

# Haemoglobinopathies encountered at Khoula Hospital, Oman

## A retrospective study

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### حالات الاعتلال الخضابي بالدم في مستشفى خولة (عمان) دراسة استيعادية

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**المخلص: الهدف:** تقييم مدى انتشار حالات الاعتلال الخضابي (الهيموجلوبين) في المرضى المحولين لمستشفى خولة (عمان) ومقارنة النتائج بدراسات أخرى بتقييم عدد كبير من الحالات. **الطريقة:** تم تقييم نتائج 27,403 حالة سواء من المرضى الداخليين بمستشفى خولة أو من المحولين إليها من مراكز صحية متعددة خلال فترة أربع سنوات بداية من يناير 2001 وحتى ديسمبر 2004 لتحديد مدى نسبة إنتشار الإعتلال الخضابي لديهم. الفوحصات المختبرية المستخدمة هي اختبار التمنجل عن طريق الذوبان والرحلان الكهربائي لخضاب الدم. **النتائج:** نسبة حاملي فقر الدم المنجلي هي 7.5% و نسبة المرضى بفقر الدم المنجلي هي 0.46%, أما نسبة الأنواع الأخرى من الاعتلال الخضابي بالدم فكانت 0.102%. هناك ترابط واضح بين نتائج هذه الدراسة و بين نتائج الترصد الوطني لاضطرابات الدم الوراثية التي أجريت بواسطة قسم البحوث و الدراسات بوزارة الصحة بسلطنة عمان. **الخلاصة:** أظهرت هذه الدراسة الاستيعادية بوضوح مدى انتشار الاعتلال الخضابي عند المرضى موضوع الدراسة لذا فيجب إعطاء إهتمام أكثر للتحقيق الصحي و الفحص الجيني لتجنب هذه المشكلة الصحية العامة بالسلطنة .

**مفتاح الكلمات:** فقر الدم . الخلية المنجلية . خَلَّةُ الخليةِ المِنْجَلِيَّةِ . اعتلال خضاب الدم . عمان.

**ABSTRACT Objective:** The objective of this study was to find out the frequency of abnormal haemoglobins (Hb) in patients referred to Khoula Hospital, Oman and compare the data from other studies by assessing a large number of patients. **Methods:** The results of 27,403 patients, either admitted to Khoula Hospital or referred to it from different health centres during the 4 years of the study from January 2001 till December 2004, were analysed for haemoglobinopathies. The laboratory methods used for detection of abnormal haemoglobins were sickle cell solubility test and haemoglobin electrophoresis. **Results:** The frequency of sickle cell trait was 7.5%, sickle cell disease 0.46% and other Hb variants were 0.102%. The results correlate well with that of the National Genetic Blood Disorder Survey carried out by the research and studies department, Ministry of Health, Sultanate of Oman, during a 4 year period from January 2001 till December 2004. **Conclusion:** This retrospective study demonstrates the high prevalence of haemoglobinopathies among the studied group of patients. More attention to the importance of health education and genetic counselling is required for the prevention of this public health problem in the country.

**Keywords:** Anaemia, Sickle Cell; Sickle Cell Trait; Haemoglobinopathies; Oman.

#### Advances in Knowledge

- The study shows that haemoglobinopathies are prevalent at a significant rate among the patient group studied.
- The study stimulates the need to conduct regular surveys to monitor haemoglobinopathies as well as prevalent genetic blood disorders in Oman.

#### Application to Patient Care

- Knowledge gained by researchers and doctors that can be applied both to the early diagnosis of haemoglobinopathies and to the management of patients with these abnormalities including genetic counselling.

**T**HE COMMONEST GENETIC BLOOD DISORDERS that cause alterations in erythrocyte morphology and rheology are sickle cell anaemia, G6PD (Glucose-6 phosphate dehydrogenase enzyme deficiency) and thalassaemias.<sup>1</sup> These inherited haemoglobinopathies are the commonest single-gene disorders; the World Health Organization estimates that about 7% of the world population are carriers.<sup>2</sup> Because of their worldwide distribution, the disorders resulting from abnormal haemoglobin structure (haemoglobinopathies) are of enormous clinical importance.<sup>3</sup>

These haemoglobin disorders occur in homozygous as well as heterozygous forms and involve the  $\beta$ -chain or the  $\alpha$ -chain. In the homozygous state, Hb A is totally lacking, and clinical manifestations are of variable severity. Individuals so affected have anaemia, for example, sickle cell anaemia. In the heterozygotes, because they rarely have phenotypic expressions of clinical significance, they are said to have the trait for abnormality, for example, sickle cell trait.<sup>1</sup>

The thalassaemias are a heterogenous group of inherited conditions characterised by defects in the synthesis of one or more of the globin chains that form the haemoglobin tetramer. The clinical syndromes associated with thalassaemia arise from the combined consequences of inadequate haemoglobin production and of unbalanced accumulation of one type of globin chains.<sup>4</sup>

The main objective of this study was to estimate the prevalence of the most common haemoglobinopathies reported at Khoula Hospital and compare the data with other studies performed in Oman.

Some studies were done before to estimate the prevalence of haemoglobinopathies in Oman. Khoula Hospital is a tertiary hospital and is the national trauma centre. It therefore gets referrals from many other hospitals in Oman, in addition to the referrals from the local health centres in Muscat; so a large number of cases is assessed every year. This provided a good opportunity for further assessment and evaluation of haemoglobinopathies, especially those investigations that were already requested by the treating doctors in the hospital departments and health centres, as this meant no additional costs or patient disturbance.

## METHODS

In this study, we used the laboratory records to collect data on blood samples sent to the laboratory from Khoula Hospital and Wattayah Polyclinic and also

those referred from health centres over a period of four years from January 2001 to December 2004. Ours is a tertiary hospital and the National Trauma Centre of the Sultanate of Oman receiving referrals from different regions and different health centres. 27,403 patients had investigations done for them as in-patients in the hospital or outpatients from different health centres. The investigations were already requested by the treating doctors in different departments in the hospital and health centres so there were no additional costs or additional financial funds needed for the study and also no additional burden on the patients either physically or financially.

All cases of haemoglobinopathies detected in the laboratory were tabulated noting the solubility sickle cell screening test results and their confirmation using the haemoglobin electrophoresis, HbL4, by Helena method.<sup>4</sup> For thalassaemia confirmation, samples were sent to the laboratory at the Royal Hospital, Muscat, where the high performance liquid chromatography (HPLC) method is done.<sup>4</sup>

During the period of study, a total number of 27,403 cases were screened by the sickle cell solubility method and 3,158 cases were subjected to haemoglobin electrophoresis.

## RESULTS

The results are charted in Figures 1, 2 and Table 1. The total number of patients assessed was 27,403 cases. Of these 90.5% were Omanis and expatriates 9.5% (Indians 6.2%; Egyptians 1.4%; Bangladeshis 0.7%, Sri Lankans 0.3% and Gulf Cooperation Council citizens 0.3%). Out of these, according to our laboratory results, 2,057 cases (7.5%) had sickle cell trait with only a small numbers of patients having sickle cell disease itself: 128 cases (0.46%). Other small groups of patients, 21 cases (0.102%), had a combination of sickle cell with abnormal haemoglobin. Sickle thalassaemias were encountered at a very low rate (0.01%).

## DISCUSSION

In a previous survey study done by the Research and Studies Department of the Oman Ministry of Health, 6,342 children under 5 years of age were taken by their parents to neighbourhood hospitals or health centres for blood collection. The study showed that the prevalence of sickle cell trait was 6%, B-thalassaemia trait (heterozygous) was 2%, B-thalassaemia homozygous was 0.07% and sickle cell disease 0.2%. The combination of

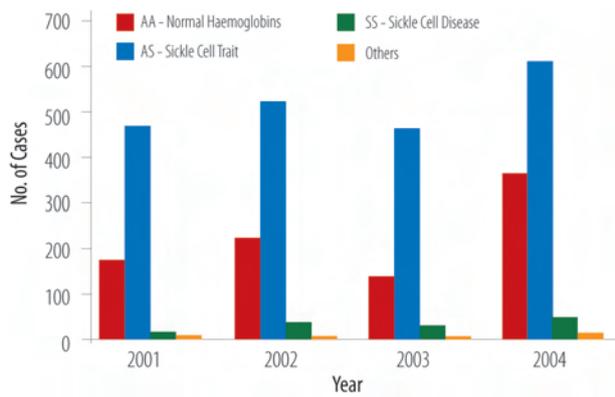


Figure 1: Values in numbers of the different haemoglobinopathies

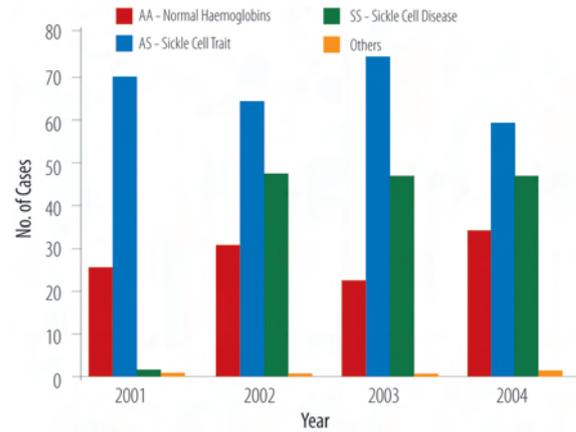


Figure 2: Percentage values of the different haemoglobinopathies

Table 1: Tables of values and percentages for the different haemoglobinopathies

Year	No. %	Nor Hb AA	SC Trait AS	SC Disease SS											Total Proc.
					FS	SE	AFS	FSD	S-	S-OM	S-Dho	AD	AE	DD	
2001	No	179	465	18	-	-	1	-	1	2	1	1	-	-	668
	%	26.8	69.6	2.69	-	-	0.15	-	0.15	0.3	0.15	0.15	-	-	-
2002	No	255	522	33	2	-	-	-	-	-	-	-	1	1	814
	%	31.3	64.1	4.05	0.25	-	-	-	-	-	-	-	0.12	0.12	-
2003	No	141	461	31	-	-	-	1	-	-	-	2	-	1	637
	%	22.1	72.3	4.87	-	-	-	0.16	-	-	-	0.31	-	0.16	-
2004	No	368	609	46	7	1	-	1	2	-	-	4	1	-	1039
	%	35.4	58.6	4.43	0.67	0.1	-	0.1	0.19	-	-	0.38	0.1	-	-
Totals	No	943	2057	128	9	1	1	2	3	2	1	7	2	2	3158
	%	29.8	65.1	4	0.03	0.03	0.03	0.06	0.01	0.007	0.003	0.025	0.007	0.007	-

AA-Normal Haemoglobin; AS-Sickle Cell Trait; SS - Sickle Cell Disease; FS-Fetal and Sickle Haemoglobin ; SE-Sickle and Haemoglobin D; AFS-Adult, Fetal and Sickle Haemoglobin ; FSD-Fetal Haemoglobin and Sickle Cell Disease; S-Th-Sickle Cell and  $\beta$ -Thalassemia ; S-OM-Sickle Cell-Oman; S-Dho-Sickle Cell-Dhofar region Oman; AD-Adult and Haemoglobin D; AE-Adult and Haemoglobin E; DD-Haemoglobin D; HBL4 -Haemoglobin Electrophoresis

sickle cell with other abnormal haemoglobins was also detected at a very low prevalence rate. Among the studied children, three quarters (74.5%) were found to be free from haemoglobinopathies and G6PD normal, the other quarter of children, either had haemoglobin abnormalities (7.5%), G6PD (16%) or had a combination of G6PD with at least one abnormal haemoglobin (2%). The prevalence rate of the total haemoglobinopathies in Oman is 9.5%.<sup>5</sup> Other abnormal haemoglobins detected in this survey were: Hb D(0.6%), Hb E(0.3%), Hb C (0.02%). The combination of sickle cell with abnormal Hb was also detected at low prevalence.<sup>5</sup>

In the study done by White et al, the frequencies of four major red cell genetic defects: sickle haemoglobin (HbS), glucose 6 phosphate dehydrogenase (G6PD), and  $\alpha$  and  $\beta$ - thalassemia, were determined in nearly 5,000 subjects from the three major peninsular Arab states, namely Yemen, the United Arab Emirates, and Oman. The frequencies of these in Oman were 0.389, 0.328, 0.024, and 0.038 respectively.<sup>6</sup>

In the Khoula laboratory study, the prevalence rate of haemoglobinopathies was found to be 8.09%; sickle cell trait formed 7.5 %, while sickle cell disease formed 0.46 % of this total. The other variants encountered (HbD, E, S-Oman, S-thalassemia, etc.) were 0.102%. Our results are consistent with previous studies performed in Oman.

Knowledge of the distribution of these genetic blood disorders is useful in health care planning and management of resources.<sup>7</sup> In populations in which there is a significant incidence of severe forms of thalassemia or sickle cell anaemia, women should be screened early in pregnancy for thalassemia and the sickle cell trait. If both parents are carriers, prevention of severe disease is possible through genetic counselling and offering prenatal diagnosis through fetal blood analysis or amniocentesis and performing fetal DNA analysis.<sup>8</sup>

Also, the major objective of screening for genetic blood disorders is the identification of individuals who would benefit from genetic counselling. Testing for haemoglobinopathies is best coordinated with comprehensive health screening programmes and integrated with meaningful education and ethical counselling.<sup>1</sup> The technique chosen for screening should be genetically diagnostic and should clearly differentiate between sickle cell trait and those disorders of haemoglobin having implications for health.<sup>9</sup>

Genetic blood disorder diseases can be prevented by establishing a proper preventive programme which includes health education, genetic counselling for heterozygotes, the improvement of curative and blood transfusion services, as well as newborn screening. The Ministry of Health in the Sultanate of Oman has recognised that genetic blood diseases are a public health problem in the country and need attention.<sup>5</sup> Many of the components of a genetic blood disorder prevention programme have already been successfully implemented in Oman, for example, neonatal screening, premariatal examination and genetic counselling.

## CONCLUSION

In conclusion, this retrospective study over 4 years demonstrated clearly the high prevalence of haemoglobinopathies among the studied group of patients. Moreover, prompt and full implementation of the genetic blood disorder disease prevention programme is likely to reduce the numbers of homozygous patients and help early detection.

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## Insulinoma: A Rare Cause of a Common Metabolic Disorder - Hypoglycaemia

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### الوَرَمُ الجَزِيرِيّ (انسولينوما) : سبب نادر للاضطراب الأيضي (الاستقلابي) واسع الانتشار - نقص سكر الدم

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**المخلص:** تقرير عن أول حالة في سلطنة عمان لمريض عماني يعاني من الورم الجزيري والذي تم استئصاله مع ذيل غدة البنكرياس بواسطة المنظار. هذه الحالة تثبت أهمية اخذ تاريخ المرض من المريض و/أو عائلته . كما يوضح هذا التقرير أهمية فحص نسبة السكر في الدم للمرضى الذين يعانون من فقدان الوعي المتكرر . وكذلك اخذ عينات دم أخرى للتأكد من نسبة السكر في المعمل ونسبة هرمون الأنسولين وبيبتايد - ج طليح الانسولين ومستويات يوريا السلفونيل - اذا كانت هناك ضرورة لذلك . واذا لم يكن باستطاعة الرنين المغناطيسي تحديد موقع الورم بالضبط . يمكن حينذاك الفحص بتخطيط الصدى بالتنظير الداخلي . أو بالتفريغ باستخدام الانديوم الثلاثي الموسوم بالاوكتيرويد لتحديد مكان الورم في البنكرياس اذا استجاب المريض الذي يعاني من انخفاض سكر الدم للعلاج بالاوكتيرويد.

**مفتاح الكلمات:** بيبتايد - ج . انخفاض سكر الدم . الجراحة بالمنظار . استئصال البنكرياس.

**ABSTRACT** We describe the first patient diagnosed with an insulinoma in Oman and successfully managed with a distal laparoscopic pancreatectomy. The importance of obtaining a good history from the patient and/or his family is stressed. All patients with loss of consciousness must have a Reflow check carried out and, if hypoglycaemic, this should be documented in the laboratory and a simultaneous serum sample stored for measurement of insulin, C-peptide proinsulin and sulphonylurea levels, if subsequently indicated. If magnetic resonance imaging fails to locate the tumour, endoscopic ultrasound of the pancreas, or indium 111 labelled octreotide scanning is indicated if the patient's hypoglycaemia has previously responded to treatment with octreotide.

**Key words:** Insulinoma; C-peptide; Hypoglycaemia; Laparoscopy; Pancreatectomy.

**H**YPOGLYCAEMIA IS A COMMON METABOLIC problem and may result from increased peripheral uptake of glucose, failure of glucose production or a combination of both. By far the commonest cause is increased peripheral glucose uptake resulting from stimulation of the insulin receptor (INS-R) by endogenous overproduction or exogenous administration of excess insulin. Rarely, hypoglycaemia is caused by increased circulating levels of molecules resembling insulin such as insulin like growth factors (IGFs) or antibodies directed against the INS-R. Hypoglycaemia also occurs in patients with advanced liv-

er disease resulting from a failure of gluconeogenesis. The role of the kidney is less certain; glucose uptake and synthesis is high normally and renal failure often results in hypoglycaemia. As insulin is degraded by the kidney, hypoglycaemia may in part be due to prolongation of its actions.<sup>1-5</sup>

Hypoglycaemia has a potential for serious neurological damage and death. The patient described here had recurrent symptoms for two years that were initially thought to result from epilepsy and later a conversion reaction. Insulinoma is rare with an incidence of only 4 per 1 million persons per year, but it is the common-

**Table 1: Simultaneous blood sampling of patient when hypoglycaemic**

Glucose	1.5	(3.5 – 5.0) mm/l
Insulin	9.0	(1.9 – 23) mIU/L
C-peptide	2	(1.5 – 4.5) ug/L
Pro-insulin	21	(6.4 – 9.4) pm/l

**Table 2: Octreotide trial 100 micrograms s/c time 0**

Time (minutes)	-15	0	30	60	120
Glucose mmol/L	1.4	1.7	1.8	1.4	1.0
Insulin mIU/L	2.1	3.4	0.3	1.9	2.0

est cause of hypoglycaemia in otherwise healthy adults who are not taking antidiabetic drugs. The median age is 47 years with a slight female preponderance of 59%. 87% of insulinomas are single benign tumours, 6% are malignant and 7% are multiple benign tumours and associated with multiple endocrine neoplasia type 1 (MEN-1).<sup>1,2</sup>

**CASE REPORT**

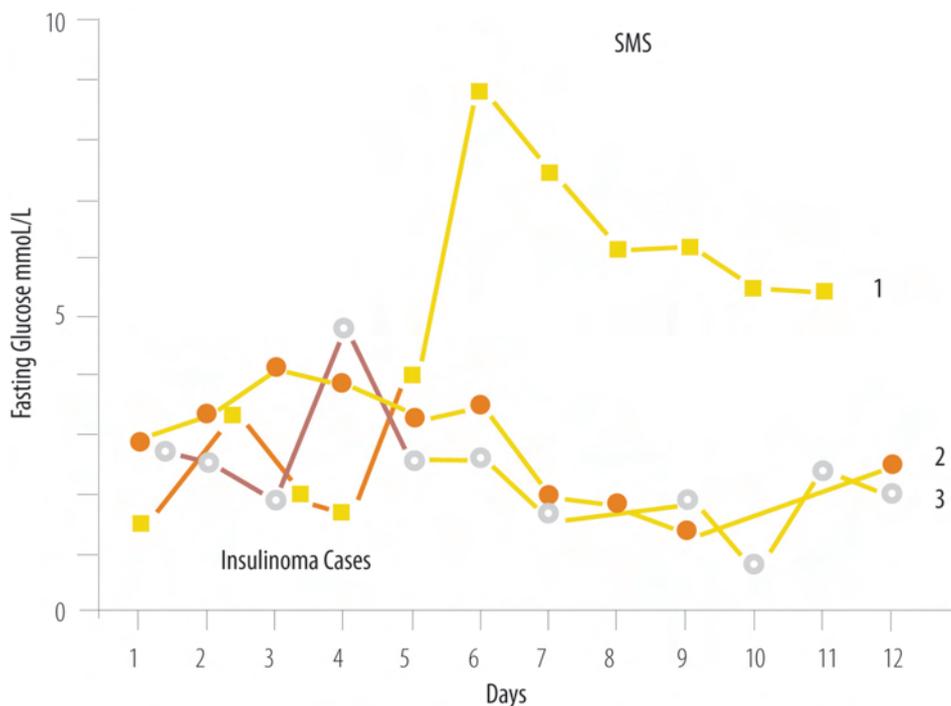
A 23 year old Omani male had a 2 year history of recurrent loss of consciousness and convulsions.

On the first day of Ramadan (Islamic month of fasting) in 2006, he presented to the Accident and Emergency Department of Sultan Qaboos University Hospital, Oman, with loss of consciousness. His blood glucose was measured by Reflocheck, a blood glucose monitor, and was found to be 1.5mmol/L. On receiving intravenous dextrose, he regained consciousness. He was then

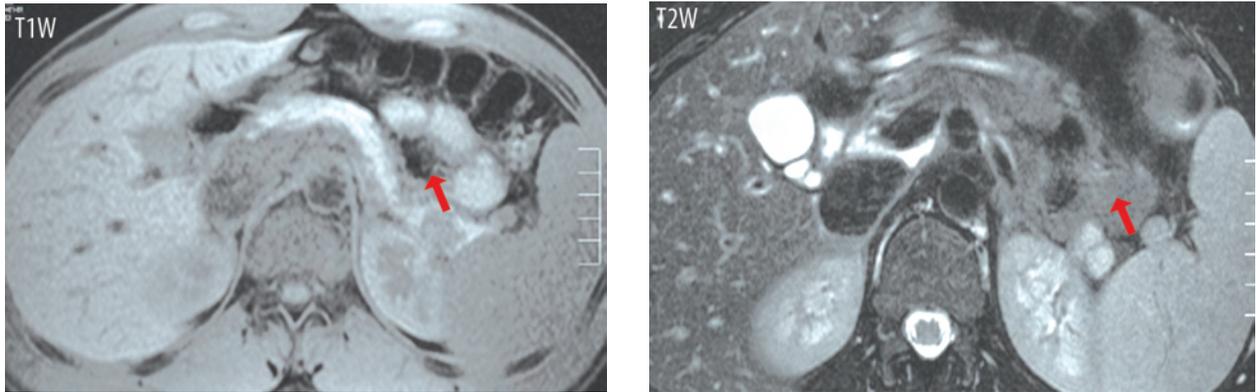
discharged with a referral letter to the endocrine clinic. This delayed his admission by two months.

His attacks had started in Ramadan 2005, when he was unable to fast for more than 10 days. A year later in Ramadan 2006, fasting became impossible for more than a few hours hence his hospital visit. The family reported that frequent meals made him less liable to attacks. There was no family history of diabetes and he was not known to have diabetes. His parents and ten siblings were healthy. His physical examination was unremarkable.

He was admitted and started on a 72 hour fast. After 8 hours, his blood glucose fell to 1.5 mmol. (Reflocheck). Blood samples were taken for laboratory confirmation of the plasma glucose, and levels of insulin, C-peptide, pro-insulin and sulphonylureas. The fast was terminated and he was given intravenous glucose. Treatment



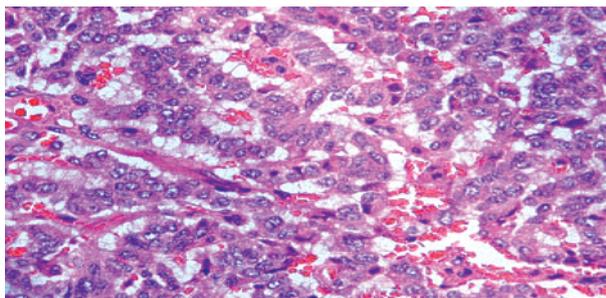
**Figure 1: A therapeutic trial of octreotide (SMS) in 3 patients with insulinomas. Insulin secretion can be inhibited, with normalisation of the blood sugar level, only in those patients whose tumours have receptors for octreotide (<50%). Only patient 1 responded**



**Figure 2:** The Patient's CT scan was normal but an MRI revealed a 1.5 x 2 cm tumour localized in the tail of the pancreas (Arrows)



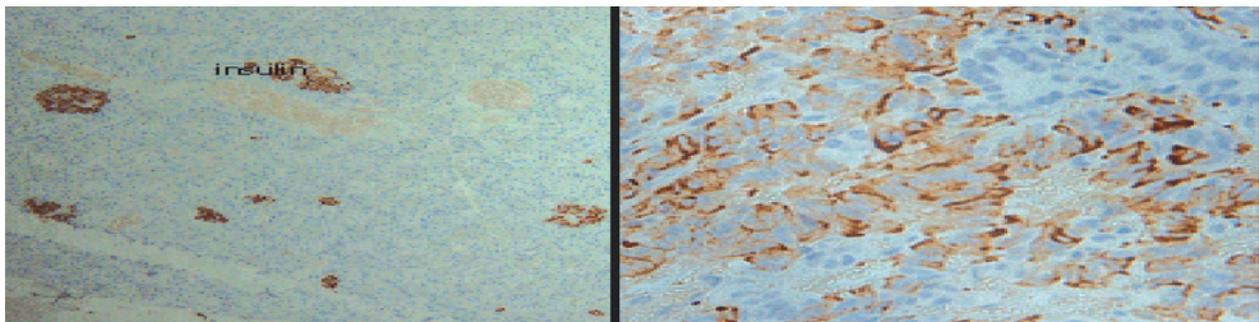
**Figure 3:** Patient's pancreatic tumour



**Figure 4:** Microscopic view of tumour

**Table 3:** WHO classification of pancreatic endocrine tumours

- 
- Well differentiated endocrine tumours
  - Well differentiated (low grade malignant) carcinoma with gross local invasion or distant metastasis
  - Poorly differentiated endocrine carcinoma small cell neuroendocrine carcinoma
- 



**Figure 5:** Insulin staining. On left normal staining, on right patient's tumour

**Table 4: Characteristics of well differentiated endocrine tumours**

Benign	Uncertain behaviour
<ul style="list-style-type: none"> <li>- No extrapancreatic spread</li> <li>- No vascular invasion &lt;2cm</li> <li>- &lt;2 mitoses/10HPF</li> <li>- &lt;2% ki-67 positive cells</li> </ul>	<ul style="list-style-type: none"> <li>- No extrapancreatic extension</li> <li>- BUT with one or more of these features:                             <ul style="list-style-type: none"> <li>&gt;2cm in size angioinvasion</li> <li>&gt;2% ki-67 positive cells</li> </ul> </li> </ul>

was started with diazoxide 50 mg three times a day, and thereafter he remained asymptomatic.

The results in Table 1 show an inappropriately high insulin concentration for the level of blood glucose. The detectable C-peptide excludes the injection of exogenous insulin as commercial insulins contain no C-peptide.<sup>1,2</sup> Sulphonylurea was not detected. These results confirm excessive and inappropriate endogenous insulin overproduction. Normally, circulating proinsulin levels account for less than 22% of the serum insulin value, but the ratio of more than 24% is seen in 90% of all insulinomas when greater than 40% malignancy is usually indicated. Our patient’s value was more than 50% and he has to be carefully followed up. An octreotide trial [Table 2] produced no significant change in blood glucose or insulin levels and therefore an octreotide scan was not done. Only 50% of insulinomas have octreotide receptors and in these cases the drug can be used therapeutically<sup>6</sup> [Fig 1] or to locate the tumour by scanning with indium III labelled hormone.

Two weeks later, he was admitted for further assessment. There had been no attacks of hypoglycaemia since starting on diazoxide. He underwent laparoscopic distal pancreatectomy<sup>7</sup> and the tumour was localized by intraoperative laparoscopic ultrasound during surgery.<sup>8</sup> The surgery was uneventful and the histopathology confirmed an insulinoma [Figs. 4-5] of “uncertain behaviour” by WHO classification [Tables 3 & 4].

Since surgery, the patient has been very well with no hypoglycaemic attacks and he is looking forward to the next Ramadan moon to undertake his fast.

**DISCUSSION**

This case illustrates the necessity of good history taking. The patient’s symptoms very clearly improved by taking food. The family gave a vivid description of how he was often too weak to walk to the table for his meals. He would sometimes sink to the ground and the family would restore him by bringing food to him. During Ramadan, by midday, he would be weak and confused

until breaking his fast. Hypoglycaemia was not, however, suspected and he was referred to neurology and psychiatric clinics. In the Mayo Clinic series of 224 cases of insulinoma as many as 20% of patients had been misdiagnosed as having neurological or psychiatric disorders.<sup>2</sup>

In this article, we have outlined a systematic approach to the investigation and management of patients with spontaneous hypoglycaemia.<sup>9</sup> The largest series in the literature is from the Mayo Clinic<sup>2</sup> where, in an 80-year period, 224 cases were seen. 87% were benign tumours, 6% were malignant, and 7% were associated with MEN-1. Their follow up shows a higher recurrence rate in patients with MEN-1 [Figure 6]. Patients with benign insulinomas had a survival rate which did not differ from that expected in the general population. This is not the case in those with malignant insulinomas [Figure 7].

MEN-1 is excluded in our patient as the pituitary CT scan and bone profile were normal. He is now free of symptoms since surgery done in November 2006. In the Mayo Clinic series, a cure has been defined as being totally free of symptoms for 6 months after removal of the insulinoma.<sup>2</sup>

The next Ramadan fast will be used to confirm the success or otherwise of his treatment.

**CONCLUSION**

The symptoms of hypoglycaemia may include loss of consciousness, convulsions and personality changes. In such a patient, hypoglycaemia should be looked for and, if found by Reflocheck, two venous samples must be taken immediately; one for laboratory confirmation of the glucose and insulin level and the other stored for C-peptide, pro-insulin and sulphonylurea measurement, if indicated. This must not delay the administration of intravenous glucose, which should be given without awaiting a result. If in such a patient hypoglycaemia is found by finger prick sampling, it is essential to take two venous samples immediately. One sample should

be taken for laboratory confirmation of the glucose and insulin levels. The other should be stored for other possible investigations (C-peptide, pro-insulin and sulphonylurea). You should then take a history from your recovering patient.

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