

Change in IgG and evolution of lung function in children with cystic fibrosis

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Abstract

Reports from the seventies and eighties have shown that cystic fibrosis (CF) patients with severe lung disease have high levels of IgG and that this is associated with worse prognosis. We decided to explore IgG level as a possible outcome parameter for lung disease severity in a cohort of pediatric CF patients treated according to current standards of care.

Seventy three CF children older than 5 years (and max 15 years old at the initial evaluation) attending the same CF center were followed during a period of 4 years. Data collection included spirometry, height, weight, sputum cultures and total IgG.

Median age at the start was 10 years. IgG z scores ± 2 SD were seen in 2.7% of patients in 2004 and 2008. Twelve patients (16%) had an IgG ± 2 SD in 2004 and this number increased to 18 (25%) in 2008. IgG z-scores were inversely correlated with FEV₁% predicted ($r = -0.323$ in 2004; $p = 0.001$). In longitudinal evaluation, changes in IgG z-score correlate inversely with changes in FEV₁% predicted ($r = -0.498$; $p = 0.001$).

We can conclude that even for CF patients treated according to current standards IgG z-score increases with age and is correlated with a decline in FEV₁.

Introduction

Cystic fibrosis (CF) lung disease is characterized by chronic endobronchial infection and inflammation, typically caused by bacteria such as *S aureus* and *P aeruginosa* [1]. It has been reported several decades ago, that CF patients with severe lung disease have raised levels of immunoglobulin G (IgG) [2,3,4,5,6]. All IgG subclass levels are also raised in these patients [6, 7, 8]. On the other hand old reports document hypo-gammaglobulinemia in up to 10.8 % of children with CF [2, 9]. Although the latter finding is still poorly understood, a relation with malnutrition was suspected.

In the above mentioned reports, high levels of IgG were in a cross sectional analysis associated with worse lung function as higher IgG would reflect more severe chronic lung

infection [4, 6, 8]. Hypo IgG on the contrary was associated with better lung function and thus prognosis [4, 9]. These older data therefore suggest that IgG level and evolution could have potential as an outcome parameter.

Over the past decades CF therapy has progressed with intensive nutritional support and aggressive treatment of lung infection as major cornerstones. Frequent and prolonged courses of oral, inhaled and intravenous antibiotics are being prescribed to slow down relentless lung infection [10]. Additionally new mucolytics have become available [11]. Few studies have addressed the prevalence of hyper- and/or hypo gammaglobulinemia and its relation with lung prognosis in CF children treated according to current standards. One pediatric CF center reported an hyper IgG (>2 sd for age) in 7.8% ($n=12$) while only 1.9% ($n=3$) had hypo IgG [12]. The former group had worse lung function and worse clinical and radiological scores when compared to matched control CF patients.

Because recent data are limited and cross sectional, we decided to study the relation between IgG and lung function over a 4 year period in a cohort of pediatric CF patients thereby exploring IgG level as possible outcome parameter for lung disease severity.

Patients and Methods

CF children attending the CF center at the University of Leuven, Belgium for follow-up were studied over a period of 4 years. Patients were included if above 5 years of age and able to perform spirometry and if data were available for the years 2004 up to 2008. Maximum age at inclusion was 15 years. Clinical data collected at each 3 monthly visit include: spirometry with FEV₁ and FVC % predicted, height and weight (expressed as z-score) and sputum cultures. Total IgG was measured twice yearly.

Sequential measurements for the years 2004, 2006 and 2008 were analyzed. For FEV₁, the best pre-bronchodilator measure of the year was used (expressed as percent predicted according to Zapletal) [13]. Other parameters were taken closest to the date of the selected lung function. Weight z-score was calculated according to Cole [14]. For each IgG result z-score was calculated using mean and SD for age (Nephelometry, Beckman –Image 800; see table 1).

Hypogammaglobulinemia was defined as IgG z-score < 2 and hypergammaglobulinemia IgG as Ig z score > 2 .

Pseudomonas aeruginosa (*Pa*) status was defined according to the Leeds criteria [15].

Table 1

Reference values for serum IgG according to age as used by the lab.

| Age | -2 SD | Mean | +2 SD |
|-------------|-------|-------|-------|
| 3–6 years | 4.78 | 8.04 | 11.29 |
| 6–9 years | 5.30 | 9.18 | 13.06 |
| 9–12 years | 5.58 | 9.06 | 12.54 |
| 12–16 years | 5.76 | 9.21 | 12.65 |
| >16 years | 7.51 | 11.56 | 15.60 |

Statistics.

Statistical analysis was performed with SPSS-18 . For continuous variables without normal distribution the Kruskal-Wallis test was used. Non-parametric correlations (Spearman) were calculated for cross-sectional and longitudinal data. For multifactorial analysis linear regression was used.

Results

For 73 CF children between the age of 5 and 15 years in 2004, sequential data were available for the period 2004-2008 (40 boys, 33 girls). Chronic *Pa* infection was present in 12 patients (16%) in 2004, and 16 (22%) and 17 (23%) in 2006 and 2008 respectively. Further patients characteristics are given in Table 2.

In 2004, 2 patients had an IgG z-score < 2 (2.7%) and this number was 1 (1.4%) and 2 (2.7%) in 2006 and 2008 respectively. Twelve patients (16%) had an IgG > 2 SD in 2004 and this number increased to 14 (19%) and 18 (25%) in 2006 and 2008.

In cross-sectional analyses, there is an inverse correlation between IgG z-scores and lung disease severity expressed as FEV₁ % predicted (for 2004 $r = -.455$ and $p = .001$; for 2006 $r = -$

.264 and $p=.02$; for 2008 $r=-.34$ and $p=.002$). In longitudinal evaluation, changes in IgG z-score correlate inversely with changes in FEV₁ between 2004 and 2008 ($r=-.498$ and $p<.001$).

Table 2
Patient characteristics.

| Median (IQR) | 2004 | 2006 | 2008 |
|---------------------------------|--------------------|--------------------|--------------------|
| Age in years | 10 (7;12) | 12 (9;15) | 14 (11;17) |
| FEV ₁ % predicted | 93 (81;106) | 96 (78;102) | 91 (78;103) |
| Weight z-score | -0.17 (-0.82;0.55) | -0.32 (-0.83;0.43) | -0.48 (-1.10;0.13) |
| IgG z-score | -.01 (-1.08-1.25) | .47 (-.57-1.85) | .52 (-.44-2.05) |

The average decline in FEV1% for a rise in IgG of +1 z score is -8.3% (95% CI -14.382—2.282). For the subgroup of patients with chronic *Pa* infection in 2004 correlation between changes in IgG z score and FEV1 was -0.596 ($p=0.01$).

The mean change in IgG z-score over 4 years was 0.43 (SD 1.46) and the mean change FEV1% -5% (SD 17%). See figure 1.

In 2004, 12 out of 73 patients (16%) were chronically colonized with *Pa*, while the same number had intermittent *Pa* isolation. In 2008 the number of chronic *Pa* infected patients increased to 17 (23%). For the group with IgG >2 SD, the proportion of chronic *Pa* patients is significantly higher compared to the group with normal IgG (Fisher exact ; $p<0.05$). As expected the median age between these groups differed as well : chronic *Pa* 13.0 years (IQR 11.3-14.8) *versus* 8.0 (IQR 6.0-11.5) years if no chronic *Pa* for the year 2004 ($p<0.001$). Since age is correlated with IgG z-score ($r=0.488$ in 2004 $p<0.001$, $r=0.394$ in 2006 $p=0.001$, $r=0.252$ in 2008 $p=0.03$), we performed a multifactorial analysis for the effect of age and *Pa* status on IgG z-score. *Pa* status was not significantly correlated with IgG z score ($p=0.8$).

Discussion

We followed IgG levels in a cohort of 73 children with CF over a 4 year period and correlated change in total serum IgG with evolution of lung function. Most importantly increase in IgG

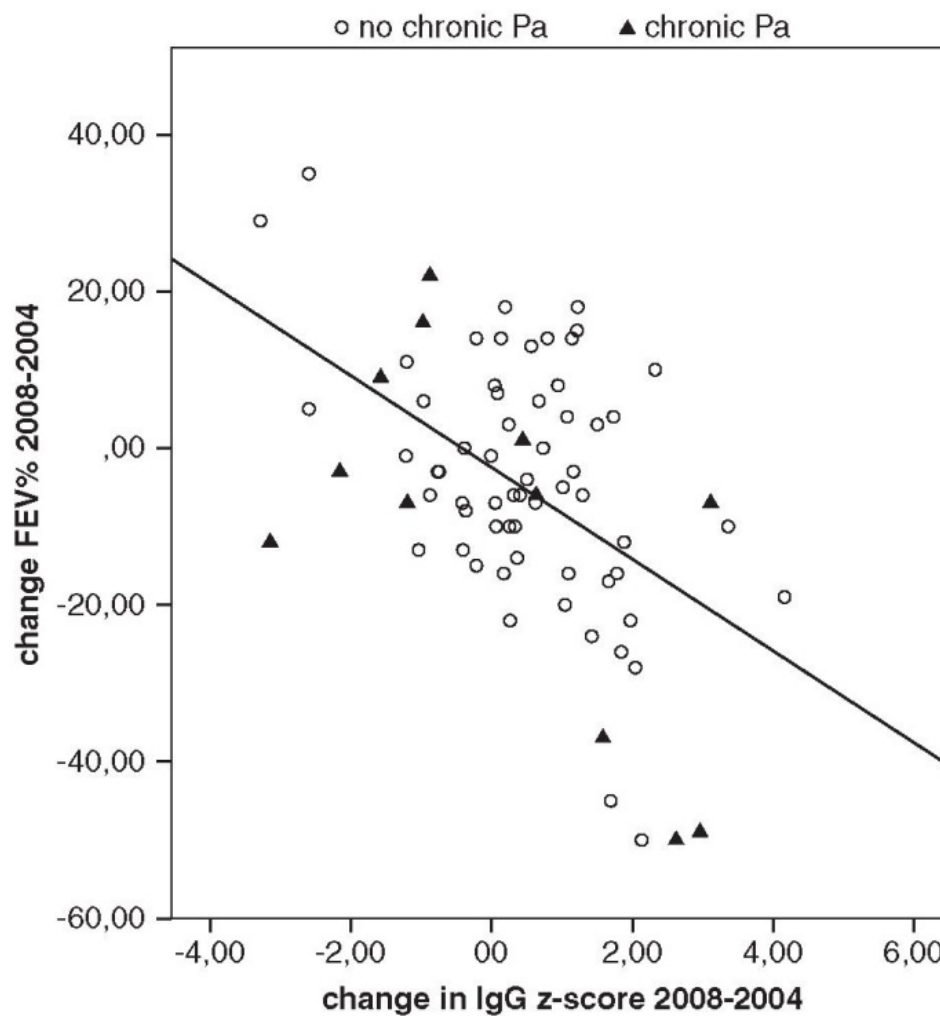


Fig. 1. Correlation between change in IgG z-score 2008–2004 and change in FEV1% 2008–2004.

z-score inversely correlates with FEV₁% decline over this 4 year period. In a cross sectional analysis, IgG expressed as z-score also correlates with FEV₁ % predicted for the 3 separate years of study (2004, 2006, 2008).

Raised levels of IgG (> 2 sd for age) were present in 12 (16%) patients at the start of the follow-up increasing to 18 (25%) 4 years later. The latter corresponds well with the 25.4% of patients with an IgG >2sd in the German CF registry for all patients under the age of 18 years. In some older publications raised IgG was prevalent in up to 30% of patients [3]. A pediatric report from 1980 [9] showed a prevalence of hyper gammaglobulinemia in 22% of children below the age of 10 years. In the German registry, raised IgG levels occurred more often in patients with chronic *Pa* infection. This was also the case in our series, however, in multifactorial analysis age rather than *Pa* status correlated with IgG z score.

At the start and the end of the follow up (median age of 10 and 14 years), only 2 (2.7%) of children had a IgG < 2 SD for age. This percentage is comparable to the report of Garside *et al* [12]. In the German CF registry (report of 2007), 3.5% of pediatric patients had an IgG < 2 SD however, the group included children from birth. In studies published in the seventies and eighties up to 11% of young CF children had hypogammaglobulinemia [2,9]. This may be attributed to malnutrition in older cohorts. To date there are however no arguments that lower IgG level have a negative prognostic value, even on the contrary [9].

The majority of reports on IgG levels in CF and correlation with lung function are cross sectional. Only in a study published in 1984 [4], longitudinal data over a period of 5 years were documented while all other older studies report cross sectional data on IgG and respiratory status. Compared with matched controls, CF patients with hypogammaglobulinemia (< 2sd) had a better prognosis [9,4].

We are aware of only 1 report correlating serum IgG with respiratory status in children with CF published in the last 10 years [12]. In this series of 154 patients with a mean age of 9.2 years, 7.8% had IgG >2 SD. About 19% of children had chronic *Pa* infection. The 12 patients with raised IgG had worse lung function as well as clinical - and X-ray scoring compared with matched controls. In our report, a higher proportion of patients had raised IgG levels (between 16% in 2004 and 25% in 2008) although the age was comparable and the proportion of chronic *Pa* somewhat lower. In the study of Garside *et al* CF children were included from diagnosis while in our study only patients older than 5 years and above were studied.

Rather than matching patients according to raised or lowered IgG levels, we correlated IgG- and lung function evolution over time in the whole cohort and found moderate correlation ($r= 0.498$) even better than the correlation between bronchoalveolar lavage elastase and FEV₁ decline [16]. In addition, IgG seemed responsive i.e. decreasing in subjects with improving lung function and rising in subjects with worsening lung function. The mean FEV % change per z-score change was 8.3%. In a disease as CF the aspecific nature of the IgG signal (an overall reflection of lung function rather than a specific antibody to one infection) may even be an advantage when used as outcome parameter. CF subjects indeed suffer from different types of infection, viral as well as bacterial, and both can contribute to lung disease.

We are aware that the cohort is not large, especially if one would like to study subgroups with or without chronic *Pa*. On the other hand, this cohort is followed up in the same CF reference center and thus receives comparable treatment.

Our main message is that also in the current era of CF treatment, IgG z-score in children with CF rises with age since chronic lung infection is progressive. Since this rise is inversely correlated with FEV₁ it most likely reflects progressive chronic lung infection. Raised IgG can thus be used in combination with other measurements like lung function and imaging as an additional parameter to evaluate if treatment is adequate or should be intensified. Although hyper IgG is less frequently found in young CF children, a rising IgG z-score in this group should prompt a review of lung infectious status.

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