Arch Argent Pediatr. 2024;122(4):e202410367

What may Pygmies teach us about short stature in very preterm infants?

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Short stature is frequently observed in preterm infants until adulthood.[1] Linear growth represents predominantly protein, lean mass, and bone mass accretion and indicates organ growth, which is dependent on the growth hormone-somatomedin axis. Weight gain represents total body mass, including fat mass, and indicates the balance between energy intake and expenditure, which is dependent on the glucose-insulin axis.[2] Although the causes of preterm weight retardation are known and have been extensively studied, the origins and consequences of linear growth retardation in this population have not been fully investigated.[2]

The objective of this article is to discuss the striking similarities observed between the evolutionary strategies of Pygmies and the neonatal adaptive strategies of preterm infants that we noted during our investigations to understand the origin of postnatal linear growth retardation in preterm infants.

Humans show considerable variations in height. In our contemporary setting, Efe hunter-gatherers in the Ituri Rainforest (Democratic Republic of Congo) are the shortest people studied in the world.[3] The origin of Pygmy short stature has been an enigma until very recently and, in our experience, knowledge about it provides fundamental data for understanding neonatal evolutionary biology.

Pygmies are born with a normal length and weight for their gestational age, as are preterm infants without intrauterine growth retardation. Based on this, it is possible to rule out genetic and prenatal causes of linear growth deficiency. During postnatal life, Pygmies grow in an isolated ecosystem with limited resources and face recurrent gastrointestinal infections due to lack of access to drinking water, leading to sustained systemic inflammation (SSI) with permanently elevated serum levels of C-reactive protein.[3] There is plenty evidence linking SSI caused by recurrent infections with the presence of short stature and growth hormone resistance in both Pygmies and children from poverty-stricken communities.[3,4] Similarly, preterm infants grow in isolation in incubators undergoing invasive procedures that promote the development of complications, such as sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia, leading to SSI associated with short stature.[2]

The growth hormone-somatomedin axis was an attractive candidate for understanding the mechanisms underlying the Pygmy phenotype. Recently, Pygmies have been shown to have somatomedin deficiency with peripheral growth hormone resistance, as do premature infants with short stature compared to controls.[3,5] Reduced growth hormone levels in Pygmies are associated

doi: http://dx.doi.org/10.5546/aap.2024-10367.eng

To cite: Cuestas E, Rizzotti A. What may Pygmies teach us about short stature in very preterm infants? *Arch Argent Pediatr.* 2024;122(4):e202410367.

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with decreased epigenetic expression of the growth hormone receptor gene. This explains why Pygmies, and probably premature infants, grow slowly during childhood and adolescence without compensatory growth, even though they have a normal growth spurt during puberty and reach adulthood ~10 cm shorter than their Bantu neighbors in the case of Pygmies and ~4 cm shorter than their full-term peers in the case of premature babies. This is consistent with the fact that the timing of puberty affects the intensity of adolescent growth, but not the final height.[1,3]

Given that chronic malnutrition may lead to low growth hormone and somatomedin levels, it is important to assess the impact of nutritional status on linear growth. It has been proven that, despite differences in adult height, the average skinfold thickness of Pygmies and their taller farmer neighbors did not differ, indicating a comparable level of nutritional health in both populations, in the same way as observed when comparing the nutritional status between preterm infants with and without linear growth retardation.[2,3,5] These findings are obviously incompatible with a simple model of growth retardation due to poor nutrition. The non-nutritional factors underlying linear growth retardation in preterm infants are not well understood. We and other authors have presented evidence that severe neonatal inflammatory diseases, mainly sepsis, bronchopulmonary dysplasia, and necrotizing enterocolitis, are associated with reduced height at 12 months of corrected age, and we recently proposed a pathophysiological mechanism to explain the association between SSI and linear growth retardation in preterm infants.[2,6,7] Subsequently, we demonstrated the inhibitory effect exerted by SSI on the growth hormone-somatomedin axis both systemically and locally by affecting bone mass formation in preterm infants.[5]

By analyzing data in the context of Pygmy life history, anthropologists have developed an elegant explanation to understand the evolution of the Pygmy phenotype. Specifically, to maximize reproductive fitness in very adverse living conditions, Pygmies experience a very early cessation of linear growth.[3] This explanation predicts an inverse relationship between adult life expectancy and final height; in fact, among contemporary Central African Pygmies, life expectancy is observed to be very short, averaging no more than 32 years.[3] There is a growing clinical interest in how people born prematurely age, get sick, and die. Some studies show that preterm adults with short stature have a burden of cardiovascular disease similar to that of individuals twice their age and have a higher proportion of short telomeres, indicating molecular evidence of advanced aging. These markers indicate an increased susceptibility to age-related diseases and provide evidence for the continued development of a high burden of early morbidity and mortality in this population.[1]

Hereditary, environmental, and stochastic factors determine a child's growth in its unique environment, but their relative contribution to phenotypic outcome and the degree of stochastic programming required to alter preterm length phenotypes are unknown because few data are available.

In summary and in conclusion, this has been a brief chronicle of our attempt to use evolutionary life history theory to understand linear growth retardation in preterm infants with SSI from adaptive neonatal strategies. ■

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