needle-like (3–10 μm). IRSA, albeit more expensive, can be used to confirm the diagnosis since CPPD and MSU have distinctive spectral peaks.

Currently, there is no definitive preventive treatment for CPPD crystal deposition disease as its pathophysiology has not been elucidated. Acute attacks may respond to aspirin, NSAIDs, and intra-articular steroids. Colchicine also appears to be helpful in alleviating acute arthritic attacks and for prophylaxis, as it does for gout. Increased joint pressure may be reduced by aspiration of joint fluid. If masses of calcified material are deposited in the joint space and fibrocartilaginous meniscus, surgical excision is an effective way to remove these

crystalline deposits, particularly for uni-articular involvement.

This case demonstrates the difficulty in diagnosis of indolent swellings in the region of the temporomandibular joint, especially in elderly patients, and the diagnosis of CPPD crystal deposition disease should therefore be given serious consideration when these features are manifest.

Final diagnosis

Calcium pyrophosphate dihydrate deposition disease.

Keywords: calcium pyrophosphate dihydrate deposition disease; pseudogout; temporomandibular joint

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Recurrent hypoglycaemia

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A 61-year-old non-diabetic man was admitted from out-patients with a three-month history of dizziness. These would generally occur when he was hungry, and would be relieved by eating. He was on no regular medication, and had no relevant medical history. Physical examination elicited an abdominal mass in the left upper quadrant which moved with respiration. Baseline investigations showed a normal blood count, urea and electrolytes, liver function tests, thyroid function tests and a short synacthen test. Computed tomography (CT) scan showed the presence of a mass present in the mid-thorax and extending down into the abdomen, the nature of which was uncertain. During his admission, he developed fasting-induced hypoglycaemia (blood sugar 1.3 mmol/l). Insulin and C-peptide levels during the episode were undetectable. Plasma β -hydroxybutyrate levels during the episode were also suppressed ($<25 \mu\text{mol/l}$). He subsequently required regular parenteral 10% dextrose infusions to maintain normoglycaemia.

Questions

- 1 What are the possible causes of his hypoglycaemia?
- 2 What further investigations are required?
- 3 What is the treatment of choice?

Table Differential diagnosis of spontaneous hypoglycaemia

	Glucose	Insulin	C-peptide	Proinsulin	BHB	GH	IGF-I	IGF-II
Normal	>3.0	<25	<100	<5	>600	NA	NA	NA
Insulinoma	<3.0	>30	>300	>20	<600	NA	NA	NA
Exogenous insulin	<3.0	>30	<100	<5	<600	NA	NA	NA
Sulphonylureas	<3.0	>30	>300	≥5—<20	<600	NA	NA	NA
Hypopituitarism	<3.0	<25	<100	<5	>600	≤1	↔	↔
IEM	<3.0	<25	<100	<5	>600	≥5	NA	NA
Liver disease	<3.0	<25	<100	<5	<600	≥5	↓	↓
Insulin receptor antibodies	<3.0	<25	<100	<5	<600	≥5	↔	↔
IGF-mediated (NICTH)	<3.0	<25	<100	<5	<600	≤1	↓	↑

BHB, β-hydroxybutyrate; IEM, inborn errors of metabolism; GH, growth hormone; IGF-I & IGF-II, insulin-like growth factors I & II; NICTH, non-islet-cell tumour hypoglycaemia; NA, not applicable

Answers

QUESTION 1

The patient has biochemically proven hypoglycaemia, but suppressed insulin, C-peptide and β-hydroxybutyrate levels. Insulinoma, exogenous insulin or sulphonylureas will characteristically result in elevated fasting serum insulin levels (table). Hypo-insulinaemic hypoglycaemia may be seen in association with insulin receptor antibodies, or non-islet-cell tumour hypoglycaemia (NICTH) secreting an insulin-like growth factor (IGF-I or IGF-II).

QUESTION 2

Measurement of IGF-I, IGF-II and big IGF-II is helpful in distinguishing between NICTH and insulin receptor antibodies. In NICTH, IGF-I levels are low and IGF-II levels are normal or slightly elevated, resulting in an abnormally low IGF-I:IGF-II ratio (<0.2). Big IGF-II levels may be elevated. Serum growth hormone may be low (≤1 mU/l) in NICTH but elevated (≥5 mU/l) in the presence of insulin receptor antibodies (table). The patient's serum IGF-I was low at 0.31 U/ml (normal range 0.09–0.86 mU/l), IGF-II was elevated at 2.21 U/ml (normal range 0.08–1.08 mU/l). The IGF-I:IGF-II ratio was thus low at 0.14 (normal >0.2) and big IGF-II was elevated at 23.0 nmol/l (<14.4 nmol/l), suggesting NICTH.

QUESTION 3

Surgical removal of the tumour can result in complete remission in cases where total excision is possible. In many malignant or locally invasive tumours, alleviation of the hypoglycaemia often follows partial removal. The patient had an excision of a large mesothelioma of the posterior mediastinum by thoracotomy. Postoperatively the hypoglycaemia settled and at six months repeat biochemistry showed normal IGF-I (1.17 U/ml), IGF-II (1.07 U/ml), IGF-I:IGF-II ratio (1.09) and big IGF (11.0 nmol/l) levels, suggesting no recurrence.

Discussion

NICTH is characterised by low plasma insulin, C-peptide and ketone (β-hydroxybutyrate) levels in the presence of spontaneous hypoglycaemia (serum glucose <3.0 mmol/l).¹ Such tumours are rare, and may be due to a number of types of tumour, including mesothelioma, hepatoma and fibroma. Hypoglycaemia occurs

Summary points

- hypo-insulinaemic hypoglycaemia may be due to non-islet-cell tumour hypoglycaemia (NICTH) or the presence of insulin receptor antibodies
- NICTH is due to excessive production of insulin-like growth factor-II (IGF-II)
- a reduced ratio of IGF-I:IGF-II, or elevated big IGF-II levels suggest NICTH
- surgical removal of the tumour can result in complete remission
- GH can alleviate symptoms while more definitive treatment is planned

as a result of excessive IGF-II or big IGF-II. IGF-I and IGF-II circulate in concentrations about 1000 times greater than that of insulin, although they possess only around 6% insulin-like activity. Hypoglycaemia would occur if IGFs were not tightly bound to their specific binding protein.²

The initial factor in the genesis of hypoglycaemia is the overproduction of IGF-II which in turn reduces growth hormone (GH) secretion in response to physiological stimulation.³ This physiological GH deficiency leads to a decreased production and secretion by the liver of both IGF-I and IGF binding proteins, especially IGF-BP3, whose presence normally reduces if not entirely removes the hypoglycaemic effect of circulating IGF-I and II.^{3,4} The reduction in IGF-BP3 results in an increase in unbound IGF-II without necessarily increasing total concentration in the plasma. The alternative hypothesis, not necessarily in conflict with the IGF-I:IGF-II ratio hypothesis, is that these tumours produce an abnormal or large IGF-II. This is postulated to be a more potent hypoglycaemic agent than regular IGF-II.³

Surgical excision removes the source of the excess IGF-II, although complete excision may not be possible with such tumours. Growth hormone therapy in such cases may be useful as it increases production of IGF-I and IGF-BP3, restoring the normal ratio of the two growth factors and reducing the unbound fraction.

Final diagnosis

Non-islet-cell tumour hypoglycaemia due to an IGF-II secreting mesothelioma.

Keywords: non-islet-cell tumour; hypoglycaemia; insulin-like growth factors

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Painless blurred vision

N Karia, P Watts

A 76-year-old normotensive woman with no previous ocular history or history of trauma, presented with one day of painless blurred vision in the right eye. Together with digoxin and isosorbide mononitrate she was also on warfarin, 3 mg a day, which had been started eight months previously as systemic anticoagulation for atrial fibrillation. She had no other significant medical history. The figure shows the anterior segment appearance of the right eye. The left eye was normal.

Figure Anterior segment of right eye

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Questions

- 1 What does the figure show ?
- 2 Given the above ophthalmic and medical history, do you think that the condition shown in the figure occurs commonly or infrequently ?
- 3 What should be included in this patient's medical management ? Should her warfarin be continued ?
- 4 Suggest her ophthalmic management.