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Monogenic diabetes mellitus in cystic fibrosis

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Monogenic diabetes mellitus in cystic fibrosis

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Abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
<i>CFTR</i>	Cystic fibrosis transmembrane conductance regulator
DM	Diabetes mellitus
FVC	Forced vital capacity
FEV ₁	Forced expiratory volume in one second
GAD	Glutamic acid decarboxylase
<i>HNF1A</i>	Hepatocyte nuclear factor 1 homeobox alpha

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3	IA-2	Tyrosine phosphatase-related antigen 2
4	ICA	Islet cell antibody
5	MODY	Maturity-onset diabetes of the young
6	OGTT	Oral glucose tolerance test
7	ZnT8	Zinc transporter 8
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ABSTRACT

We present a non-consanguineous family of three siblings who presented with diabetes mellitus (DM), two of whom had genetically confirmed cystic fibrosis (CF), with one pancreatic-sufficient mutation in the CF transmembrane conductance regulator (*CFTR*) gene ($\Delta F508/R117H;IVS8-5T$). A detailed history revealed family members from three successive generations diagnosed with “type 1” or “type 2” diabetes, leading to genetic investigations for monogenic DM. A heterozygous frameshift mutation in the hepatocyte nuclear factor 1 homeobox alpha (*HNF1A*) gene (c.404delA) was subsequently confirmed in all three siblings, which is known to cause monogenic diabetes and is exquisitely sensitive to sulfonylurea therapy. Following this diagnosis, both siblings with CF and *HNF1A* monogenic diabetes were started on gliclazide therapy, whilst their older brother who had been wrongly diagnosed with type 1 diabetes was switched from insulin to gliclazide; all with excellent therapeutic responses.

INTRODUCTION

Cystic fibrosis (CF) is the commonest single gene disorder causing life-limiting respiratory disease in the Caucasian population worldwide, with the $\Delta F508$ mutation (c.1521_1523delCTT) in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene being the most prevalent. CF-related diabetes (CFRD) affects 20.4-50% of adults with CF,[1-4] and early initiation of insulin significantly decreases mortality in these patients.[3] However, pancreatic-sufficient mutations in *CFTR* exist which are less likely to cause CFRD,[5] and other forms of diabetes mellitus (DM) should therefore be particularly considered in their presence. We present a family of siblings who presented with DM on a background of CF, who were eventually found to also have monogenic diabetes.

CASE 1

Patient A was referred at the age of 12 years because of an abnormal OGTT (2-hour plasma glucose 12.6 mmol/l) on a background of CF (confirmed compound heterozygous *CFTR* mutation ($\Delta F508/R117H;IVS8-5T$), usually associated with pancreatic sufficiency).[6] From a respiratory point of view, she had been relatively stable with a body mass index (BMI) of 25.4 kg/m² (+2.2 SDS), Shwachman score of 95-100/100,[7] a Northern chest X-ray score of 0-3/20,[8] a forced expiratory volume in one second (FEV₁) of 62-112% predicted, and a forced vital capacity (FVC) of 72-107% predicted throughout the course of her care. She had never required intravenous antibiotics for CF.

Further investigations revealed an HbA_{1c} of 40 mmol/mol, detectable fasting insulin (11.2 mU/l) and C-peptide (1165 pmol/l (normal range 365-1655)), and negative

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3 glutamic acid decarboxylase (GAD) and islet cell (ICA) autoantibodies. A decision
4 was made to defer treatment, but a repeat OGTT a year later remained abnormal (2-
5 hour plasma glucose 14.7 mmol/l). Around this time her younger sister with CF was
6 also diagnosed with DM (Case 2), and a more detailed family history revealed an
7 older brother with “type 1 diabetes” (Case 3), as well as a father and paternal
8 grandmother with “type 2 diabetes” (Figure 1). Her father had been treated with
9 metformin, gliclazide and saxagliptin since the age of 23 years. The family was of
10 Caucasian origin and there was no parental consanguinity.
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22 Given the family history of three successive generations with DM, patient A was
23 tested for monogenic diabetes (positive predictive value for monogenic diabetes
24 testing >75.5%).[9] Next generation sequencing and subsequent Sanger sequencing
25 revealed a heterozygous frameshift mutation (c.404delA) in the hepatocyte nuclear
26 factor 1 homeobox alpha (*HNF1A*) gene which is known to be associated with
27 monogenic diabetes.[10-12] However, initial continuous glucose monitoring (CGM)
28 revealed largely normal blood glucose concentrations (3.2-8.1 mmol/l), and as such
29 sulfonylurea treatment was postponed until she developed intermittent
30 hyperglycaemia (11-12 mmol/l) five months later. Unfortunately, commencement of
31 gliclazide 10 mg once daily led to recurrent hypoglycaemia and treatment was
32 suspended. Serial CGM revealed rising blood glucose readings after two years off
33 gliclazide (10.8-13.8 mmol/l). Following a rise in HbA1c to 51 mmol/mol, gliclazide
34 was restarted and gradually increased to 10 mg twice daily with mostly stable blood
35 glucose concentrations (4-7 mmol/l) and subsequent reduction in her HbA1c (43
36 mmol/mol).
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CASE 2

Patient B was referred at the age of 7 years in view of an abnormal OGTT one year after patient A (2-hour plasma glucose 15.7 mmol/l). A diagnosis of CF had previously been confirmed on genetic testing (same genotype as patient A). From a respiratory point of view she had a BMI of 23.2 kg/m² (+2.7 SDS), Shwachman score of 84-96/100, a Northern score of 1-5/20, a FEV₁ of 73-104% predicted, and a FVC of 64-131% predicted throughout the course of her care. Prior to referral she had been admitted twice for intravenous antibiotics for CF.

Given the family history, *HNF1A* mutation testing was performed concurrently with patient A, confirming the same genotype. Her initial HbA1c was 41 mmol/mol but initial CGM readings showed high postprandial blood glucose concentrations (8-9.7 mmol/l), thus gliclazide 10 mg once daily was commenced. Like her sister, treatment had to be temporarily suspended for recurrent hypoglycaemia 15 months into treatment. However, serial CGM revealed worsening hyperglycaemia (11.9-13.3 mmol/l) with a rising HbA1c (51 mmol/mol) five months after cessation. Gliclazide was restarted and gradually increased to 10 mg twice daily with mostly stable blood glucose concentrations (4-10 mmol/l) and subsequent reduction in her HbA1c (48 mmol/mol).

CASE 3

In view of the familial diagnosis of monogenic diabetes, genetic testing was also performed on patient A and B's older brother, who did not have CF, confirming the same *HNF1A* mutation. He had presented with polyuria and polydipsia and been diagnosed with type 1 diabetes at 16 years. However, he had remained on very low

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3 doses of insulin (0.38 units/kg/day) with a normal HbA1c (40 mmol/mol) and
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5 negative GAD and ICA autoantibodies. Following this, he was switched to gliclazide
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7 which was gradually increased to 20 mg twice daily. Genetic tracing of the remaining
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9 affected family members is currently underway.
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11 12 13 **DISCUSSION**

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15 To our knowledge, this is the first report in the literature of a family with both CF and
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17 monogenic DM confirmed by genetic testing, highlighting the need to consider non-
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19 CFRD forms of DM, particularly in patients who harbour pancreatic sufficient *CFTR*
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21 mutations. “Classical” class I-III mutations such as $\Delta F508$ are associated with
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23 pancreatic insufficiency in a homozygous or compound heterozygous state as they
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25 interfere with *CFTR* production or regulation.[13] The presence of another class IV-V
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27 mutation where residual *CFTR* function remains, such as R117H, generally results in
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29 pancreatic sufficient-CF.[13] The Clinical and Functional Translation of *CFTR*
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31 (*CFTR2*, <https://www.cftr2.org/>) registry[6] should therefore be consulted to
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33 determine the likelihood of pancreatic insufficiency and the need to perform further
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35 investigations as this may have management consequences. Regardless of CF
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37 genotype, differential diagnoses should include type 1 diabetes (in the presence of
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39 autoantibodies or acute-onset hyperglycaemia with significant ketosis),[14, 15] or
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41 monogenic diabetes (in the presence of DM in successive generations, especially
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43 without autoantibodies, or the presence of non-insulin dependence in any member
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45 diagnosed before 25 years of age, especially without obesity or signs of insulin
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47 resistance).[16]
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3 Monogenic diabetes accounts for 1-2% of all diabetes cases, and are due to autosomal
4 dominant single gene mutations which ultimately lead to β cell dysfunction.[16] Of
5 these, *HNF1A* mutations are commonest, often presenting in adolescence.[12]
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HNF1A, HNF1B and HNF4A are transcription factors regulating pancreatic β cell development and function.[17, 18] Patients with *HNF1A* mutations typically have fasting euglycaemia but post-OGTT hyperglycaemia, raised high-density lipoprotein concentrations, and a reduced renal glucose threshold.[16] These patients are extremely sensitive to sulfonylureas, as illustrated by patients A and B's initial hypoglycaemia.[19] However, progressive β cell failure ensues, and continued monitoring is necessary, with insulin often being required several years later.

A probability calculator has been developed for diagnosing monogenic diabetes (<http://www.diabetesgenes.org/content/mody-probability-calculator>) with up to 91% sensitivity and 94% specificity.[9] Diagnosis of monogenic diabetes is crucial, as some forms are amenable to sulfonylurea therapy (*KCNJ11*, *ABCC8*, *HNF1A*, *HNF4A*),[16] whilst others may warrant screening for extrapancreatic complications (*KCNJ11*, *HNF1B*, *WFS1*, *MIDD*).[16]

In conclusion, the family presented here illustrates the need for clinicians managing patients with CF to consider other causes of DM in this cohort. Recognition of non-CFRD forms of diabetes can have important long-term implications for screening (for other autoimmune disorders in type 1 diabetes) or treatment (as in monogenic diabetes).

CONTRIBUTORS' STATEMENT

Dr. Gan obtained informed consent, drafted the initial manuscript, and reviewed and revised the final manuscript for publication.

Drs. Bhatt, Denvir, Randell and Sachdev reviewed and revised the final manuscript for publication.

All authors were involved in the multidisciplinary care of this family, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

None declared.

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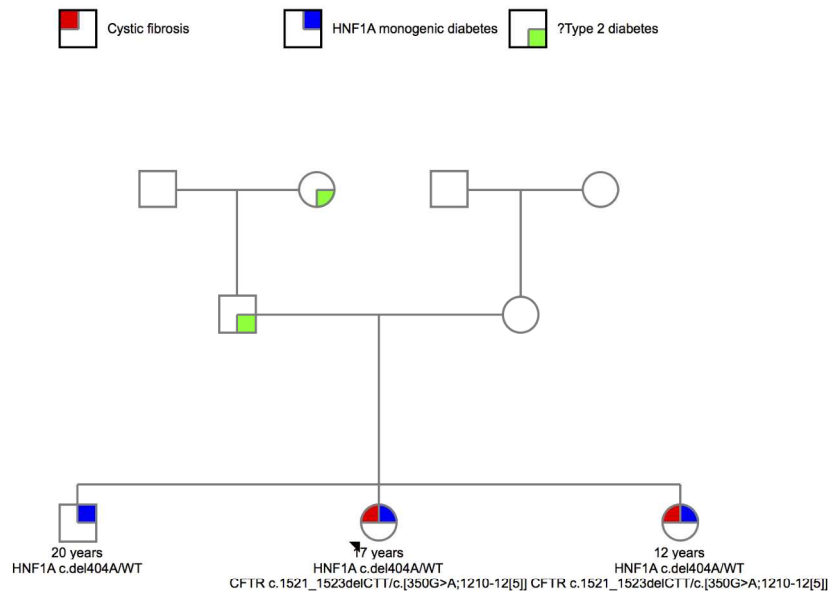
None required.

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Genogram illustrating case 1 (proband, 17 years), case 2 (12 years) and case 3 (20 years). For uniformity, the CFTR mutations are annotated using the nomenclature for coding DNA (i.e. c.1521_1523delCTT = ΔF508, c.[350G>A;1210-12[5]] = R117H;IVS8-5T). WT, wild-type allele.

637x492mm (150 x 150 DPI)

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