Insulinoma in childhood: clinical, radiological, molecular and histological aspects of nine patients

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Abstract

Background: Insulinomas are a rare cause of hyperinsulinaemic hypoglycaemia (HH) in children. The clinical features, investigations, management and histology of these rare pancreatic tumours in children have not been described in a large cohort of patients.

Methods: We conducted a retrospective review of cases diagnosed between 2000 and 2012, presenting to two referral centres in the United Kingdom. Clinical, biochemical, imaging (magnetic resonance imaging (MRI) and 6-L-18F-fluorodihydroxyphenylalanine (18F-DOPA) PET/CT scanning) and histological data were collected.

Results: Nine children (age range 2–14.5 years) were diagnosed during the study period at Great Ormond Street Hospital (n = 5) and Royal Manchester Children’s Hospital (n = 4). The combination of abdominal MRI scan (7/8) and 18F-DOPA PET/CT scan (2/4) correctly localised the anatomical location of all insulinomas. Before surgery, diazoxide therapy was used to treat hypoglycaemia, but only four patients responded. After surgical resection of the insulinoma, hypoglycaemia resolved in all patients. The anatomical localisation of the insulinoma in each patient was head (n = 4), uncinate process (n = 4) and tail (n = 2, one second lesion) of the pancreas. Histology confirmed the diagnosis of insulinoma with the presence of sheets and trabeculae of epithelioid and spindle cells staining strongly for insulin and proinsulin, but not for glucagon or somatostatin. Two children were positive for MEN1, one of whom had two separate insulinoma lesions within the pancreas.

Conclusions: We describe a cohort of paediatric insulinoma patients. Although rare, insulinomas should be included in the differential diagnosis of HH, even in very young children. In the absence of a single imaging modality in the preoperative period, localisation of the tumour is achieved by combining imaging techniques, both conventional and functional.

Introduction

Hyperinsulinaemic hypoglycaemia (HH) is an important cause of recurrent and severe hypoglycaemia during infancy and childhood. Though rare, it is one of the commonest causes of hypoglycaemia, causing significant neurological deficit. HH is caused by unregulated insulin secretion, which results in severe and recurrent hypoglycaemia. Inappropriate insulin secretion inhibits glycogenolysis, gluconeogenesis, lipolysis and ketogenesis.
that prevents generation of ketone bodies (alternative energy sources) leading to neuroglycopaenia and hypoglycaemic brain injury.

In children, congenital hyperinsulinism (CHI) is the most common cause for HH and it typically presents in early infancy. The incidence of severe CHI is estimated at 1:50 000 (1). Beyond infancy, HH may also be due to another diagnosis – insulinoma, a neuroendocrine tumour of the pancreas, which has been described mostly in adults. It is estimated that insulinoma occurs once in 250 000 persons/year (2). The incidence of insulinoma has not been estimated in children. Insulinoma can occur either in isolation or in association with multiple endocrine neoplasia type 1 (MEN1), with a lifetime prevalence of 10% among adults carrying mutations in MEN1 (3). Around 6% of insulinomas occur in patients with MEN1 (3). Most insulinomas are benign: 5–10% are malignant (2).

An insulinoma is clinically suspected in the presence of Whipple’s triad (symptoms and/or signs compatible with hypoglycaemia, a low measured plasma glucose concentration, and resolution of symptoms and signs when glucose concentrations are raised). However, a particular problem for evaluating hypoglycaemia in infants and children is that it may not be possible to satisfy all components of Whipple’s triad, because young children cannot dependably recognise and/or communicate their symptoms. Insulinomas are difficult to detect in adults, as symptoms can be non-specific and present for a long period before diagnosis. In children, the presenting clinical features are also non-specific; importantly, the biochemical features of HH do not differentiate between CHI and insulinoma. Childhood insulinomas are considered to be exceedingly rare with only single case reports in the literature. Therefore, information about the disease patterns of childhood insulinoma is limited. The rarity of insulinoma and the absence of large cohort studies prompted us to examine two large cohorts of children with HH. We describe the clinical, radiological, molecular and histological aspects of nine patients with childhood insulinoma.

Subjects and methods

To identify the study cohort, we reviewed the database of children with HH managed at the two referral centres: Great Ormond Street Hospital, London and Royal Manchester Children’s Hospital. Nine patients with a diagnosis of insulinoma were identified from the database from 2000 to 2012. The clinical data was collected retrospectively from the medical notes.

All patients were managed as per common protocols for managing hypoglycaemia due to HH. The diagnosis of HH was based on clinical symptoms of hypoglycaemia and finding detectable insulin at the time of hypoglycaemia. All children with HH were screened for mutations in the common genes causing CHI, ABCC8 and KCNJ11. Abdominal MRI scan with contrast was performed in eight children to identify signal changes correlating with probable insulinoma in the region of the pancreas. Four patients diagnosed after 2007 were also investigated with 6-L-18F-fluorodihydroxyphenylalanine (18-F-DOPA) PET/CT scan as per routine investigation policy in children with HH. In one patient, a localised lesion had already been ascertained on 18-F-DOPA PET/CT scan and hence MRI scanning was not undertaken.

The diagnosis of insulinoma was confirmed by the histological examination of excised pancreatic tissue. On the basis of the findings of radiological and surgical exploration, insulinoma was further classified into single or multiple and benign or malignant. Once the diagnosis of insulinoma was confirmed, genetic testing was carried out for MEN1. In those carrying MEN1 mutations, the presence of pituitary, parathyroid and other pancreatic tumours were assessed (4).

Results

Table 1 describes the clinical, radiological, molecular and surgical characteristics of patients with insulinoma in our cohort. Five patients with insulinoma were managed at the Great Ormond Street Hospital for Children, and four were managed at the Royal Manchester Children’s Hospital. The cohort consisted of five females and four males.

The age of onset of clinical symptoms ranged from 2.0 to 14.5 years. Clinical symptoms developed in two patients between 2 and 5 years of age, in four patients between 5 and 10 years of age and in three patients between 10 and 15 years of age.

The duration of symptoms before the diagnosis of HH was established, ranging from 1 month to 3 years with an average of around 10 months. All patients developed neurological symptoms of hypoglycaemia. Three patients were treated for seizure disorders with antiepileptic medications (2M, 3M and 6F). The fasting tolerance was limited and ranged from 2.5 to 6 h. Preoperatively, euglycaemia was maintained in four patients with diazoxide (1F, 3M, 5M and 7F) and in one patient with
<table>
<thead>
<tr>
<th>Patient ID and gender (M/F)</th>
<th>1F</th>
<th>2M</th>
<th>3M</th>
<th>4F</th>
<th>5M</th>
<th>6F</th>
<th>7F</th>
<th>8F</th>
<th>9M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td>3 years 4 months</td>
<td>5 years</td>
<td>7 years 6 months</td>
<td>8 years</td>
<td>8 years</td>
<td>10 years 8 months</td>
<td>8 years</td>
<td>10 months</td>
<td>13 years 13 years 15 years</td>
</tr>
<tr>
<td><strong>Duration of symptoms before referral</strong></td>
<td>1 year 4 months</td>
<td>4 months</td>
<td>2 years</td>
<td>12 months</td>
<td>3 years</td>
<td>8 months</td>
<td>1 month</td>
<td>2 months</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>Fast tolerance (h)</strong></td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3.5</td>
<td>6</td>
<td>4.5</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Blood glucose (mmol/l)</strong></td>
<td>1.9</td>
<td>2.2</td>
<td>1.5</td>
<td>1.1</td>
<td>0.8</td>
<td>1.6</td>
<td>2</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Insulin (mIU/l)</strong></td>
<td>5.7</td>
<td>4.5</td>
<td>Partial response to diazoxide</td>
<td>5.8</td>
<td>Responsive to diazoxide</td>
<td>66.3</td>
<td>Not responsive to diazoxide and octreotide</td>
<td>85</td>
<td>Responsive to diazoxide</td>
</tr>
<tr>
<td><strong>MRI scan</strong></td>
<td>ND</td>
<td>Lesion on the head of pancreas</td>
<td>Lesion on the uncinate process</td>
<td>Lesion on the head of pancreas</td>
<td>Normal appearance of pancreas</td>
<td>Lesion on the head of the pancreas anterior to the portal vein</td>
<td>Lesion on the uncinate process</td>
<td>Lesion on the uncinate process</td>
<td>Lesion on the head of pancreas</td>
</tr>
<tr>
<td><strong>PET/CT scan</strong></td>
<td>Focal uptake in uncinate process of pancreas</td>
<td>ND</td>
<td>Poor uptake in uncinate process of pancreas</td>
<td>ND</td>
<td>Focal lesion at the junction of tail and body of pancreas</td>
<td>ND</td>
<td>ND</td>
<td>Diffuse uptake</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Localisation of lesion</strong></td>
<td>PET/CT and peripancreatic lymphadenectomy and postoperative histology</td>
<td>Subtotal</td>
<td>MRI scan and postoperative histology</td>
<td>Partial</td>
<td>MRI scan and postoperative histology</td>
<td>Partial</td>
<td>PET/CT and peripancreatic lymphadenectomy</td>
<td>Subtotal</td>
<td>MRI scan and histology</td>
</tr>
<tr>
<td><strong>Type of pancreatectomy</strong></td>
<td>Focal lesionectomy</td>
<td>Subtotal</td>
<td>MRI scan and postoperative histology</td>
<td>Partial</td>
<td>MRI scan and postoperative histology</td>
<td>Partial</td>
<td>PET/CT and peripancreatic lymphadenectomy</td>
<td>Subtotal</td>
<td>MRI scan and histology</td>
</tr>
<tr>
<td><strong>Site and size of lesion on pancreas</strong></td>
<td>Uncinate process, 1 cm</td>
<td>Head, 1 cm</td>
<td>Uncinate process and tail, 1.5 cm</td>
<td>Between head and body, 1.5 cm</td>
<td>Tail, 1.2 cm</td>
<td>Head, 1.2 cm</td>
<td>Uncinate process, 0.8 cm</td>
<td>Uncinate process, 2 cm</td>
<td>Head, 1.2 cm</td>
</tr>
<tr>
<td><strong>Mutation for MEN1</strong></td>
<td>Negative</td>
<td>Positive c.249_252del-GTCT (deletion at codons 83-84)</td>
<td>Positive c.628_631delA-CAG (deletion at codons 210–211)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td><strong>Additional endocrinopathies</strong></td>
<td>Nil</td>
<td>Parathyroid adenoma after 5 years of presentation</td>
<td>Screening for MEN associated endocrinopathies ongoing</td>
<td>Nil</td>
<td>Nil</td>
<td>Missed clinical follow-up</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

ND, not done.
diazoxide and additional cornstarch in feeds (2M). Three patients were unresponsive to diazoxide and octreotide (4F, 8F and 9M).

All patients were negative for ABCC8/KCNJ11 mutations. Preoperatively, abdominal MRI scan was performed in eight patients and was successful in identifying an abnormality of the pancreas in seven patients while it was normal in one patient (5M). The pancreatic lesions on MRI scan typically had a low-signal density on T1-weighted images and a high-signal density on T2-weighted images (Fig. 1 of patient 3M). Four patients underwent 18-F-DOPA PET/CT scanning: in two patients (1F and 5M) increased uptake and localised retention of isotope18-F-DOPA on the pancreas suggested a solitary lesion (Fig. 2 of patient 1F) and in one patient (3M) a well-defined reduced uptake was identified and correlated anatomically to an abnormality on MRI scan. We did not identify any atypical clinical presentation or histology feature in 3M to account for the reduced uptake of18-F-DOPA on PET/CT scanning. One patient had diffuse uptake of 18-F-DOPA on PET/CT scan (8F). All children underwent pancreatic surgery, following which euglycaemia was achieved. In follow-up assessment, all children remained euglycaemic, suggesting that in 1–12 years of follow-up, recurrence of insulinoma was not observed.

Perioperative frozen section histology was carried out in all cases to confirm the site of the lesion and the completeness of excision. The histological diagnosis of insulinoma was confirmed in all cases. The lesions showed well-demarcated nodules of endocrine tissue without hyperplasia of the exocrine components (Fig. 3). There was a fibrous pseudocapsule at the perimeter of the lesion and the surrounding pancreatic tissue was compressed, but was otherwise normal. The neoplastic cells were spindle shaped and epithelioid with abundant eosinophilic cytoplasm and rounded or oval, regular nuclei (Fig. 3A, B and C of patient 3M). Two types of gross histology were seen, one which comprised sheets of uniform spindle-shaped cells with open nuclei with stippled chromatin (4F and 7F) and the others showing a trabecular pattern. Mitotic figures were very sparse. There was strong cytoplasmic staining of the tumour cells with antibodies to insulin and proinsulin. Apart from one patient (2M) in whom scattered glucagon and somatostatin-immunoreactive cells were seen, the lesions had no staining for glucagon, somatostatin or pancreatic polypeptide. There was no necrosis or haemorrhage and no infiltration of the pseudocapsule, blood vessels or lymphatics or of the surrounding pancreas.

Some variations were noted. In patient 5M, the lesion was non-encapsulated and poorly circumscribed with islands of normal pancreatic tissues within the lesion. Patient 3M had two disconnected lesions with a larger lesion in the uncinate process and a smaller different lesion in the tail of the pancreas, both of which were removed by partial pancreatectomy.

Two patients were positive for known MEN1 mutations (2M and 3M). Both are under regular review for evolving endocrinopaties associated with the MEN1
syndrome. Patient 2M was diagnosed with parathyroid adenoma 5 years after presentation with insulinoma, which was surgically removed. In patient 3M, no endocrinopathy has been identified till date.

Discussion

Insulinomas have the highest incidence in the fifth and sixth decades (2). Presentation during childhood is extremely rare. We have described a relatively large cohort of patients who presented during childhood with insulinoma in the UK over a 12-year period. Our case series shows that insulinomas can occur at a very young age and is a rare but important diagnosis in the investigation of children with HH. While CHI is the most common cause for persistent and recurrent hypoglycaemia in infancy (5), the possibility of insulinoma should be considered, especially in those with HH presenting beyond infancy.

The diagnosis of insulinoma in adults can be delayed, with only 20% of cases being diagnosed within a year of onset of symptoms (6). In comparison, children in our cohort with insulinoma also experienced symptoms of hypoglycaemia for a prolonged duration (an average of 10 months) before the diagnosis of HH was confirmed. Neuroglycopenic symptoms (with seizures and syncopal episodes) were frequent in this cohort, suggesting a greater severity at presentation, in contrast to adults with insulinoma.

In our cohort, all children were initially treated with diazoxide, but only four children were responsive (high doses of 10–20 mg/kg per day) and one was partially responsive. This observation is in contrast to the better response to diazoxide in adults, before surgery (7, 8, 9). Patients with GCK/GLUD1 mutation can present beyond infancy with insidious onset of hypoglycaemic episodes, which are usually responsive to diazoxide (10, 11). Clinical or biochemical evidence of protein sensitivity should prompt mutation analysis for GLUD1 (11). In our patients, the diagnosis of CHI was considered, but genetic investigations for GCK/GLUD1 were not carried out as children did not present with clinical characteristics suggestive of GCK/GLUD1. Nonetheless, it would be prudent to consider mutations in GCK/GLUD1 causing CHI before pursuing imaging investigations for the diagnosis of an insulinoma.

It is understood that neuroendocrine cells take up and retain 18F-DOPA in focal CHI (12, 13). Similar principles may apply to insulinoma, although the results of 18F-DOPA PET have been generally inconsistent in published adult cohorts (14, 15). In our cohort, the success
rate of $^{18}$F-DOPA PET/CT scan was 50% (2/4), which is inconsistent with a recent report in which insulinoma was localised in all three children who underwent $^{18}$F-DOPA PET/CT scan (16).

In our cohort, MRI alone localised pancreatic lesions in 88% (7/8) of patients. In adult studies of insulinoma, the utility of MRI scanning has been variable, with success rates varying between 30 and 85% (17, 18, 19), which could be attributable to the small tumour size at the time of diagnosis (17). Patient 5M, in whom MRI scan was non-confirmatory, had a tumour size similar to that in other children. Even though multiple modes of diagnostic techniques have been applied for preoperative localisation, none can be considered as gold standard. The intra-arterial calcium stimulation has been used variably in adults and children (16, 18). Endoscopic ultrasonography and radio-nucleotide scanning using radioactive tracers of octreotide have not been successful in children (16). Other modalities, such as spiral CT scans, intraoperative ultrasound (20, 21) and GLP1 receptor scintigraphy (22), need further evaluation in children. Based on our experience and evidence from the literature, we recommend MRI scan as a first line of investigation for insulinoma. Development of novel sequences including diffusion-weighted imaging and novel software programmes may further improve pre-operative localisation with MRI scan (17).

In our cohort, two patients were diagnosed with the MEN1 syndrome, one of whom developed a parathyroid adenoma later. In adults, the 20-year recurrence risk has been observed to be higher (21%) in patients with MEN1 than in those without MEN1 (7%) (2). In view of the small but distinct possibility of recurrence and the prospect of an evolving endocrinopathy, all patients in our cohort are being carefully followed up with suitable transition to adult endocrine services.

In one of the earliest descriptions, Mann et al. (1969) (23) summarised 39 published cases of insulinoma in children. From a historical perspective, although the entity of CHI had not been defined at the time; most cases (15/24) were in children older than 4 years and were therefore probably insulinosmas. In recent years, there has been a clear histopathological differentiation of insulinoma from CHI. Focal lesions (Fig. 3D, E and F) are characterised by the presence of a conglomeration of islet cells without a clear margin of demarcation with additional ductal components and the presence of insulin and glucagon staining. Focal lesions have large endocrine cells with large cytoplasm and large nuclei which are pleomorphic, irregular and angular in shape and >3–5 times the size of the nearby acinar nuclei (24). By contrast, insulinoma (Fig. 3A, B and C) is well localised with fibrous septa separating it from normal tissue with the absence of exocrine pancreatic components. Insulinoa is also characterised by abundance of insulin secreting cells with large nucleoli (with very little pleomorphism) and abundant eosinophilic cytoplasm arranged in a trabecular pattern or as sheets of uniform spindle-shaped cells (25). Mostly, there is an absence of glucagon-secreting cells, although immunohistochemical staining to glucagon, somatostatin and chromogranin has been previously reported in a proportion of patients with insulinoma (26). Similarly, one patient (2M) in our study had scattered glucagon and somatostatin immune-positive cells in the tumour.

**Conclusions**

We have described nine cases of insulinoma in children managed in two large cohorts over a 12-year period. The differential diagnosis of children presenting beyond infancy with HH should include insulinoma, even in those in early childhood. Based on our experience and availability of MRI in most centres, we recommend MRI scan as the first line of investigation of childhood insulinoma, with due consideration given to other imaging modalities as second-line investigations. All children with insulinoma should be carefully followed up for tumour recurrence and evolving endocrinopathy should be screened in those carrying MEN1 mutations.
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