Original Article

Trends in Presentation and Management of Endogenous Hyperinsulinaemic Hypoglycaemia Over the Last Three Decades at a Tertiary Care Centre (1992–2022)

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Abstract

Introduction: Endogenous hyperinsulinaemic hypoglycaemia (EHH) is characterized by inappropriate insulin secretion from pancreatic beta cells despite low blood glucose concentrations. We aimed to evaluate the secular changes in presentation and management of EHH due to insulinoma/non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) at our centre. **Methods:** This was a single-centre ambispective study (2014–2022). The clinical, biochemical, hormonal and radiological parameters (n = 63) collected as part of this study were compared with our earlier studies (1992–2005, n = 31; and 2006–2013, n = 35) and with other centres across the world. **Results:** A total of 63 patients (39 males) with a preoperative diagnosis of EHH (insulinoma, n = 58; and NIPHS, n = 5) and a mean age of 40.7 years were studied. The mean lag time from the onset of symptoms to diagnosis decreased from 4.6 years during the first study period to 1.9 years during this study period. However, the majority presented with fasting hypoglycaemia of 98.4%, and both fasting and postprandial hypoglycaemia of 32%. Exclusive postprandial hypoglycaemia was present in 1.7% of insulinoma. A histopathological diagnosis of insulinoma was made in 52 patients and nesidioblastosis in two patients. Intraoperative ultrasonography (IOUS) and intraoperative palpation (IOP) yielded 100% sensitivity, while endoscopic ultrasonography (EUS) and 68Ga-DOTA-Exendin-4 positron emission tomography/computed tomography (PET/CT) yielded sensitivity of 86% and 85%, respectively, for localizing insulinoma. Resolution of hypoglycaemia was noted in 53 of 57 (93%) patients who underwent surgery with a preoperative diagnosis of insulinoma. **Conclusion:** We observed a trend towards earlier diagnosis of EHH, increased patient numbers and availability of nuclear imaging techniques for preoperative localization in the last decade compared to earlier.

Keywords: Endogenous hyperinsulinism, GLP-1 receptor imaging, hyperinsulinaemic hypoglycaemia, hypoglycaemia, insulinoma, nesidioblastosis

Introduction

Endogenous hyperinsulinaemic hypoglycaemia (EHH) is characterized by inappropriate insulin secretion from pancreatic beta cells despite low plasma glucose. Aetiologies for EHH include insulinoma, non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), sulfonylurea-induced hypoglycaemia, autoimmune hypoglycaemia and post-gastric bypass hypoglycaemia. Insulinoma, a pancreatic neuroendocrine tumour (NET), is the most common cause of EHH. With advancements in diagnostic modalities, the preoperative localization of culprit lesion has improved. This has been reported from our centre[1,2] as well as other centres.[3]

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Two series on insulinoma were published from our centre, first with 31 patients from 1992 to 2005,[1] and another with 35 patients from 2006 to 2013.[2]

Insulinoma is a rare disorder, with the incidence of 1–4 cases per million per year[4-6] and hence difficult to study through

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prospective design. We therefore planned an ambispective study to characterize the changes in presentation and management of EHH at our centre, in comparison with previous data. We have additionally included NIPHS in this analysis, as these cases have overlapping clinical and biochemical presentation with insulinoma, and present significant management challenges.

Materials and Methods

This was a single-centre ambispective study, conducted in the Department of Endocrinology and Metabolism of a tertiary care hospital in North India. Subjects were recruited retrospectively from 1 January 2014 till 31 October 2021 {as data till 31 December 2013 was already published},[2] and prospective recruitment was conducted for subjects from 1 November 2021 till 31 May 2022. The clinical, biochemical, hormonal and radiological parameters were compared with our earlier studies[1,2] and studies from other centres.

Inclusion criteria were patients diagnosed as hyperinsulinaemic hypoglycaemia {serum insulin and C-peptide values of ≥3 µIU/mL and ≥0.6 ng/ml, respectively, during hypoglycaemia (venous plasma glucose ≤54 mg/dl)}. Patients with hypoglycaemia due to insulin, oral medications, insulin autoantibodies, hypopituitarism, hypoadrenalism or factitious hypoglycaemia were excluded. Insulin and C-peptide were measured on an autoanalyzer (Cobas e411, Germany) using electrochemiluminescence assay (since 2006). Before 2006, they were measured using radioimmunoassay kit. To ensure quality control, the quality control provided with the kit was used. After the institutional ethics committee approval, data pertaining to clinical characteristics, diagnosis, imaging techniques, surgical findings and outcomes were extracted and analysed using the Statistical Package for Social Sciences (SPSS).

A combination of available radiological techniques, including abdominal ultrasonography (USG), contrast-enhanced multiphase computed tomography (CT), multiphase magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), 68Ga-DOTANOC positron emission tomography (PET)/CT and 68Ga-DOTA-Exendin-4 PET/CT, was used to localize tumour preoperatively. In cases where lesion could not be localized, or there was discrepancy among the results of imaging techniques, selective arterial calcium stimulation test (SACST) was employed to look for gradient in insulin rise after stimulation and localize territory of possible lesion.[7] Intraoperatively, lesions were further confirmed using intraoperative ultrasonography (IOUS) and intraoperative palpation (IOP). Tissue specimens were sent for histopathology and characterized with parameters, such as mitotic index, Ki-67 index, synaptophysin and chromogranin, and tumour was graded using the World Health Organization (WHO) criteria.[8] The results of preoperative localization were compared with intraoperative findings, as well as histopathological confirmation for determining sensitivity of various preoperative localization tests. Histopathology was taken as the gold standard.

Ethical aspect

Ethics clearance was obtained from the institute ethical committee (EC approval letter no. IECPG-618/28.10.2021, RT-01/27.04.2022, date of issue: 28.04.2022). For participants who were recruited prospectively, written informed consent was obtained for the use of the patient data for research purposes. The work done was in compliance with the Declaration of Helsinki.

Results

Between 2014 and 2022, a total of 63 patients received a preoperative diagnosis of EHH, 58 due to insulinoma and five due to NIPHS. Patients with insulinoma had biochemical EHH, and the preoperative imaging modalities suggested the presence of a pancreatic lesion, while those with NIPHS had biochemical EHH and negative preoperative pancreatic imaging. Of the 58 patients with preoperative diagnosis of insulinoma, 57 underwent surgery and one patient with arterial collaterals in the pancreatic head underwent ethanol ablation. Of these 57 patients, 52 were found to have a NET on histopathology (confirming insulinoma), four had normal histopathology and one had histopathological evidence of nesidioblastosis. Of the five patients with preoperative diagnosis of NIPHS, two underwent surgery, one had histopathological evidence of nesidioblastosis and the other had normal histopathology. Thus, a histopathological diagnosis was achieved in 54 patients, with 52 having insulinoma and two having nesidioblastosis.

A total of 63 patients (males, n = 39) were evaluated. The mean age was 40.7 ± 16.1 years, with a range of 8–88 years. Fasting hypoglycaemia was present in 62 patients (98.4%), and both fasting and postprandial hypoglycaemia in 20 patients (31.7%). One patient demonstrated exclusive postprandial hypoglycaemia. This patient on histopathology was found to have insulinoma at the head of the pancreas. The demographic and clinical profile of the study participants, in comparison with our case series published earlier,[1,2] is provided in Table 1.

Forty-seven patients (74.6%) had spontaneous hypoglycaemia and 16 (25.4%) required a supervised prolonged fast to induce hypoglycaemia for critical sample. During prolonged fast, 13 of 16 (81.3%) manifested hypoglycaemia within 24 hours, 15 of 16 (93.8%) had hypoglycaemia within 36 hours, and only one patient required fast beyond 48 hours (hypoglycaemia at 52 hours). The mean duration of fast was 17.95 ± 13.56 hours.

The mean plasma glucose during hypoglycaemia was 34.1 ± 8.9 mg/dl, with concomitant serum insulin of 49.63 ± 45.8 µIU/ml, C-peptide of 6.61 ± 4.47 ng/ml, growth hormone of 1.83 ± 2.8 ng/ml and cortisol of 11.6 ± 5.1 ug/dL. The mean glycated haemoglobin was 4.7 ± 0.52% [Table 2].

Contrast-enhanced multiphase CT (100%) and IOUS (100%) were most commonly used, while 68Ga-DOTA-Exendin-4 PET/CT (50%) was used least frequently. The sensitivity of preoperative localization was calculated among 52 patients who had a final histopathological diagnosis of pancreatic

Table 1: Demographic and clinical profile of the study participants (2014–2022) and comparison with our previous cohorts (1992–2005 and 2006–2013)

Parameter	Study period (1992–2005, n=31) (1)	Study period (2006–2013, n=35) (2)	Study period (2014–2022, n=63)	Total period (1992–2022, n=129)
Male: female	16/15	19/16	39/24	74/55
Mean age (y)	38.4±12.8	37.5±13.8	40.75±16.14	38.9
Age range (y)	15-60	14-65	8-88	8-88
Duration of symptoms (y)	4.6	3.3	1.97	3.29
Pre-prandial hypoglycaemia	31 (100)	35 (100)	62 (98.4)	128 (99.2)
Both pre- and postprandial hypoglycaemia	4 (13)	13 (37.14)	20 (31.7)	37 (28.7)
Excessive hunger	22 (70)	28 (80)	20 (31.7)	70 (23.3)
Weight gain	16 (54)	26 (74.28)	35 (55.6)	77 (59.7)
Palpitations	8 (25)	22 (62.5)	35 (55.6)	65 (50.4)
Sweating	8 (25)	31 (88.57)	44 (69.8)	83 (64.3)
Tremors	8 (25)	26 (74.28)	30 (47.6)	64 (49.6)
Giddiness	23 (75)	30 (85.7)	35 (55.6)	88 (68.2)
Loss of consciousness	16 (54)	30 (85.71)	39 (61.9)	85 (65.9)
Persistent cognitive dysfunction	8 (25)	3 (8.5)	4 (6.3)	15 (11.6)
Seizures	13 (42)	18 (51.42)	16 (25.4)	47 (36.4)
History of antiepileptic drugs	6 (19.35)	18 (51.42)	20 (31.7)	44 (34.1)
History of psychotropic drugs	4 (12.90)	12 (34.28)	9 (14.3)	25 (19.4)

Table 2: Biochemical parameters of the study participants (2014–2022) and comparison with our previous cohorts (1992–2005 and 2006–2013)

Parameter	Study period (1992–2005, n=31) (1)	Study period (2006–2013, n=35) (2)	Study period (2014–2022, n=63)	Total period (1992–2022, n=129)
Spontaneous hypoglycaemia	12/31 (38.7)	31/35 (88.6)	47 (74.6%)	90 (69.8)
Prolonged fast required for diagnosis	19 (61.3)	4 (11.4)	16 (25.4)	39 (30.2)
Mean duration of fast (h)	20.4±7.1	23.3±7.9	17.95±13.56	20.6
Mean plasma glucose (mg/dl)	25±8.3	33.6±7.8	34.09±8.89	34.2
Concomitant insulin (µIU/ml)	44.9	42.3	49.63±45.8	45.6
Concomitant C-peptide (ng/ml)	4.7	6.1	6.61±4.47	5.8
HbA1c (%)	4.2	4.6	4.7±0.52	4.5

NET (insulinoma). The localization sensitivity was highest for IOUS (100%) and IOP (100%), followed by EUS (85.7%), 68Ga-DOTA-Exendin-4 PET/CT (84.6%), contrast-enhanced MRI (79.3%), contrast-enhanced multiphase CT (77.1%), 68Ga-DOTANOC PET/CT (62.8%) and abdominal USG (17.5%). The sensitivity of various localization techniques as they became available over the last 30 years is compared in Table 3.

Five patients whose diagnosis was not clear on preoperative imaging modalities underwent SACST. Of these, three had diffuse rise following calcium stimulation, while two had focal rise, one each following calcium injection into gastroduodenal artery and proximal splenic artery. In the former group, only one patient underwent surgery, with histopathological diagnosis being nesidioblastosis, while in the latter group, both patients underwent surgery and had histopathology-confirmed insulinoma in the pancreatic head and tail, respectively.

Among 58 patients with preoperative diagnosis of insulinoma, eight (13.8%) were associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome, while the rest were sporadic. Patients were identified as having MEN-1 syndrome if they had associated tumour of parathyroid and/or pituitary gland or positive family history of MEN-1. Among patients with MEN-1-related insulinoma, Primary hyperparathyroid (PHPT) was the most commonly associated endocrine neoplasm (7/8, 87.5%). Of the seven patients with PHPT, five were diagnosed during routine serum calcium and Parathyroid hormone (PTH) screening at admission, while the remaining two were already diagnosed before the admission. For PHPT, all patients underwent surgery: subtotal parathyroidectomy in four and focused parathyroidectomy in three. Other MEN-1-associated endocrine tumours included pituitary adenoma in three patients (prolactinoma, n = 2; non-functioning pituitary adenoma, n = 1), and gastrinoma in two patients. Three patients had tumours involving all three endocrine glands, that is pituitary, parathyroid and pancreas. Three patients had a family history of MEN-1 syndrome.

All patients with MEN-1-associated insulinoma had spontaneous hypoglycaemia after admission and did not require supervised fast. Patients with MEN-1-related insulinoma were younger, had lower body mass index, higher

Table 3: Sensitivity of preoperative localization techniques in this study compared with our previous studies[1,2]

Localization technique	Study period (1992–2005, n=31)[1]	Study period (2006–2013, n=35)[2]	Study period (2014–2022, n=63)
USG	15.8%	16.7%	17.7%
Conventional CECT	10%	25%	Not done
Dual-phase CT	57.1%	Not done	Not done
Multiphase CT	Not available	79.3%	77.1%
Conventional MRI	30.8%	Not done	Not done
Multiphase MRI	Not available	85%	79.3%
EUS	Not available	95%	85.7%
68GaDOTA NOC PET/CT	Not available	25%	62.8%
EXENDIN PET/CT	Not available	Not available	84.6%
IOUS	Not available	93%	100%
IOP	Not available	91%	100%

serum PTH, greater number of pancreatic lesions and required longer hospital admission [Table 4].

A total of 57 patients with a preoperative diagnosis of insulinoma underwent surgery. Of these 57 patients, 21 underwent enucleation ± cystojejunostomy, 19 underwent distal pancreatectomy ± splenectomy, nine underwent Whipple's procedure ± total pancreatectomy, five underwent median pancreatectomy, two underwent enucleation + distal pancreatectomy, and one underwent explorative laparotomy (which had to be abandoned). Fifty-three (93%) patients had resolution of hypoglycaemia post-surgery, 36 (63.2%) required insulin in the postoperative period for rebound hyperglycaemia, and 12 (21.1%) required insulin at discharge. Seven (12.3%) patients developed exocrine pancreatic insufficiency, 16 (28.1%) had hyperkalaemia in the postoperative period, and 22 (38.6%) had postoperative complications requiring pigtail insertion/interventions. Fifty-two (91.2%) patients had histopathological evidence of insulinoma.

Two patients had histopathologic evidence of nesidioblastosis: One had a preoperative diagnosis of NIPHS and the other had a preoperative diagnosis of insulinoma. The first patient had a total of four admissions in the endocrinology ward and underwent total pancreatectomy after repeated negative preoperative imaging and SACST suggestive of diffuse rise. The patient required insulin and pancreatic exocrine replacement therapy after the surgery. The second patient had conflicting preoperative imaging findings: Multiphase CT showed lesion in the pancreatic head, while 68Ga-DOTANOC PET/CT and EUS suggested a lesion in the pancreatic tail, and contrast-enhanced MRI study was negative. The patient underwent distal pancreatectomy; in the postoperative period, hypoglycaemia persisted, and the patient was discharged on frequent complex carbohydrate diet and oral prednisolone. At the last follow-up, the patient had developed Cushing's stigmata and persistently required prednisolone.

Table 4: Difference between MEN-1-associated insulinoma and sporadic insulinoma

	Sporadic	MEN-1	*P*
Age (years)	41.85	33.13	0.155
Duration of admission (days)	44.89	66.25	0.032
BMI (Kg/m^2)	32.07	24.95	0.577
HbA1c (%)	4.71	4.67	0.944
iPTH (pg/ml)	48.99	144.41	<0.001
Number of lesion	1.19	2.25	0.01
Size of lesion (cm)	1.765	1.732	0.9

Discussion

In this ambispective study, we evaluated clinical, biochemical profile and surgical outcomes of 63 patients with EHH suspected to be due to insulinoma (n = 58) or NIPHS (n = 5) admitted to our hospital between 2014 and 2022. This work complements our data on EHH due to insulinoma published earlier,[1,2] spanning between 1992 and 2013, and provides trends in presentation and management of this rare condition.

Insulinomas are rare, but most common functioning pancreatic NET. These tumours are typically single, small and hypervascular, with 90% measuring <2 cm and 30% measuring <1 cm in diameter. Approximately 10% are multiple, 10% are malignant, and 16% are associated with MEN-1 syndrome.[4-6] NIPHS is a rarer condition, characterized by a) endogenous hyperinsulinism not related to insulinoma, b) predominant postprandial hypoglycaemia and c) histopathological evidence of beta cell hypertrophy and budding of islet cells from periductal epithelium. Previously, this condition was termed as 'nesidioblastosis'; however, this term is currently restricted to histological appearance and not to describe the clinical state of islet cell dysfunction.[9]

Two series on insulinoma were previously published by us, one in 2006,[1] and another in 2014.[2] The number of cases has increased from 31 in our first series (13 years; 1992–2005) to 35 in the second series (7 years; 2006–2013) and 63 in the current series (including 58 suspected insulinoma and 52 histopathology-proven insulinoma over 8 years; 2014–2022). This increase in number could be attributed to increased awareness among medical fraternity about this condition and more referrals, given the growth of the multidisciplinary

team managing this condition in our centre. Unlike the international data suggesting slight female preponderance,[3,4] we always had a slight male preponderance. Studies from other centres of India have similarly shown slight male preponderance.[10,11] This series documented a wider age range at presentation, from 8 to 88 years, even though the mean age at presentation remained nearly the same through the years (from 38 to 41 years). A relatively early detection was seen as the average duration between symptoms and diagnosis was found to decrease from 4.6 years in earlier series to <2 years in this series. The clinical presentation has remained relatively consistent over the last two study periods, with fasting hypoglycaemia in nearly all cases, and combined fasting and postprandial hypoglycaemia in nearly one-third of cases. Only one among 58 (1.7%) patients of insulinoma presented with exclusive postprandial hypoglycaemia.

Nearly 75% of patients had spontaneous hypoglycaemia and did not require a supervised fast, while the remaining 25% needed supervised fast to induce hypoglycaemia. A clear trend is discernible in our cohort, as only 39% of patients manifested spontaneous hypoglycaemia in the 1992–2005 period, increasing to 89% during the 2006–2013 period, with a slight decline to 75% during the 2014–2022 period. A similar trend has been observed in data reported from the Mayo Clinic.[3] These data suggest that in the majority of patients, hypoglycaemia occurs without the need for the cumbersome 72-h fast. Among those patients who required prolonged fast, hypoglycaemia occurred in <24 hours in 81%, <36 hours in 94% and <72 hours in 100%. These data again mirror that from the Mayo Clinic, wherein 65% of patients terminated test in <24 hours, 84% in <36 hours, 93% in <48 hours and 99% in <72 hours.[12]

For preoperative localization of insulinoma, contrast-enhanced multiphase CT and IOUS were the most common modalities employed, and similar to our previous study,[2] IOUS and IOP demonstrated high sensitivity for localization of insulinoma. Glucagon-like peptide-1 (GLP-1) receptor imaging using 68Ga-DOTA-Exendin-4 PET/CT was a useful addition in our analysis and yielded a high sensitivity of 85% among 26 patients who underwent it. Previous studies[13,14] have similarly reported high sensitivity of GLP-1 receptor-based functional imaging in localizing insulinoma (6/6, 100% and 19/20, 95%, respectively). Unlike morphological imaging and somatostatin receptor-based imaging, GLP-1 receptor-based functional imaging is specific for insulinoma (only insulinomas highly express GLP-1 receptors and show intense uptake of the radiolabelled GLP-1 analogue) and is especially helpful in the setting of multiple pancreatic NETs (such as MEN-1 syndrome) to differentiate insulinoma from other functional or non-functional pancreatic NETs.[15] Notably, the sensitivity of 68Ga-DOTANOC-PET/CT was found to increase from 25% in our earlier analysis to 62% in this analysis. A possible explanation is that a doubtful lesion on DOTANOC PET-CT previously deemed negative would now be interpreted in sync with other more sensitive imaging modalities (such as Exendin-4 PET-CT) that increase the confidence in correctly identifying it as the culprit lesion.

Among patients with preoperative diagnosis of insulinoma (n = 58), eight (13.8%) were found to have MEN-1 syndrome. As expected, PHPT was the most commonly associated endocrine abnormality (7/8, 87.5%) in such patients and three patients had a positive family history of MEN-1 syndrome. Compared to those with sporadic disease, patients with MEN-1-associated insulinoma were younger, leaner, manifested higher serum PTH levels, had greater number of pancreatic lesions and had longer hospital stay. A recent study similarly reported that younger age, multifocal pancreatic NETs and positive family history are features that differentiate MEN-1-related from sporadic insulinomas.[16] The presence of these features and associated endocrine abnormalities should prompt one to suspect MEN-1 syndrome in patients with insulinoma.

Among patients undergoing surgical intervention for suspected insulinoma (n = 57), enucleation (n = 21) and distal pancreatectomy (n = 19) were the most common procedures. More than 90% of patients had resolution of hypoglycaemia post-surgery. Nearly two in every three patients needed insulin in the postoperative period for rebound hyperglycaemia, while nearly one in every five patients required insulin at time of discharge. The preoperative diagnosis of insulinoma was confirmed by histopathology in 52 of 57 (91%) patients. We also encountered two patients with histopathology-proven nesidioblastosis, one with a preoperative diagnosis of NIPHS and the other with preoperative diagnosis of insulinoma. The first patient was a typical case of NIPHS, wherein multiple admissions and preoperative procedures including SACST failed to locate a focal lesion, and decision for total pancreatectomy was taken considering the recurrent and severe hypoglycaemia episodes. This patient had resolution of hypoglycaemia after total pancreatectomy and required insulin and pancreatic exocrine replacement at discharge. However, the preoperative diagnosis in the second case was that of a doubtful insulinoma and the patient underwent distal pancreatectomy. As expected, the patient did not achieve resolution of hypoglycaemia and requires ongoing medical management.

Nesidioblastosis (or NIPHS) is an important differential diagnosis of insulinoma, but is rare in adults, accounting for only 0.5–7% of all cases of EHH. This condition leads to proliferation of beta cells throughout the pancreas and presents a significant management challenge. Treatment options include dietary modifications and pharmacological agents, such as diazoxide, acarbose, verapamil, glucocorticoids and somatostatin analogue in milder cases (or patient not willing/fit for surgery) and partial or total pancreatectomy in severe cases.[17,18] In a retrospective analysis of 32 EHH,[19] five cases of nesidioblastosis were reported, each of which underwent 70% of distal pancreatectomy (removing all pancreatic tissue to the left of the superior mesenteric vessels). Three of these five cases had resolution of hypoglycaemia, while two experienced recurrences which were successfully treated with verapamil. The

authors concluded that 70% of distal pancreatectomy results in fairly successful outcome in adult nesidioblastosis and verapamil is useful in patients with recurrence following the surgery.[19]

One patient underwent EUS-guided ethanol ablation of pancreatic NET as during laparotomy, there were extensive arterial collaterals due to portal cavernoma surrounding the NET at the head of the pancreas, because of which planned enucleation was abandoned. Post-intervention, the size of the NET reduced from 1.8 cm to 1.4 cm and became less hypoechoic at day 3. Further insulin and C-peptide levels reduced from 22.3 to 4.3 uIU/ml and 6.5 to 1.2 ng/ml, respectively. The patient had excellent response, with no hypoglycaemic episodes till the last follow-up. A recent review also showed excellent success rate of 98.5% with EUS-guided ablations, with the majority of targeted NETs being in head of pancreas.[20]

Ours is the largest series of HPE-proven EHH/insulinoma from India (n = 129) and the second largest in the world. This study clearly defines trend in improvement in diagnosis, in terms of earlier diagnosis as well the emergence of sensitive imaging techniques leading to better and more accurate preoperative localization. We also noted a trend for decreased reliance on 72-h fast to induce hypoglycaemia. Paediatric and MEN-1 cases were also included in our analysis, further showing diversity and heterogeneity of cases.

This study has various limitations. Firstly, a large component of this study is retrospective. However, considering the rarity of insulinoma, this is the most pragmatic approach to study rare diseases. Secondly, follow-up of cases after discharge was limited, as the majority of patients did not visit after they were cured. Thirdly, insulin staining was not conducted on histopathology specimens of patients with insulinoma. Therefore, confirmation of insulinoma in multifocal PNET or in case of MEN-1 could not be conducted with certainty.

Conclusion

We observed a clear trend towards earlier diagnosis of EHH and a decreased need for 72-h fast. Noninvasive molecular imaging techniques, such as 68Ga-DOTA-Exendin PET/CT, are now available to ascertain the functionality of the lesions. Currently, a combination of radiological and functional imaging is helpful to localize the lesion and manage EHH, especially in multifocal disease, such as MEN-1 syndrome.

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Authors' contribution

Dr Setu Gupta, Dr Alpesh Goyal, Dr Viveka *P* Jyotsna and Dr Nikhil Tandon were involved in conceptualizing the study, gathering information and statistical analysis. Dr Devasenathipathy Kandasamy, Dr Shipra Agarwal and Dr Nishikant Damle were involved in the radiological investigations, histopathological diagnosis and nuclear medicine scans, respectively. Dr Sujoy Pal was involved in the surgery and postoperative management of the patients. All authors were involved in writing, revision, reading and approving the manuscript for publication.

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Conflicts of interest

There are no conflicts of interest.

Data availability

Data pertaining to this manuscript will be made available on request.

References

1. Jyotsna VP, Rangel N, Pal S, Seith A, Sahni P, Ammini AC. Insulinoma: Diagnosis and surgical treatment. Retrospective analysis of 31 cases. Indian J Gastroenterol 2006;25:244-7.
2. Jyotsna VP, Pal S, Kandasamy D, Gamanagatti S, Garg P, Raizada N, *et al*. Evolving management of insulinoma: Experience at a tertiary care centre. Indian J Med Res 2016;144:771.
3. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, *et al*. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab 2009;94:1069–73.
4. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: A 60-year study. Mayo Clin Proc 1991;66:711–9.
5. Vaidakis D, Karoubalis J, Pappa T, Piaditis G, Zografos GN. Pancreatic insulinoma: Current issues and trends. Hepatobiliary Pancreat Dis Int 2010;9:234-41.
6. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005; 19:783–98.
7. Thompson SM, Vella A, Thompson GB, Rumilla KM, Service FJ, Grant CS, *et al*. Selective arterial calcium stimulation with hepatic venous sampling differentiates insulinoma from nesidioblastosis. J Clin Endo Metab 2015;100:4189–97.
8. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, *et al*. Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol 2022;33:115–54.
9. Tsujino M, Sugiyama T, Nishida K, Takada Y, Takanishi K, Ishizawa M, *et al*. Noninsulinoma pancreatogenous hypoglycemia syndrome: A rare case of adult-onset nesidioblastosis. Intern Med 2005;44:843-7.
10. Anakal MG, Kalra P, Dharmalingam M, Indushekhar S, Rao V, Prasanna Kumar KM. Insulinoma case series: Experience of a tertiary care center. Indian J Endocrinol Metab 2014;18:858-62.
11. Manjunath PR, George B, Mathew V, Bantwal G, Ayyar V. "Riding high on low fuel"—Our experience with endogenous hyperinsulinemic hypoglycemia. Indian J Endocrinol Metab 2017;21:655–9.
12. Service FJ, Natt N. The prolonged fast. J Clin Endocrinol Metab 2000;85:3973-4.
13. Christ E, Wild D, Forrer F, Brändle M, Sahli R, Clerici T, *et al*. Glucagon-like peptide-1 receptor imaging for localization of insulinomas. J Clin Endocrinol Metab 2009;94:4398-405.
14. Christ E, Wild D, Ederer S, Béhé M, Nicolas G, Caplin ME, *et al*. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: A prospective multicentre imaging study. Lancet Diabetes Endocrinol 2013;1:115-22.
15. Antwi K, Nicolas G, Fani M, Heye T, Pattou F, Grossman A, *et al*. 68Ga-Exendin-4 PET/CT detects insulinomas in patients with endogenous hyperinsulinemic hypoglycemia in MEN-1. J Clin Endocrinol Metab 2019;104:5843-52.
16. Opalińska M, Gilis-Januszewska A, Morawiec-Sławek K, Kurzyńska A, Sowa-Staszczak A, Bogusławska A, *et al*. Differences in clinical

characteristics, treatment, and outcomes of sporadic and MEN-1-related insulinomas. Endokrynol Pol 2023. doi: 10.5603/EP.a2023.0049.
17. Qintar M, Sibai F, Taha M. Hypoglycemia due to an adult-onset nesidioblastosis, a diagnostic and management dilemma. Avicenna J Med 2012;2:45-7.
18. Schwetz V, Horvath K, Kump P, Lackner C, Perren A, Forrer F, *et al*. Successful medical treatment of adult nesidioblastosis with pasireotide over 3 years: A case report. Medicine (Baltimore) 2016;95:e3272.
19. Witteles RM, Straus II FH, Sugg SL, Koka MR, Costa EA, Kaplan EL. Adult-onset nesidioblastosis causing hypoglycemia: An important clinical entity and continuing treatment dilemma. Arch Surg 2001;136:656-63.
20. El Sayed G, Frim L, Franklin J, McCrudden R, Gordon C, Al-Shamma S, *et al*. Endoscopic ultrasound-guided ethanol and radiofrequency ablation of pancreatic insulinomas: A systematic literature review. Therap Adv Gastroenterol 2021;14:17562848211042171. doi: 10.1177/17562848211042171.