multiple pancreatic lesions[1,11]. In this patient, the tumour is positive for Chromogranin and CD56 but negative for Beta catenin and CK7. The Ki-67 index was low (<2%).

IV. Conclusion

Insulinoma is a rare cause of hypoglycaemia. Due to its rarity, and variability of symptoms (Neuroglycopenic and sympathoadrenal) diagnosis is often missed or delayed. Diagnosis can be achieved clinically, examining biochemical markers as well as radiological images. Localization of Insulinoma is vital as complete excision yield 100% curative rate.

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