ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

Had it happened without Christmas? Thoracic emphysema and Allergic Bronchopulmonary Aspergillosis in a juvenile CF-patient with G551D receiving ivacaftor

Jochen G. Mainz, Nina Erdmann, Franziska Duckstein, Carlos Zagoya

Please cite this article as: Mainz JG, Erdmann N, Duckstein F, *et al*. Had it happened without Christmas? Thoracic emphysema and Allergic Bronchopulmonary Aspergillosis in a juvenile CF-patient with G551D receiving ivacaftor. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00758-2020).

Had it happened without Christmas?
- Thoracic emphysema and Allergic Bronchopulmonary Aspergillosis in a juvenile CF-patient with G551D receiving ivacaftor-

Jochen G. Mainz[1, 2, 3], Nina Erdmann[1], Franziska Duckstein[1], Carlos Zagoya[1]

[1] Cystic Fibrosis Center, Brandenburg Medical School (MHB) University. Klinikum Westbrandenburg, Brandenburg an der Havel, Germany

[2] CF-Center, Jena University Hospital, Jena, Germany

[3] Faculty of Health Sciences, joint Faculty of the Brandenburg University of Technology Cottbus-Senftenberg, the Brandenburg Medical School Theodor Fontane and the University of Potsdam, Germany

* Correspondence:

Professor Dr. Jochen G. Mainz, Cystic Fibrosis Center, Brandenburg Medical School (MHB) University. Brandenburg an der Havel, Klinikum Westbrandenburg, Germany, Klinik für Kinder- und Jugendmedizin. Hochstrasse 29, 14770 Brandenburg an der Havel, Germany. Phone: +49 3381-411800. Fax: +49 3381-411809.

E-mail: j.mainz@klinikum-brandenburg.de

Take home message:

Potent CFTR-modulators improve CF manifestations far beyond expectations including reduction of risks for typical CF complications. Nevertheless, to our knowledge this is the first report on a patient who developed life-threatening ABPA and emphysema after overwhelming improvements.

Running Head: Not without Christmas

Keywords: Cystic fibrosis, gating mutation, CFTR, modulation

To the Editor:

We report on a then thirteen-year-old female patient with cystic fibrosis (CF) compound heterozygous for the mutations G551D and N1303K. Despite history of intermittent pulmonary colonisation with *P.aeruginosa* and moderate pulmonary haemorrhages before initiating ivacaftor, our patient still had a good pulmonary function (FEV_1: 95-105%pred.) at baseline. Furthermore, she had a stable nutritional status by pancreatic enzyme replacement therapy (PERT) above 7,000IE Lipase/kg body weight/day. Nevertheless, when the CF-Transmembrane Conductance Regulator (CFTR)-modulator ivacaftor was introduced in April 2013 and approved for CF-patients carrying a gating mutation, i.e. G551D [1-3], she improved considerably. Her pulmonary function increased by more than 20% to above–average; resulting in an FEV_1: 128% pred. (=3.43l). Simultaneously, the patient reduced and eventually stopped her enzyme substitution. Yet, her nutritional status remained stable (BMI >50.percentile) without increase in stool frequency or other clinical signs of maldigestion. In parallel, her sweat-chloride improved from 87.5 to 29.6 mmol/L (to the normal range). It is noteworthy that she took trumpet lessons and even joined her school's big band in her leisure time.

Rather unexpectedly, on December 28, 2013, the patient was admitted to hospital for severe dyspnoea and hypoxia with only 85% of transcutaneous oxygen saturation. Chest X-ray ruled out new pulmonary infiltrates, albeit it revealed a cervical-thoracic emphysema (see Figure.1). While inhalation of beta2-agonists only had marginally positive effects, she stabilised considerably with oxygen supplementation, so that attending physicians proceeded without a CT scan. Pulmonary function testing on December 29 revealed a drop in FEV_1 to 35%predicted (0.94l) and a massive hyperinflation (residual volume 298%predicted).

Initial treatment with oral ciprofloxacin did not stabilise her clinical status and microbiological cultures from sputum as well as infection parameters in blood remained negative with C-reactive protein below 5 mg/L and leucocyte counts within the normal range; only the proportion of eosinophils was considerably increased at 12%. Previously, the patient's total and specific IgE and IgG against *Aspergillus (A.) fumigatus* had been slightly elevated.

Nevertheless, the patient's critical clinical status together with history of changes in the living environment prompted our therapy:

For long, the family kept a guinea pig in their living room. That year, however, they decided to place their Christmas tree at the space usually occupied by the pet's hutch. In order to put up the tree, the pet's cage was moved into our CF patient's bedroom, together with its hay for bedding. Presumably, the resulting exposure of the patient to *A.fumigatus* allergens in the guinea pig's bedding was a root cause for her exacerbation. To make matters worse on Christmas Eve, unaware of her inflamed airways due to allergen-exposure, our patient played Christmas carols on her trumpet near the Christmas tree.

We initiated a therapy for Allergic Bronchopulmonary Aspergillosis (ABPA) including systemic steroid treatment combined with itraconazole. Four days later, laboratory findings confirmed our decision: total IgE levels, which were previously slightly elevated at 517kU/L, sky rocketed to 13,858kU/mL. At the same time, other markers of ABPA increased significantly (specific IgE and IgG for *A.fumigatus* 14.80→54.30kU/L, and 75.50→128mg/L, respectively; ABPA-specific IgE against recombinant *A.fumigatus* antigens 4 and 6: 1.88→8.63kU/L, and 3.44→ >100.00kU/L, respectively).

With cessation of allergen exposure and start of the addressed systemic therapy, the patient stabilised considerably in the coming days, reaching FEV1 and FVC values of 108 and 122%pred after only two weeks. In parallel, her total IgE as well as all further markers for ABPA normalised in the following months (see Figure 1).

Discussion:

The reported living environmental changes as cause for the patient's crucial exposure to *A.fumigatus*, well-known to be abundant in hay, triggered her first manifestation of ABPA [4]. Enhanced central airway pressure when playing the trumpet added to the resulting severe airway inflammation and obstruction as key clinical symptoms of ABPA, which we surmised to be causative for her cervical and pulmonary interstitial emphysema. A combination of both

prompted critical pulmonary deterioration and hypoxia, so that the patient required hospitalisation, oxygen supplementation and urgent medical treatment.

Our case report is noteworthy, as our patient had stabilised prior to this threatening exacerbation under therapy with ivacaftor to an extent beyond our and the patient's expectation: pulmonary function reached outstanding values and pancreatic function recovered to the extent that PERT could be ceased without revealing symptoms of maldigestion and weight loss.

The highly potent CFTR-modulator ivacaftor is available for patients carrying the rare G551D mutation since 2012 [2, 3]. In vitro, it enhances the opening probability of defective CFTR-channels in so-called gating-mutations like G551D up to 50% [5]. In these, a dysfunctional channel is present in apical membranes of exocrine glands [6]. Despite its considerably higher complexity, such effects can now also be achieved for more than 60% of CF patients carrying the most frequent mutation F508del [7]. In patients homozygous for F508del, in the endoplasmatic reticulum, the defectively folded channel protein is disposed of during intracellular CFTR-processing. Now, in the US and many European countries, the triple-combination of two potent CFTR-correctors (tezacaftor and elexacaftor) allows further processing and presence of the channel on cell surfaces in patients carrying only one F508del mutation. Here again, ivacaftor as a third component enhances opening probability of the ion-channel [7]. As with CF patients with a gating mutation treated with ivacaftor, triple modulating therapy leads to a mean FEV_1-increase above 10%. At the same time, it allows a considerable gain of weight in often malnourished patients. Future will reveal whether pancreatic insufficiency may be compensated to some extent, as a recent publication on 3 CF-siblings carrying a G551D mutation suggests [8].

Most interestingly, our case report shows that substantial improvement of pulmonary and extra-pulmonary involvement in CF patients receiving a potent CFTR-modulating therapy does not protect against ABPA, a typical CF-complication [4]. Moreover, our patient revealed the highest hyperergic immunological response on exposition to aspergillus allergens that we

ever saw, with IgE levels at the limit of the measurement range. Consequently, we still must take into account CF-typical complications like ABPA, even if under CFTR-modulator therapy patients improve to an extent seen in our juvenile patient [9-11].

Our case report contradicts expectations deriving from recent publications which suggest that recovery of CFTR function would reduce susceptibility to ABPA, as disposition for hyperergic immunological reactions, e.g. to mould:

On the one hand, in a mouse model, Allard et al. showed that *A.fumigatus* hyphal Ag exposure in CFTR-deficient and DeltaF508-mutant mice generates an enhanced Th2-immune response with profound lung inflammation [12]. In humans, mutations in the *CFTR*-gene appear to be a single relevant risk factor for development of ABPA. In a systematic review, the risk for development of ABPA was calculated with an odds ratio of 10.39 in subjects carrying a CFTR mutation (95% CI, 4.35–24.79) [9]. Hence, effective CFTR-modulation should be expected to reduce such a risk.

On the other hand, therapy with CFTR-modulators was shown to reduce CF patients' airway colonisation with *A.fumigatus* [13]. Furthermore, overshooting inflammatory responses against *A.fumigatus* was shown to decline significantly during CFTR-modulating therapies: Aspergillus-induced reactive oxygen species (ROS), liberated from CF-patients' mononuclear (PBMCs) and polymorphonuclear cells (PMNs), were elevated in CF patients, compared to healthy controls. Remarkably, pre-treatment with ivacaftor alone ($p < 0.01$) or in combination with lumacaftor ($p < 0.01$) led to a significant reduction of this overshooting inflammatory response. Therefore, CFTR modulation is expected to have immunomodulatory effects preventing Aspergillus-induced inflammation in CF.

However, these effects on PMNs may not be crucial in ABPA where the lymphatic system assumes a central role, with liberation of T-helper (TH)-2 cytokines like Interleukin (IL)-4, IL-5 and IL-13, leading to abundant production of total and specific IgE and IgG antibodies by B-lymphocytes directed against *A. fumigatus* and to a hypersensitivity reaction.

In present literature, we did not find reports on effects of CFTR-modulators on lymphatically-driven hypersensitivity ABPA-reactions according to type I (IgE) and type III (IgG-immunocomplexes) mediated reactions, as classified by Coombs and Gell.

In conclusion, only a combination of two factors associated with the Christmas season – i.e. the changes in our patient's living environment as well as her traditional Christmas Carolling – caused classical CFTR-associated complications of ABPA, despite her previous substantial success of improvements with CFTR-modulating therapy. Further studies are required to understand these complex interactions.

Acknowledgements: The authors are grateful for the patient's support and continuous interest. We thank Prof. Dr. Hans-Joachim Mentzel, Jena, for the provision of the patient`s chest X-ray.

Support statement: This work did not receive external support.

References

1. Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, Sagel SD, Hornick DB, Konstan MW, Donaldson SH, Moss RB, Pilewski JM, Rubenstein RC, Uluer AZ, Aitken ML, Freedman SD, Rose LM, Mayer-Hamblett N, Dong Q, Zha J, Stone AJ, Olson ER, Ordonez CL, Campbell PW, Ashlock MA, Ramsey BW. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *The New England journal of medicine* 2010: 363(21): 1991-2003.
2. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, Mainz JG, Rodriguez S, Li H, Yen K, Ordonez CL, Ahrens R, Group VXS. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013: 187(11): 1219-1225.
3. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, Griese M, McKone EF, Wainwright CE, Konstan MW, Moss R, Ratjen F, Sermet-Gaudelus I, Rowe SM, Dong Q, Rodriguez S, Yen K, Ordonez C, Elborn JS. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *The New England journal of medicine* 2011: 365(18): 1663-1672.
4. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri R, Brody AS, Light M, Skov M, Maish W, Mastella G, Participants in the Cystic Fibrosis Foundation Consensus C. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003: 37 Suppl 3: S225-264.
5. Van Goor F, Hadida S, Grootenhuis PDJ, Burton B, Cao D, Neuberger T, Turnbull A, Singh A, Joubran J, Hazlewood A, Zhou JL, McCartney J, Arumugam V, Decker C, Yang J, Young C, Olson ER, Wine JJ, Frizzell RA, Ashlock M, Negulescu P. Rescue of CF airway

epithelial cell function in vitro by a CFTR potentiator, VX-770. *P Natl Acad Sci USA* 2009: 106(44): 18825-18830.
6. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *The New England journal of medicine* 2005: 352(19): 1992-2001.
7. Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, Ramsey BW, Taylor-Cousar JL, Tullis E, Vermeulen F, Marigowda G, McKee CM, Moskowitz SM, Nair N, Savage J, Simard C, Tian S, Waltz D, Xuan F, Rowe SM, Jain R, Group VXS. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *The New England journal of medicine* 2019: 381(19): 1809-1819.
8. Mainz JG, Arnold C, Hentschel J, Tabori H. Effects of Ivacaftor in Three Pediatric Siblings With Cystic Fibrosis Carrying the Mutations G551D And F508del. *Arch Bronconeumol* 2018: 54(4): 232-234.
9. Agarwal R, Khan A, Aggarwal AN, Gupta D. Link between CFTR mutations and ABPA: a systematic review and meta-analysis. *Mycoses* 2012: 55(4): 357-365.
10. Lebecque P, Pepermans X, Marchand E, Leonard A, Leal T. ABPA in adulthood: a CFTR-related disorder. *Thorax* 2011: 66(6): 540-541.
11. Mueller C, Torrez D, Braag S, Martino A, Clarke T, Campbell-Thompson M, Flotte TR. Partial correction of the CFTR-dependent ABPA mouse model with recombinant adeno-associated virus gene transfer of truncated CFTR gene. *J Gene Med* 2008: 10(1): 51-60.
12. Allard JB, Poynter ME, Marr KA, Cohn L, Rincon M, Whittaker LA. Aspergillus fumigatus generates an enhanced Th2-biased immune response in mice with defective cystic fibrosis transmembrane conductance regulator. *Journal of immunology* 2006: 177(8): 5186-5194.
13. Currie AJ, Main ET, Wilson HM, Armstrong-James D, Warris A. CFTR Modulators Dampen Aspergillus-Induced Reactive Oxygen Species Production by Cystic Fibrosis Phagocytes. *Front Cell Infect Microbiol* 2020: 10: 372.