Regulators of growth plate maturation

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Catch-up growth: testing the hypothesis of delayed growth plate senescence in humans

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After a period of growth inhibition, the linear growth rate usually exceeds the normal range. This phenomenon, known as catch-up growth, was first described more than 40 years ago by Prader et al (1). It has been observed in humans and other mammals, after a wide variety of growth-inhibiting conditions, including malnutrition, Cushing syndrome, hypothyroidism, growth hormone deficiency, and many other systemic diseases (2).

Tanner proposed the hypothesis that catch-up growth is regulated by a central nervous system mechanism that compares the individual's actual body size to an age-appropriate set point and then adjusts the growth rate accordingly (3). However, this hypothesis is not supported by observations that transient growth inhibition within a single growth plate is followed by local catch-up growth in rabbits (4). This local catch-up growth suggests a mechanism intrinsic to the growth plate. Evidence from animal studies suggests that catch-up growth is due, in large part, to a delay in growth plate senescence. Growth plate senescence refers to the normal, programmed changes that occur in the growth plate over time. With increasing age, there is a decrease in the linear growth rate, the chondrocyte proliferation rate, the height of the growth plate, and the number of cells in each growth plate zone (5).

Animal studies suggest that growth plate senescence is not a function of time per se, but of cell proliferation (6). In particular, growth plate chondrocytes may have a finite proliferative capacity that is gradually exhausted, causing growth to slow and eventually to stop (6;7). Conditions that suppress growth plate chondrocyte proliferation conserve the proliferative capacity of the chondrocytes, thus slowing senescence. Consequently, after transient growth inhibition, growth plates retain a greater proliferative capacity, are less senescent, and, hence, show a greater growth rate than expected for age, resulting in catch-up growth.

However, the relationship between catch-up growth and delayed growth plate senescence has only been studied in rabbits (6) and rats (8). Thus it is not known whether catch-up growth is caused by delayed growth plate senescence in humans. Testing this hypothesis in humans is more difficult because most of the known hallmarks of growth plate senescence require microscopic examination of the growth plate. In children, we are restricted to indirect measures of growth plate senescence, including bone age and linear growth rate. Bone age assesses the degree to which the embryonic cartilaginous skeleton has been transformed into the adult bony skeleton. Bone age has been used as a surrogate marker for growth plate senescence (9) on the basis of 2 lines of evidence. First, the determination of bone age is based partly on the thickness of the radiolucent bands between the epiphyses and metaphyses, and thus bone age depends in part on growth plate height, a structural marker of senescence (7). Second, bone age is inversely associated with the remaining linear growth potential. This association is the basis for most height prediction methods (10). Thus bone age is associated with a functional marker of senescence, the decline in growth potential of the growth plates.

If catch-up growth in humans is indeed due to delayed growth plate senescence, and if bone age is a marker for growth plate senescence, then catch-up growth should be associated with delayed bone age. Abundant clinical data support this association. A delayed bone age is observed in essentially all conditions that impair growth, including nutritional, endocrine, rheumatologic, gastrointestinal, heart, lung, and kidney disease (11). Thus multiple conditions, which span the breadth of pediatric medicine, are all associated with growth inhibition, bone age delay, and, if the condition resolves, catch-up growth. This broad association supports the hypothesis that catch-up growth in humans is due, at least in part, to delayed growth plate senescence.

Linear growth rate can also be used as a marker for growth plate senescence. With age, the linear growth rate declines dramatically. The human fetus grows at a rate of over 100 cm/y. By birth, the linear growth rate has decreased to 50 cm/y, and in later childhood to 5 cm/y. In humans, this

decline is briefly interrupted by the pubertal growth spurt, after which the growth rate declines to zero. Animal studies suggest that this decline in growth rate is due to a mechanism intrinsic to the growth plate (4).

We propose that the linear growth rate in prepubertal children can be used to test the hypothesis that catch-up growth in children is due to delayed growth plate senescence. If catch-up growth is due solely to a delay in growth plate senescence, then the linear growth rate of a child experiencing catch-up growth should be equal to the growth rate of a normal younger child. Thus the growth curve during catch-up growth should represent a simple time shift of the normal growth curve of a younger child (Figure 1, A). A steeper curve would suggest that other (or additional) mechanisms besides delayed senescence are responsible for the catch-up growth.

As a first test of this approach, we examined catch-up growth in children with celiac disease placed on a gluten free diet. We reanalyzed data from an earlier study (12) using a new mathematical approach designed to test our hypothesis. A total of 28 prepubertal children, consisting of 9 boys (chronological age [CA] 3.9 ± 3.0 years, bone age [BA] 3.6 ± 2.5 years, height standard deviation score SDS for CA 21.3 ± 1.1, BMI SDS 20.1 ± 1.0, mean ± SD) and 19 girls (CA 3.9 ± 3.4 yr, BA 3.2 ± 2.7 yr, height SDS for CA 21.4 ± 1.0, BMI SDS 20.7 ± 1.1), from the Netherlands with celiac disease were included in this study. The following inclusion criteria were used: (1) symptoms and small intestinal biopsy typical for celiac disease, (2) no signs of puberty, and (3) no other known diagnoses or treated diseases. Height was measured 0.5, 1, 2, 3, 6, 12, 18, 24, 30, 36, and 50 months after introduction of a gluten-free diet with standard equipment. The study was approved by the hospital ethical committees, and informed consent was obtained from parents and/or patients.

The height at initiation of treatment was used to determine the baseline height age, defined as the age at which the median height for normal children was equal to the child's baseline height. For each child we then calculated the baseline growth delay, defined as the chronological age at initiation of treatment minus the height age at initiation of treatment. The growth delay for each child was calculated only once, using the data from the baseline visit. For each subsequent data point, we calculated the adjusted age, defined as the chronological age at that visit minus the baseline growth delay. Use of the adjusted age rather than the chronological age allowed us to assess whether growth was normal for a younger child, that is, whether the child's growth curve represented a simple time shift of the normal growth curve. We therefore calculated the child's height SDS for adjusted age. A similar analysis was done using initial bone age instead of height age. Our hypothesis predicts that the height SDS for adjusted age would remain close to 0 SDS over time (Figure 1, B, dashed curve). An increasing SDS for adjusted age (Figure 1, B, solid curve) would indicate that the growth rate was increased even for adjusted age, which would not be consistent with the delayed senescence hypothesis.

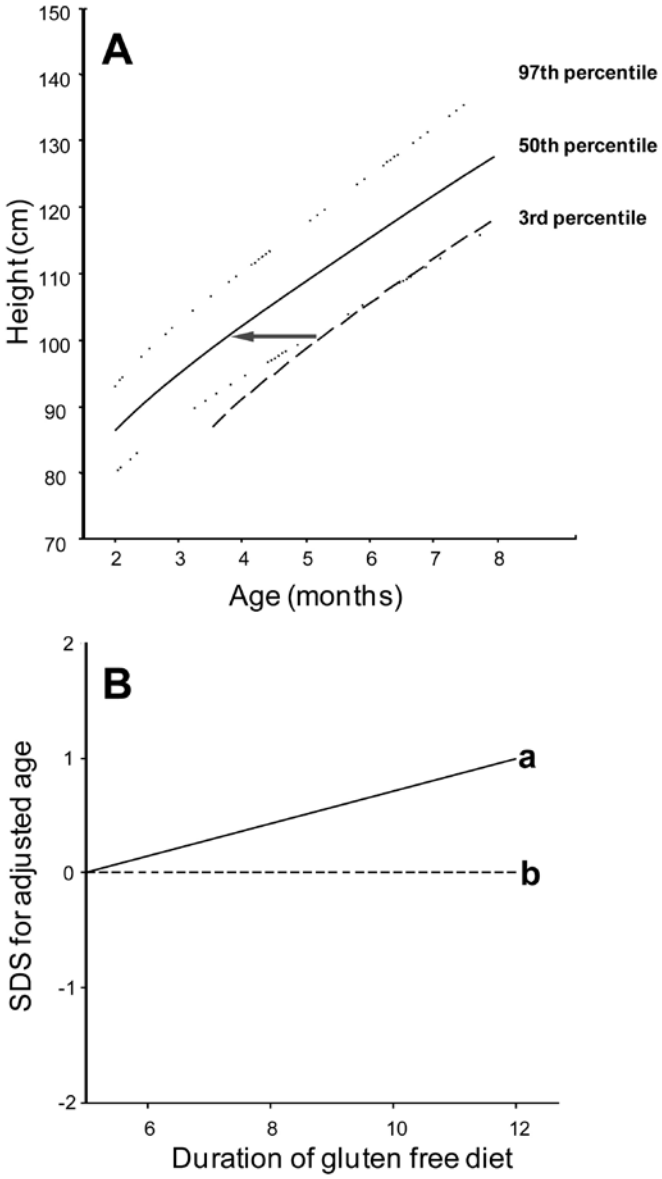

Figure 1

Theoretical catch-up growth curves predicted by the delayed senescence hypothesis. A, The delayed senescence hypothesis predicts that the height curve during catch-up growth (dashed line) should represent simple time-shift of normal (50 percentile, solid line) height curve. B, Therefore the delayed senescence hypothesis also predicts that, during catch-up growth, height should remain normal for a younger child (based on initial height age). Consequently, the height SDS for adjusted age should remain close to 0 (curve b). If the height SDS for adjusted age increases over time, this would indicate that the child's growth rate is rapid even for a younger child (curve a). Curve a would be inconsistent with the delayed senescence hypothesis.

The height SDS for chronological age (Figure 2, A) at onset of gluten-free diet was 21.5, and in the following 36 months this value increased to 20.6 SDS,12 indicating that the linear growth rate was greater than normal for CA. Thus these children experienced catch-up growth.

However, height SDS for adjusted age on the basis of initial height age remained very close to 0 SDS (Figure 2, B), and height SDS for adjusted age on the basis of initial bone age did the same (Figure 2, C), although with a wider 95% confidence interval (SEM 0.23-0.34) compared with the analysis with height age (SEM 0.02-0.19). Both analyses indicate that the growth rate was normal for a younger child based on initial height age and bone age. Specifically, at baseline, the height age was 0.7 ± 0.8 years less than the CA, and the BA was 0.7 ± 1.0 year (mean ± SD) less than the CA. Subsequently, the children grew at a rate that was normal for a child 0.7 years younger than chronological age. The larger SEM values for the analysis with BA probably reflect the subjective nature and lower precision of BA measurement compared with height measurement. Because linear growth and bone maturation reflect longitudinal bone growth at the growth plate, the data imply that growth plate function was appropriate for a younger child.

These findings are therefore consistent with the hypothesis that catch-up growth is due to delayed senescence of the growth plate. Indeed, if the height SDS for adjusted age had increased or decreased over time, it would have implied that mechanisms other than growth plate senescence were involved. Although the actual data match the predictions of the delayed senescence hypothesis well, they do not provide a definitive proof of the hypothesis; it is possible that the catch-up growth is due to a completely different mechanism that happens to produce a growth curve that is a time-shift of the normal curve. For example, the neuroendocrine hypothesis, that catch-up growth is regulated by a central nervous system mechanism, does not predict any specific growth pattern, and therefore the current findings neither support nor refute that hypothesis. It is also possible that a gluten-free diet does not fully reverse the growth inhibition, or compliance with a gluten-free diet was not fully accomplished, and thus the observed catch-up growth curve was artifactually dampened.

Indeed, anecdotal observations of individual children have shown catch-up growth curves that appear too steep to be consistent with a delayed senescence mechanism alone (3;13). These observations suggest that an additional mechanism may contribute to human catch-up growth in some conditions, although it is possible that these individual cases might instead reflect individual confounding factors, for example, a pubertal growth spurt superimposed on catch-up growth.

We conclude that the pattern of catch-up growth during recovery from celiac disease is consistent with the hypothesis of delayed growth plate senescence. Analogous studies could be performed in children experiencing catch-up growth after other conditions. The delayed senescence hypothesis predicts that the time course of catch-up growth will vary dramatically with the age of the subjects studied. In infancy, the normal grow rate declines rapidly. Thus delayed growth plate senescence should produce a markedly increased growth rate in infants, and catch-up growth should occur over a brief time course. Conversely, in older children, the hypothesis predicts that catch-up growth should occur gradually, over years. Perhaps in the future, the resolution of noninvasive imaging methods will improve to the point where the histologic markers of growth plate senescence can be assessed in humans. Until then, we may have to extrapolate from animal studies, relying on bone age and linear growth rate to provide indirect tests of the delayed senescence hypothesis in children.

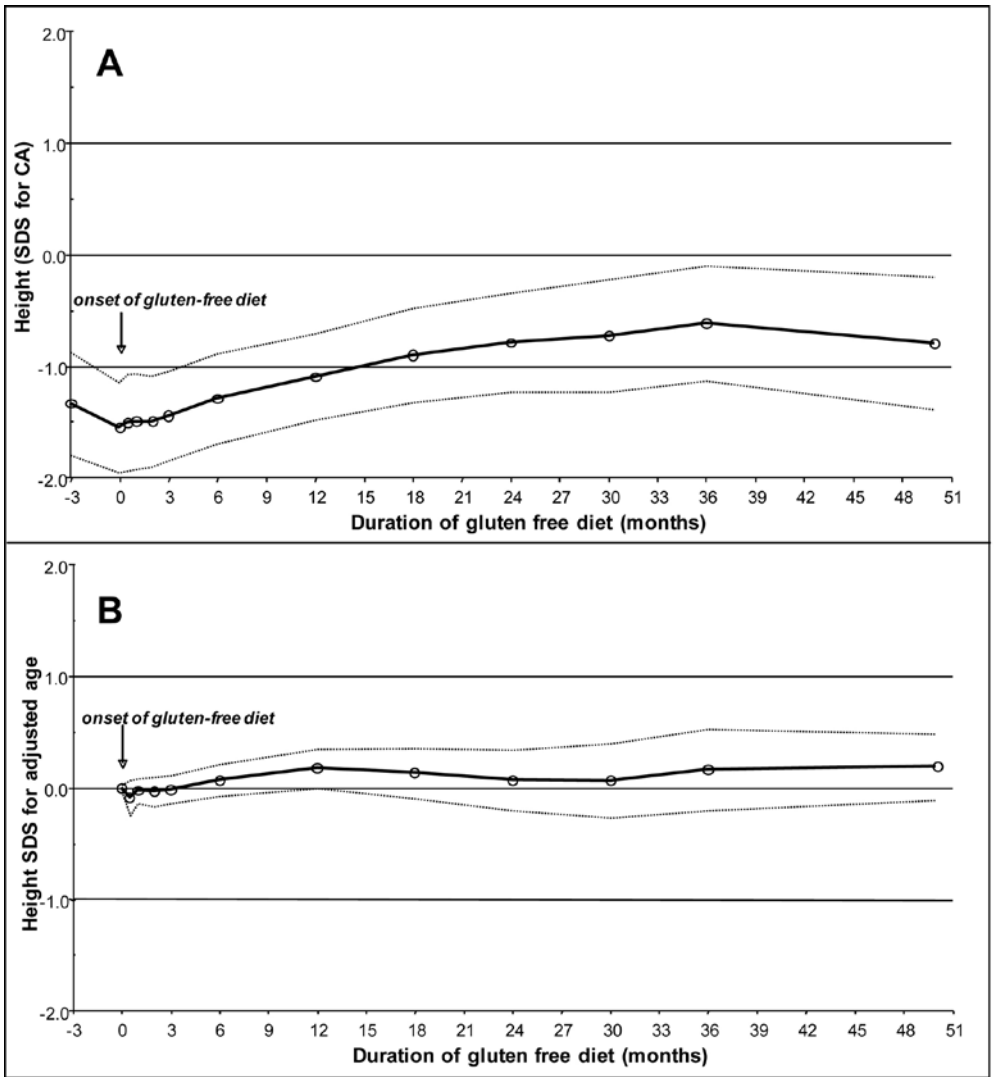

Figure 2

Height SDS for chronological age (A) and for adjusted age (B and C) after institution of a gluten-free diet for celiac disease. A, Before initiation of the gluten-free diet, the average height SDS for chronological age (CA) was negative, indicating short stature. On the gluten-free diet, the height SDS increased, indicating catch-up growth B, Age was adjusted for height age (HA) at diagnosis. C, Age was adjusted for bone age (BA) at diagnosis. The upper and lower curves in each panel represent 95% confidence interval of the mean. In both B and C the height SDS for adjusted age remained close to 0, indicating that growth was normal for a younger child.

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