Case Report

A rare cause of hypoglycaemia

Robert Sciberras

Abstract

This paper describes a case study concerning a young man on treatment for psychiatric illness who developed severe episodes of hypoglycaemia. After several investigations, lithium therapy was implicated. Stopping this treatment resulted in the patient being relieved of these episodes.

A rare cause of hypoglycaemia

F.A. is a 36 year old male health care worker with a long-standing history of psychiatric illnesses and repeated admissions to the Psychiatric Short-Stay Ward. The depressive illness was precipitated by an accident in a previous work-place. Other past history included hypertension of 4 years duration and spinal surgery for a prolapsed disc in 2006.

The patient is married to a diabetic lady, who is on gliclazide and metformin. She monitors her own blood glucose at home using a glucose meter.

F.A. was referred in October 2008 complaining of recurrent hypoglycamic attacks occurring approximately every 2 days for the past 4 weeks. The low glucose levels ranging between 2.2mmol/L and 2.7mmol/L were documented by his wife using her glucose meter. The hypoglycaemic attacks were typical and included excessive sweating, tremors, nausea and at times, episodes of confusion. The episodes were relieved by the patient ingesting a large bar of chocolate followed by sugary drinks.

Keywords

Psychiatric illness, lithium therapy, hypoglyacemia

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The patient was on clozapine 25mg, ½ tablet three times a day, lithium 400mg tabs, 600mg at night, mianserin 10mg, two tablets three times a day and paroxetine 20mg two tablets in the morning and one tablet in the evening. His blood pressure was well controlled with amlodipine 5mg once daily.

There were no other systemic complaints, and no relevant family history. There was no recent change in appetite or weight. Examination was unremarkable. Given his work-place and also his home situation, surreptitious ingestion of oral hypoglycaemic agents was suspected but subsequently eliminated as the cause for his attacks. At his place of work he did not have access to any hypoglycaemic agents. At home, his wife kept her medications under lock and key particularly because the couple had two small children. She could also account for all her tablets. Psychiatric consultation concerning whether any of the psychiatric medications could be causing hypoglycaemia proved negative. All investigations including thyroid function tests were normal. Serum lithium level was 0.45mmol/L (normal range 0.6-1.2mmol/L). The patients did not present a history of lithium toxicity.

The patient was admitted to Gozo General Hospital for monitoring at the end of October 2008. During admission two hypoglycaemic attacks occurred and were witnessed by the author. The glucose levels were 2.6mmol/L and 2.7mmol/L respectively. The hypoglycaemic attacks had to be aborted rapidly by dextrose infusion as the patient became very symptomatic, confused and on the point of becoming aggressive. Blood tests were taken during the hypoglycaemia: C-Peptide level was 5.85ng/ml (normal range is 0.80-4.00ng/ml), insulin level was 31.0microU/ml (normal range 2.0-25.0microU/ml), and proinsulin level was 88pmol/L (normal range is 6.4-9.4pmol/L). These levels were inappropriately high for a patient with hypoglycaemia.

An insulinoma was suspected and an urgent computerised axial tomography of the abdomen was carried out, including 1.5mm slices at the pancreatic level. This was reported as normal.

Meanwhile hypoglycaemic episodes were still occurring in spite of continuous dextrose infusion and so the patient was started on prednisolone 10mg three times a day. This medication put an end to the hypoglycaemic episodes and the patient was discharged home pending further investigations.

An Indium-111 octreotide scintigraphy was performed on the 17th of December 2008, 4 hours and 24 hours following intravenous administration of 160MBq of Octreoscan. Both whole body and

SPECT images were acquired. There was no abnormal focus of tracer accumulated in the abdomen. Physiological activity was seen in liver, spleen and kidneys with intestinal activity evident at 24 hours. It was therefore concluded that there was no definite evidence of insulinoma. However sensitivity of octreotide scintigraphy is in the range of only 50% (see discussion below). Surgical consultation resulted in the patient being scheduled for exploratory laparotomy which might have included total pancreatectomy. At the eleventh hour the surgery was postponed due to repeated hypoglycaemic episodes. During one of these episodes, blood investigations showed an insulin level of 22microU/ml (reference range 2.0-25.0microU/ml), C-peptide level of 3.64ng/ml (reference range 0.80-4.00ng/ml), and proinsulin level of 30.4pmol/L (reference range 6.4-9.4pmol/L). The patient was started on diazoxide 50mg, four tablets three times a day and discharged home on the 10th of March 2009.

Two days later the patient was admitted urgently to hospital complaining of fever of 102 degrees Fahrenheit, severe muscle aches and pains, shortness of breath and inability to walk due to generalized weakness and stiffness. There was no wheezing or rash. His eosinophil count was normal. The symptoms had started on initiating diazoxide therapy. A reaction to the medication was suspected, the drug withdrawn and all symptoms resolved. At this point, lithium therapy started to be suspected to be causing the hypoglycaemic episodes in this patient. The dose of lithium was reduced to 400mg at night and the patient discharged. The rest of the medication was kept at the same dose throughout the investigative period. Further visits at out-patients revealed that no further episodes of hypoglycaemia were occurring since reduction of lithium therapy, in spite of the steroids being tailed down. Lithium was eventually reduced to 200mg at night and steroids completely stopped on the 27th of April 2009.

On the 15th of May 2009, the patient was admitted to hospital for a prolonged fasting test. He was advised not to eat anything between 4.00 pm and 8.00 am the following morning. He was allowed to drink water only. Blood glucose was monitored every hour. There were no low blood glucose readings. At 8.00 am, a 75g glucose oral drink was administered. Three hours later the patient suffered a symptomatic hypoglycaemic attack with blood glucose falling to 2.5mmo/L. The insulin level checked at this time was 11.0microU/ml (normal range 2.0-25.0microU/ml), C-peptide level was 3.73ng/ml (normal range 0.8-4.00ng/ml) and proinsulin level was 61.7pmol/L (normal range 6.4-9.4pmol/L). At this point, therefore, the patient was not having spontaneous hypoglyaemic episodes but had a late one precipitated by a glucose load. The lithium therapy was eventually tailed off by the end of June 2009.

The prolonged fasting test was repeated on the 23rd of July 2009. Serum lithium level was <0.10mmol/L (normal range 0.6-1.5mmol/L), and this confirmed that the patient had indeed stopped lithium therapy as instructed. During the fast, the patient did not have hypoglycaemic episodes. At 8.00 am, a 75g glucose load was administered and the patient was observed for six hours later and was allowed to drink water only. Contrary to the first prolonged fasting test, the blood glucose estimations every 30 minutes were stable and there were no hypoglycaemic episodes after the glucose load.

The patient is still being seen regularly at the hospital out-patients department. He is well and has had no further problems since. A letter to the Medicine Authority has been sent reporting the adverse effects caused by lithium and diazoxide.

Discussion

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorders (manic-depressive disorder) and in the prophylaxis of recurrent depression (unipolar illness or unipolar depression). A literature search for the association of lithium therapy with hypoglycaemia did not reveal significant results. Pinelli *et al* reported neonatal hypoglycaemia with maternal lithium therapy, apart from Ebstein's anomaly, cyanosis, rhythm disturbances and thyroid dysfunction.[1] Shah *et al* performed five-hour oral glucose tests (OGTT) in nine patients receiving lithium therapy and in seven control patients.[2] During GTT mean nadir serum glucose was significantly lower in the lithium-treated patients as compared to controls. The study suggested that chronic lithium treatment may be associated with symptomatic and biochemical hypoglycaemia during OGTT due to a rise in serum cortisol but lack of appropriate rise in plasma glucagon concentrations. Other hormonal effects were studied by Grof *et al*.[3] In this study, lithium treatment resulted in a dramatic reduction in prolactin and growth hormone response to insulin hypoglycaemia. The reduced prolactin response to hypoglycaemia was also confirmed by Grof *et al*.[4] However, other studies tend to contradict these findings. In the intact rat, lithium was found to inhibit glucose- and tolbutamide-induced insulin release, which in turn, causes glucose intolerance and prevents tolbutamide-induced hypoglycaemia.[5] The literature describes one report of a patient with lithium toxicity who presented with hypoglycaemia, acneform lesions, hypothyroidism and nephrogenic diabetes insipidus.[6] However the case study presented above was not a case of lithium toxicity as was proved by repeated blood tests.

The first oral glucose tolerance test also suggested a rebound type of hypoglycaemia. This could explain the fact that when the patient presented originally, his eating chocolate bars to alleviate a hypoglycaemic attack was in fact triggering the next one. The levels of pro-insulin were very high (up to 9 times the upper laboratory reference range). Pro-insulin has weak insulin-like biological activity of its own right, but a much longer half-life than insulin. It might therefore have contributed to a reactive-type of hypoglycaemic reactions. A diagnostic problem which was encountered was the fact that the octreotide scan is not always helpful, since the false negative rate could reach up to 50% due to different types of somatostatin receptors present in this tumour type.[7,8,9]

The duration of the prolonged fasting tests might not be the recommended one, however in this case it served its purpose since the difference between the 2 tests occurred after the glucose challenge; when the patient was on lithium there was

severe hypoglycaemia and while off lithium the patient did not suffer any adverse events. So the two scenarios were directly comparable. Furthermore, stopping lithium therapy has resulted in the total absence of further hypoglycaemic episodes to date, virtually ruling out insulinomas since no definite treatment for these tumours was undertaken. Furthermore the patient has not developed other conditions e.g. diabetes mellitus.

It is clear that further studies need to be carried out in order to investigate the role of lithium in causing hypoglycaemia. However any patient on lithium suffering from recurrent episodes of hypoglycaemia may need a review of psychiatric treatment.

Acknowledgements

The author acknowledges the input of Dr. Mario Cachia in suggesting that lithium therapy could cause hypoglycaemic episodes.

References

1. Pinelli JM, Symington AJ, Cunningham KA, Paes BA: Case report and review of the perinatal implications of maternal lithium use. Am J Obstet Gynecol. 2002 Jul;187(1):245-9
2. Shah JH, DeLeon-Jones FA, Shickler R, Nasr S, Mayer M, Hurks C: Symptomatic reactive hypoglycaemia during glucose tolerance test in lithium-treated patients. Metabolism. 1986 Jul; 35(7):634-9.
3. Grof E, Grof P, Brown GM, Downie S. Lithium effects on neuroendocrine function. Prog Nueropsychopharmacol Biol Psychiatry. 1984; 8(4-6):541-6.
4. Grof E, Brown GM, Grof P: Neuroendocrine strategies in affective disorders. Prog Neuropsychopharmacol Biol Psychiatry. 1983; 7(4-6):557-62.
5. Shah JH, Pishdad G: The effect of lithium on glucose- and tolbutamide-induced insulin release and glucose tolerance in the intact rat. Endocrinology. 1980 Nov;107(5):1300-4.
6. Heng MC: Lithium carbonate toxicity. Acneform eruption and other manifestation. Arch Dermatol. 1982 Apr;118(4):246-8.
7. Modlin IM & Tang LH. Approaches to the diagnosis of gut neuroendocrine tumors: the last word (today). Gastroenterology. 1997;112:583–90.
8. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M, Reubi JC et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. European Journal of Nuclear Medicine. 1993;20:716–31.
9. Schillaci O, Massa R & Scopinaro F. ^{111}In-pentetreotide scintigraphy in the detection of insulinomas: importance of SPECT imaging. Journal of Nuclear Medicine. 2000;41:459-62.

Donation of a clinical-skills simulation model by Bayer-Schering Pharma

The Department of Obstetrics and Gynaecology within the Faculty of Medicine and Surgery has been the recipient of a simulation model aimed at assisting the development of clinical skills by medical students. The Zoe® Gynaecologic Simulator was kindly donated by Mr. Simon Delicata who is the local representative of the international-based company Bayer-Schering Pharma. The model consists of a full-sized adult female lower torso designed as a training tool developed to assist health professionals to teach the processes and skills required to perform certain gynaecological procedures.

Bayer Schering Pharma AG is an international healthcare company that is committed to sustainable development in various fields of healthcare including gynaecology. The present donation is a clear example of the commitment being shown by the company of the positive inter-relationship between industry and academia. The company has strongly supported the Department of Obstetrics and Gynaecology throughout the last years. It has set up the annual Bayer-Schering Pharma Prize in Obstetrics & Gynaecology that is awarded to the student who obtains the highest aggregate mark in the speciality during the final examinations of the Medicine and Surgery course. In addition, the company has sponsored publications on the history of midwifery education and on the history of gynaecology in Malta prepared by the Department. The present gift is a welcome addition to the educational tools armamentarium of the Faculty since it helps augment the clinical skills simulation laboratories being set up by the Faculty.