

CASE REPORT

Non islet cell tumor hypoglycaemia in a metastatic Leydig cell tumor

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Abstract

Non islet cell tumour hypoglycaemia (NICTH) is a rare cause of hypoglycaemia associated with malignancy and can be considered as a paraneoplastic syndrome. The hormonal factor associated with this condition is big IGF II, which exerts negative feedback effect and decreases the production of growth hormone and insulin. Due to low growth hormone levels, hepatic production of IGFBP 3 (the main binding protein of IGF II) is impaired. Excess free big IGF II is thus available for binding with insulin receptors to cause hypoglycaemia. Treatment options are either surgical removal of the tumour, administration of growth hormone, glucocorticoids or combination of treatments. A case of metastatic Leydig cell tumour causing NICTH has been discussed and the mechanism of NICTH hypoglycaemia and the treatment is outlined.

Non Islet Cell tumour induced hypoglycaemia (NICTH) is a rare cause of recurrent fasting hypoglycaemia caused by production of Insulin like Growth Factor II (IGF II) by the tumour [1]. Various tumour types have been associated with this syndrome including carcinoma and sarcoma, but most often it occurs secondary to a large tumour of mesenchymal origin like mesothelioma, fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma and hemangiopericytoma [2]. In this paper we discuss a case of NICTH associated with a malignant Leydig cell tumour.

Case Report

A 75-year-old man was diagnosed with Leydig cell tumour of his right testicle in October 1999. The tumour was malignant from the onset with wide spread vascular invasion. CT scan of abdomen showed widespread metastases to inguinal and pelvic lymph nodes. He had palliative radiotherapy to his right groin in March 2000 without any significant reduction in the tumour bulk. Palliative chemotherapy was declined by him due to concerns regarding side effects. Metastatic lymphadenopathy progressed in the inguinal, para aortic and retroperitoneal

regions causing obstructive uropathy. Renal function deteriorated and a CT scan of his abdomen in December 2000 showed hydronephrosis of right kidney due to obstruction of the right ureter by the hugely enlarged retroperitoneal lymph nodes. It was planned to stent the obstruction in his right kidney but just prior to this he became acutely unwell.

He was found unconscious by his wife at home in January 2001. He was severely hypoglycaemic and capillary blood glucose was unrecordable on the glucometer by paramedics and he was resuscitated with 100 ml of 50% dextrose and transferred to our hospital. On examination, he was alert, orientated and looked cachectic. His pulse was 70 beats per minute in sinus rhythm, blood pressure 140/70 mm Hg and afebrile. Heart sounds were normal and chest clear and no focal neurological signs. Abdominal examination showed a large, irregular, hard mass of lymph nodes (confirmed on CT scan in December 2000). Laboratory results showed; haemoglobin of 9.3 gm/dl, white blood cell count 16 000/dl, platelet 534 000/dl, ESR 42mm/hour, sodium 138 mmol/L, potassium 4.2 mmol/L, urea 12.6 mmol/L and creatinine 146 mmol/L, glucose 0.7 mmol/l. Liver function tests were deranged with mild elevation of liver enzymes and low protein.

Random cortisol 928 nmol/L, making adrenocortical insufficiency unlikely. Serum insulin was <3 mmol/L and C peptide was undetectable. Insulin like Growth Factor I (IGF I) was 9 nmol/L (5–22 nmol/L) and IGF II was extremely high at 118.2 nmol/L. The molar ratio of IGF II and IGF I was 13.1, and any value of IGF II AND IGF I ratio greater than 10 is regarded highly significant. [16]. Growth hormone was 2 mIU/L.

He was treated with continuous intravenous 10% dextrose (1 litre every 6–8 hours) along with intravenous dexamethasone 2 mg four times a day. His general condition improved; nevertheless he had hypoglycaemia on stopping the dextrose infusion. He was given subcutaneous human recombinant growth hormone, starting at 8 mU and gradually increased to 32 mU per day. Hypoglycaemia resolved gradually and dextrose infusion was discontinued 4 days after starting growth hormone. He was too unwell to have surgical debulking of the metastatic tumour mass. Following a detailed discussion with the patient and his family, a conservative approach was planned. Renal function progressively deteriorated and he died ten days after his admission.

Discussion

The frequency of diagnosis of new cases of NICTH has increased in the recent years due to increased awareness and availability of appropriate tests related to hypoglycaemia [3]. Diagnosis is characterised by constant hypoglycaemia, suppressed serum insulin, C peptide and growth hormone levels. Serum IGF I is low but IGF II may be normal or elevated [4]. These criteria were fulfilled in our patient.

The development of hypoglycaemia has been linked to secretion of IGF II by the tumour and circulating IGF binding protein (IGFBP) [5]. A large tumour bulk is necessary to make sufficient IGF II to cause the syndrome [6]. Increased expression of IGF II genes have been reported in various cancers [7]. Human chromosome 11p 15 contains the imprinted IGF II gene and also tumour suppressor genes H19 and P57 KIP2. In NICTH, the IGF II gene product is over expressed. There is loss of imprinting of the IGF II gene, leading to abnormal gene expression and decreased expressions of H19 and P57 KIP2 genes (tumour suppressor genes) [6]. IGF II derived from tumour cells represents a truncated form of pro IGF II, with molecular weight ranging from 10 to 20 kD, instead of fully processed 7.4 kD peptide form [8]. IGF II binds with IGFBP3 forming a 150 kD ternary complex which consists of IGF II, IGFBP 3 and an acid labile (a) subunit (ALS). Normally, this amounts to

70–80% of circulating IGF II and a small percentage of IGF II is bound in a binary complex with IGFBP 3, which is less than 60kD. In NICTH, IGFBP 3 and ALS production is reduced and the ability to form the ternary complex is impaired [9]. As a consequence tumour derived IGF II appears in smaller binary complex of IGF II-IGFBP3. This complex has an increased clearance rate compared to the 150kD complex. The binary complex can cross the interstitial space and therefore, has increased bioavailability in binding with the insulin receptors.

IGFBP3 is produced by the liver under the influence of growth hormone [10]. Initially IGF II secreted by the tumour is bound to the IGF binding protein in the plasma. Due to high turnover rate of the tumour a huge amount of tumour derived IGF II is available in the circulation. This produces a negative feedback on the pituitary to suppress growth hormone secretion and therefore hepatic production of IGFBP 3 is impaired. Tumour derived IGF II forms the binary complex and binds to the insulin receptors to cause hypoglycaemia.

Surgical intervention by removing the tumour bulk causes a decline in tumour derived IGF II, thus relieving hypoglycaemia [11]. Other therapeutic options prior to surgery include glucagon, human recombinant growth hormone (hGH) and glucocorticoids [12]. The response of NICTH to hGH causes immediate relief of hypoglycaemia [13]. With hGH treatment serum concentrations of immunoreactive IGFII, IGF I and IGFBP 3 rises [14]. It is speculated that increased availability of both IGFBP 3 and ALS might promote formation of the high molecular weight ternary complex and consequently control the insulin like activity of the circulating IGF II [11]. Glucocorticoid treatment normalises the binding protein profiles [15]. A possible explanation is that the glucocorticoid induces enzymes that normally convert pro IGF II into mature IGF II, thus suppressing big IGF derived from the tumour. Glucocorticoids also increase serum acid labile subunit level and restore the formation of ternary complex and thus relieving hypoglycaemia. Where surgical intervention is not possible, treatments with hGH or glucocorticoids are both effective and beneficial. In cases of intractable hypoglycaemia as seen in our case, a combination of both therapies may be tried.

Leydig cell tumour accounts for only 1–3% of all testicular neoplasm. They present as testicular lumps and mostly benign but 10% are malignant. Our patient presented with testicular lump associated with extensive metastasis of intra abdominal and inguinal lymph nodes. Studies have been done on response of different hormones and intra cellular mediators on cultured Leydig tumour cells. During

our literature search we found a case report of Cushing Syndrome presenting as a feature of metastasis of Leydig cell tumour [13].

In summary NICTH is a paraneoplastic manifestation of a variety of tumours. Although the condition can be fatal, it is amenable to treatment using growth hormone, glucagon and steroids whilst awaiting removal of tumour bulk by surgery. This is the first reported case of metastatic Leydig Cell tumour presenting as NICTH and we have highlighted the pathophysiological process underlying this.

References

- [1] Zapf J. Role of Insulin like Growth factors (IGF II) and IGF binding proteins in extrapancreatic tumour hypoglycaemia. *Journal of Internal Medicine* 1993;234:543–52.
- [2] Zapf J. Insulin like growth factors binding protein and tumour hypoglycaemia. *Trends in Endocrinology and Metabolism* 1995;6:37–42.
- [3] Marks V, Teale JD. Investigation of Hypoglycaemia. *Clinical endocrinology* 1996;44:133–6.
- [4] Marks V, Teale JD. Inappropriately elevated plasma insulin like Growth Factor II in relation to suppressed insulin like growth factor I in the diagnosis of Non Islet cell tumour. Hypoglycaemia *Clinical Endocrinology* 1990;33:87–8.
- [5] Baxter RC. The role of insulin like growth factors and their binding proteins in tumour hypoglycaemia. *Hormone Research* 1996;46:195–201.
- [6] Bertherat J, Logie A, Gicquel C, Mourrieras F, Luton JP, Le Bouc Y. Alteration of 11p15 imprint region s and the IGF system in a case of recurrent non-islet tumour hypoglycaemia (NICTH). *Clinical Endocrinology* 2000;53:213–20.
- [7] Werner H, Le Roith D. New concepts in regulation and function of insulin like growth factors: implication for understanding normal growth and neoplasm. *Cell Mol Life Sci* 2000;57(6):932–42.
- [8] Hoekman K, van Doorn J, Gloudemans T, Massen JA, Schuller AGP, Pinedo HM. Hypoglycaemia associated with production of insulin like growth factor II and insulin like growth factor binding protein 6 by a haemangiopericytoma. *Clinical Endocrinology* 1999;51:247–53.
- [9] Baxter RC, Daughaday WH. Impaired formation of ternary insulin like growth factor binding protein complex in patients with hypoglycaemia due to non-islet cell tumours. *Journal of Clinical Endocrinology and Metabolism* 1991;73:696–702.
- [10] Marks V. *Colour Atlas of Clinical Endocrinology*. Mosby Wolfe Medical Communications 1998;20.1–20.18.
- [11] Teale JD, Marks V. Glucocorticoid therapy suppresses abnormal secretion of big IGF II by non islet cell tumour inducing hypoglycaemia (NICTH). *Clinical Endocrinology* 1998;49:491–8.
- [12] Teale JD, Blum WF, Marks V. Alleviation of non islet cell tumour hypoglycaemia by growth hormone therapy is associated with changes in IGF binding protein 3. *Annals of Clinical Biochemistry* 1992;29:314–23.
- [13] Khaleeli A, Perumainar M, Spedding AV, Teale JD, Marks V. Treatment of tumour induced hypoglycaemia with human growth hormone. *Journal of Royal Society of Medicine* 1992; 85:303.
- [14] Papadimitris C, Alvizaki M, Pantazopoulos D, Nakapoulou L, Athanassiades P, Dimopoulos MA. Cushing syndrome as the presenting feature of metastatic Leydig cell tumour of testis. *Urology* 2000;56:153.
- [15] McNulty SJ, Furlong N, Al-Jubouri MA, Hardy KJ. Dexamethasone-treatment of choice in IGF 2 mediated non islet cell tumour hypoglycaemia? *Journal of Endocrinology* 1998;156(Suppl.):44.
- [16] Marks V, Teale JD. Tumours producing hypoglycaemia. *Diabetes/ Metabolism Revs* 1991;7:79–91.