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Growth Monitoring to Detect Children with Cystic Fibrosis

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Key Words
Growth · Auxology · Screening · Cystic fibrosis · Malnutrition

Abstract
Background/Aims: Cystic fibrosis (CF) in infancy and childhood is often associated with failure to thrive (FTT). This would suggest that in countries without a newborn screening program for CF, FTT could be used as a clinical screening tool. The aim of this study is to assess the diagnostic performance of FTT for identifying children with CF. ***Methods:*** Longitudinal length and weight measurements up to 2.5 years of age were used from CF patients (n = 123) and a reference group (n = 2,151) in The Netherlands. Growth measurements after diagnosis were excluded. We developed five potential screening rules based upon length, weight and body mass index (BMI) standardized by age and gender (SDS). Outcome measures were sensitivity, specificity and positive predictive value (PPV). ***Results:*** BMI SDS had the highest sensitivity at low false-positive rates. An efficient scenario is a BMI SDS below –2.5 SD in combination with a decrease in BMI SDS of at least 0.5 SD. This scenario had a sensitivity of 32%, a specificity of 98.3% and a PPV of 0.75%. ***Conclusion:*** In the absence of a newborn screening program, young children with FTT for BMI are candidates to consider testing for CF.

Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in the Caucasian population [1]. In Caucasian European newborns the incidence is about 1:2,500, whereas in Caucasian North American newborns the incidence is approximately 1:3,500 [1, 2]. The symptoms of CF usually start at an early age and include meconium ileus, recurrent respiratory symptoms (cough, wheeze, pneumonia), steatorrhea, diarrhea, abdominal distension and failure to thrive (FTT) (slowed

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growth) [3, 4]. Newborn screening programs for CF have been introduced in several countries. In areas where there is no such program, CF is often diagnosed late, because the presentation of the symptoms is variable [5–7]. Diagnostic delay can lead to malnutrition [8], deterioration in lung function, an increase in immunoglobulin levels and a reduced life expectancy [9–12]. The standard diagnostic strategy is a sweat test after recognition of symptoms or a positive family history, followed by further laboratory testing and DNA analysis [13].

Several studies have compared the growth pattern of CF patients with that of healthy children [14–20]. Many cases show FTT for weight, length and body mass index (BMI). At the age of 1 year, mean weight and length standardized by age and gender (SDS) generally do not exceed –1.3 and –1 SD, respectively [14–18]. It is suggested that FTT for weight [14, 15, 17] and BMI [17] is more severe in girls than in boys. Mean BMI SDS for girls was approximately –1.2 SD at the age of 1 year, while this was –0.8 SD for boys [17]. A decrease in weight corrected for height was most pronounced in children with predominantly pulmonary symptoms [19], and height and weight of CF patients who were not colonized with *Pseudomonas aeruginosa* were within normal limits [20]. Most children experienced catch-up growth after diagnosis.

In countries where no newborn screening program for CF is available, many cases of CF are detected based on pulmonary and/or gastrointestinal symptoms and signs in combination with FTT. In other infants and children with CF, such clinical features are mild or subclinical and FTT may be the first symptom. In such children the diagnosis is often made relatively late. The interpretation of growth data in infancy and early childhood is difficult, because there is no consensus about the definition of FTT [21] nor about cutoff points for referral. Also for CF, there are no data on the diagnostic value of various expressions of FTT (length for age, weight for age, BMI for age) nor on the sensitivity and specificity of the possible cutoff points. The aim of this study is to assess the diagnostic performance of growth-based criteria for detecting CF. This could improve the efficiency of growth monitoring as a tool to detect CF as early as possible.

Patients and Methods

Patients

Longitudinal length and weight data of the patients with CF were collected retrospectively in the year 2005 from three major CF clinics in The Netherlands: Erasmus MC – Sophia Children's Hospital in Rotterdam, University Hospital Maastricht, and Haga/Juliana Children's Hospital in The Hague. Additional growth information of these children was obtained from physicians in the Regional Child Health Care Centers with permission from the patient or his or her parents. The following information was obtained from the patient files: date of birth, date of referral, gender, ethnicity, perinatal information (birth weight, length, gestational age), date of diagnosis of CF and DNA mutation. If ethnicity was not recorded, it was assessed based on the patient's first and family name according to an algorithm reported earlier [22]. We included only growth data before or at diagnosis, with a maximum at the age of 2.5 years. In total, 123 children were available.

Reference Sample

A reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in The Netherlands during 1988–1989 [23]. Of this cohort, longitudinal data of length and weight of children from birth to 2.5 years of age were available. The length and weight distributions from birth to 2 years of these children were previously described by Herngreen et al. [24].

Screening Rules

We developed several screening rules based upon growth (table 1). The rules are meant to serve as criteria for referral to specialist care. The same rules have also been examined for the detection of children with celiac disease [25]. Each of these rules combines several parameters, such as a certain amount of a decrease in SDS over some time period. Table 1 provides the explanation of the individual parameter in the rules studied. In a simulation analysis, we varied each parameter to see how the diagnostic performance of each rule would change.

We used the following five rules:

(1) The first rule *(delta rule)* refers a child if an absolute change in length SDS, weight SDS or BMI SDS occurs. For example, if a child has two weight measurements, one measurement at the age of 6 months and one at the age of 1.5 years, it will be referred according to the delta rule with parameter $g_1 = -2$ (see table 1) if its weight decreases by more than 2 SD during this period.

(2) The second rule *(extended delta rule)* is equal to the first rule with the extra condition that the second measurement must have a low SDS (for example below –1.5 SD).

(3) The third rule *(slowed growth rule)* signals whether an abnormal slowed growth for length, weight or BMI occurs in terms of change in SDS per year in combination with a current low SDS. Slowed growth requires measurements taken at least 3 months apart. For example, if a child has two length measurements, one measurement at the age of 7 months and one measurement 6 months later, it will be referred according to the slowed growth rule with parameters $g_3 = -1$ and $f_2 = -1.5$ (see table 1) if the difference between the second and first length measurement per year exceeds 1 SD (which corresponds to a decrease of 0.5 SD within 6 months) and if the second measurement is below –1.5 SD.

(4) The fourth rule *(conditional weight gain rule)* signals whether a child's conditional weight gain SDS is below a certain value, in combination with the extra condition of a low weight SDS [26, 27]. The conditional weight gain rule accounts for regression to the mean.

Table 1. Growth screening rules with their definitions, interpretation of the used parameters and cutoff (simulation) values (see Methods section for details)

Screening rule	Definition	Parameter	Interpretation	Simulation values
Delta rule[a]	For ages 0 to 2.5 years, refer if			
	$(SDS_2 - SDS_1) < g_1$	g_1	Change in SDS	–0.5, –1, –1.5, –2, –2.5, –3
Extended delta rule[a]	For ages 0 to 2.5 years, refer if			
	$SDS_2 < f_1$, and	f_1	SDS cutoff level below which the SDS_2 must lie	–1, –1.3, –1.5, –2, –2.5
	$(SDS_2 - SDS_1) < g_2$	g_2	Change in SDS	–0.5, –1, –1.5, –2, –2.5, –3
Slowed growth[a]	For ages 0 to 2.5 years, and			
	$X_2 - X_1 \geq 3/12$ refer if		Minimal 3-month interval between ages X_1 and X_2	
	$SDS_2 < f_2$, and	f_2	SDS cutoff level below which the SDS_2 must lie	–1, –1.3, –1.5, –2, –2.5
	$(SDS_2 - SDS_1)/(X_2 - X_1) < g_3$	g_3	Change in SDS per year	–0.5, –1, –1.5, –2, –2.5
Conditional weight gain rule	For ages 0 to 2.5 years, refer if			
	Weight $SDS_2 < f_3$ and	f_3	SDS cutoff level below which the SDS_2 must lie	–1, –1.3, –1.5, –2, –2.5
	Weight SDS_{gain} = (weight SDS_2 – r weight SDS_1)/($\sqrt{1 - r^2}$) < g_4	g_4	Change in SDS	–0.5, –1, –1.5, –2, –2.5
Absolute SDS rule[a]	For ages 0 to e_1 years, refer if	e_1	Age (in years) at which the referral level changes	0, 0.5, 1
	$SDS < f_4$	f_4	SDS cutoff level before age e_1	–1, –1.3, –1.5, –2, –2.5, –3, –3.5
	For ages e_1 to 2.5 years, refer if			
	$SDS < f_5$	f_5	SDS cutoff level after age e_1	–1, –1.3, –1.5, –2, –2.5, –3

Several screening rules based upon growth were studied. Each screening rule consists of parameters that we have varied. Delta rule: refer when there is a decrease in SDS (crossing SDS lines). Extended delta rule: see delta rule plus a low SDS (crossing SDS lines with a low SDS as a result). Slowed growth rule: refer when there is a decrease in SDS per year plus a low SDS. Conditional weight gain rule: refer when there is a decrease in SDS per year accounted for regression to the mean (the amount of regression to the mean depends on the correlation of body weight across age) plus a low SDS. Absolute SDS rule: refer when a child has a low SDS. For more details, see 'Screening Rules'.

[a] Calculated for length, weight and BMI.

(5) The fifth rule *(absolute SDS rule)* refers a child if the length SDS, weight SDS or BMI SDS is low. An example is to refer if a child's length SDS is below –2 ($e_1 = 0$ and $f_5 = -2$).

Some parameter settings effectively select a subset of data. Rules 1–4 need the availability of multiple measurements. The rules were tested only on children for whom appropriate data were available. In the case of three or more measurements, all possible pairs of measurements were calculated. For example, if weight is measured at ages A, B and C, the method calculates the weight gain for the intervals AB, BC and AC.

Statistical Analysis

Each screening rule was implemented using S-Plus Version 7.0.3 for Microsoft Windows (2005), and was applied to both sets of longitudinal data. We calculated sensitivity, specificity and positive predictive value (PPV) for each rule under several scenarios. A scenario is a unique combination of parameter values. The rules were ordered according to their sensitivity at high levels of specificity. A higher sensitivity at the same level of specificity results in a better performance. The results were plotted as a receiver operating characteristic (ROC) plot, but scaled to a different axis than conventionally in order to view the area of most interest (high specificity). Scenarios of rules up to 2% false-positive rates were presented in detail, because low false-positive rates are desirable from a societal perspective. PPV was calculated assuming that the mean incidence of CF is 1 per 2,500 live births in the Caucasian population [2]. Tables of agreement and differences between rules in both the CF-group and reference group were calculated, because such tables provide insight into the diagnostic performance for different subsets of the data.

Length, weight and BMI measurements were expressed as SDS using the Dutch reference growth data [28, 29]. In preterm infants (gestational age <37 weeks) length and weight SDS were corrected for gestational age. For most children, gestational age was calculated as the number of weeks that have passed since the first day of the last menstrual period accounting for the average menstrual cycle length. This gestational age was confirmed with the measurement from an ultrasound examination between 8 and 12 weeks. The intrauterine growth charts from the Swedish reference population was used to express SDS up to the age corresponding with 40 weeks of gestation [30]. Between 40 and 42 weeks an interpolation between the growth curve of the Swedish reference population and that of the Dutch reference population was used. From 42 weeks of gestation till the age of 2 years, SDS was calculated on ages corrected for gestational age, using the Dutch reference growth data.

We assumed that a child would be referred if his or her growth pattern met the criteria of a given screening rule at the earliest age possible. All rules were dealt with separately, meaning that the same child could be referred according to each separate rule.

Table 2. General characteristics of the CF patients

Characteristics (n = 123)	
Male	51%
Ethnicity	
Dutch/European	91%
Turkish	2%
Moroccan	1%
Others	4%
Unknown	2%
Median (range) age in years at time of diagnosis	0.59 (0–15)
Children with diagnosis at birth[1]	3%
Children diagnosed <1 year	62%
Children with ≥2 measurements between birth and diagnosis	64%
Mean (SD) length SDS at time of diagnosis[2]	–1.08 (1.13)
Mean (SD) weight SDS at time of diagnosis[2]	–1.60 (1.35)
Mean (SD) BMI SDS at time of diagnosis[2]	–1.13 (1.79)
DNA	
Homozygous for dF508	47.2%
Heterozygous for dF508[3]	20.3%
Others[3]	3.3%
Unknown	29.3%

[1] One of their siblings is known with CF or the neonate presents with meconeum ileus.

[2] Based on children with at least one measurement between 6 months before or 3 months after diagnosis.

[3] Mutations other than dF508 were: 'A455E', 'G542X', 'N1303K', 'R1162X', 'R553X', '1717-1G>A' 'IVS17bTA', 'Q552P', 'R1066C', 'S1251N', 'G542x', '1677d', 'G178R', 'Q493X' and '3659delC'.

The Medical Ethical Committee of the Leiden Academic Hospital approved the study protocol. Informed consent was obtained from all parents and/or patients.

Results

Table 2 contains the general characteristics of the 123 CF-patients. Mean weight SDS at time of diagnosis was –1.7 SD for girls and –1.5 SD for boys (not statistically significant, data not shown).

ROC Curves

Figure 1 shows the ROC plot of the five best screening rules. The diagonal line indicates where sensitivity is equal to 100-specificity. In other words, a scenario on this line is not able to discriminate between the CF group and the reference group. The BMI extended delta was most successful in terms of high sensitivity at a low false-positive rate. Of the rules that consider only length, the length extended delta rule had the best diagnostic performance. All other rules that considered length and weight separately had sensitivities below 20% at a 2% false-positive rate.

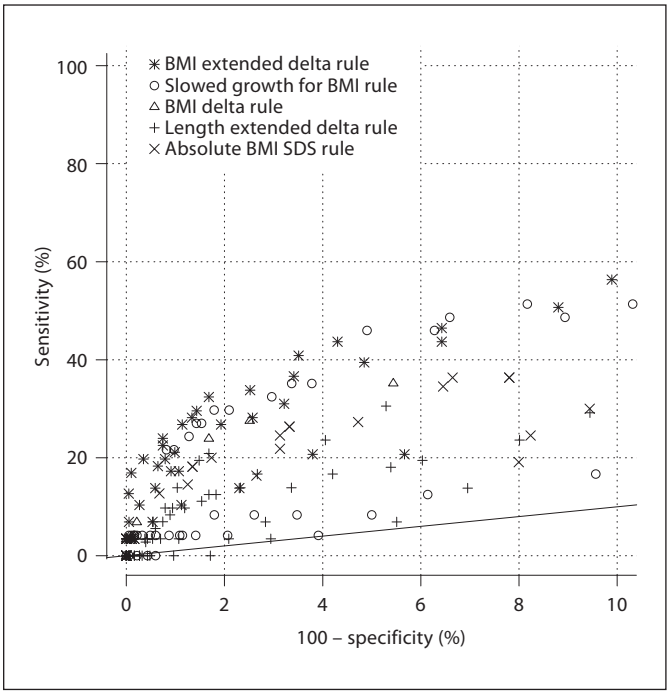

Fig. 1. ROC plot of efficient screening rules to detect CF.

Scenarios of the Best Screening Rule

A very strict version of the BMI extended delta rule is a BMI SDS below –2 SD combined with a decrease in BMI of >3.0 SD between birth and 2.5 years of age. This scenario correctly identified 17% (95% CI 8–26) of the CF children, while 99.9% (95% CI 99.8–100) of the reference children were correctly labeled as disease-free. The PPV of this scenario is approximately 6%. For example, if a boy has a BMI of +1 SD at 3 months of age and if he crosses three SDS lines (SDS 0, –1 and –2) before the age of 2.5 years, then the boy has a 6% probability of having CF. Less strict rules identify more children, but the probability of having CF rapidly decreases. For example, in children with a BMI SDS below –2 SD and a decrease in BMI SDS of >1 SD between birth and 2.5 years of age, the probability of having CF is only 0.47%.

Diagnostic Performance of the Rules

Table 3 presents the properties of the five best rules, in terms of sensitivity and PPV at approximately 2% false-

Table 3. Simulation values and the percentage of detected CF children (sensitivity) with approximately 2% false-positives (=98% specificity)

Rule	Growth	Simulation values			Sensitivity (95% CI)	False-positives (95% CI)	PPV
Extended delta rule	BMI	$f_1 = -2.5$	$g_2 = -0.5$		32 (21–43)	1.7 (1.1–2.3)	0.75%
Slowed growth	BMI	$f_2 = -2.5$	$g_3 = -0.5$		27 (13–41)	1.5 (1.0–2.0)	0.71%
Delta rule	BMI		$g_1 = -3$		24 (14–34)	1.7 (1.1–2.3)	0.56%
Extended delta rule	Length	$f_1 = -2.5$	$g_2 = -0.5$		21 (11–31)	1.7 (1.1–2.3)	0.49%
Absolute SDS rule	BMI	$e_1 = 1$	$f_4 = -3$	$f_5 = -2.5$	20 (13–27)	1.7 (1.1–2.3)	0.47%

positives. About 32% of all CF children and 1.7% of the reference children had a BMI SDS below –2.5 SD and a decrease in BMI SDS of more than 0.5 SD (PPV = 0.75%). If this rule would have been used, median referral age would be almost 3 months earlier than the observed age at diagnosis. For example, if a girl has a BMI SDS on the –2 SD line at 6 months of age, and her BMI crosses the –2.5 SD line 3 months later, she will be referred according to the above scenario. Her probability of actually having CF is 0.75%.

The best rule using length as a parameter was the extended delta rule. Referral is warranted if length SDS is below –2.5 SD and if a decrease in length SDS of >0.5 SD occurs between birth and 2.5 years of age.

Agreement

Contingency tables of agreement between rules in the CF group and in the reference group revealed that, except for the absolute BMI SDS rule, the diagnostic performance changed only slightly when looking at different subsets in the data. Sensitivity of the absolute BMI SDS rule was 5% higher (from 20 to 25%) for the children with at least two measurements. Therefore, this rule should actually be at the third position instead of the fifth in table 3.

Discussion

Our study shows that a combination of a low BMI SDS (<–2.5 SD) and a decrease of BMI SDS over the previous period (>0.5 SD) is the most sensitive rule to detect CF at an acceptable false-positive rate (1.7%). However, even for this rule, the PPV is low (0.75%), and for all scenarios PPV ranged from 0.5 to 6%. Thus, at best, only 1 in 16 children that are referred according to BMI SDS actually have CF. While such a yield is low in absolute terms, one should realize that the prevalence of CF in the open population is about 1:2,500. Thus one could also argue that screening on BMI SDS is useful since it will increase the probability of identifying CF from 1:2,500 to 1:16.

With respect to the possible generalizability of our results, future studies on other CF patients must be awaited. However, the decrease of weight, length and BMI over time until diagnosis observed in our study is similar to the findings of earlier studies [14–20], suggesting that the proposed screening rules may apply to other populations as well.

The reference sample is a nationally representative sample of infants who remained healthy over the 2.5 years of study. Although the incidence of CF of 1 CF patient per live births would suggest that there may be 1 case with CF in the reference sample (n = 2,151), the absence of clinical features of CF makes it far more likely that the reference sample did not comprise any case of CF. Even if one assumes the presence of 1 case of CF, this would only have a very small (negative) effect on the estimated specificity and PPV.

Screening rules for growth monitoring can be divided into rules with respect to a single measurement, with respect to velocity (e.g. a decrease in SDS or kg/year), and combinations. Traditionally, rules based on velocity have been considered as a better screening tool. However, such rules are more sensitive to measurement error than rules based on single growth measurements. Voss et al. [31] reported that height velocity lacks the precision to provide a reliable index of growth in short children. In our study, measurement errors may have led to more variation in velocity in the reference group and in the CF group. Therefore, one may need stricter cutoff values. Despite this phenomenon, it appears that velocity is a more informative predictor of CF than a single measurement. We found similar results for the detection of children with celiac disease [25].

The term 'failure to thrive', though used for a long time, suffers from a lack of consensus on its definition [21]. Some authors define FTT as weight or height falling below the third or fifth centile, or falling off two major centiles of the standard National Center for Health Statistics growth chart. Others state that malnutrition (weight <80% of ideal body weight for age) should be present to state that a child is failing to thrive [32, 33]. We believe that our approach, including studying the diagnostic performance of various definitions of FTT, is a fruitful basis for a discussion of the concept of FTT. While we have shown that BMI SDS and its decrease is useful for detecting CF and celiac disease, body length is superior to BMI in detecting girls with Turner's syndrome [34]. The optimal definition depends on the pathological causes of growth failure in infants.

In countries where newborn screening for CF is not available, growth monitoring (including assessment of BMI and its change over time), combined with a thorough medical history and physical examination, may be considered as the best screening procedure for CF. In infants and toddlers with an increased probability of CF, a sweat test is the next step. The diagnostic performance of the sweat test is known to vary, and widely different practices and standards in sweat testing are used. As a follow-up of this study, it would be interesting to investigate the diagnostic properties of sweat testing in combination with referral for FTT. Note that such a study would require that sweat testing is performed according to an evidence-based guideline [35].

Newborn screening has shown beneficial effects on the prognosis of CF and has been implemented in several countries [8–12]. In countries where such program is absent, we suggest the clinician to consider testing for CF (i.e. a sweat test) in the diagnostic work-up in infants and young children with FTT, with or without clinical features suggestive for CF. The most sensitive growth parameter is a combination of a low BMI SDS at examination and a decrease of BMI SDS over the previous period. Referral criteria implemented in a computer system in Community Child Health Care Centres can be helpful to perform the calculations. We recommend that future research with larger samples of children with CF should be performed to further optimize referral criteria.

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