Patterns of Catch-Up Growth

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From embryogenesis to young adulthood, growth rate declines dramatically. This deceleration in growth velocity is most extreme in infancy with a more subtle slowing in growth velocity through mid-childhood, interrupted by the pubertal growth spurt, after which the growth rate gradually declines to zero.[1] While in the first years of life the length of healthy infants can cross the percentiles toward their genetic target height (TH) SDS, height tends to remain within a narrow "channel" on the growth charts between 3 years and the onset of puberty, close to the same percentile or SDS position. The tendency to keep to this narrow and predictable track of growth is called "canalization."[2] An SDS change of >0.25/year is rarely seen in longitudinal growth studies on normal children.[3]

A large variety of growth-retarding illnesses, including hypothyroidism, celiac disease (CD), malnutrition, Cushing syndrome or chronic steroid treatment, and growth hormone (GH) deficiency, can lead to a slowing in growth with a downward deviation from the standard growth curve. After release from these growth-inhibiting conditions, exaggerated acceleration in linear growth can occur. In 1963, Prader et al[4] and Tanner[5] introduced the term "catch-up growth" to describe this period of rapid linear growth in children that followed a period of growth inhibition, leading toward their original growth channel. The term catch-up growth is also used for the growth acceleration seen in ~85% of infants born small for gestational age (SGA),[6] although in these cases there is usually no information about the foregoing downward deviation.

The term catch-up growth is mostly used for height. Catch-up growth has been defined as "a height velocity above the statistical limits of normality for age or maturity during a defined period of time, following a transient period of growth inhibition; the effect of catch-up growth is to take the child towards his/her pre-retardation growth curve."[7] Even though this definition would imply that for a proper assessment of catch-up growth the full growth trajectory has to be evaluated (up to adult height), only few studies on catch-up growth have included all parts of this trajectory (the phases of growth inhibition, growth acceleration, growth maintenance, and puberty and the achieved adult height in comparison with the genetic growth potential). Furthermore, several alternative definitions of catch-up growth have been used, for example (in children born SGA) reaching an SDS of >−2 for the reference population[8] or a cut-off of a change of >0.67 SDS in the first year.[9] Data on the growth curve after the initial phase of catch-up growth and on the adult height corrected for mid-parental height (TH) are often lacking, presumably because of the difficulties in obtaining frequent growth data over long periods of time. In only a few studies, for example in GH deficiency,[10,11] hypothyroidism,[12,13] and CD,[14] have data on the complete pattern of catch-up growth including data on adult height been described.

Catch-up growth also occurs for other growth parameters, such as body weight, body composition, head circumference, and body segments (sitting height and leg length). For example, catch-up growth observed in the early stages after treatment of CD is generally characterized by an initial weight increase before height catches up, thus an initial rise of body mass index.[14] A mismatch between catch-up growth in height and in abdominal fat is seen in babies born preterm or SGA, in which there is greater increase in adiposity than height, which has been associated with a higher risk of cardiovascular disease.[15]

CD	Celiac disease
GH	Growth hormone
SGA	Small for gestational age
TH	Target height

Parameters of Catch-Up Growth

We have previously argued[16] that the first year height velocity is not suitable as the sole parameter for catch-up growth, because it is highly variable, lacks precision, and incompletely depicts catch-up growth.[17] In addition, the average height velocity for age is highly dependent on the height percentile of the child. For example, if height is to stay on 3rd percentile, a height velocity at approximately the 25th percentile is needed.[16] Furthermore, from a series of height velocities one cannot get a good impression of the position of the patient's height versus the population's reference charts.

A better parameter of catch-up growth, particularly when assessed over the full trajectory, is height SDS and its change over time.[16] There is no agreed cut-off criterion for catch-up growth, and we suggest that a sustained increase in height SDS toward the height SDS before the start of growth retardation would suffice as definition. One would expect that the size and speed of the height SDS change during the first years of catch-up growth depend on the distance between height SDS and TH SDS, as well as on age. In fact, this has been observed for GH deficiency.[18]

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Potential Mechanisms of Catch-Up Growth

We have previously discussed the 2 main hypotheses that have been proposed to explain catch-up growth: the neuroendocrine hypothesis and the growth plate hypothesis.[7] The neuroendocrine hypothesis was proposed by Tanner in 1963 and is based on the classical endocrine concept of central steering of processes.[5] Tanner suggested that a mechanism—possibly located in the hypothalamus—is able to compare the size of the body with the individual's expected size for that age. This was called a "time tally." If a mismatch is recognized, the body is encouraged to continue growing at a faster-than-normal rate. When the mismatch becomes less distinct, the growth velocity will decrease.[5] So far, no experimental evidence for this hypothesis has been collected.

The growth plate hypothesis is based on an old concept proposed by Osborne and Mendel in 1914, who showed that prolonged nutritional deprivation in the rat was followed by growth at an age well beyond the normal growth period of the species. They suggested that age is not the limiting factor for growth but that growth is limited by the intrinsic capacity for growth of the tissue itself.[19] After further work in this area by Williams,[20] a study in rabbits by Baron et al[21] gave this hypothesis its present shape by suggesting that the mechanism for catch-up growth is intrinsic to the growth plate. They proposed that catch-up growth arises from a delay in normal growth plate senescence. During normal growth plate senescence, the proliferative rate of the growth plate chondrocytes diminishes with each successive stem cell cycle. Thus, growth plate senescence is not a function of time per se but rather a function of the cumulative number of divisions the stem cells have undergone. After cessation of suppression of proliferation, in Baron et al's experiments by glucocorticoids or hypothyroidism, the cumulative number of stem cell divisions is lower than expected. After the suppression of proliferation, the cells therefore begin to proliferate at a faster rate than the nonexposed cells, leading to local catch-up growth.[21]

None of the 2 hypotheses gives a fully satisfactory explanation for the mechanism of catch-up growth in humans. The neuroendocrine hypothesis lacks experimental support, and the growth plate hypothesis can only explain one specific type of catch-up growth.[22]

Published Patterns of Catch-Up Growth

In 2 seminal articles,[23,24] Tanner distinguished 3 different growth patterns that potentially lead to the same (normal) adult height. In the first pattern (A), the cessation of the growth restriction is followed by an increased height velocity (up to 4 times the mean velocity for chronologic age), which fully eliminates the growth deficit. When the original growth curve is achieved, height velocity returns to normal. In the second pattern (B), the growth-restricted child grows slightly faster than normal for age but at a normal velocity for bone age, resulting in a longer growth period and a normal adult height. The third pattern (C) shows a growth velocity at the average level for chronologic age but with delayed bone maturation, resulting in growth that goes on for longer than usual. As noted by Tanner and by ourselves, type C formally cannot be considered catch-up growth, because by definition "velocity" should be above normal for age,[16,24] and we do not discuss this further.

Type A catch-up growth is seen as the classic example of catch-up growth and has been reported for several children, such as in some of the cases in the first reports of Prader et al[4] and Tanner.[25] This pattern can be seen in some infants and young children after growth restriction due to CD when a gluten-free diet is introduced,[14] in the majority of young children with hypothyroidism after treatment with levothyroxine,[13] and in many children with GH deficiency who are receiving GH treatment. Children with CD show on average a type B catch-up growth, with a height velocity that is consistent with height age and bone age,[22] conforming to the hypothesis of delayed senescence.[21,26] Another example of type B catch-up growth was given in a report on 2 men with hypopituitarism, in whom GH treatment was started at age 22.7 and 24.3 years at a bone age of 13-14 years. At ages 27.9 and 29.1 years, respectively, they had gained 22 and 21 cm in height, and their growth velocity was normal for their bone age.[27]

An Intermediate Type of Catch-Up Growth (Type AB)

We noticed that some catch-up growth curves of children with CD,[14,22,28] hypothyroidism,[13,29] GH deficiency,[11] and preterm born children[30,31] showed a catch-up growth pattern inconsistent with the classic types described by Tanner. Instead, they showed an increased growth velocity in the first years of treatment, followed by a stabilization of height SDS about half of the initial height SDS and genetic TH for a number of years, and a delayed pubertal growth spurt, after which they finally reached an adult height that was close to TH (or lower). If this pattern was arbitrarily defined as a failure to catch up toward the target range (TH $\pm$1 SD) within 3 years and further growth toward adult height of >1 SD, it was observed in 4 of 11 children (aged 1.2-10.1 years) with primary hypothyroidism and 2 of 8 children with GH deficiency (aged 0.4-9.3 years) (J.W., unpublished analysis of data reported by Ranke et al[13] and Sas et al[11]). For illustrative purposes, we show the growth curve of a boy with GH deficiency, who participated in a dose-response study,[11] in comparison with the theoretical curves for type A and B catch-up growth (Figure 1). This type of catch-up growth is intermediate between types A and B. We suggest calling this form "catch-up growth type AB," which is characterized by an initial faster growth than normal for bone age, which then passes into a phase of stable height SDS, which remains below TH SDS, until the delayed puberty causes an increase of height SDS toward TH SDS.

It is unclear why in some children catch-up growth is abrogated halfway and in others it continues until TH SDS is reached. We speculate that if the underlying disease remains active (eg, inadequately treated CD), treatment is