REVIEW

Do we need to test for maturity onset diabetes of the young among newly diagnosed diabetics in Saudi Arabia?

Suzanne Elkholy a,b,*, Amer A. Lardhi c

a Department of Pediatrics, King Fahd Military Medical Complex, Dhahran, Saudi Arabia
b Ain Shams University, Cairo, Egypt
c Department of Pediatrics, King Fahd Hospital of the University, Al-Khobar, University of Dammam, Saudi Arabia

Received 8 November 2010; accepted 18 January 2011

Abstract    Monogenic forms of diabetes are still rare and not well understood. Their prevalence among children and young adults at diagnosis is thought to be between 1% and 2% of cases of diabetes. However, awareness of these conditions may be lacking, and screening for them genetically is not routinely undertaken, even when the clinical picture may point to their probability. The aim of this work is to identify the indicators for suspecting cases of monogenic diabetes beyond the neonatal period in children and young adults in Saudi Arabia, and to provide a draft for baseline investigations for those suspected cases, depending on available resources. The implications of the diagnosis of such conditions would be better management of cases, providing genetic counseling to families and planning health resources.

© 2011 International Journal of Diabetes Mellitus. Published by Elsevier Ltd. All rights reserved. doi: 10.1016/j.ijdm.2011.01.006

1. Introduction

Will my child need insulin for life?

When a family is given the diagnosis of diabetes for their child, this is the most commonly asked question we hear where we practice. Type 1 diabetes remains the most common type of diabetes diagnosed in children and young adults. Therefore, we usually advise parents that insulin will be needed for life. There is however an increasing incidence of type 2 diabetes with the global endemic of obesity and other rare types of monogenic diabetes. In these conditions, insulin may not be needed for life.

In Saudi Arabia, there is increased consanguinity with first degree cousin marriages, which is not only allowed but socially favored. Hence genetic disorders like monogenic diabetes may be more prevalent. Therefore, it would be logical to consider monogenic forms of familial diabetes in the differential
diagnosis of newly diagnosed cases. The exact prevalence of monogenic diabetes is not known in Saudi Arabia.

2. Aim of the work

The aim of the current work is to look at a possible algorithm for diagnosing monogenic diabetes among children and young adults beyond the neonatal period, in an area of high consanguinity in the middle-east. The literature will be searched for evidence of when to suspect monogenic diabetes and according to the clinical picture, what genetic tests to request.

We will also search the literature for the best management of diagnosed cases, genetic counseling of families and implications for other family members. Cases of monogenic diabetes presenting in the neonatal period will not be discussed, as they are beyond the scope of this work, and the main aim is to differentiate type 1 diabetes from monogenic forms.

2.1. What is monogenic diabetes?

Monogenic diabetes is not a single diagnosis. It is a group of disorders mostly dominantly inherited, causing beta cell dysfunction [1]. They are usually caused by single gene defects that can occur de novo in a child, but more commonly, a family history is present [2]. The importance of making the diagnosis is that there may be implications for the child in the form of a change in treatment from insulin to oral hypoglycemics, and for the family in diagnosing other family members and counseling for future pregnancies. The health care implications noted are the change to a less costly treatment and, in some cases, no need for treatment at all.

2.2. Clinical picture

Mostly presenting with hyperglycemia, and being in the pediatric age group, patients are given the diagnosis of type 1 diabetes [3]. The point that may direct the attention of the pediatrician/diabetologist to the possibility of monogenic diabetes is the occurrence of diabetes in the family, in particular a dominant type of inheritance such as 2–3 generations of diabetes [4]. This criterion can sometimes be challenging, with the increasing number of families with type 2 diabetes. However, as maturity onset diabetes of the young (MODY) genes do not exclude type 2 diabetes [5], a positive family history should still be taken into consideration.

It is therefore our view that more weight should be placed on a typical autosomal dominant type of family history of diabetes in the family. Other sporadic cases of diabetes in the family should also alert the physician to the possibility of genetic conditions, as a family history of diabetes is found in only 2–4% of type 1 diabetes patients [6]. With positive consanguinity in the family, this gives even more significance to a positive family history. The prevalence of consanguinity in Saudi Arabia is 56%, with first-degree cousins reaching up to 40% [7–9]. Although most types of MODY are transferred by autosomal dominant inheritance, which is generally not increased in consanguineous marriages, there are some autosomal recessive presenting types, e.g., MODY 4.

The second point that alerts to the possibility of monogenic diabetes is reduced insulin requirement. Children with type 1 diabetes usually require between 0.75 and 1 U/kg/day, and this can change with activity, diet, age with great individual variations as well. When children are controlled with around 0.5 U/kg/day of insulin achieving good control the possibility of monogenic diabetes has to be raised [10].

The third indicator for testing for MODY is preserved insulin secretion after the honeymoon phase, which is generally agreed as 3 years from onset of type 1 diagnosis [1]. Endogenous secretion is tested for by detectable C-peptide (> 200 nmol/l) with blood glucose level of 8 mmol/l [1]. Insulin level is not used, as the children are usually on exogenous insulin as treatment, and C-peptide is a true reflection of endogenous insulin production. The preserved endogenous insulin production can explain the lack of ketosis, with hyperglycemia seen in many cases of monogenic diabetes at presentation [11].

The fourth indicator to consider, which in our view would be the earliest to detect at presentation, is the absence of auto antibodies in the pancreatic islets. It is recommended that a variety of antibodies be measured at the diagnosis of type 1 diabetes, when the results of these antibodies are negative, the likelihood of monogenic diabetes is greatest. Although up to 30% of type 1 diabetes cases may have negative antibodies at diagnosis, when all antibodies are negative, together with the absence of stigmata for insulin resistance, this indicator can be of most value [12–14].

Type 2 diabetes in children is occurring with increased frequency [15]. MODY genes have been identified in a number of cases of type 2 diabetes in adults, and the occurrence of the gene does not exclude the diagnosis of type 2 diabetes [5]. The diagnosis of type 2 diabetes in children may not be correct, however, if the child is of normal body weight [16], with no signs of insulin resistance specially acanthosis nigricans [17], and with normal fasting levels of C-peptide [18].

2.3. Clinical indicators for MODY

2.3.1. History

Child is generally well prior to presentation, with possible coincidental finding of hyperglycemia. Positive family history of 2–3 generations of at least one side of the family carries the highest value, followed by a positive family history of diabetes in a parent. Positive consanguinity in the family will generally increase the likelihood of genetic diseases but the exact incidence in monogenic diabetes has not been reported. Although most MODY cases are known to be autosomal dominant, some types, e.g., MODY 4 have presentations of mild diabetes in heterozygous state.

2.3.2. Examination

The child is usually well on physical examination, with no signs of diabetic ketoacidosis, which may be the case for up to 20–40% of cases of type 1 diabetes [19]. The child’s body mass index (BMI) is within an acceptable range for age and sex.

No clinical stigmata of insulin resistance as acanthosis nigricans.

No manifestations of syndromic insulin resistance, e.g., hirsutism, lipodystrophy, etc.

On follow up, metabolic control is achieved with low doses of insulin and minimal effort regarding diet control and exercise, at least initially.
2.3.3. Laboratory investigations

Hyperglycemia may be severe, but may be mild and only with fasting in some cases of monogenic diabetes [1]. Ketones are usually negative on presentation, but may be present [19]. Auto antibodies against pancreatic islets are negative [12]. On follow up; residual C-peptide levels beyond the honeymoon period.

In our opinion, if a child or young adult fulfills most of the above criteria, he or she will benefit from genetic testing for MODY.

Now that we suspect, what to do?

When faced with a clinical scenario, as above, it is tempting to look for a “genetic diagnosis for MODY”. Some genetic laboratories provide a clinical sheet to be filled in by the referring physician, which would include history, clinical findings and biochemical investigations. Experts in these labs will then direct the testing towards the most probable diagnosis, based on these findings. This may not be the case in all centers when a specific test needs to be requested; otherwise it will be financially unacceptable to run the panel for the full range of monogenic diabetes. It will therefore be useful to have clinical and laboratory indicators for different types of MODY, and hence, advise the lab as to which diagnostic test is required.

Neither types 1 and 2 diabetes has a diagnostic test, whereas monogenic diabetes can be diagnosed by genetic tests in about 80% of cases at present [1].

2.4. Indicators for type of MODY

Some forms are easily distinguishable, owing to major clinical findings, e.g., MODY 4. Mutation of insulin promoter factor-1 α, which is required for both endocrine and exocrine functions of the pancreas. Therefore, cases of MODY 4 will have exocrine pancreatic insufficiency, as well as being extremely rare [20,21].

Another type, MODY 5, is caused by mutation of HNF 1β, which is a transcription factor that can cause extra pancreatic diseases such as uterine hypoplasia in females, and hypospadius in males. Other distinctive findings are non diabetes related renal problems like oligomeganephrons, renal cysts and hypoplastic glomerulonephric cysts [22]. These findings can be detected by abdominal and renal ultrasound, which are non invasive and cost effective investigations and can guide towards the diagnosis.

Other forms of monogenic diabetes, MODY 3 (most common type), MODY 1 and glucokinase deficiency (GKD) do not have clinically distinct features, and may need an oral glucose tolerance test (OGTT) for diagnosis.

2.5. Value of OGTT for diagnosis of MODY

Type 1 diabetes presents with insidious onset of polyuria, polydipsia, polyphagia and loss of weight or acute onset of DKA [23]. Oral glucose tolerance is not usually required for diagnosis, as random venous blood glucose is usually above 11.1 mmol/l, which is the cut off for acceptable as defined by WHO criteria for diagnosing diabetes [24].

When suspecting a case to be monogenic diabetes or type 2 diabetes, an OGTT may help to reach a diagnosis and narrow the differential to the type of MODY. The test, however, requires the child to be present in the ward/day unit for a few hours after an overnight fast, and may be difficult for small children. It is not without complications, especially rebound hypoglycemia if hyper-insulinism is an association, and it requires monitoring of the child.

Stride et al. [25] assessed Oral Glucose tolerance in a multi center trial involving 362 individuals with genetically diagnosed MODY, including 162 patients below 20 years of age. In this study, patients were off treatment either as insulin or oral hypoglycemics for 1 week prior to the OGTT. This is not feasible when a child is newly diagnosed as having diabetes, and guidelines require the start of insulin treatment unless a molecular diagnosis proves MODY, and then the gradual withdrawal of insulin, followed by the introduction of oral agents, is started under strict supervision. Children as young as 2 years of age experienced OGTT during this study. This, however, needs to be performed only in highly specialized centers.

However, what is learned from this study is very valuable. The authors recommend that impaired fasting glucose alone, without the need for OGTT, may be helpful in cases of GKD. More than 70% of patients with GKD at less than 20 years of age had impaired fasting blood glucose. This may not be noted in very young children, but impaired fasting levels were seen on retesting.

If patients with GKD underwent OGTT, the increment of plasma glucose was noted to be small (less than 3.0 mmol/l) compared to patients with hepatocyte nuclear 1 alpha (HNF 1α) [25]. HNF 1α patients, however, had normal fasting blood glucose in all cases below 20 years of age. Some of them had normal glucose tolerance, especially those below 10 years of age. However, the overall conclusion drawn from the study when including all age groups has shown a large increment in blood glucose during OGTT (> 3.0 mmol/l) [25].

Another mutation of HNF 4α gene causes similar clinical picture to HNF 1α but are less common [11]. Patients have lower renal threshold, and may present at an older age than HNF 1α. This group of patients’ OGTT was not studied by Stride et al.

The study by Stride et al. has shed first light on the glucose tolerance in cases of MODY, and also provided information about progression of different types. It would be most useful to screen family members of affected individuals before sending them for genetic testing, or to test individuals early on in the course of the disease, to decide which test to send for screening.

We see this as most feasible in young adults who are metabolically stable and with no evidence of ketosis. They have to be educated about screening for blood glucose and ketones and reporting to hospital immediately in cases of hyperglycaemia or positive ketonemia or ketonuria.

We do not propose to keep children off treatment for a week prior to an OGTT test when one doubts the diagnosis of diabetes, as type 1 remains the most common cause. If there is strong family history of MODY in family and criteria previously defined, treatment can be started then blood sent for genetic testing. Initially for HNF 1α gene the most common of MODY, or the glucokinase gene, if the child has impaired fasting glucose.
A summary of the clinical criteria of different types of MODY and relative prevalence in UK [1] is shown in Table 1. Unfortunately, no similar data are available in the Middle East. There is one study postulating MODY as a presentation in “Non Insulin dependent Diabetes” presenting in young adults in Saudi Arabia [26], but no genetic testing was conducted. A case report of the first family of MODY in Saudi was reported by our group in 2008 [27]. The case presented with hyperglycemia for many months, as noted by the mother, who was also diabetic. The child had normal BMI, no acanthosis nigricans and positive family history of diabetes in family. Her antibody screen was negative, and genetic diagnosis revealed HNF 4α mutation in the child, one affected brother and her father who also had diabetes. A younger sister had the mutation but was euglycemic.

Therefore, we feel that awareness of the diagnosis and clinical findings will lead to the suspicion of MODY and earlier diagnosis.

### 3. Treatment of MODY

As previously mentioned, monogenic forms of diabetes are a group of disorders with distinct clinical features and pathophysiology. Therapy would therefore be directed towards the metabolic condition of the patient, and individualized according to the specific diagnosis and possible outcome.

Diagnosis of cases with glucokinase mutation may be difficult in children, as previously mentioned, due to mild incidental fasting hyperglycaemia. Currently there appears to be no benefit in treating patients in the pediatric age group, as fasting hyperglycaemia remains stable even without treatment, with HbA1c being just above the acceptable range [25]. Microvascular and macrovascular complications are rarely seen, even without treatment in these patients [28].

The real challenge is to treat patients with HNF 1α mutations who were previously diagnosed as type 1, and started on insulin. Once molecular diagnosis is available, the possibility of discontinuing insulin needs to be discussed with the family [29]. In our experience, most pediatricians would prefer to gradually reduce insulin doses before introducing oral hypoglycemics.

Patients with HNF 1α usually respond to sulphonylurea in much lower doses than those used for type 2 treatment [30]. Patients may even be managed by diet initially, but this will need close follow up in terms of adherence, to avoid the deterioration of metabolic control. Families should be advised that the need for treatment is expected, as progressive deterioration of beta cell function is anticipated. They can be maintained on sulfonylurea for a long time, with very good control. Insulin may be needed in some cases.

Patients with mutations of HNF 4α would also benefit from sulfonylurea, but would be expected to require insulin should beta cell dysfunction progress [31].

### 4. Recommendations for follow up

There are no current guidelines for the management of MODY in children and young adults. Stride et al. [25] provided a model for progression for HNF 1α and HNF 4α (being clinically similar) as well as GKD.

Therefore, the recommendations that could be drawn are that patients with glucokinase may not need treatment and could just be followed up by serial fasting blood glucose. We suggest serial glycated hemoglobin may be helpful to recognize continued high blood glucose that would indicate remote possibility of microvascular or macrovascular complications (Figs. 1 and 2).

HNF 1α and HNF 4α, however, need to be followed up and treated as mentioned above. These types are known to be associated with microvascular and macrovascular complications, and therefore I postulate that the same recommendations as those for type 1 diabetes be followed.

It should be noted that current knowledge of prognosis and long term follow up for these conditions remain limited, due to smaller number of patients diagnosed when compared to type 1 and type 2 diabetes. The case for the pediatric population is even worse when there are no randomized controlled trials for the management of these cases in the pediatric age group. Most data is extracted from the adult population, and few long term studies are available so far.

We would therefore recommend that children and young adults with HNF 1α and HNF 4α mutations be followed up

<table>
<thead>
<tr>
<th>Table 1</th>
<th>summary of clinical criteria of different types of MODY and relative prevalence in UK [1].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Number of families identified in UK</td>
</tr>
<tr>
<td>HNF 1α (MODY3)</td>
<td>Dominant</td>
</tr>
<tr>
<td>HNF 4α (MODY1)</td>
<td>Dominant</td>
</tr>
<tr>
<td>Glucokinase (MODY2)</td>
<td>Dominant (may not be diagnosed in parents as mild)</td>
</tr>
</tbody>
</table>
according to current guidelines for Type 1 diabetes, until more research is available to allow special guidelines for this group of patients.

5. Implications for other family members

With the diagnosis of any genetic disorder comes the question of testing other family members and the implications of a positive test. Adults have the legal right to consent to be tested for genetic disorders and know if they are affected or non-affected carriers, or free from the disorder. They can then make informed choices about jobs, partner’s future pregnancies, etc. However, these tests, when undertaken, need to be under the guidance and counseling of health care professionals who are experts in the field of genetic disorders, and can provide reliable information. The financial burden of these tests on the health care authorities needs to be taken into account as well.

Minors, however, present a further challenge. Parental consent from biological parents or individuals with parental responsibilities needs to be sought in all situations. Unless the child is clearly affected by a genetic condition and molecular diagnosis will aid diagnosis and guide treatment, ethically genetic testing can be a problem. For example, a genetic disorder may be manifest at a later stage in life, and the knowledge of its possibility will limit life choices for the child unnecessarily. On the other hand, knowledge of a condition that may not have presented clinically yet may initiate early follow up and delay, or prevent complications.

Therefore, offering genetic testing to families is dependent on the nature of the disease and what is known of its mode of inheritance and natural course. In cases of monogenic diabetes, it is our view, that all family members would benefit from screening by OGTT in cases of HNF mutation, and this is also recommended by Stride et al. [25]. GKD patients’ family members however would benefit from only serial fasting blood glucose estimation.

Those positive by screening can be offered genetic testing. Females in the child bearing period would generally benefit, as they would be prone to diabetes associated with pregnancy.

6. Recommendations for future research

We recommend that cases of suspected familial diabetes seek genetic testing for common forms of MODY. Collaboration and communication between different centers in different countries in the same region will allow a larger number of patients to be identified, and therefore, follow up and prognostic conclusions can be drawn more effectively. OGTTs can be performed on patients in specialized centers, to allow for guidance on the molecular genetic testing of suspected cases. Insulin should not be denied to any child or young adult with newly diagnosed diabetes, whose metabolic condition is not stable, awaiting OGTT or genetic studies.

7. Summary

The incidence of monogenic forms of diabetes has not been identified in Saudi Arabia. In our experience of working with children and young adults with diabetes, our group has identified one family and reported it. Whether there are more cases undiagnosed remains unknown. More awareness of the disorder is needed for better diagnosis and management.

Therefore, as an answer to our initial question, testing for MODY should not be considered routinely. It should be offered to select cases, where clinical and biochemical indicators dictate. We propose the algorithm in this work as an initial framework, which can be reviewed and modified in the future.
References


