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REVIEW

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

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KEYWORDS

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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.

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

Abbreviations: BMI, body mass index; GKD, glucokinase deficiency; HbA1c, haemoglobin A1c; HNF 1α, hepatocyte nuclear 1 alpha; HNF 4α, hepatocyte nuclear 4 alpha; MODY, maturity onset diabetes of the young; OGTT, oral glucose tolerance test

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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 hyperglycaemia. 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., hirsuitism, 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.