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CASE REPORT

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Non-pulmonary CFTR-related symptom improvement with ivacaftor in p.Phe508del/p.Arg117His (7T) cystic fibrosis

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Abstract

Diagnosis and management of CRMS/CFSPID and cystic fibrosis (CF) with mild phenotypes remains challenging, and this extends to expanding practice with the use of CFTR modulators. We describe a case of an 18-year-old man with p.F508del/p.Arg117His(7T) initially presenting with CRMS/CFSPID. He went on to be diagnosed with pancreatic sufficient CF with minimal lung disease. However, he has had significant CFTR-related symptoms with recurrent pancreatitis and chronic sinusitis. These non-pulmonary symptoms resolved following introduction of the CFTR modulator ivacaftor. Care for those with mild CF phenotypes, CRMS/CFSPID and those with CFTR-RD must be individualized, and open dialogue, education and patient centred care is necessary to ascertaining which patients might benefit from management in a multidisciplinary CF clinic and treatment. There may be a role for expanding the use of CFTR modulators to include non-pulmonary manifestations of CFTR dysfunction in some cases.

KEYWORDS

CFTR modulators, CFTR-related disease (CFTR-RD), cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID), Ivacaftor

INTRODUCTION

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1] There are over 2000 known mutations across a number of mutation classes that result in a heterogenous phenotype, ranging from classic pancreatic insufficient CF to CFTR related diseases and even no evidence of disease despite mutations in each allele.[1] The diagnosis of CF can be challenging for those who do not have typical symptoms, and this can raise issues about how they should be managed and whether it is appropriate to use CFTR modulators.[2,3]

There are a number of mutations known to cause a variable phenotype, in particular the CFTR exon 4 Arg117His mutation.[2,4] This mutation exhibits reduced channel conductivity compared with wild type CFTR.[2] The variable phenotype is partly explained by variations in the intron 8 polythymidine branch acceptor site, with sequences of 5, 7 and 9 thymidines that cause variable exon 9 splicing.[2] When Arg117His (or R117H) is *in cis* with 5T (and a non-function mutation on the other allele) the likely phenotype is pancreatic sufficient CF.[2] As Arg117His is responsive to CFTR activator therapy these patients may benefit from ivacaftor.[5] When Arg117His is *in cis* with 7T (and a non-function mutation on the other allele) the phenotype can vary from pancreatic sufficient CF (uncommon, penetrance 3%) to CFTR diseases (e.g., sinusitis, pancreatitis, or absent vas deferens) or nothing.[2] When infants with Arg117His (7T) and a non-functioning mutation are detected by newborn screening they are invariably healthy and it can be difficult to know how to follow these infants and whether CFTR modulators should be used.[4]

We describe a case of an 18-year-old male with the genotype p.Phe508del/p.Arg117His (7T) whose non-pulmonary symptoms have benefited from treatment with ivacaftor. We aim to explore the difficulties in diagnosis in some cases, and the challenges in understanding the role for CFTR modulator treatment.

CASE REPORT

An 18-year-old male is managed in the CF clinic. He was initially identified following newborn screening with an elevated immunoreactive trypsinogen and p.Phe508del on a 12-mutation screening panel. He was asymptomatic and had borderline sweat chloride tests (34 mmol/L aged 6 weeks, 31 mmol/L aged 10 weeks, 55 mmol/L aged 2 years). Extended genetic testing demonstrated genotype Arg117His(7 T) on the other allele. He was seen 6 monthly in a non-CF respiratory clinic.[4] At age 3 years of age he had recurrent cough, and at that time his sweat chloride was 67 mmol/L (CF range >60 mmol/L). He was then diagnosed with CF and seen in the multidisciplinary CF clinic.

Between the ages of 3–5 years he had recurrent pulmonary exacerbations with *Haemophilus infleunzae* cultures from sputum and bronchoalveolar lavage. He was managed with regular antibiotics, rhDNase and twice daily airway clearance. He required one admission to hospital for a pulmonary exacerbation. Since then he has had minimal pulmonary involvement, with a normal chest CT scan at age 17 years and FEV1 103%. He is pancreatic sufficient with BMI 90th percentile.

The patient's main issues have been recurrent pancreatitis and sinusitis. Biologically confirmed pancreatitis was troublesome from ages 8 to 16 years, and was successfully treated on multiple occasions with low fat diet, anti-oxidants and intermittent pancreatic enzyme replacement. Other anatomical or medication causes were excluded, and additional testing including *SPINK 1* and *PRSS 1* mutations have been negative. Sinusitis became problematic around 14 years of age and was confirmed on imaging. At times it has been debilitating (unable to attend school) with significant sinus pain and headache despite vigorous management with intranasal steroids and nasal washes. He has also had skin issues including high sweat volumes, multiple unspecified 'sores' and poor wound healing.

At the age of 16 years he was commenced on the CFTR activator ivacaftor. After 3 months of treatment his sweat chloride was 34 mmol/L. He has had significant improvement in his CFTR related symptoms, with no further episodes of pancreatitis or sinusitis. This has been life changing for him. He is able to enjoy a normal diet without abdominal pain, his sinuses no longer feel full and his headaches have resolved. He does not need therapy for pancreatitis or his sinuses. His skin is much better with the sores resolving and wound healing improved. He has completed high school and started first year of university. He is now transitioned to adult care.

DISCUSSION

We have described a patient with initial cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID).[6] Despite subsequently being diagnosed with CF, he went on to have minimal lung disease but significant symptoms in other organ systems more consistent with CFTR related disease (CFTR-RD). These non-respiratory symptoms significantly affected his quality of life, and he has gone on to have substantial benefit from CFTR modulator treatment. This case highlights a number of issues regarding diagnosis and management of young people with less common CF presentation and phenotype.

Diagnosis and follow up of infants with indeterminate diagnosis following abnormal newborn screening remains challenging.[6] Cystic fibrosis is most commonly identified on newborn screening with elevated immuno-reactive trypsinogen (IRT), and diagnosis is then confirmed with elevated sweat chloride and genetic testing.[1] Whilst for most infants this is straightforward, there remain a proportion of asymptomatic infants who screen positive and go on to have equivocal (30–59 mmol/L) or negative (<30 mmol/L) sweat tests with genetic variants of unclear phenotypic consequences.[6] Our patient fell in to the CRMS/CFSPID category with a borderline sweat test and Arg117His (7T), a variant of varying clinical significance.[6] This group of CRMS/CFSPID infants has increased with widespread newborn screening (NBS) and more extensive genetic panels.[6] Screening programs must consider the implications of abnormal screening in management, counselling and follow up of these infants and families.[2,4] The majority of CRMS/CFSPID infants go on to be healthy carriers, but a minority will develop CFTR related disease (CFTR-RD) or, like our patient, CF.[5] This patient was the only person from our reported cohort of 8 patients with p.F508del/Arg117His (7T) (five from NBS and three healthy siblings) who has returned to the CF clinic.[4] Guidelines for management and follow up of CRMS/CFSPID are predominantly based on consensus opinion, with limited evidence for best practice.[6] The majority recommend follow up with a clinician experienced in CF with clear education, monitoring and repeat testing over time.[6] This proved to be appropriate in the case of our patient, who was initially followed up by a respiratory physician 6 monthly in a non-CF clinic and moved to a CF clinic following evolution of symptoms and an elevated sweat chloride at 3 years.

Management of these children with CRMS/CFSPID requires flexibility, and it is not always clear who benefits from management in a multidisciplinary CF clinic. This may also be true for those with CFTR-RD. Admission to CF clinic allows access to multidisciplinary care and funding for expensive therapies such as CFTR modulators. However, admission to the CF clinic is not appropriate for the majority of CRMS/CFSPID children since the vast majority will be healthy carriers, and they risk over-medicalisation, iatrogenic harm, unnecessary burden of treatment, infection risk and increased anxiety.[6] Following the diagnosis with CF, our patient had an early course in keeping with what we usually see in pancreatic sufficient CF, but later the issues with suppurative bronchitis resolved such that we questioned the

value of treatment in the CF clinic. However, once he developed significant pancreatitis and sinusitis, mediated by CFTR (i.e., CFTR related-disease), he benefited from a multidisciplinary team with knowledge of conditions of CFTR dysfunction. Whilst some children may not have CF by consensus definition, CFTR-RD can cause significant symptom burden in the form of recurrent pancreatitis, sinus disease, isolated bronchiectasis and male infertility.[7] These can have substantial impact on quality of life, such as in our patient. While we often measure quantitative parameters such as lung function, admission days and BMI, what matters most to patients may be better captured in quality of life assessments. With both CRMS/CFSPID and CFTR-RD open dialogue, education and patient centred care is necessary to ascertaining which patients might benefit from treatment.

CFTR modulators are clearly of value to a large number of people with CF, and quality of life parameters such as CFQ-R has been shown to improve in patients given CFTR modulators in trials.[3] Furthermore, there are reports of benefit from ivacaftor use for non-pulmonary manifestations such as pancreatitis.[8] Our patient had significant benefit with use of ivacaftor, with marked improvement in non-respiratory symptoms and subsequent quality of life. It is possible that an expanded use for CFTR modulators could include some individuals with CFTR-RD. However, this needs to be based on symptom development and not genotype alone, a challenge when in most cases CFTR modulator eligibility is based on genotype. Given most (i.e., 97%) people with p.F508del/p.Arg117His (7T) do not develop CF or CFTR-RD it would be inappropriate to treat them all with modulator therapy. Some of the symptoms, such as absent vas deferens, are unlikely to respond. In fact, the clinical trials on the use of ivacaftor in patients with Arg117His, even those with the 5T intron 8 variant, are far from convincing.[5] The CFTR modulators have side effects and should only be used when the known benefits outweigh the risk. For these reasons the availability of CFTR modulators is not sufficient to advocate for screening programs to include Arg117His or other mutations of variable penetrance.

Diagnosis and management of CRMS/CFSPID and CF with mild phenotypes remains challenging, and this extends to expanding practice with the use of CFTR modulators. Care for those with mild CF phenotypes, CRMS/CFSPID and CFTR-RD must be individualized, but there may be a role for expanding the usual pulmonary indications of CFTR modulators in some cases.

AUTHOR CONTRIBUTIONS

Stephanie Kuek: Collected clinical history and data, drafted the initial manuscript, reviewed, and revised the manuscript. **John Massie**: Conceptualization, supervision. Reviewed, and revised the manuscript.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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