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Case report

Case report: Three adult brothers with cystic fibrosis (delF508-delF508) maintain unusually preserved clinical profile in the absence of standard CF care

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ABSTRACT

We present three cases in this report. Three adult brothers, homozygous for the delF508 cystic fibrosis mutation, have maintained an unusually preserved clinical condition even though they did not attend a CF Clinic during their childhood, do not attend a CF Clinic now, and do not follow standard CF care guidelines. The brothers use an alternative CF treatment regimen on which they have maintained normal lung function, height/weight, and bloodwork, and they utilize less than half the recommended dosage of pancreatic enzymes. The brothers culture only methicillin-sensitive Staphylococcus aureus, and have never cultured any other bacteria. Highly effective modulator therapies, such as elexacaftor/tezacaftor/ivacaftor, do not substantially reduce infection and inflammation in vivo in CF patients, and thus these three case reports are of special note in terms of suggesting adjunct therapeutic approaches. Finally, these three cases also raise important questions about standard CF care guidelines.

1. Introduction

Cystic fibrosis (CF) is a serious and life-shortening genetic disorder affecting approximately 70,000 persons worldwide [1]. Respiratory failure is the foremost cause of death in CF patients, and lung transplantation is often considered in end-stage CF disease. For those born with CF in the last five years, median predicted survival age is now 44, which is decades longer than survival rates in the recent past [2]. Indeed, new advances in CF modulator therapy and CF gene therapy may eventually provide a normal life expectancy for these individuals.

A key approach in fighting the ravages of CF while waiting for more advanced treatments to be developed has been to slow the inexorable decline in lung function. Typical rate of lung function decline in CF is approximately −1.2 to −1.6 FEV1% per year [3]. Rate of decline is strongly associated with type of CF mutation. The three most severe classes of CFTR, Classes I, II, and III, represent defects in protein production, protein processing, and protein regulation, respectively [4]. The most common CF-causing mutation is delF508, occurring in 70% of cases, which is a Class II mutation [5]. Being homozygous for the delF508 mutation confers a severe phenotype, including pancreatic insufficiency and a steeper rate of decline in lung function over time [6]. In the United States, it is estimated that approximately 50% of those with cystic fibrosis are homozygous for delF508 [7]. Standard clinical care for severe mutation cases is often aggressive, including but not limited to daily airway clearance, use of pancreatic enzymes at the level of 500-2,500 lipase units/kg/meal (and enteric feeding if adequate weight percentile cannot be maintained), common and repeated use of oral, inhaled and intravenous antibiotics, daily intake of water-miscible versions of fat-soluble vitamins, and quarterly CF Clinic visits where lung function parameters and cultures of lung bacteria and fungi are assessed [8,9]. Pulmonary exacerbations often result in hospitalization, which may occur one or more times per year, typically lasting 14–21 days and including intensive antibiotic treatment and chest physical therapy. Everyday treatment burden is high, with estimates of 2–3 hours per day, with adherence at an estimated 50% or less [10]. The mean annual cost of standard supportive CF care in the US in 2016 (in 2019 dollars), before CFTR modulator therapies, was estimated to average $77,143, with severe non-transplant cases experiencing multiple pulmonary exacerbations costing on average triple or quadruple that amount [11]. With the average cost of elexacaftor/tezacaftor/ivacaftor (Trikafta) treatment currently over $311,000 per year, average standard supportive CF care costs were expected to double in 2019 [12] and increase further over time, perhaps quadrupling, with wider adoption of that treatment by all eligible patients.

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Here we report on three adult brothers who are delF508 homozygotes, and yet who have maintained an unusually preserved clinical profile in the absence of standard CF clinical care. At the time of this writing, Brother A is 23 years old, Brother B is 21 years old, and Brother C is 18 years old. They are full-blooded siblings.

2. Case reports

2.1. Brother A

Brother A, now aged 23, was born full-term weighing 10 lbs. 2 oz. to a carrier mother experiencing gestational diabetes who subsequently breastfed him. His weight percentile decreased significantly over time, and at 6 months, after a course of oral antibiotics for a suspected ear infection, he developed a severe Vitamin K deficiency manifesting in quarter-sized black bruises on his body, as well as Pseudo-Bartter Syndrome. He was hospitalized until IV fluids stabilized his condition and normalized his electrolytes. Vitamin K shots were also administered. At 9 months of age, he was diagnosed with cystic fibrosis, and the genetic mutation analysis identified him as a delF508 homozygote. Between the time of his hospitalization and his diagnosis, he suffered from malnutrition with accompanying protein edema and his weight percentile, which had been over 97th percentile when born, was under the 5th percentile adjusted for age and sex. Once started on pancreatic enzymes (CREON 5) after diagnosis, his weight percentile increased to approximately the 30th percentile.

Approximately one year after diagnosis, the parents of Brother A elected to depart from standard CF care, including an election to stop attending the CF Clinic, while continuing to be under the care of their family pediatrician. The treatment plan for the brothers is described in detail in a later section. The only prescription medicine taken during his childhood and continuing to this day remains CREON 5/6, with Brother A utilizing 4 CREON 5/6 per meal, less than half the lowest recommended dose for his weight. In the teen years, Brother A experienced three episodes of heat exhaustion requiring IV fluid stabilization in an emergency room, has had one endoscopic sinus cleaning for sinus pain at age 20, and also underwent an appendectomy for appendicitis at age 23, but otherwise has had no major clinical issues, though exhibiting digital clubbing. Brother A played ice hockey throughout his childhood and teen years. His height, weight, lung function, and lab results at age 23 are provided in Table 1.

Table 1
Clinical parameters, Brother A.

Brother A, age 23, delF508/delF508, all tests performed June–August 2020	
Height, Height percentile for men	6′0”, 84th percentile
Weight, Weight percentile for men	218 lbs., 72nd percentile
BMI	29.6 (overweight)
Blood pressure	146/84
FVC (percent predicted)	6.95 L (124%)
FEV1 (percent predicted)	5.21 L (108%)
FEV1/FVC (percent predicted)	74.96%
PEF (percent predicted)	14.67 L/second (about 160%)
$\%SpO_2$	97%
CF Lower Respiratory Culture (LabCorp version)	Light Growth, Staphylococcus aureus (methicillin sensitive)
Hemoglobin A1c	5.2% (Normal; normal range 4.8–5.6)
C-Reactive Protein	<1 mg/L (Normal; normal range 0–10)
Vitamin D, 25-Hydroxy	39.1 ng/mL (Normal; normal range 39–100)
Beta Carotene	6 μg/dL (Normal; normal range 3–91)
Vitamin A	68.8 μg/dL (High; normal range 18.9–57.3)
Vitamin E (Alpha Tocopherol)	27.6 mg/L (High; normal range 5.9–19.4)
Vitamin E (Gamma Tocopherol)	0.6 mg/L (Low; normal range 0.7–4.9)
Total Protein	7.5 g/dL (Normal; normal range 6.0–8.5)
Albumin	4.9 g/dL (Normal; normal range 4.1–5.2)
Bilirubin, Total	0.5 mg/dL (Normal; normal range 0–1.2)
Bilirubin, Direct	0.13 mg/dL (Normal; normal range 0–0.40)
Alkaline Phosphatase	100 IU/L (Normal; normal range 39–117)
AST (SGOT)	24 IU/L (Normal; normal range 0–40)
ALT (SGPT)	47 IU/L (High; normal range 0–44)

2.2. Brother B

Brother B, now aged 21, was born full-term, weighing 8 lbs. 8 oz., the mother supplementing with oral glutathione (GSH) during the pregnancy and subsequently breastfeeding him. Brother B has never attended a CF Clinic, was diagnosed at 2 weeks of age, and was under the care of the family's pediatrician only. Brother B's only prescription medication during his childhood was CREON 5/6, just as with Brother A, utilizing 4 capsules per meal. Brother B has never needed to be hospitalized or have surgery or antibiotics. While Brother B does not exhibit digital clubbing; when recovering from respiratory viruses, he does manifest a cough that lingers longer than it lingers for his brothers, though the cough ultimately resolves. Brother B played ice hockey in childhood and teen years, as well as participated in gymnastics, cross-country running, track and field, and weight-lifting. His height, weight, lung function, and lab results at age 21 are provided in Table 2.

2.3. Brother C

Brother C, now aged 18, was born full-term weighing 9 lbs. 2 oz., the mother supplementing with oral glutathione (GSH) during the pregnancy and subsequently breastfeeding him. Brother C has never attended a CF Clinic, was diagnosed at 2 weeks of age, and was under the care of the family's pediatrician only. Brother C's only prescription medication during his childhood was CREON 5/6, just as with Brothers A and B, utilizing 4 capsules per meal. Brother C has never needed to be hospitalized, or have surgery or antibiotics. Brother C does not exhibit digital clubbing. Brother C played ice hockey in childhood and teen years, as well as participated in gymnastics. His height, weight, lung function, and lab results at age 18 are provided in Table 3.

3. Description of treatment

Given the severity of the genotype involved and the almost complete non-adherence to standard CF guidelines (with the exception of a significantly lower-than-average dose of prescription pancreatic enzymes and a standard dose of water-miscible fat soluble vitamins), the

Table 2
Clinical parameters, Brother B.

Brother B, age 21, delF508/delF508, all tests performed June–August 2020	
Height, Height percentile for men	5′ 10 ½”, 67th percentile
Weight, Weight percentile for men	157.8 lbs, 19th percentile
BMI	22.3 (normal)
Blood pressure	122/70
FVC (percent predicted)	4.81 L (133%)
FEV1 (percent predicted)	3.13 L (101%)
FEV1/FVC (percent predicted)	65.07%
PEF (percent predicted)	6.75 L/second (93%)
$\%SpO_2$	92%
CF Lower Respiratory Culture (LabCorp version)	Light Growth, Staphylococcus aureus (methicillin sensitive)
Hemoglobin A1c	5.3% (Normal; normal range 4.8–5.6)
C-Reactive Protein	<1 mg/L (Normal; normal range 0–10)
Vitamin D, 25-Hydroxy	34.9 ng/mL (Normal; normal range 0–100)
Beta Carotene	6 μg/dL (Normal; normal range 3–91)
Vitamin A	53.2 μg/dL (Normal; normal range 18.9–57.3)
Vitamin E (Alpha Tocopherol)	15.4 mg/L (Normal; normal range 5.9–19.4)
Vitamin E (Gamma Tocopherol)	0.3 mg/L (Low; normal range 0.7–4.9)
Total Protein	7.2 g/dL (Normal; normal range 6.0–8.5)
Albumin	4.7 g/dL (Normal; normal range 4.1–5.2)
Bilirubin, Total	1.0 mg/dL (Normal; normal range 0–1.2)
Bilirubin, Direct	0.25 mg/dL (Normal; normal range 0–0.4)
Alkaline Phosphatase	88 IU/L (Normal; normal range 39–117)
AST (SGOT)	24 IU/L (Normal; normal range 0–40)
ALT (SGPT)	25 IU/L (Normal; normal range 0–44)

Table 3
Clinical parameters, Brother C.

Brother C, age 18, delF508/delF508, all tests performed June–August 2020	
Height, Height percentile for men	5′ 11 ½ ”, 78th percentile
Weight, Weight percentile for men	153.6 lbs., 15th percentile
BMI	21.1 (normal)
Blood pressure	121/71
FVC (percent predicted)	6.44 L (127%)
FEV1 (percent predicted)	5.07 L (116%)
FEV1/FVC (percent predicted)	78.73%
PEF (percent predicted)	13.93 L/second (155%)
$\%SpO_2$	97%
CF Lower Respiratory Culture (LabCorp version)	Moderate Growth, Staphylococcus aureus (methicillin sensitive)
Hemoglobin A1c	5.4% (Normal; normal range 4.8–5.6)
C-Reactive Protein	2 mg/L (Normal; normal range 0–10)
Vitamin D, 25-Hydroxy	27.9 ng/mL (Low; normal range 30–100)
Beta Carotene	6 μg/dL (Normal; normal range 3–91)
Vitamin A	48.4 μg/dL (Normal; normal range 18.8–54.9)
Vitamin E (Alpha Tocopherol)	13.8 mg/L (High; normal range 5.0–13.2)
Vitamin E (Gamma Tocopherol)	0.7 mg/L (Low; normal range 0.8–3.8)
Total Protein	7.2 g/dL (Normal; normal range 6.0–8.5)
Albumin	4.6 g/dL (Normal; normal range 4.1–5.2)
Bilirubin, Total	0.3 mg/dL (Normal; normal range 0–1.2)
Bilirubin, Direct	0.10 mg/dL (Normal; normal range 0–0.4)
Alkaline Phosphatase	127 IU/L (Normal; normal range 56–127)
AST (SGOT)	27 IU/L (Normal; normal range 0–40)
ALT (SGPT)	36 IU/L (Normal; normal range 0–44)

preserved clinical profile of these three brothers is noteworthy. However, the family developed a regimen that went well beyond pancreatic enzymes and water-miscible vitamins. The treatment regimen is provided in Table 4.

4. Discussion

There are several possibilities for the preserved clinical status of these three brothers in the absence of standard CF care:

a) They avoided the CF Clinic setting. Recent research [13] has shown that Pseudomonas infections are more prevalent and lung function lower among CF patients in standard care versus CF patients in a telemedicine setting. It is possible these three brothers benefitted from not attending a standard CF Clinic, especially since during their childhood years at the turn of the century, Clinic infection control was not emphasized. For example, during Brother A's first few CF Clinic visits as an infant, families were expected to wait together in a communal area with communal toys, and health care professionals at the Clinic wore neither masks nor gloves as they moved from exam room to exam room.

b) With the exception of Brother A, Brothers B and C have used no antibiotics at all. Brother A has only used antibiotics three times in his life; the first use in infancy precipitated Pseudo-Bartter Syndrome, leading to his diagnosis with cystic fibrosis. The other two uses were incident to endoscopic sinus scraping and an appendectomy. Recent research has shown the importance of the gut microbiome in maintenance of health (including respiratory function), digestion and immune signaling, and this is true in the case of cystic fibrosis as well [14–16]. As David Pride, Associate Director of Microbiology at UC San Diego, notes in an address to the 2019 North American Cystic Fibrosis Conference [17], “It is important to preserve our microbiomes because they play important roles in preventing pathogens from establishing infections, in the development of our immune systems to recognize and kill pathogens, and in metabolic processes such as the digestion of foods. Indiscriminate uses of antibiotics can have profound and long-lasting effects upon our microbiomes by killing many of the bacteria that make up our microbiome; thus, limiting their use may aid in keeping us healthy.” Prevalent, sometimes chronic, antibiotic use among CF patients results in a significant gut dysbiosis [18]. In addition, it has been noted that aggressive antibiotic use in CF, usually incident to the first manifestation of Staphylococcus aureus (SA), may allow Pseudomonas aeruginosa a greater foothold [19], and that aggressive treatment of Pseudomonas may, in turn, promote drug resistance and may allow additional bacteria, such as Stenotrophomonas maltophilia, an opportunity to proliferate [20]. Perhaps a preserved gut microbiome due to non-use of antibiotics may have played a role in the brothers' preserved clinical condition; this may also help account for the brothers' significantly lower level of need for pancreatic enzymes. Perhaps also the decision not to aggressively treat their light to moderate growth of methicillin-sensitive SA may have precluded additional bacteria, including drug-resistant bacteria, from emerging.

c) Other standard daily CF treatments were not employed, either, which might help account for their preserved clinical condition. For example, the brothers do not use bronchodilators; and beta-2 agonist bronchodilators, such as albuterol, have recently been shown to significantly reduce delF508 CFTR activation [21]. This reduction is even evident when CFTR modulators are used, with the finding of a more than 60% reduction of modulator-corrected CFTR activation in vitro, “sufficient to abrogate VX809/VX770 modulation of F508-del CFTR” [21]. In addition, the brothers do not use DNase, which has been associated with increased levels of neutrophil elastase in past research [22]. Last, after Brother A transitioned to his new treatment regimen at approximately 23 months of age, chest percussive therapy (CPT) was discontinued, and neither Brother B nor C underwent CPT at all. A Cochrane meta-review found that while CPT constituted the lion's share of treatment time burden in CF, the evidence that outcomes of CPT differed from no CPT was “very low quality” [23].

d) Glutathione (GSH) is heavily emphasized in the brothers' daily regimen. Levels of GSH are strongly decreased in the extracellular milieu of CF patients, as its efflux from epithelial cells is compromised by CFTR mutation [24]. In the non-CF research literature, GSH in its ratio of reduced to oxidized forms (GSH:GSSG) has been shown to be the foundation of redox signaling in the body; GSH is also the body's primary water-soluble antioxidant and a potent mucolytic, and conserves NO through formation of GSNO. Given its pivotal roles, it is not surprising to find that GSH deficiency is noted in several other severe respiratory illnesses besides CF, including ARDS, COPD, IIP, IPF, IRDS, and DFA, and GSH deficiency is a key catalyst for (and GSH dosing a key treatment of) cachexia [24]. The use of GSH in the treatment of CF may reduce systemic inflammation, lessen the viscosity of mucus, and catalyze the efficacy of the immune system, including through GSNO. Indeed, a clinical study by Visca et al. found significantly increased BMI [25], significantly increased lung function [26], and even improved bacteriological results [27] from the daily use of oral glutathione in children with CF at a dose of 30 mg/lb body weight/day, spread out over 3–4 doses, over a time period of 6 months. In addition, the parents of these brothers noted a sudden increase in both saliva and appetite in Brother A after glutathione (GSH) was introduced when he was two years of age. Brothers B and C, on GSH from two weeks of birth (and with the mother supplementing with oral glutathione throughout pregnancy with these two brothers), never displayed low saliva or low appetite. The preserved clinical status of these three brothers may perhaps be related to this glutathione-heavy regimen.

e) Other aspects of the brothers' regimen may offset their disease condition. The use of probiotics [28], the heavy emphasis on antioxidants in addition to glutathione (such as C, CoQ10, Alpha-lipoic acid, D, E, etc. [29]), amino acids (such as cysteine [30], carnitine [31], choline [32,33], taurine [34], and glycine [35]), curcumin [36], and additional digestive support beyond enzymes (lecithin, bile acid). It is possible that some or all of these supplementation efforts also helped to preserve the clinical status of the three brothers. In

Table 4
Description of Daily Regimen.

A. Oral Supplements

Taken in the morning	Taken at lunch and at dinner	Taken at bedtime
1 ABDEKs tablet	3 x 500 mg GSH	3 x 500 mg GSH
1 x 250 mg Alpha Lipoic Acid	3 GSH-Curc Caps* (Theranaturals)	3 GSH-Curc Caps
1 x 3 mg Boron	4 CREON 6 enzymes	1 x 500 mg Vitamin C
1 x tablet Cal-Mag-Zinc**	1 x 500 mg Vitamin C	Alternating days:
1 x 500 mg L-Carnitine	1 x 1200 mg Lecithin capsule	Xlear nasal spray or
1 x 500 mg Choline	1 x 1000 mg Bile Acid Factors (Jarrow)	Biocidin throat spray
1 x 60 mg Co-Q-10		
1 x 200 mcg Chromium Picolinate		
1 x 665 mg Curcumin		
3 x 10,000 IU Vitamin D3		
2 x 500 mg DHA		
1 x 400 IU Vitamin E		
1 x 800 mcg Folic Acid		
1 x 1000 mg Glycine		
1 x 100 mcg Vitamin K		
! x 1000 mg MSM		
1 x 600 mg NAC		
1 x 500 mg Taurine		
1 capsule Probiotics (Kyo-dophilus)***		
3 x 500 mg GSH		
3 GSH-Curc Caps		
4 CREON 6 enzymes		
1 x 500 mg Vitamin C		
1 x 1200 mg Lecithin capsule		
1 x 1000 mg Bile Acid Factors (Jarrow)		

* Each GSH-Curc Cap contains 300 mg GSH, 200 mg Curcumin, 50 mg NAC, 300 mg Vitamin C, and 3 mcg Selenomethionine
** Each Cal-Mag-Zinc capsule contains 1000 mg Calcium, 600 mg Magnesium, 15 mg Zinc
*** Each Probiotic capsule (Kyodophilus) contains 3 billion cells of Lactobacillus and Bifidobacterium

B. Aerosolized Glutathione, 1-2 times per week

3 GSH-Plus capsules**** (Theranaturals) in approximately 3 ml cooled boiled distilled water, Pari neb
**** Each GSH-Plus capsule contains 200 mg GSH and 55 mg Sodium Bicarbonate as a buffering agent.

addition, exclusive breastfeeding of CF infants has been linked to significantly higher FEV1 at age 5 (difference significant at $p \leq 0.001$ between breastfed and formula fed CF infants), perhaps contributing to the preservation of lung function beyond that time frame [37].

f) Modifier alleles may be present. While no in-depth analysis of the brothers' genetic profile has been performed beyond the identification of their CF mutations, there are known modifier alleles that serve to lessen (or exacerbate) the severity of CF (see, for example [38]). It is possible all three brothers inherited some propitious set of modifier alleles.

5. Conclusion

In conclusion, while it is encouraging and heartening that new CF therapies, such as elexacaftor/tezacaftor/ivacaftor (Trikafta) and other HEMT (highly effective modulator therapies), now exist, it is instructive

to consider how this family was able to preserve the clinical condition of three brothers, all delF508 homozygotes, in the absence of those therapies, and even in the absence of standard CF care. While HEMT certainly increase CFTR activity, there is substantially less effect on infection and inflammation in vivo [39]. As recently noted by Singh et al., "[I]f infection and inflammation become uncoupled from CFTR activity in established disease [due to HEMT use], drugs targeting CFTR may need to be initiated very early in life, or *used in combination with agents that suppress infection and inflammation*" [39; emphasis ours]. These case reports may speak to that proposition.

Furthermore, each possible explanation for that preservation is an occasion for reflection on the current standard of CF care. We may feel to ask questions such as, "From the point of view of the patient's health, is the entire concept of the CF Clinic inherently flawed? Is the frequent, sometimes chronic, use of antibiotics and certain other medications in CF care a real double-edged sword for CF patients, with disadvantages possibly outweighing advantages in many cases? Are there measures we can take now, relatively inexpensive measures such as the use of glutathione (GSH) and other antioxidants and amino acids, that will help preserve the clinical status of CF patients, and that might synergize with cutting-edge treatments such as CFTR modulators to improve and safeguard health to an even greater degree, and which should be initiated as early in life as possible, possibly while the fetus is still *in utero*?" The experience of these three brothers, so removed from standard CF care and yet so well preserved in their clinical status, highlights the need to consider such questions more urgently than we perhaps have heretofore considered them.

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