

Spontaneous hypoglycaemia and pleural fibroma: role of insulin like growth factors

N E Moat, J D Teale, R E Lea,
A W Matthews

Abstract

Spontaneous hypoglycaemia was the presenting feature of a man with a large subpleural fibroma. Preoperative and postoperative studies support the view that the tumour induced hypoglycaemia was due to the secretion of peptide hormones by the tumour.

It has long been recognised that tumours other than those of pancreatic islet cells may present with spontaneous hypoglycaemia.¹ They are usually large mesenchymal tumours and include pleural fibromas.² Of the numerous hypotheses explaining this phenomenon, the most plausible is that the tumour secretes substances with insulin-like activity.³

Case report

A 57 year old non-smoker with no relevant medical history presented with two episodes of confusion, unusual behaviour, and sweating that were relieved by food. On examination he had finger clubbing and there was dullness to percussion with reduced breath sounds over the left upper chest. A chest radiograph and computed tomogram showed a large rounded mass occupying the upper half of the left hemithorax. Percutaneous needle biopsy showed a spindle cell tumour, suggesting a subpleural fibroma.⁴ His fasting blood glucose concentration was 2.1 mmol/l. Plasma insulin, C peptide, and growth hormone concentrations were also low given the presence of hypoglycaemia (table). Further investigations showed that the plasma concentration of insulin like growth factor I (IGF I) was

abnormally low when compared with relevant reference values, whereas that of IGF II was normal; thus the IGF I : IGF II ratio was considerably reduced (table).

At operation a large tumour was found, arising from the parietal pleura at the left apex, compressing but not invading the lung. The tumour was completely excised and macroscopically was an encapsulated, lobulated mass measuring 16 × 10 × 16 cm. Histological examination showed fibroblastic proliferation with regions of increased cellularity typical of a subpleural fibroma.⁴ The mitotic rate was high for this type of tumour.

The patient made an uneventful recovery and had no further hypoglycaemic episodes. The biochemical studies were repeated six months later and fasting blood glucose, insulin, and growth hormone concentrations were in the normal range. The concentration of IGF I and the IGF I : IGF II ratio had returned to the normal range (table).

Discussion

Tumour induced hypoglycaemia was first described by Doege in 1930.¹ A large variety of tumours have been implicated, particularly those involving fibrous proliferations. In a review of 368 cases of pleural fibroma there was a 4% incidence of spontaneous hypoglycaemia; this was more likely to occur with larger tumours and those with a high mitotic rate.² Non-islet cell tumours may secrete peptides with insulin like activity.³ The insulin like growth factors (I and II) are polypeptides with a weak insulin like effect. Unlike most peptide hormones they are bound strongly to specific binding proteins in blood. The production of both insulin like growth factors and their main binding protein is usually controlled by growth hormone. Insulin like growth factors suppress growth hormone secretion by negative feedback. The published evidence concerning their concentrations in patients with tumour associated hypoglycaemia is contradictory.^{3,5} These discrepancies may be explained by methodological differences and difficulties in assaying these peptides.⁶

Further evidence in favour of the production of insulin like growth factors are the high concentrations of messenger RNA for IGF II in excised mesenchymal tumours.⁷ Autonomous secretion of insulin like growth factor II by such tumours may lead to suppression of plasma growth hormone concentrations and

Wessex Regional
Cardiothoracic
Centre, Southampton
General Hospital,
Southampton
SO9 4XY
N E Moat
R E Lea

Department of
Clinical Biochemistry
and Clinical Nutrition,
St Luke's Hospital,
Guildford GU1 3NT
J D Teale

Department of
Medicine, Queen
Alexandra Hospital,
Portsmouth PO6 3LY
A W Matthews

Reprint requests to:
Mr N E Moat, Royal
Brompton National Heart
and Lung Hospital, London
SW3 6NP.

Accepted 22 August 1991

*Biochemical data immediately before and six months after surgical excision of a pleural fibroma**

	Glucose (mmol/l)	Growth hormone (mU/l)	IGF I (U/ml)	IGF II (U/ml)	IGF I : IGF II
Reference value	3.5-5.5	>10†	0.3-1.2	0.4-1.3	>0.2‡
Preoperative	2.1	2.9	0.15	1.08	0.14
Postoperative	5.2	14.7	1.24	0.96	1.29

IGF—insulin like growth factor.

*Insulin and C peptide were detectable postoperatively but not preoperatively.

†During hypoglycaemia.

‡See Teale and Marks.⁵

hence to low concentrations of IGF I and the main binding protein.⁸ Although some binding proteins that are not dependent on growth hormone exist, reduction of the major binding protein might lead to an increased amount of unbound, biologically active free peptide for any given plasma concentration.⁹

Our patient had hypoinsulinaemic hypoglycaemia and noticeably suppressed growth hormone and IGF I concentrations but with a concentration of IGF II that was, inappropriately, near the upper end of the normal range. The ratio of IGF I to IGF II, which is normally fairly constant,⁵ was grossly abnormal. Postoperatively the concentration of all these peptide hormones returned to within the normal reference ranges, including the IGF I : IGF II ratio. These data imply that autonomous secretion of IGF II by the subpleural fibroma was responsible for the presenting symptom of spontaneous hypoglycaemia. Although these tumours may be very large at presentation, radical surgical excision is usually possible and is the preferred treatment. Tumour recurrence is almost invariably local, and in a few cases has led to the recurrence of spontaneous hypoglycaemia.¹⁰

This case gives weight to the view that some cases of tumour associated hypoglycaemia are due to secretion by the tumour of peptides that

have both insulin like and growth factor activity.

- 1 Doege KW. Fibrosarcoma of the mediastinum. *Ann Surg* 1930;92:955-61.
- 2 Briselli M, Mark EJ, Dickerson GR. Solitary fibrous tumors of the pleura. Eight new cases and review of 360 cases in the literature. *Cancer* 1981;47:2678-89.
- 3 Gordon P, Hendricks CM, Kahn CR, Megyesi K, Roth J. Hypoglycemia associated with non-islet-cell tumour and insulin-like growth factors. *N Engl J Med* 1981;305:1452-5.
- 4 Herbert A. Pathogenesis of pleurisy, pleural fibrosis, and mesothelial proliferation. *Thorax* 1986;41:176-89.
- 5 Teale JD, Marks V. 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. *Clin Endocrinol (Oxf)* 1990;33:87-98.
- 6 Zapf J, Walter H, Froesch ER. Radioimmunological determination of insulin-like growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumor hypoglycemia. *J Clin Invest* 1981;68:1321-30.
- 7 Daughaday WH, Emanuele MA, Brooks MN, Balbato AL, Kapadia M, Rotwein P. Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. *N Engl J Med* 1988;319:1434-40.
- 8 Ron D, Powers AC, Pandian MR, Godine JE, Axelrod L. Increased insulin-like growth factor II production and consequent suppression of growth hormone secretion: a dual mechanism for tumor induced hypoglycemia. *J Clin Endocrinol Metab* 1989;68:701-6.
- 9 Merimee T. Insulin-like growth factors in patients with non-islet cell tumors and hypoglycemia. *Metabolism* 1986;35:360-3.
- 10 Okike N, Bernatz PE, Woolner LB. Localised mesothelioma of the pleura. *J Thorac Cardiovasc Surg* 1978;75:363-72.

Thorax 1991;46:933-935

Endoscopic bougie and balloon dilatation of multiple bronchial stenoses: 10 year follow up

J B Ball, J C Delaney, C C Evans,
R J Donnelly, C R K Hind

Abstract

This paper reports 10 year follow up data on four patients who underwent mechanical dilatation of multiple bronchial stenoses (sarcoidosis two cases, berylliosis one case, idiopathic stenoses one case). Two patients enjoyed symptomatic and physiological improvement during the nine years before they presented with a recurrence of stenosis. The other two had recurrences sooner, and improved only slightly after they had started prednisolone treatment.

In 1981 the Liverpool Cardiothoracic Centre reported four cases in which bougie dilatation at rigid bronchoscopy was used successfully to treat multiple bronchial stenoses.¹ Ten years later we have reviewed the outcome. Two of the patients have biopsy proved sarcoidosis, one idiopathic bronchostenoses, and one berylliosis.

Case reports

CASE 1

A 51 year old man was diagnosed as having pulmonary sarcoidosis in 1971 by endobronchial biopsy. During 1973-8 he developed progressive exertional dyspnoea and had recurrent chest infections. He presented in 1979 with breathlessness on mild exertion, stridor, fixed wheeze in the left midzone, and reduced breath sounds at both apices. The flow-volume loop suggested central airway obstruction and tomography showed bilateral bronchial stenoses.

Fibreoptic bronchoscopy showed multiple fibrotic stenoses with pale, non-erythematous mucosa. The segmental bronchi of the right upper lobe were narrowed to 0.5-2.0 mm and the right middle lobe bronchus to 3.0 mm. In the left lung the diameters of the orifices of the upper lobe, lingula, and lower lobe bronchi

Cardiothoracic
Centre, Liverpool
L14 3PE

J B Ball
C C Evans
R J Donnelly
C R K Hind

Arrowe Park Hospital,
Wirral L49 5PE
J C Delaney

Reprint requests to:
Dr Hind

Accepted 11 June 1990