

Monogenic Diabetes, Case Series from Four Arab Countries

Khadiga Eltonbary^{1,2}

Department of ¹Pediatrics, Faculty of Medicine, Ain Shams University, Egypt.

Department of ²Pediatrics, Dr. Soliman Fakeeh Hospital, Saudi Arabia

*Corresponding author: Khadiga Yehia Elsayed Eltonbary, **Mobile:** (+20)01010477244, **E-Mail:** khadigadoc@yahoo.com

ABSTRACT

Background: Monogenic diabetes results from the inheritance of a mutation in a single gene. It may be dominantly or recessively inherited or may be de novo. **Patients and Methods:** Five cases were described in a single center in Jeddah, all were products of first cousin marriage. Three infants aged 2-3 months, including two siblings from Egypt and one from Saudi Arabia were found to have diabetes after hospital admission for gastroenteritis. The fourth case (Yemeni) was admitted with anemia and failure to thrive, picked up during routine clinic visit at the age of four months, hyperglycemia was detected during routine hospital workup. The fifth case is a four years old Jordanian child with accidental finding of hyperglycemia during routine workup during admission for pneumonia, with history of gestational diabetes and an affected grandparent. All patients, but the fifth, was started on insulin after collecting samples from patients and parents for molecular genetic testing. **Results:** The first three patients were diagnosed with Wolcott Rallison, having mis-sense mutation of EIF2AK3 and all expired by almost the age of 6-7 months. Thiamine responsive megaloblastic anemia was confirmed with homozygous SLC19A2 mutation in the Yemeni patient. Last child showed typical profile of fasting hyperglycemia and with the typical family history, was diagnosed on clinical basis as Glucokinase MODY. **Conclusion:** Awareness with different forms of monogenic diabetes is essential for early diagnosis, especially in countries with high rates of consanguineous marriage. Genetic diagnosis is also mandatory in management, especially in the first six months of life.

Keywords: Glucokinase, Monogenic diabetes, Neonatal diabetes, Wolcott Rallison.

INTRODUCTION

Monogenic diabetes results from the inheritance of a mutation in a single gene. It may be dominantly or recessively inherited or may be a de novo mutation⁽¹⁾.

Although, monogenic diabetes represents only small proportion of diabetes cases in children and adolescents group, but to date, up to 50 genetic mutations have been described⁽²⁾. Detecting the underlying genetic defect improves the understanding of pathophysiology and facilitates management⁽³⁾.

Although recent breakthroughs have been made in discovering the genetic abnormalities that rise to monogenic forms, it is believed that 80% of such instances remain undetected and are labelled monogenic based on clinical criteria⁽⁴⁾.

Clinical suspicion has been the main motivation for detecting monogenic forms of diabetes for many years. The presence of neonatal diabetes, which can be transitory or persistent, is one of the most critical characteristics that signals to potential. In teenagers and young adults, an autosomal dominant pattern with a family history of diabetes is another key clue⁽⁵⁾.

Saudi Arabia is a country with lots of expats mainly from other Asian and Arab countries. Arab countries are reported to have the highest rates of consanguineous marriages in the world, and primarily first cousin marriages, reaching up to 25-30% of all marriages⁽⁶⁾. The aim was to report different cases of monogenic diabetes that are common among Arab communities with high rates

of consanguinity and to highlight the need for genetic testing when suspicion of monogenic forms is high.

SUBJECTS AND METHODS

Five cases were reported in a single center in Jeddah. Dr. Soliman Fakeeh Hospital is a tertiary center in western area of Saudi Arabia.

Three infants including two siblings from Egypt and one from Saudi Arabia were found to have diabetes after hospital admission as cases of gastroenteritis and dehydration (aged 2-3 months) at diagnosis, later they presented with hepatomegaly and a picture of hepatorenal failure. The fourth case (Yemeni) was referred from primary care center when she was found to be pale and failing to thrive during a routine visit for vaccination.

The fifth case was a four years old Jordanian child who was found to have hyperglycemia during routine workup after hospital admission with pneumonia.

All patients, but the fifth, was started on insulin after collecting samples from patients and parents for molecular genetic testing for different forms of monogenic diabetes. Diabetes was defined by blood sugar of ≥ 200 mg/dl in more than one occasion, glutamic acid decarboxylase autoantibodies (GAD) was done (except for 5th) using ELISA and glycated hemoglobin (HbA1C) was done for all except the patient presenting with anemia and instead, a fructosamine test was sent out. Genetic analysis was performed in the Exeter Molecular Genetic Laboratory using custom designed Agilent Sure Select Target



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Enrichment, which allows detection of base substitutions (SNVs), small insertions and deletions (indels) and partial/whole gene deletions and duplications (CNVs), after obtaining written informed consent from parents.

Ethical statement:

Ethical approval of Dr. Soliman Fakeeh Hospital for publishing patient’s data was obtained. Written consents were taken from parents to report their cases.

RESULTS

The first three patients were products of consanguineous (1st cousin) marriage. First patient was Saudi girl, with a healthy 4 years old sibling. She was presented to emergency room at the age of two months, with an attack of gastroenteritis and dehydration with mild metabolic acidosis. Patient was admitted initially to pediatric intensive care unit, initial laboratory results revealed a blood sugar level of 429 mg/dl, HbA1C of 7.6, pH: 7.3 and HCO₃ of 14 mmol/l.

Patient had no phenotypic features of any skeletal dysplasia, she improved and started on neutral protamine Hagedorn (NPH) insulin and diluted short acting insulin aspart on demand with hyperglycemia. Sample for genetic testing revealed the diagnosis of Wolcott Rallison. At the age of six months, patient was readmitted with another attack of gastroenteritis, hepatomegaly and elevated liver enzymes; initial SGPT of 1381 IU/L and SGOT of 932 IU/L with a total bilirubin of 1.2 mg/dl. Patient rapidly deteriorated with a picture of hepatorenal failure and expired after 12 days. The next two patients were siblings originally from Egypt (Behira). First presented with an attack of dehydration and persistent vomiting at the age of two months. Investigations confirmed hyperglycemia and started on subcutaneous insulin. The patient lost to follow up and reported to have an attack of hepatitis and expired during a visit to Egypt. His sibling presented at the age of three months with hypotonia, hyperglycemia and diagnosis of diabetes were confirmed and was started on insulin. Thyroid functions and liver function tests were normal, however in five weeks she was admitted with jaundice and elevated transaminases and she expired. Genetic test confirmed diagnosis of Wolcott Rallison. These three

cases were all born at term with normal birth weight and there was no family history of diabetes.

The fourth case was for a four and half months old girl, second in order to first cousin parents with a healthy 35 months old sibling. She was referred by the primary care physician after her visit for vaccination. She was pale and failing to thrive since birth. Initial blood count showed an Hb level of 5.1 gm/dl MCV 98 fl, platelets of 145,000/mm³ with a normal total and differential leucocyte count. Routine blood sugar test showed hyperglycemia. No acidosis or ketosis was reported. Iron studies were normal and patient received blood transfusion initially but parents refused totally to consent for bone marrow test.

Fructosamine level was slightly elevated (315 mmol/l) and the patient was started on NPH insulin only with a minimal dose of 0.3 u/kg/day and blood sugar was controlled. Nine weeks later, genetic test revealed a diagnosis of thiamine-responsive megaloblastic anemia (TRMA) syndrome due to a homozygous mutation in the SLC19A2 gene.

Auditory brain stem response and echo-cardiography were done for the patient and she was found to have severe bilateral sensory neural hearing loss. From diagnosis and until genetic results came back she had another two transfusions and was then started after diagnosis on high dose thiamine and kept on NPH without need for further transfusion. Recently she was shifted to basal insulin Glargine.

The last patient was a four years old Jordanian boy, third in order of first cousin consanguineous parents. Grandfather had diabetes, controlled only with diet and mother reported gestational diabetes. None of them was obese or even overweight. He was found to have hyperglycemia during routine workup after hospital admission with pneumonia. With monitoring of blood sugar, the patient showed a pattern of mild fasting hyperglycemia <200 mg/dl, postprandial blood sugar was always in the normal range with an HbA1C of 5.8%. After counselling of parents about the high clinical suspicion of glucokinase genetic mutations, parents refused signing for genetic testing and understood the need to screen any other siblings with overt diabetes as the father still may carry the same mutation.

Table (1): Describe the general characteristics of the five reported patients

Case No.	Age at presentation (months)	Inheritance pattern	Initial blood sugar	Associated defects	Genetic defect	Outcome
1	2	AR	429	Hepatitis	EIF2AK3	Deceased
2	2	AR	398	Hepatitis	EIF2AK3(novel mutation)	Deceased
3	3	AR	275	Hepatitis	EIF2AK3(novel mutation)	Deceased
4	4	AR	169	Megaloblastic anemia/Sensory neural hearing loss	SLC19A2	On basal insulin
5	49	AD	253	None	Not done	Not on Insulin

DISCUSSION

Monogenic diabetes should be considered when a patient does not seem to fit with the clinical or laboratory criteria of type 1 or type 2 diabetes, especially in neonatal period, where monogenic diabetes is highly suspected⁽⁴⁾.

Early diagnosis is mandatory to avoid acute complications and to initiate treatment early as some common forms of neonatal diabetes, like KCNJ11 and ABCC8 (pancreatic ATP-dependent potassium channel genes), respond usually to sulfonyl urea⁽⁷⁾.

Consanguinity, which is common among Arab population, is highly suspicious in several monogenic forms of diabetes. Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disease, which should be highly suspected in cases with neonatal/early-onset diabetes. It is associated with skeletal dysplasia and growth retardation. Other associations include frequent episodes of acute liver failure, renal dysfunction, exocrine pancreas insufficiency, hypothyroidism, bone fractures and recurrent infections but with varying severity. Mutations in the gene encoding the eukaryotic translation initiation factor 2 kinase 3 (EIF2AK3), which is required for translation regulation during the unfolded protein response in beta cells, cause WRS⁽⁸⁾.

Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disease. Thiamine uptake into cells is disturbed leading to decreased activity of enzymes associated with thiamine pyrophosphate. This disorder has been linked to mutations within the SLC19A2 gene that encodes a functional thiamine transporter. Megaloblastic anemia, diabetes mellitus, and sensorineural deafness are the main symptoms of this condition. Other tissues that can be also affected include brain and retina⁽⁹⁾.

The diagnosis of TRMA should be suspected in the presence of megaloblastic anemia, especially in populations with high consanguinity rates. Treatment is with high thiamine supplementation, insulin is still required for some patients especially during pregnancy⁽¹⁰⁾.

With an estimated prevalence of 1 in 1,000 people, nonprogressive hyperglycemia linked to the glucokinase gene (GCK) is the most common cause of monogenic diabetes. GCK is the beta cell glucose sensor and is also responsible for hepatic regulation of glucose release and storage⁽¹¹⁾. Carriers of heterozygous mutations are asymptomatic and are diagnosed incidentally with laboratory testing or routine screening with hyperglycemia during childhood, pregnancy (most common) and acute infections^(4, 12). On the other hand,

homozygous mutations are associated with overt diabetes mostly in neonatal period.

CONCLUSION

Awareness with different forms of monogenic diabetes is essential for early diagnosis, especially in countries with high rates of consanguineous marriage. Genetic diagnosis is also mandatory in management, especially in the first six months of life, when insulin is not always the solution.

Compliance with ethical standards

Conflict of interest: The author declares no conflict of interest.

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