Nesidioblastosis : A Review of Anaesthetic Implications : Case Report = مراجعة و تقييم آثار مرض نسيديوبلاستوسيس على التخدير

Article *in* Sudan Medical Journal · December 2016

DOI: 10.12816/0033262

CITATIONS
0

READS
136

1 author:

Hadab Ahmed Mohamed
University of Khartoum
22 PUBLICATIONS **17** CITATIONS

SEE PROFILE

Sudan Medical Journal
المجله الطبيه السودانيه

Sudan Med J 2016 December;52(3):140-145

Case Report

Nesidioblastosis, a review of anaesthetic implications

Hadab A Mohamed, MD

Faculty of Medicine, University of Khartoum

مراجعة وتقييم أثار مرض نسيديوبلاستوسيسعلى التخدير

د. هداب أحمد محمد، دكتوراه تخدير-جامعة الخرطوم
استاذ مشارك، كلية الطب جامعة الخرطوم

الخلاصة:
هذا التقرير عن طفل حديث الولاده عانى من مرض نسيديوبلاستوسيس واجريت له جراحة لإزالة 90% من غدة البنكرياس تحت التخدير العام. الغرض من هذا التقرير هو تنوير وتمليك القارئ بالمعلومات الاساسية عن هذا المرض النادر المهدد للحياة وتأثيراته المحتملة على التخدير.
عرض الطفل لاول مره على اخصائى الاطفال لمعاناته من نوبات صرع متكررة ونقص دائم فى مستوى السكر بالدم وتمت معالجته حينها بالحقن الوريدى لمحلول السكر 10% وعقار الجلوكاقون والإستيرويد وأدوية لمعالجة الصرع. خضع الطفل بعدها لعملية إزالة 90% من غدة البنكرياس تحت التخدير العام بعد ان شُخص بانه يعانى من مرض نسيديوبلاستوسيس. تم قياس مستوى السكر فى الدم بصورة منتظمة اثناء العملية وبعدهاوقد لوحظ بانه عانى من بعض نوبات إرتفاع سكر الدم بعد العملية وتم معالجتها بحقن عقار الإنسلين. أفاق الطفل من التخدير بدون مضاعفات وتم تحويله لغرفة العناية المكثفة لمزيد من المراقبة ولاحقا تم تخريجه الى المنزل بصحة جيدة وبدون المعاناة من نقص السكر او نوبات الصرع.

Summary
This is a case report about an infant who presented with nesidioblastosis and underwent 90% pancreatectomy under general anaesthesia. The report aims at highlighting the basic information and anaesthetic implications of a rare, yet life threatening condition. The infant presented with repeated convulsions and persistent hypoglycaemia, and was treated with 10% dextrose infusions, glucagon, steroids and anticonvulsants. Subtotal pancreatectomy was performed after reaching the diagnosis of nesidioblastosis. Blood glucose was regularly monitored during the intra and postoperative periods where the infant had few episodes of hyperglycaemia following subtotal pancreatectomy but was maintained euglycaemic by using insulin. Recovery from anaesthesia was smooth and the infant was referred to the ICU, and later discharged home, free of convulsions and hypoglycaemia.

Keywords: Anaesthesia, nesidioblastosis, insulinoma, hypoglycaemia, convulsions, drug therapy, pancreatectomy, newborn.

Corresponding author
Hadab A Mohamed
Email:hadabadarob@gmail.com

Introduction

Nesidioblastosis of infants, and its histological equivalent in adult's noninsulinoma pancreatogenous hypoglycaemic syndrome (NIPHS), are rare neuroendocrine causes of hyperinsulinaemic hypoglycaemia. The condition is characterized by pancreatic hyperplasia due to new generation of excess number of islet cells arising from the exocrine pancreatic ductal epithelium. The excess number of islet cells results in increased secretion of insulin and persistent hypoglycaemia.

Insulinoma is the major neuroendocrine cause of hyperinsulinaemic hypoglycaemia while nesidioblastosis and NIPHS are relatively rare.

In comparison to pancreatic hyperplasia seen with nesidioblastosis, an insulinoma is caused by tumour arising mainly from pancreatic islet cells that produce excessive amounts of insulin.

The distinction between the two conditions may be difficult as the clinical presentation may be similar. While hypoglycaemia is mainly persistent and usually present postprandially with nesidioblastosis, an episodic fasting hypoglycaemia is common with insulinoma. Although equivocal, tumour

localization studies, e.g. CT scan, ultrasound and insulin stimulation studies, may help to distinguished insulinoma from nesidio-blastosis, but the exact diagnosis is histopathological. These studies may reveal a focal abnormality in insulinoma while only showing a diffuse hyperplasia of the pancreas on imaging cases with nesidioblastosis.

Neonatal nesidioblastosis was first described by George F Laidlaw in 1938[(1)]. Adult onset nesidioblastosis (NIPHS), which was first described in 1975[(2)], is commonly associated with gastric bypass surgery or drug induced hypoglycaemia. These conditions, if not treated early, may lead to irreversible brain damage and death. Although drug therapy is an option, surgical resection of the pancreas remains the only definitive treatment.

Case report

A 9 days old, 3.5 kg male baby, presented with refractory convulsions without history of any precipitants e.g. febrile illness. The baby was the outcome of a non-complicated vaginal delivery from a non-diabetic mother.

The clinical examination revealed no systemic abnormalities.

A blood sugar of 26 mg/dL was the only abnormality detected on doing routine investigations (CBC, urine analysis, urea, creatinine, electrolytes and blood sugar). An infusion of 10% glucose was started together with IV phenytoin (20 mg/kg loading followed by 3 mg/kg/dose twice daily) and cefuroxime (150 mg/kg/day).The child was active and normally feeding when free of convulsion. Serial blood sugar measurements in the range between 17 to 33mg/dL, while the baby was off glucose, raised the suspicion of nesidioblastosis. Accordingly, CT brain, abdominal ultrasound and lumbar puncture were then performed to reveal a moderately enlarged pancreas. A positive glycaemic response to 0.1 mg/kg IM glucagon confirmed the diagnosis, which was further supported by failure to control hypoglycaemia and convulsions despite the steady increases in the rate of glucose infusion. Other diagnostic investigations, such as serum insulin, C-peptide and proinsulin levels, were not available in our country when the patient presented for the first time in 2004. A subtotal pancreatectomy was then planned.

The preoperative investigations were as follows: Hb 13.2 g/dL, PCV 40%,TWBCs $4X10^9$/L, RBS 105 mg/dL, BUN 5 mg/dL, Na^+ 129 meq/ L, K^+ 3.5 meq/L and Ca^{++}9.5 mg/L.

The baby arrived to the operating theatre with the 10% dextrose infusion flowing. A fasting blood sugar sample prior to induction of anaesthesia was 106 mg/dL. Standard monitoring was applied (Pulse oximeter, BP, ECG, temperature, urinary catheter and pericordial stethoscope) and the infant was then premedicated with an IV0.02 mg/kg atropine (i.e. 0.7 mg) prior to induction with halothane in O_2. A 3 millimeter internal diameter endotracheal tube was inserted at deep level of anaesthesia, aided with the administration of 2 mg/kg suxamethonium IV. Anaesthesia was then maintained with halothane in O_2 and N_2O and muscle relaxation was maintained with pancuronium 0.1 mg/kg initially followed by intermittent doses (0.02 mg). Blood sugar was measured every 15 minutes using a glucometer and the rate of infused dextrose was scaled accordingly. The blood sugar was observed to be more than 300 mg/dL for one hour following 90% pancreatectomy; accordingly the 10% glucose infusion was replaced with5% dextrose solution. The intraoperative blood loss was estimated to be 60 ml and this was replaced promptly. At the end of the surgery, which lasted about one and half hours, the infant was rewarmed and reversed from muscle relaxants following good spontaneous attempts of breathing, using atropine 0.02 mg/kg and neostigmine 0.05 mg/kg IV and was shifted to the ICU department for further monitoring.

In the ICU, no convulsions were noted but the first three readings of blood sugar were in the range of 270 to 300 mg/dL. Accordingly, the rate of dextrose infusion was reduced and intermittent insulin doses were given. Blood sugar returned to normal values three hours later. The blood sugar was maintained at the upper limit of normal during the first three postoperative days after which the infant

started to resume his breast oral feeds. The histopathology revealed normal pancreatic acini with increase in the number of islets of Langerhans. Between the acini were seen clusters of islet cells, suggestive of nesidioblastosis.

On discharge, at the tenth postoperative day, the patient was free of hypoglycaemia and convulsions, but was prescribed an anticonvulsant and was asked to monitor blood sugar daily till the next appointment with the neonatologist.

Discussion

Nesidioblastosis is a rare neuroendocrine disorder of infants, with focal or diffuse adenomatous hyperplasia of the pancreatic islet cells of Langerhans that produce excessive amounts of insulin. Adult onset hyperinsulinaemic hypoglycaemia, with beta cell hypertrophy, has been reported following Roux-en-Y gastric bypass surgery and hypoglycaemic drug administration.

Insulinomas a neuroendocrine tumour deriving mainly from pancreatic islet cells that produce excessive amounts of insulin. It was first described by Harris in 1924[3]. Pancreatic tumour as a cause of insulinoma can be benign (90%) or malignant (usually metastasize to the liver). 10% of insulinomas are multiple, particularly if the condition is part of multiple endocrine neoplasia type 1 syndrome (MEN 1).

Both insulin and C-peptide, together with their precursor proinsulin, are secreted in large quantities in the circulation, resulting in periodic (insulinoma) or persistent (nesidioblastosis) hypoglycaemia, with the consequent neurological presentation.

The clinical presentation of either cause of hypoglycaemia may be non-specific, remain unrecognized and occasionally misdiagnosed. There are reports of long-standing insulinoma with marked adaptation to extreme hypoglycaemia with near-normal plasma insulin levels[4]. In our case, the infant presented with a history of convulsion from the third day onwards. At the time of presentation, blood sugar was 26 mg/dL and the baby was treated with 10% dextrose infusions and I.M. glucagon (0.1 mg/kg) to control hypoglycaemic convulsions.

Insulinoma may affect all age groups, but is more common in middle age with slight female predominance (The male to female ratio is 2:3).

The hypoglycaemia resulting from insulinoma is usually precipitated by ingestion of alcohol, fasting, or prolonged exercise, but is not physiological, as the excess secretion continues despite the hypoglycaemia. Patients usually tend to overeat in an attempt to relive symptoms and hence get overweight.

In patients with insulinoma, hypoglycaemic symptoms appear when the plasma glucose falls below 50 mg/dL and, if hypoglycaemia persists, neuroglycopenic symptoms appear at glucose levels below 45 mg/dL. These central nervous system symptoms occur due to neuronal deprivation of glucose that leads to central nervous system stimulation. Therefore, symptoms can be divided into either adrenergic, resulting from the catecholaminergic response to hypoglycaemia (anxiety, tremor, nausea, hunger, sweating and palpitations) or neuroglycopenic (headache, lethargy, dizziness, diplopia, blurred vision, amnesia, seizures and, in more severe cases, confusion or coma). Initial seizure may be self-limiting because of a sympathetically mediated insulin antagonism, but as the disease progresses, adverse neurological consequences of low blood glucose will follow.

The presence of Whipple's triad is pathognomonic[5]:

1. A history of repeated attacks of hypoglycaemia,
2. Serum blood glucose levels less than 50 mg/100 ml during a symptomatic period.
3. Relief of symptoms by glucose administration.

Hypoglycaemia in term infants is defined as a blood sugar less than 30 mg/dL in the first 3 days and 40 mg/dL thereafter[6]. On the first presentation our infant showed a blood sugar much below this value (26 mg/dL), with neuroglycopenic presentation (convulsions).

Failure of endogenous insulin

secretion to be suppressed in the presence of hypoglycaemia is the hallmark of insulinoma. The Endocrine Society Clinical Guideline recommended the following diagnostic criteria[7]:

1. Plasma concentrations of glucose less than 55 mg/dL (3.0 mmol/L)
2. Insulin of at least 3.0 μU/mL (18 pmol/L)
3. C-peptide of at least 0.6 ng/mL (0.2 nmol/L)
4. Proinsulin of at least 5.0 pmol/L

Trans-abdominal or intraoperative ultra-sonography, CT scan or MRI and insulin stimulation tests are available tools to localize the tumour.

In this case, we had a high index of suspicion of nesidioblastosis despite not doing insulin, C-peptide and proinsulin levels, as these investigations were not available in our country at that time. The diagnosis of nesidioblastosis was assumed depending on the persistent hypoglycaemia, convulsions, response to dextrose infusion, hypoglycaemia while the baby was off glucose, the positive glycaemic response to 0.1 mg/kg IM glucagon, negative CT brain, negative CSF study and abdominal ultrasound that revealed moderately enlarged pancreas. The diagnosis of nesidioblastosis was later confirmed histologically.

Solitary tumours of insulinoma are surgically resectable. If widespread metastasis is present, palliative treatment should be initiated.

Medical treatment is used in the preoperative period and as a sole treatment to relieve the burden of hypoglycaemic symptoms if widespread metastasis is present or if the patient is deemed surgically unfit.

The medical treatment consists of:

- Dietary modification: Frequent small diets to avoid symptoms of hypoglycaemia.
- Diazoxide: Reduces insulin secretion.
- Hydrochlorothiazide: Counteracts the oedema and hyperkalaemia secondary to diazoxide and potentates its hyperglycaemic effect.
- Somatostatin analogue octreotide: Prevent hypoglycaemia.
- Glucagon: Suppresses insulin secretion.
- Phenytoin: In addition to its anticonvulsant property, it inhibits the release of insulin from β-cells.
- Glucocorticoids: Suppress insulin-mediated glucose uptake and augment glucose release.

Sizonekis[8] observed remission on 60% cases where diazoxide therapy was continued for 4-6 years. The same study documented an increase in blood glucose level from 19.8 to 109 mg/dL following glucagon. Only a minimal increase in blood glucose level (from 32.4 to 41.4%) was observed with hydrocortisone. In low resource areas the un-availability of some of these drugs may limit the selection or tip the balance toward surgical management. Fonkalrud[9] recommended early pancreatic resection to obviate the occurrence of mental retardation resulting from frequent hypoglycaemic convulsions.

Surgical resection is the only curative procedure for nesidioblastosis and benign insulinomas, with 90% cure rate.

Glucagon was used initially in this infant to manage the intractable hypoglycaemia that does not respond well to dextrose infusion. Subtotal pancreatectomy was then decided.

In cases of insulinoma, subtotal pancreatectomy with enucleation of tumors from the pancreatic head and uncinate processes is often recommended over simple enucleation because of frequent prevalence of multiple tumors in patients with MEN1.

Anaesthetic management

Maintenance of adequate glycaemic control during the preoperative, operative and postoperative periods is the main goal of anaesthetic management of insulinoma and nesidioblastosis.

These patients can easily go into hypoglycaemic attacks if kept fasting for long periods, during surgical manipulation of the pancreas or if glucose infusion is withheld.

A thorough preoperative assessment, with documentation of all preexisting neurologic damage, which has occurred as a result of previous hypoglycaemic episodes, is mandatory. Apprehensive adults may be premedicated with anxiolytics.

An intravenous line should be inserted preoperatively and connected to 10% dextrose

in water to maintain plasma glucose in the range of 100 to150 mg/dL[10]. Drugs inhibiting the release of insulin should be discontinued to attenuate their exaggerated postoperative hyperglycaemic effects. Glucagon should be available in the theatre for emergency use.

The main intraoperative concern is to maintain glycaemic control, namely prevention of intraoperative hypoglycaemic episodes. Serious hypoglycaemia should be expected upon tumor manipulation, while hyperglycaemia is inevitable following tumor removal. Signs of both hypo and hyperglycaemia may be masked by general anaesthesia, hypovolaemia or by the autonomic response to surgical stimulation. The only certain sign of hypoglycaemia is a low blood glucose level. Accordingly, repeated monitoring of blood sugar is mandatory.

The 10% dextrose infusion should be terminated half an hour prior to completion of pancreatic resection in order to reduce the severity of the postoperative hyperglycaemic response.

General anaesthesia results in increased blood glucose concentrations related to increased circulating catecholamines, cortisol and glucagon levels. Although some anaesthetic agents can influence glucose and insulin homeostasis, there is no specific consensus regarding the selection of anaesthetic agents in patients undergoing pancreatectomy. In general, the main aim of anaesthetic management is to prevent hypoglycaemia until pancreatic resection is achieved and to control rebound hyperglycaemia encountered soon after resection.

The selected anaesthetic agents should decrease the cerebral metabolic rate for oxygen. In this respect, propofol and thiopentone are more superior to ketamine for induction of anaesthesia. Inhalation induction was used in this infant as all agents also decrease cerebral metabolic rate to oxygen. In addition, the anaesthetic agents used should have a beneficial effect on glucose and insulin homeostasis.

Enflurane and halothane have the beneficial effect of inhibiting pancreatic insulin release; this effect being more pronounced with enflurane.

During surgery, opioid may be used to supplement analgesia and glucocorticoids, that stimulate glycogenolysis by insulin antagonism, may be administered.

In addition to standard anaesthetic monitoring, repeated assessment and maintenance of blood glucose values are essential. Intraoperative blood glucose assessment is essential for detection and prevention of the deleterious effects of hypoglycaemic episodes encountered upon pancreatic manipulations. Accordingly, it is essential to regularly monitor blood glucose level prior to induction of anaesthesia and then every 15-30 minutes till discharge from the recovery room.

The first three postoperative readings of blood sugar in this case were in the range of 270 to 300 mg/dL. Accordingly the rate of dextrose infusion was reduced and intermittent insulin doses were prescribed

Usually, the blood glucose rapidly rises in the immediate postoperative period. This could possibly be attributed to catecholamine release due to stress of surgery, residual glycaemic effect of I.M. glucagon administered the previous night or hydrocortisone given at induction of anaesthesia.

This may take several hours to several days during which strict monitoring of blood glucose should be instituted and small doses of insulin or glucose may be needed to assure euglycaemia. Postoperative analgesia is mandatory to alleviate the painful surgical incision.

A long term follow-up would be necessary to ensure that the baby remains euglycaemic and to assess for neurological development.

In conclusion, Nesidioblastosis is a neonatal neuroendocrine disorder characterized by hyperplasia of the pancreatic islet cells that produce excessive amounts of insulin, producing persistent hypoglycaemia. Clinical, biochemical and imaging tests are required to differentiate the condition from insulinoma. Subtotal resection of the pancreas is the definitive treatment. A large swing in blood

sugar is usually observed during manipulation and following resection of pancreas. Accordingly, peri and postoperative euglycaemia should be maintained by regular blood sugar monitoring and administration of glucose or insulin as appropriate.

The anaesthetic management should aim at decreasing cerebral metabolic rate to oxygen, providing beneficial influence on glucose and insulin homeostasis and maintaining euglycaemia through regular assessment and maintenance of blood glucose and avoidance of excessive fasting.

References

1. Laidlaw GF. Nesidioblastoma, the islet tumor of the pancreas. Am J Pathol 1938; 14:125-34.
2. Albers N, Löhr M, Bogner U, Loy V, Klöppel G. Nesidioblastosis of the pancreas in an adult with persistent hyperinsulinaemichypoglycemia. Am J ClinPathol 1989;91:336-40.
3. Harris S. Hyperinsulinism and dysinsulinism. JAMA 1924;83:729-33.
4. 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.
5. Pulver JJ, Cullen BF, Miller DR, Valenta LJ. Use of the artificial beta cell during anesthesia for surgical removal of an insulinoma. Anesth and Analg 1980;59(12):950-2.
6. La Franchi, Stephen MD. Hypoglycaemia of infancy and childhood. Paediatric Clinics of North America 1987;34(4): 961-82.
7. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J ClinEndocrinolMetab 2009;94:709-28.
8. Pierre SC. Hypoglycaemia paediatric endocrinology physiology, patho-physiology and clinical aspects. 2nd edition. Edited by Bertrand J, Rappaport R, Sizonenko P. USA:Williams and Wilkins;1993.p.583-97.
9. Fonkaisrud Eric, Trout Hugh, Lippe Barbara. Idiopathic hypoglycaemia in infancy: surgical management. Arch Surg 1974;108:801-4.
10. Muir JJ, Endres SM, Offord K, van Heerden JA, Tinker JH. Glucose management in patients undergoing operation for insulinoma removal. Anaesthesiology 1983;59:371-5.