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BRIEF COMMUNICATION

Clinically-Defined Maturity Onset Diabetes of the Young in Omanis

Absence of the common Caucasian gene mutations

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داء السُّكَّرِيّ البادِئ عِنْدَ النُّضْج المحدد سريريا عند البالغين العُمانيين صغار السن

غياب المورّثات الجينية الشائعة في الغرب

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الملخص: **الهدف:** نستقبل أعدادا متزايدة من المرضى صغار السن المصابين بداء السكر الذي تشابه خصائصه السريرية مرض السكري البادىء عند النضج حيث التاريخ الأسري يشير الى تأثر مورّث أحادي، مع غياب الدليل الذي يشير الى وجود داء السكري من النوع الأول ذي المناعة الذاتية. الهدف من هذه الدراسة تحديد مسؤولية الطفرات الوراثية الثلاثة (العامل الكبدي النووي 4α ، والعامل الكبدي النووي – 1α، والجلوكوكاينيز) الاكثر شيوعا بين المرضى الغربيين من عدمه عند البالغين العُمانيين صغار السن. **الطريقة:** تمت الدراسة في مستشفى جامعة السلطان قابوس بسلطنة عُمان، حيث تم اختيار عشرين مريضا بالغا من صغار السن ممن لهم تاريخ أسَري باحتمالية التوريث بمورّث واحد بفترة تقل عن (18) شهرا، وكان متوسط الأعمار (25) سنة مع وسيط منسب كتلة الجسم (29). أجري التحري لوجود مضادات المناعة الذاتية ضد خلايا البنكرياس الجزيرية – نوع ب– و نازِعُ الكَرْبُوكسيل لحامض الجلوتاميك وكان سلبيا. وافق أربعة عشر مريضا على إجراء تحري فحص الدم الوراثي وتم إرساله لوحدة البروفيسور هاترسلي فَي كلية الطب بباكستر (المملكة المتحدة)، حيث تم فحص الحَمْضُ الرِّيْبِيُّ النَّوَوِي مَنْزُوع الأوكسجين للطفرات الجينية في الاكسون (10–1) من انزيم نازِعُ الكَرْبُوكسيل لحامض الجلوتاميك والاكسون (10–2) من مورّثات العامل الكبدي النووي(1α) والعامل الكبدي النووي (4α)، الطفرات الوراثية الأكثر شيوعا في اوروبا. **النتائج:** لم يتم العثور على أي من الطفرات الوراثية المذكورة في أي من المرضى. **الخلاصة:** في هذه المجموعه الصغيرة من المرضى العمانيين البالغين صغيري السن الذين تطابق حالتهم السريرية داء السكري البادِئ عِنْدَ النُّضْج لم يتم العثور على أي من الطفرات الوراثية الثلاث الأكثر شيوعا في الغرب. وهذا قد يكون ناتجا من وجود طفرات جديدة في المرضَى العمانيين أو أن هؤلاء المرضى يعانون من داء السكري من النوع الثاني نتيجة لتوريث بعض المورّثات التي تشكل خطرا في الاصابة المبكرة بداء السكري من النوع الثاني الذي يتميز بوجود مقاومة كبيرة للانسولين ناتجة عن السمنة .

مفتاح الكلمات: داء السكري – النوع الثاني، داء السُّكَّرِيُّ البادِئُ عِنْدَ النُّضْج، طفرات، داء السكري العائلي، البالغين الصغار، عُمان.

ABSTRACT: ***Objectives:*** We are seeing a progressive increase in the number of young patients with clinically defined maturity onset diabetes of the young (MODY) having a family history suggestive of a monogenic cause of their disease and no evidence of autoimmune type 1 diabetes mellitus (T1DM). The aim of this study was to determine whether or not mutations in the 3 commonest forms of MODY, hepatic nuclear factor 4α (HNF4α), HNF1α and glucokinase (GK), are a cause of diabetes in young Omanis. ***Methods:*** The study was performed at Sultan Qaboos University Hospital (SQUH), Oman. Twenty young diabetics with a family history suggestive of monogenic inheritance were identified in less than 18 months; the median age of onset of diabetes was 25 years and the median body mass index (BMI) 29 at presentation. Screening for the presence of autoimmune antibodies against pancreatic beta cells islet cell antibody (ICA) and glutamic acid decarboxylase (GAD) was negative. Fourteen of them consented to genetic screening and their blood was sent to Prof. A. Hattersley's Unit at the Peninsular Medical School, Exeter, UK. There, their DNA was screened for known mutations by sequencing exon 1-10 of the GCK and exon 2-10 of the HNF1α and HNF4α genes, the three commonest forms of MODY in Europe. ***Results:*** Surprisingly, none of the patients had any of the tested MODY mutations. ***Conclusion:*** In this small sample of patients with clinically defined MODY, mutations of the three most commonly affected genes occurring in Caucasians were not observed. Either these patients have novel MODY mutations or have inherited a high proportion of the type 2 diabetes mellitus (T2DM) susceptibility genes compounded by excessive insulin resistance due to obesity.

Keywords: Diabetes Mellitus, Type II; Diabetes mellitus, maturity onset; MODY; mutations; Diabetes, familial; Young adults; Oman.

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Advances in Knowledge

1. It would appear that the maturity onset diabetes of the young mutations common in Caucasians are rare in Oman.

Application to Patient Care

1. Families with mutations of the beta cells potassium ATP channels may be identified and thus the use of insulin avoided

Diabetes mellitus (DM), both types I and II, is common worldwide and now affects more than 5% of all obese adolescents;[1-4] however, optimal investigation and management is still unclear. Doctors often struggle to provide the best therapy, especially in regions where lifestyle changes in the last one or two generations have contributed to the diabetogenic risk.

In Oman, as in other countries of the Arabian Peninsula, type 2 diabetes (T2DM) especially and other complex, multifactorial disorders have reached epidemic levels.[5] We are now seeing a progressive increase in the number of young Omani diabetics (<25 years) with a family history indicating a monogenic cause of their disease and who have no evidence of type 1 diabetes mellitus (T1DM). These patients have clinically defined maturity onset diabetes of the young (MODY), a disorder resulting from mutation in 6 different genes causing deficient insulin secretion. They are often misdiagnosed as T1DM and treated with insulin. However, some patients have mutations in the genes encoding HNF1α or β-cell potassium adenosine triphosphate (K-ATP) channels both of which respond well to low dose sylphonylurea (SU) therapy. To date, we have identified three such families (not included in the present study) who were able to discontinue insulin and continue on SU therapy alone. Clearly therefore, MODY exists in Oman and in this study we have screened an additional 14 patients for common MODY mutations.

Methods

Twenty young diabetics with a family history suggesting monogenic inheritance [Figure 1], and whose antibodies against pancreatic beta-cells islet cell antibodies (ICA) and glutamic acid decarboxylase (GAD)) were negative, were identified in less than 18 months. Of these 14 patients, whose characteristics are shown in Table 1, consented to genetic screening and their blood was sent to the Molecular Genetics Laboratory at the Peninsular Medical School, Exeter, UK. There, their DNA was screened for known mutations by sequencing exon 1-10 of the glucokinase gene and exon 2-10 of the HNF1α and HNF4α, the commonest forms of MODY in Europe[6] using the DNA ABI PRISM® 3100 Genetic Analyzer,

Results and Discussion

In this small group of young Omani diabetics, we expected to find several with known MODY mutations, particularly as we have already identified 3 different MODY families responsive to SU therapy. Surprisingly, this was not the case and mutations in the three commonest forms of MODY were not observed, although all had family histories suggestive of a monogenic cause of their disease and no evidence of T1DM. How might this be explained? Either these patients had novel MODY mutations or have inherited one or more of the T2DM susceptibility genes. Novel mutations cannot be ruled out as, in a recent and larger Danish study, mutations were found in only half the patients with clinically defined MODY, as ours.[7] Interestingly, patients with clinically defined MODY in Mexico and China[8,9] have few of the documented mutations occurring in Caucasians which suggests that our Omani MODY patients may have novel gene mutations as well. However, we suspect that early onset T2DM is more likely, particularly as the median BMI in our study group was 29, an additional factor associated with early onset disease.

MODY is a familial monogenic form of diabetes with autosomal dominant inheritance and high penetrance of 80–95%. In contrast to type 1 and type 2 diabetes, MODY usually develops below 25 years[6,10] [Figure 2]. Currently there are 6 identified gene mutations, three of them, HNF1α, HNF4α and glucokinase, are common and account for >80% of MODY cases in Europe and North America, while others are rare (HNF1β, insulin promoter factor 1 and neurogenic differentiation factor 1).[10] Some of the MODY patients will not

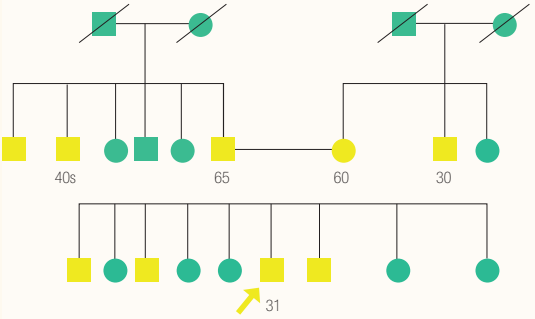
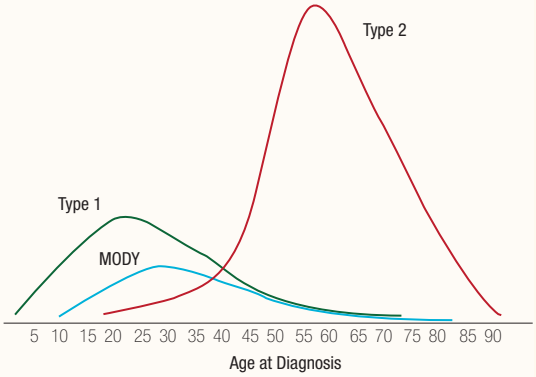


Figure 1: Pedigree of index Omani patient. The numbers indicate the age at diagnosis



Legend: MODY = maturity onset diabetes of the young
Figure 2: *Age at onset with differnt types of diabetes*

Table 1: Details of the 14 patients with a family history suggesting a monogenic cause of their disease. Shown is the median and range of age and BMI at diagnosis. Four were taking insulin alone and 10 oral hypoglycaemic agents.

Age at diagnosis/Yr Median	Sex	BMI	Therapy	GAD / ICA
20 (12-40)	10 M	29	INS	Negative
	4 F	20-41	OHA	Negative

Legend: BMI = body mass index; GAD = glutamic acid decarboxylase; ICA =islet cell antibody; INS = insulin; OHA = oral hypoglycaemic agents

have a known gene mutation (MODY X), but efforts are on going to determine the responsible mutations.[10, 11]

With young patients, the clinician should distinguish between T1DM (with autoimmune destructions of the beta-cells and insulin dependence), monogenic defects due to the maturity onset of diabetes in the young (MODY) and T2DM which is multifactorial.[3,12,13] With their early age of onset, patients with single gene disorders such as MODY are often misdiagnosed as T1DM and inappropriately treated with insulin.[12,14-16] This is unfortunate as patients with glucokinase deficiency (GKD) have few complications and rarely require treatment.[13,17] Furthermore, patients with transcriptions factor mutations (such as HNF1α and neonatal Kir6.2) respond dramatically to sulphonylurea medication.[14] Recently, we have successfully switched diabetics, from three families, from insulin of many years duration to oral SUs. Although monogenic DM in the UK is only estimated to occur in 1–2% of the diabetic population (i.e. up to 40,000 patients), in Oman the incidence of monogenic disease is probably much higher due to the higher rate of consanguinity.

Mutagenesis screening is expensive so we are now actively screening candidate patients using a trial of SU therapy. Screening is carried out in patients aged <30 years who are taking insulin, have a positive family history and no GAD or ICA antibodies. Of the 10 patients studied so far 3 have gratifyingly responded to low dose SU therapy. This trial is currently in progress, together with screening of the patients for the T2DM susceptibility genes which are currently known to be associated with T2DM.[18-21]

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