

Prediabetes in three siblings of a Nigerian boy with type 1 diabetes mellitus: Is this a case of familial clustering?

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ABSTRACT: We report a case of a 9-year-old Nigerian boy with confirmed type 1 diabetes (T1D) and whose three elder siblings (sisters) had pre-diabetes, defined by impaired fasting blood glucose, using the ISPAD most recent criteria. The fasting blood glucose levels of the siblings of the index patient were 6.1mmol/L, 5.9mmol/L and 5.6mmol/L, respectively. On insulin therapy, the boy's diabetes was well controlled with no hypoglycaemic episodes. The father of the index patient has type 2 diabetes mellitus and his diabetes was initially controlled with oral glucose-lowering agent for 10 years before switching to insulin therapy in the last seven years, following poor glycaemic control with the initial therapy. The three siblings of the index patient are currently being followed up with periodic retesting, using fasting and/or 2-hour postprandial blood glucose determinations as suggested in ISPAD recent guideline. Conclusion: A high index of clinical suspicion of diabetes mellitus is required in the siblings of any child with type 1 diabetes.

Key words: Familial clustering, genetics, impaired fasting blood glucose, pre-diabetes, type 1 diabetes

INTRODUCTION

Prediabetes, is defined as impaired fasting glucose (blood glucose level between 5.6mmol/L and 6.9mmol/L).¹ Impaired fasting glucose (IFG) is an intermediate stage in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes.² IFG is a measure of disturbed carbohydrate metabolism in the basal state.¹ Individuals with prediabetes are at increased risk of developing diabetes, diabetes complications and cardiovascular disease.²⁻⁴ The natural history of prediabetes is variable, with about 25% progressing to diabetes, 50% remaining in the abnormal glycaemic state, and 25% reverting to normoglycaemia over an observational period of 3-5 years.^{4,5} In 2005-2006, the prevalence of prediabetes among adolescents in the United States aged 12-19 years, using the ADA criteria was 13.1%.⁶ Reports of recent studies show that the incidence of pre-diabetes is increasing in children.⁷

Type 1 diabetes (T1D) is a multifactorial disease

with a strong genetic component. It is characterized by autoimmune destruction of pancreatic β cells. The human leucocyte antigen (HLA) region is a cluster of genes located within the major histocompatibility complex (MHC) on chromosome 6p21.⁸ It is estimated that HLA accounts for 40-50% of familial clustering and the strongest genetic association with T1D is conferred by HLA class II gene alleles.⁸ In addition to MHC class II associations, other different genetic loci contribute susceptibility to T1D.⁹ Examples include: (1) the insulin (INS) VNTR (variable number tandem repeats),¹⁰ (2) the Arg620 Trp single nucleotide polymorphism (SNP) at PTPN22 (protein tyrosine phosphatase nonreceptor 22),¹¹ (3) the noncoding SNPs at IL2RA,¹² (4) the variants in the CTLA4 locus.¹³ All these T1D-associated genes are expressed in cells with immune function, and all except INS have been associated with other immune disorders.⁹ Two recent genome-wide association studies have separately identified two loci that confer T1D risk. These loci are

16p13 locus¹⁴ and Chr12q13 locus.⁹ The effect of the insulin gene appears to vary with ethnicity, with lesser effect in non-Caucasian population.¹⁵ By dephosphorylating and inactivating T-cell receptor-associated Csk kinase, PTPN22 appears to be involved in preventing spontaneous T-cell activation.¹⁶ These considerations provide the link between the well-recognized associations of type 1 diabetes with genetic factors. Thus, providing an explanation for the increased incidence in some families, of the concordance rates in monozygotic twins and the ethnic and racial differences in prevalence rates.^{17,18}

Although the risk of developing T1D is increased in relatives of individuals with the disease, the risk is relatively low. This risk depends on which HLA haplotypes are shared.⁸ From multiple family pedigrees and HLA typing data, it is estimated that if a sibling shares both HLA D haplotypes with an index patient the risk for that individual is 12% to 20%; for a sibling sharing only one haplotype, the risk for T1D is 5% to 7%; and with no haplotypes in common the risk is only 1% to 2%.¹⁹ Indeed, Redondo et al,²⁰ stated that approximately 85% of new cases of T1D occur in persons without an affected first-degree relative. Approximately 13% of children and adolescents who develop T1D have a parent or sibling with diabetes.²¹ Dahquist and Gothefors²¹ reported that among children with newly diagnosed diabetes, 2-3% have a mother with T1D, 5-6% have a father with T1D, and 4-5% have a brother or a sister with T1D. The study of familial clustering is a central theme in genetic epidemiology. Familial clustering refers to the occurrence of a disorder at a higher frequency in first-degree relatives of an affected person compared to the general population.²² One widely used measure of familial clustering is the sibling recurrence risk ratio (s), which is defined as the ratio of risk of disease manifestation, given that one's sibling is affected, as compared with the disease prevalence in general population.²²

The purpose of this paper is to report a case of a Nigerian boy with T1D and whose three elder sisters had impaired fasting blood glucose (prediabetes). It is hoped that this report will encourage clinicians to assess for prediabetes in siblings of children with type 1 diabetes.

CASE REPORT

The patient is 9-year old boy with a 3-day history of polyuria and polydipsia. There was no significant weight loss. His father is known have type 2 diabetes which

was diagnosed 17 years ago. He had been on oral glucose-lowering agent for the first 10 years but switched to insulin in the past 7 years because unsatisfactory response to oral glucose-lowering agent. The ages of the father and mother are 51 and 47 years, respectively. Physical examination revealed weight 57kg (> 95th percentile), height 160cm (> 95th percentile) and body mass index, BMI 22.3kg/m² (> 95th percentile). No acanthosis nigricans. External genital examination revealed testicular volume 4ml bilaterally, stretched penile length 6cm and pubic hair Tanner stage 2. A diagnosis of a diabetes mellitus (newly diagnosed) was made. Laboratory investigations confirmed that he has type 1 diabetes mellitus. The laboratory findings at initial diagnosis are summarized in Table 1. His elder sister who accompanied him to the laboratory for fasting blood glucose (FBG) measurement decided to check her own fasting blood glucose and the result revealed that she has impaired fasting blood glucose (FBG 6.1 mmol/L). This prompted the measurement of FBG for his other two sisters. The laboratory findings in the three elder sisters are summarized in Table 2. The BMI of the siblings are as follows: first sibling BMI = 26kg/m²; second sibling BMI = 24kg/m²; and third sibling BMI = 21kg/m². The patient is the only son of his parents. He is currently in his first year in the Junior Secondary School. In relation to main meals, he was placed on rapid-acting insulin (Lispro) 5 units, 6 units and 4 units in the morning, afternoon and evening respectively. He also takes a long-acting insulin (glargine) 20 units at bedtime, between 9-10 pm. Total daily dose of insulin is 0.6U/kg/day. With this insulin regimen, the boy's diabetes is well controlled with no hypoglycaemic episodes. Consent was obtained from the parents of the patients. His blood glucose range were FBG 4.8-6.7mmol/L; prelaunch BG 4.3-6.9mmol/L and pre-dinner BG 4.1-6.4mmol/L. He is being followed up in the outpatient clinic. Other initial laboratory findings are summarized in Table 1. The three siblings of the index patient are currently being followed up with periodic retesting, using fasting and/or 2-hour postprandial blood glucose.

The age and laboratory findings in the three sisters of the index patient is summarized in Table 2 and it shows that their fasting blood glucose levels were in the prediabetic range.

DISCUSSION

In the index patient, the diagnosis of type 1 diabetes mellitus (T1DM) was based on the presence of clas-

Table 1. Summary of laboratory findings at initial diagnosis.

| Laboratory parameter | Results | Normal limits | Comments |
|-------------------------|--------------|------------------|-----------|
| Fasting blood glucose | 20.5 mmol/L | 3.0-6.1 mmol/L | Very high |
| HbA1C | 9.9% | 4.0-5.6% | Very high |
| Plasma triglyceride | 15.23 mmol/L | 0.31-1.08 mmol/L | Very high |
| Total serum cholesterol | 7.45 mmol/L | 3.11-5.16 mmol/L | High |
| C-peptide | 183 pmol/L | 364-1655 pmol/L | Low |
| GAD autoantibodies | <5IU/ml | 0-10 | Negative |
| IA-2 autoantibodies | < 10IU/ml | 0-20 | Negative |

GAD = glutamic acid decarboxylase IA-2 = Insulinoma-associated protein-2

Table 2. Summary of laboratory findings in three siblings of the index patient.

| Laboratory parameter | Age (years) | Results | Comments |
|-----------------------|-------------|------------|-------------------------------|
| Fasting blood glucose | | | |
| Sibling 1 | 21 | 6.1 mmol/L | Pre-diabetic value |
| Sibling 2 | 18 | 5.9 mmol/L | Pre-diabetic value |
| Sibling 3 | 15 | 5.6 mmol/L | Pre-diabetic value |
| HbA1C value | | | |
| Sibling 1 | 21 | 5.9% | Pre-diabetic value |
| Sibling 2 | 18 | 5.8% | Pre-diabetic value |
| Sibling 3 | 15 | 5.6% | Just below pre-diabetic value |

sical symptoms of diabetes mellitus, fasting hyperglycaemia (20.5mmol/L), elevated HbA1C (9.9%), and low C-peptide level. These findings are in keeping with the most recent International Society of Pediatric and Adolescent Diabetes (ISPAD) established criteria for the diagnosis of type 1 diabetes.¹ In addition, with insulin therapy, the boy's diabetes was well controlled with no hypoglycaemic episodes. The fasting blood glucose levels in the three elder sisters of the index patient were abnormal and met the most recent ISPAD and American Diabetes Association (ADA) criteria for the diagnosis of prediabetes (impaired fasting blood glucose).^{1,2}

The presence of prediabetes in the three sisters of the index patient is an interesting finding. This implies that all the four children in this family have an abnormal carbohydrate metabolism. The clinical implication is two folds. First, the three sisters are at increased risk of developing diabetes, diabetes complications and cardiovascular disease.² Secondly, the presentation of familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes (maturity onset diabetes of the young; MODY), which accounts for 1-4% of paediatric diabetes cases.^{23,24} As stated in ISPAD guideline, it is appropriate to always define monogenic diabetes by its

genetic subgroups.¹ The benefits of making a specific molecular diagnosis include prediction of expected clinical course of the disease and guiding individual case management. In addition, such specific molecular diagnosis has important implications for family members by promoting genetic counselling and extended genetic testing in other family members and this may lead to reclassification of their type of diabetes.²⁵ However, we could not investigate the siblings of the patient for monogenic diabetes because of inadequate of laboratory facilities in the setting where we practice. This represents one of the challenges of management of such clinical condition in resource-limited countries. The parents of these children declined oral glucose tolerance test (OGTT) for their daughters because of the fear that it could worsen their daughters' clinical condition. We, therefore, continued follow up with periodic retesting, using fasting and/or 2-hour post-prandial blood glucose level determinations as suggested in ISPAD recent guideline.¹ The father of these children is known to have type 2 diabetes which was diagnosed 17 years ago (at the age of 34 years). His blood glucose was initially controlled on oral glucose-lowering agent for the first 10 years but had to switch to insulin in the last 7 years because of unsatisfactory glycaemic control while on oral glucose-lowering

agent. Such switch from oral glucose-lowering agent to insulin therapy is a well documented phenomenon in the management of adulthood type 2 diabetes (T2D).²⁶ This switch in therapy is because of the progressive nature of T2D and the relative insulin deficiency that develops in individuals with long-standing diabetes mellitus.

Some of the risk factors for type 1 diabetes (T1D) in the siblings of the index patient need consideration. First, the age (9 years) of the index patient at diagnosis of T1D. A higher risk for T1D for siblings of an index patient who was diagnosed at a young age (below the age of 10 years) has been reported.²⁷⁻²⁹ In this regard, the sisters of the index patient are also at increased risk for development of T1D. The reason for this observation is not clear. However, Harjutsalo et al,²⁷ suggested that genetic effects in such families may be particularly strong. They proposed that a young age at onset in the first child diagnosed with T1D indicate an overall increased lifetime risk for T1D in siblings and that the process leading to diabetes seems more rapid in such siblings. Another explanation which has been proposed is that genetic or environmental factors that

precipitate earlier onset of T1D in the proband are shared with the first-degree relatives (FDRs) and may also increase their risk for T1D.²⁹ The male-sex status has been reported as a risk factor for T1D in siblings.²⁷ The index patient is a male, further pointing towards increased risk of T1D among his siblings. In the index patient, it is the father and not the mother that has diabetes mellitus. This finding concurs with the known fact that the risk of T1D in the offspring is higher when the father has diabetes compared with the mother. Studies have shown that T1D is 2-3 times more common in offspring of diabetic men (3.6-8.5%) compared with diabetic women (1.3-3.6%) and the increased cumulative risk in offspring of T1D fathers (4-9%) was higher compared with offspring of T1D mothers (2-3%).^{28,29} The reason for this parental sex difference is still unknown, although several hypotheses have been proposed e.g., genomic imprinting and immunologic tolerance in utero.^{30,31} Although familial aggregation accounts for about 10% of cases of T1D,³² there is no recognizable pattern of inheritance. In conclusion, a high index of clinical suspicion of diabetes mellitus is required in the siblings of a patient with T1D.

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