A Diagnostic Challenge in the Management of Unlocalised Persistent Hyperinsulinaemic Hypoglycaemia of Infancy: A Case Report and Review of Literature

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Abstract

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is an uncommon condition that leads to hypoglycaemia in newborn or infancy. The responsible lesion can be either focal or diffuse within the pancreas. Being a rare disease entity in our locality, we describe our experience in managing an infant with focal PHHI that could not be localised by pre-operative investigations. Furthermore, a review of the literature is discussed.

Key words

Hyperinsulinism; Hypoglycaemia; Infant; Management

Introduction

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is an uncommon condition that leads to hypoglycaemia in newborn or infancy. The majority of cases are sporadic and the estimated incidence is 1 in 50,000 live births. Babies with neonatal type are usually large for gestational age and frequently present with symptomatic hypoglycaemia soon after birth, although late presentation is sometimes encountered in the infantile type. The diagnosis is suggested by the findings of high serum insulin level and low ketone level at the time of hypoglycaemia. Delayed diagnosis or inadequate treatment can lead to permanent neurological impairment. Various radiological and biochemical tests have been introduced to localise the tumour. The condition can be treated with medical therapy but if it fails or is inadequate, pancreatectomy can be offered to prevent subsequent complications of hypoglycaemia, especially neurodevelopmental impairment.

Case Summary

Our patient is a 4-month-old boy who is the second child in the family. His mother had impaired glucose tolerance during pregnancy and was managed by diet control only. Antenatal scanning was otherwise normal.

He was born at full term by normal vaginal delivery. Birth weight was 3.54 kg. The Apgar scores were 9 and 10 at 1 minute and 5 minutes respectively. At 25 hours of life, he developed bradycardia and desaturation which required admission to the intensive care unit. Urgent blood tests showed severe hypoglycaemia with a glucose level of 0.8 mmol/L, ketone was negative and he was not acidicotic. He was managed with intravenous glucose replacement and blood sugar was initially stabilised. However, he remained...
dependent on intravenous glucose supplement despite full enteral feeding. Subsequent tests revealed a persistently high fasting insulin level of 32 mIU/L. The diagnosis of hyperinsulinaemic hypoglycaemia was thus made. After he failed the first line treatment, octreotide injections and intravenous glucose were employed. At the same time, MRI of the pancreas was performed in an attempt to locate the possible focal adenoma. However, no pancreatic lesion could be identified in the scan. Subsequently, PET-CT scan (Figure 1a), Octreotide isotope scan (Figure 1b) were carried out and all these investigations failed to identify a focal pancreatic lesion. Advanced technique such as selective pancreatic arterial calcium stimulation with hepatic vein insulin sampling and transhepatic portal venous insulin sampling were not carried out due to limited experience and associated surgical risk. Although genetic screening can help to differentiate between focal or diffuse disease, it would not aid in surgical planning since there is no suspicious location in preoperative imaging. Furthermore, it is a time consuming investigation.

Over the next few weeks, his condition became more dependent on regular octreotide injection with dosage gradually increased. At last, a 98% subtotal pancreatectomy was decided. At operation, a normal sized pancreas was found with no obvious focal lesion seen. We did not perform intra-operative frozen section because it was difficult to determine the location of sectioning given all pre-operative imaging were negative. Besides, it will not help in guiding the extent of resection even if a pathology is identified in certain biopsy site. Oral feeding was resumed on day 5 post-operation with full feeding established on day 10. His blood sugar level was optimal under insulin infusion at the early stage and he became insulin independent at subsequent follow up. Neurodevelopment was appropriate for age upon follow up at 15 months.

Subsequent pathological examination of the resected specimen showed a focus of adenomatous hyperplasia measuring 4 mm in size at the body of the pancreas near the head side. It stained positively for insulin, with very occasional islet cells containing enlarged nuclei. The overall features were consistent with focal hyperinsulinism (Figure 2).

**Discussion**

Hypoglycaemia in infancy usually results from inappropriate over-secretion of insulin, although certain metabolic diseases have recently been reported to be the responsible causes. While nesidioblastosis was the old term to describe this condition, persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is now more commonly used. It can be sporadic or familial. Since 1989, 2 different forms of pancreatic lesion causing PHHI have been described. Diffuse PHHI accounts for 70% of the cases and focal PHHI accounts for the remaining 30% in sporadic cases. They usually have similar clinical presentation although subsequent management usually differs.

![Figure 1](image_url)  
**Figure 1** Imaging modalities used to determine the location of focal pancreatic lesion in persistent hyperinsulinaemic hypoglycaemia of infancy. (a) Axial PET-CT scan taken at the level of pancreas. (b) Octreotide isotope scan. No focal lesion can be detected in both scans.
With the advances in genetic studies, a number of genetic mutations have been shown to be associated with this condition. Nonetheless, PHHI remains a challenging and difficult disorder to manage and often results in permanent neurological impairment. Early diagnosis and adequate treatment are the keys to management. Diagnosis is made on both clinical and biochemical parameters. Levitt-Katz et al. defined hyperinsulinism of infancy as persistently inappropriate insulin secretion during hypoglycaemia and associated with low circulating levels of ketones bodies. While these are the usual biochemical findings, the clinical presentations can vary. About 50 to 68% patients present with symptomatic hypoglycaemia in the first week of life and some present as late as 8 months. Seizure is another common presentation. Very occasionally, the condition can present with sudden cardiac arrest due to severe hypoglycaemia. Classically, the child that suffers from this condition is usually large for gestational age although it is not absolute. If this condition is not recognised at an early stage, neurodevelopment can be impaired. This variation in clinical presentation may be attributable to the heterogeneity of mutation and genetic expression.

Having established the diagnosis of PHHI, the next step will be localisation in order to facilitate surgical intervention.

Figure 2  (a) Photomicrograph of H&E section of pancreas showing a focus of adenomatous hyperplasia consisting of anastomosing trabeculae, 2-3 cell thick. The cells display uniform small round nuclei and abundant eosinophilic cytoplasm (magnification x 25). (b) Immunohistochemical stains for insulin (with biotin blocking) show positive staining for this adenomatous focus (left panel). The right panel shows in contrast the relative size of positive stained islet cells (magnification x 25).
since it is the best treatment if a focal lesion is detected. Besides the usual imaging techniques, a more specific investigation of choice for this condition is selective sampling of pancreatic vein, first described by Brunelle in 1989. In modern days, laparoscopy is another useful tool in helping to locate the tumour. Nevertheless, they all have limitation in sensitivity especially when small lesion is encountered. More recently, \(^{18}\text{F}-\text{fluoro-L-dihydroxyphenylalanine} \left(\text{[^{18}F]DOPA}\right)\) positron emission tomography (PET) scans have been advocated for localising focal lesion in congenital hyperinsulinism. This is believed that the tumor can take up amino acid precursors, such as L-dihydroxyphenylalanine, and decarboxylate them to dopamine. It has high accuracy and is useful in guiding surgical excision in a recent study. Unfortunately, this is not available yet during the management of the child. After all, our patient gives a good illustration of a focal lesion that has eluded all pre-operative investigations.

Management aims at maintaining normoglycaemia and preventing neurodevelopmental impairment. For acute hypoglycaemia, intravenous glucose infusion is usually needed. However, this cannot be employed as long term treatment. Diazoxide and octreotide, which can inhibit insulin secretion, are specific therapies for infants with PHHI. Nonetheless, there are patients who are resistant to this drug, as they do not possess the specific receptor channel (β-cell) \(K_{\text{ATP}}\) and \(K_{\text{PHHI}}\) activity. If medical therapies fail, surgery should be considered early. There has been report comparing the outcomes of medical therapy alone with pancreatic resection. Despite the fact that patients who received surgery usually had more severe disease, their outcome was better than those who were treated medically. It was concluded in that study that medically treated patients had a higher incidence of neurodevelopmental deficit compared with the surgically treated patients. However, the outcome between medical and surgical treatment is still debatable.

The form of surgery varies with the pre-operative findings, and the extent of pancreatectomy remains controversial. If a focal lesion can be identified, local resection should be considered. On the other hand, 95% near total pancreatectomy has been the treatment of choice for diffuse or unlocalised PHHI, taking into account the risk of recurrence and surgical complication. The major complication of pancreatectomy is the development of diabetic mellitus. The reported incidence of insulin-dependent diabetes after pancreatectomy was conflicting between different centers, which may be due to the different definitions of the extent of surgery.

In summary, we present our experience in managing a child who suffered from PHHI. The major challenge in this patient was the difficulty in diagnosing the focal lesion as all the pre-operative investigations could not locate the lesion. This dilemma here was thus the extent of surgery. We finally carried out a 98% near-total pancreatectomy because we believed the recurrence rate of hypoglycaemia would be lower, and that re-operation would be more difficult and carry a high risk of complications. The discovery of a focal lesion here meant that we had performed excessive resection for our patient. Despite this, he made an excellent recovery and blood glucose was well controlled without insulin injection up to present moment. We look forward to the long term outcome of this child.

References


