Paediatric Respiratory Reviews 15 (2014) 28–32

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Controversies in the Evaluation and Treatment of Sickle Cell Disease

Somatic Growth and Lung Function in Sickle Cell Disease

Tina Catanzaro, Anastassios C. Koumbourlis *

Division of Pulmonary & Sleep Medicine, Children's National Medical Center/ George Washington University, School of Medicine, Washington DC, USA

EDUCATIONAL AIMS

The reader will:

- Learn the evidence regarding growth disparities between healthy controls and patients with sickle cell disease across different age groups.
- Review the relationship between anthropometric measurements such as height, weight and BMI and lung function in patients with SCD.
- Become familiar with the challenges that the inhomogeneity of sickle cell disease presents in applying findings of subgroup studies to larger populations.

ARTICLE INFO

Keywords:
Sickle cell disease
Growth
Lung function
Nutrition
Children
BMI

SUMMARY

Somatic growth is a key indicator of overall health and well-being with important prognostic implications in the management of chronic disease. Worldwide studies of growth in children and adults with SCD have predominantly shown delayed growth (especially in terms of body weight) that is gradual and progressive in nature. However, more recent studies have shown that a substantial number of patients with SCD have normal weight gain whereas some are even obese. Height in patients with SCD is not universally affected even among those with suboptimal weight gain, whereas some achieve the same or greater height than healthy controls. The relationship between somatic growth and lung function in SCD is not yet clearly defined. As a group, patients with SCD tend to have lower lung volumes compared with healthy controls. These findings are similar across the age spectrum and across ethnic/racial lines regardless of the differences in body weight. Several mechanisms and risk factors have been proposed to explain these findings. These include malnutrition, racial differences and socioeconomic status. In addition, there are structural changes of the thorax (specifically the anterio-posterior chest diameter and anterio-posterior to lateral chest ratio) specific to sickle cell disease, that potentially interfere with normal lung growth. Although, caloric and protein intake have been shown to improve both height and weight, the composition of an optimal diet remains unclear. The following article reviews the current knowledge and controversies regarding somatic growth and its relationship with lung function in sickle cell disease (SCD) as well as the role of specific deficiencies of certain micronutrients.

INTRODUCTION

Sickle cell disease (SCD) is a well described hemoglobinopathy characterized by vaso-occlusive episodes that may lead to severe multisystem complications including painful vasooclusive episodes, acute chest syndrome, renal infarction and stroke [1]. SCD has been also associated with impaired growth that was originally reported in the 1930s but received little attention for nearly 40 years [2,3]. The systematic study of the topic started in the 1970s with a series of studies in Jamaican children and adults with sickle cell disease [4–7]. The initial studies concentrated on the basic anthropometric measurements (height, weight) in relation to the overall skeletal maturation. Subsequent studies focused on nutritional aspects and more recently on the energy requirements of patients with SCD in an effort to understand the causes of the poor growth [8–23].

* Corresponding author. Children's National Medical Center, 111 Michigan Ave, N.W., Washington, DC 20010. Tel.: +1 202 476-2642; fax: +1 202 476-5864.
E-mail address: akoumbou@childrensnational.org (A.C. Koumbourlis).

1526-0542/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.prrv.2013.10.003

The manifestations of poor growth include suboptimal weight gain and/or suboptimal height. Poor weight gain (failure to thrive) is characteristic of almost all chronic conditions that are present in infancy (e.g. congestive heart failure due to congenital heart disease). If the condition is prolonged and/or severe the height is also affected. Studies in patients with cystic fibrosis (CF) have shown that the weight-for-age percentile (WAP) early in life is directly correlated with the height-for-age percentile (HAP) later in life. Specifically, those patients with WAP below the 10th % early in life, are expected to achieve a lower HAP compared with those whose WAP is above the 10th % [24].

There is also evidence that poor weight gain is associated with abnormalities in lung function. Studies in patients with CF have shown that there is a direct correlation between the WAP and the Forced Expiratory Volume in the first second (FEV_1), with an incremental increase in the FEV_1 for each increment in the WAP. In addition, patients with high WAP seem to have fewer pulmonary exacerbations, fewer hospitalizations and better overall survival. Conversely, patients whose BMI declined, have shown a similar decline in their lung function as well [24–26]. Although the pathophysiology of CF is obviously very different than that of SCD, it is possible that similar relationships between somatic growth and lung function may exist among patients with SCD as well. This article reviews the current knowledge and controversies regarding somatic growth and its relationship with lung function in SCD.

Body Weight in SCD

Jamaica has a large but contained population with SCD. Investigators in Jamaica compared body weight and height in relation to bone age in children, adolescents and young adults with SCD and healthy controls. They found that, as a group, patients with SCD had lower weight (adjusted for bone age) than the healthy controls [4–7]. The difference was very pronounced for male patients but rather minimal for female patients, suggesting the influence of hormonal factors. Subsequently, similar findings have been reported from virtually all parts of the world including North and South America, India, the Caribbean, Europe and several African countries that have substantial prevalence of SCD (a detailed summary of most of these studies up to 2007 can be found in an excellent review by Al-Saqladi et al. [27]).

There is currently general agreement that the weight of patients with SCD is normal at birth and remains so during the first few months of life, effectively excluding the possibility that the poor growth is congenital in origin. As longitudinal studies have shown the delayed growth is gradual and progressive in nature. Significant and progressive deficits in both weight and height can be found by 2 years of age. Most importantly, the poor weight gain is accompanied by delayed skeletal maturity that is clinically evident by 8 years of age [23]. Most investigators from around the world report that the weight of patients with SCD continues to be suboptimal throughout childhood and adolescence and into adulthood [27]. However, newer studies have challenged these assumptions reporting not only normal growth but even the presence of obesity [28–30]. There is also evidence that the effect of SCD on weight differs between males and females as well as between races [13,29,31].

Height in SCD

The effect of any disease or condition on the patients' height has potentially significant implications for lung function because height is far more closely associated with lung growth than weight [32]. This is because tall individuals tend to have a larger thorax than shorter individuals that is assumed to be the reason why they have larger lung volumes. Children and adolescents with SCD tend to be shorter compared with healthy controls. Initially, the short stature was attributed to endocrine causes such as thyroid abnormalities and hypogonadism. However, as Luban et al. [9] reported, the pituitary gonadotropins increase appropriately with puberty, and the gonadal end organ hormones also seem to be responsive in a manner similar to that seen in non-SCD individuals. An interesting finding from the Jamaican studies was that, despite the suboptimal height among children and adolescents with SCD, adult male patients with SCD were as tall or even taller than the healthy controls. The authors attributed this finding to the fact that boys with SCD have delayed skeletal maturation associated with delayed sexual maturation. As a result the fusion of the epiphyses of the long bones occurs much later than in healthy adolescents thus allowing the linear growth to continue much longer [5–7,10]. The delayed maturation does not have any effect on the weight that remains suboptimal throughout life. This discrepancy between weight and height is an important difference between patients with SCD and patients with other chronic diseases such as CF in whom the suboptimal growth seems to affect both the height and the weight.

Unfortunately, achieving normal height in adulthood is not accompanied by normal lung growth as one would expect in the general population. To explain this discrepancy, Stevens at al. [10] suggested that patients with SCD have a different body shape that may prevent the normal lung growth. Specifically, they found that children with homozygous Hb-SS SCD had an average decrease in weight, height, sitting height, limb length, interacromial and intercristal diameters as well as skinfold thickness. Most importantly they found that their patients with SCD have increased anterioposterior chest diameter, and increased antero-posterior to lateral chest ratio than healthy controls. This shape resembles the shape of pectus carinatum and could potentially interfere with normal lung growth.

It should be noted that the findings of the Jamaican studies on height are not universal. In fact, in most studies from different countries, both height and weight are reported as being lower among patients with SCD compared with healthy controls [27]. This raises the possibility that there may be genetic differences between different racial and/or ethnic groups that allow some but not all to achieve normal height. On the other hand, there are also many studies (Table 1) that show that the height among patients with SCD is close to or normal during childhood whereas the weight is generally below the predicted normal levels.

Table 1
Comparisons of anthropometric data and indices of lung function (mean±SD)

Author (Year)-Country	Age (years)	Height (cm) Patients (Controls)	Weight (kg) Patients (Controls)	BMI	FVC Patients (Controls)	FEV_1 Patients (Controls)
Pianosi et al.(1993)-Canada [33]	14±4	154±17	42±12	–	89±7 (%pred)	88±10(%pred)
Santoli et al.(1996)-France [34]	29±8	169±9/–	60±11	21±4	83±13(%pred)	86±17(%pred)
Sylvester et al.(2004)-UK [35]	10±2	139±14 (142±16)	33±11(41±15)	–	1.7±0.6L (2.1±0.8)	1.5±0.5L (1.9±0.7)
Klings et al.(2006)-USA [36]	31±9	170±10	61±12	21±4	84±4(%pred)	83±16(%pred)
Vendramini et al.(2006)-Brazil [37]	20±2	169±10 (169±8)	57±7 (70±16)	–	3.4±0.7L (4.2±0.8L)	2.9±0.5 (3.6±0.6L)
Akgul et al.(2006)-Turkey [38]	18±7	–	–	18±3	83±12(%pred)	82±12(%pred)
Sen et al.(2009)-Turkey [39]	28±7	167±8 (167±9)	61±11 (63±12)	–	79±–(%pred)	75±–(%pred)