EVOLUTION OF DISEASE IN PEOPLE WITH CYSTIC FIBROSIS CARRYING 2 NONSENSE MUTATIONS IN EUROPE

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Introduction

Cystic fibrosis (CF) is the most common severe autosomal recessive disease in Europe. Nearly 5% of people with cystic fibrosis (pwCF) worldwide carry a nonsense mutation on both alleles resulting in a premature termination codon (PTC). This percentage is even higher is some countries in south and east Europe. [1] For those patients, no efficient targeted therapy is available yet [2, 3]. Limited information is available on their clinical status.

Aims

The main objective of this study was to compare disease severity among pwCF carrying 2 alleles with PTC mutations (PTC/PTC), pwCF compound heterozygous for F508del and PTC (F508del/PTC) and pwCF homozygous for F508del (F508del+/+).

Methods

The European Cystic Fibrosis Society Patients Registry (ECFSPR) annually collects data on pwCF from 40 countries in Europe and neighboring countries and contains now data from 2008 to 2021. Data are provided to ECFSPR under existing ethical approvals and data governance structures. Analysis for this study was based on data from 23 countries in ECFSPR between 2008 and 2019. The study was restricted to middle and high-income European countries to avoid bias due to geo-economical disparities since the PTC/PTC genotype is significantly more frequent in South Eastern low-income countries, compared to the F508del+/+ genotype mostly found in the Northern Europe high income countries.

To compare the different demographic and clinical characteristics between the three mutation groups, Fisher exact test with multiple comparison option was used for categorical variables, and Kruskal-Wallis nonparametric test with multiple comparison option for numerical variables.

As marker of disease severity three endpoints were analyzed in detail: Forced Expiratory Volume in 1 second percentage of predicted (FEV_1pp), chronic Pseudomonas aeruginosa (cPsA) colonization and death. Multiple regression models were fitted to test whether the genotype was significantly associated with these endpoints, after accounting for adjusting factors already known to be associated with clinical evolution of the disease: gender, age, country income group, Body Mass Index (BMI), chronic Burkholderia Cepacia Complex and insulin-dependent diabetes, FEV_1pp (included only in the model on cPsA and survival) and cPsA (included only in the model on FEV_1pp).

Evolution of FEV_1pp over time was modeled using a mixed effect multiple linear regression model, where age at FEV_1pp measurement was included with a restricted cubic spline with 3 knots, the interactions between age and mutation group and between age and all adjusting factors were included as fixed effects, while individual and country were included as random effects.

CPsA colonization was modelled with a mixed-effect multiple logistic regression model, including individual and country as random effects.

A Cox multiple regression model, using age as a timescale, was fitted to evaluate the effect of genotype on survival. A country variable was included as a cluster.

Results

Data of 26.228 pwCF were studied, 21.317 (81.3%) were F508del+/+, 4254 (16.2%) were F508del/PTC and 657 (2.5%) were PTC/PTC. Large variations in the frequency of pwCF from each mutation group were observed between countries, with a higher prevalence of PTC/PTC in South and Eastern Europe.

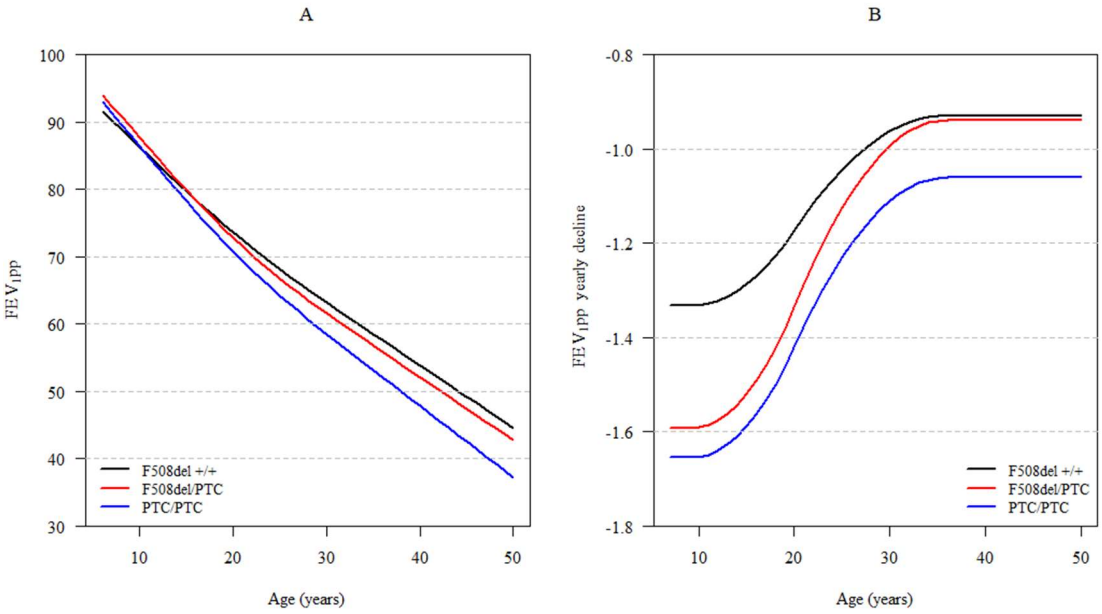
Overall, pwCF with a PTC/PTC genotype were significantly younger than those with a F508del/PTC or F508del+/+ genotype, with unexpectedly more male pwCF and less frequent diagnosis by neonatal screening among F508del+/+ patients. The carriage of at least 1 PTC was associated with a lower BMI as compared to F508del homozygotes.

FEV_1pp varies over ages, differently between the 3 mutation groups ($p<0.001$). As compared to F508del+/+ pwCF, PTC/PTC and F508del/PTC pwCF exhibited a significantly faster rate of decline from 7 years ($p<0.001$) until respectively 30 years ($p=0.048$) and 27 years ($p=0.034$). This resulted in sustained significantly lower FEV_1pp in comparison to F508del homozygotes, a difference which became significant from the age of 17 years for PTC/PTC ($p=0.036$), and from the age of 21 years for F508del/PTC pwCF ($p=0.022$). Although this never reached the significant level, the PTC/PTC pwCF tended to have a more rapid FEV_1pp yearly decline than the F508del/PTC pwCF and had a significantly lower FEV_1pp than F508del/PTC from 21 years ($p=0.043$).

Infection rate of cPsA were significantly higher in PTC/PTC versus F508del homozygotes from the multiple logistic regression analysis (Odds Ratio(OR)=1.32, $p=0.011$).

The multiple Cox regression model outlined that pwCF younger than 18 years PTC/F508del or PTC/PTC had a significantly higher mortality risk than those with the F508del+/+ genotype (hazard ratio (HR)=2.35, $p<0.001$ and HR=2.55, $p=0.05$ respectively). Even PTC/PTC pwCF older than 18 years have higher risk of death in comparison to F508del+/+, but the ratio is not statistically significant.

Figure 1. FEV_1pp values (panel A) and FEV_1pp yearly decline (panel B), according to age and mutation groups.



Conclusions

Nonsense mutations decrease the survival and accelerate the course of respiratory disease in children and adolescents with Cystic Fibrosis. In particular, our study shows that pwCF carrying at least one PTC exhibited a significantly faster rate of yearly respiratory decline until ~ 30 years and that mortality of children and adolescents with one or two PTC alleles was significantly higher than that of their F508del homozygous pairs. Moreover, infection with chronic PsA was more frequent in patients carrying 2 PTC when compared to PTC/F508del or F508del homozygous patients.

These data highlight the urgent need to develop targeted interventions for patients carrying nonsense mutations in the CFTR gene.

References

[1] De Boeck K., Zolin A., Cuppens H. et al. The relative frequency of CFTR mutation classes in European patients with cystic fibrosis. Journal of Cystic Fibrosis, 2014; 13(4):403-409.

[2] Bienvenu T, Lopez M, Girodon E. Molecular diagnosis and genetic counseling of Cystic Fibrosis and Related Disorders: New Challenges. Genes (Basel). 2020;11(6).

[3] Bell S.C., Mall M.A., Gutierrez H. et al. The future of cystic fibrosis care: a global perspective. The Lancet Respiratory Medicine, 2020; 8(1): 65-124.