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Original Article

Incorporating genetic potential when evaluating stature in children with cystic fibrosis

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Abstract

Objective: The 2002 Cystic Fibrosis Foundation (CFF) practice guidelines recommend adjusting for genetic potential when evaluating height status in children with CF. However, there is paucity of data to support this recommendation. We compared three methods of classifying short stature: unadjusted height percentile <10th, Himes adjusted height percentile <10th, and unadjusted height below the CFF target height lower bound.

Patients and methods: Data from 3306 children with parental heights documented in the 1986–2005 CFF Patient Registry were analyzed.

Results: Mean height percentile of CF children (33rd) was lower than their parents' (mothers' 53rd, fathers' 57th), and 80% of CF children were below the average of their parental height percentiles. In children with short parents, Himes adjusted height percentile was significantly higher than unadjusted height percentile (27th vs. 8th), whereas the opposite was found in children with tall parents (Himes adjusted at 18th vs. unadjusted at 49th). Consequently, the prevalence of short stature decreased from 52% to 22% in children with short parents and increased from 8% to 34% in children with tall parents after Himes adjustment. In children with discrepant classification on short stature before and after Himes adjustment, percent predicted forced expiratory volume in one second was negatively associated with unadjusted height percentile but positively associated with Himes adjusted height percentile. In children with short parents, the CFF method underestimated the prevalence of short stature (9%) compared to the Himes method (22%).

Conclusion: Without adjustment of genetic potential, the prevalence of short stature is underestimated and the association between height and lung function is biased.

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Keywords: Cystic fibrosis; Height; Parent–child relationship; Short stature; Lung function

1. Introduction

Height is both a hereditable trait and a feature of growth that is profoundly impacted by nutrition and disease. It is important that the genetic contribution to height be considered when evaluating the influence of nutrition and disease on attained height, especially for children with chronic diseases such as cystic fibrosis (CF). According to the 2004 Cystic Fibrosis Foundation (CFF) Patient Registry Annual Report, 15% of CF children had heights below the 5th percentile without adjusting for their genetic potential [1]. The prevalence of short stature in CF children is likely to be different if the contribution of genetic potential is accounted for. One possibility is that the prevalence of short stature in CF children may be overestimated, because parents of CF patients may be shorter than normal adults, as reported by a recent Italian study [2]. Alternatively, the prevalence of short stature in CF children would be underestimated if their parents have normal/tall stature, as revealed in our previous analysis using data from a

Abbreviations: CF, Cystic fibrosis; CFF, Cystic Fibrosis Foundation; FEV_1, Forced expiratory volume in one second.

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single CF center [3]. In either case, it is important to separate the effects of genetic potential versus disease impact in order to provide optimal clinical care.

The genetic potential for height is commonly estimated from parental stature. However, methods for utilizing parental stature to adjust the child's stature vary [4–10]. The 2002 CFF consensus report [10] recommended a simple method to estimate genetic potential, namely, calculation of target height range based on parental heights, when evaluating height status in children with CF [7]. The concept of this method is that a healthy and well-nourished child's attained adult height shall reflect his/her genetic potential. The CFF target height method [7,10] is intuitive to interpret and convenient to use, but has not been validated in the CF population. Clinical applications also reveal limited use because the CFF target height range is very large (e.g., for boys, 176±10 cm spans the 7th to the 93rd percentile on the CDC growth chart, ref [11]). This means that even if a child's height is substantially below the target height, he/she most likely would remain above the lower bound of the target height range and thus be considered as meeting his/her genetic potential.

Another method, developed by Himes et al. [8], also utilizes parental heights to adjust the child's height. This method [8] is based on statistical modeling of age-specific relationships between mid-parental heights and children's heights using data from the Fels Longitudinal Study [12]. Nevertheless, Himes method [8] requires the use of large reference tables to calculate an "adjusted height", making it impractical for use in routine clinical settings.

The objectives of this study are to utilize the 1986–2005 CFF Patient Registry to: 1) compare the difference between unadjusted height to Himes adjusted height percentiles [8] and their associations to lung function, and 2) examine the agreement between the CFF target height method [7,10] and the Himes adjusted height method [8] in classifying short stature.

2. Subjects and methods

2.1. Study population

The CFF Patient Registry documents the diagnosis and follow-up evaluations of patients with CF who are seen at accredited centers in the United States [13]. Data from 3510 children older than 2 years of age who had self-reported parental heights available were identified from the 1986–2005 CFF Patient Registry. Of these, 204 patients with parental heights less than 100 cm (likely due to inch–centimeter conversion or recording errors) were excluded from analysis. The most recent height measurement between age 2 to 18.5 years for each patient was used for analysis. Sex- and age-specific percentiles and *Z*-scores for height were calculated by using the reference values from 2000 CDC growth charts [11].

2.2. The CFF target height method

This method [7,10] uses parental heights to predict the genetic potential for a child's adult height, referred as the target height, which is calculated by mid-parental height plus 6.5 cm for boys or mid-parental height minus 6.5 cm for girls. A 10 cm-range above (upper bound) and below (lower bound) the target height for boys (9 cm for girls) is then applied to define the range of normal variation for target height. If the child's height is below the lower bound of his/her target height, he/she is considered to be below genetic potential. The procedure to calculate the CFF target height and range [7,10] is described in detail in Appendix A. In an example illustrated in Fig. 1, the child's CFF target height is 166.5 cm (7th percentile), with a lower bound at 156.5 cm (0.2th percentile). His unadjusted height at age 15 (5th percentile) is above his target height lower bound (0.2th percentile) and therefore he is meeting his genetic potential.

2.3. The Himes adjusted height method

This method [8] does not directly predict the child's genetic potential for height. Instead, it attempts to eliminate the influence of tall and short parental stature on the child's stature by generating an "adjusted height", which represents the child's height as if his/her parents had average stature. Therefore, Himes adjusted height presumably reflects the impact of nutrition and disease on the child's height. The procedure to calculate Himes adjusted height [8] is described in detail in Appendix A. In the example illustrated in Fig. 1, Himes adjusted height percentile is 22nd. If 10th percentile were used to define short stature, this boy would be classified as "short" by unadjusted height percentile (5th) but "normal" by Himes adjusted height percentile (22nd).

2.4. Assessment of agreement between the CFF method and the Himes method

Direct comparisons between the CFF [7,10] and the Himes [8] methods are not possible because the CFF method does not give an adjusted height. Since our purpose of utilizing a parental height adjustment method is to identify short stature, it is logical to compare the CFF [7,10] and the Himes [8] methods based on their agreement in classifying short stature. When we compared the CFF lower bounds with the 2000 CDC growth charts reference values at age 20, we found that 10 (9) cm lower bound corresponds to the 7th percentile cutoff point, when target height at age 20 is at the population mean, i.e., 50th percentile. Therefore, we applied two cutoffs, <5th and <10th, to Himes adjusted percentile [8] to define short stature and compared each of these two cutoffs to the CFF target height lower bound [7,10].

2.5. Association of height percentile to lung function

The associations of unadjusted height and Himes adjusted height [8] to the lung function parameter, percent predicted forced expiratory volume in one second (%FEV_1), were evaluated. %FEV_1 was calculated according to the Wang equations [14]. For this analysis, only patients older than 6 years of age and having %FEV_1 data were included.

2.6. Statistical analysis

Statistical analyses were performed by using SAS (version 9.13, SAS Institute, Inc, Cary, NC) and R (http://www.r-project.org).

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