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Catch-up growth gluten-free diet
celiac disease growth
epiphyseal growth malnutrition

Dedicated to Dr. Guido Fanconi on the occasion of his 80th birthday

Catch-up Growth in Malnutrition, Studied in Celiac Disease After Institution of Gluten-free Diet

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Extract

Celiac disease provides a model for investigation of one form of infantile malnutrition occurring under fully controlled circumstances. Thirteen patients aged 9–15 months were followed for a period of at least 3 years while they were on a strict gluten-free diet.

Observed values for height, weight, bone age, metacarpal diameter, and cortical thickness are compared with the normal range based on local standards, and the results are expressed as standard scores. The mean curves of these data are presented in Figures 1 and 2. At the time of diagnosis and the beginning of diet (zero time), all variables were retarded, and standard scores were significantly below normal in height ($P < 0.01$), weight ($P < 0.001$), bone age ($P < 0.01$), metacarpal cortex ($P < 0.05$), and diameter ($P < 0.001$). Weight was significantly more depressed than height ($P < 0.01$), bone age ($P < 0.001$), metacarpal cortex ($P < 0.001$), and diameter ($P < 0.001$). Height was significantly more depressed than bone age ($P < 0.05$). As the patients recovered, weight caught up faster than the other measurements; weight was not significantly below normal after the patients had been on a gluten-free diet for 6 months and it reached normal values between 6 months and 1 year after initiation of diet. Height and bone age did not reach normal levels until after 2 years of treatment, although the values were no longer significantly depressed after 1 year on the diet. Cortical thickness was no longer significantly depressed after 6 months on the diet; it reached normal values by 6 months to 1 year after initiation of diet, and then showed an overshooting type of catch-up with values remaining significantly elevated at 2 years ($P < 0.05$) and 3 years ($P < 0.05$) after the onset of diet. Metacarpal diameter showed a slow steady catch-up growth which remained below normal throughout the follow-up period although the values were no longer significantly below normal 3 years after patients had begun diet.

The study provides evidence that children aged 1 year (± 3 months) who suffer from malnutrition caused by celiac disease catch up completely in weight, height, bone age, and metacarpal cortical thickness during a dietary treatment period of 3 years.

Speculation

Poor physical growth resulting from this type and this degree of malnutrition in the second half of the 1st year of life is completely remediable. Permanent somatic sequelae from a similar severity of late infantile malnutrition in underdeveloped countries, therefore, might not be inevitable, provided that the therapeutic program is optimal and adverse factors do not continue to operate.

Introduction

The phenomenon of catch-up growth after illness is well recognized [35]. It has been thought that severe infantile malnutrition, as seen in developing countries, causes long term or even permanent aftereffects [23, 28, 32, 41, 43]. In such studies, however, the genetic growth potential of the population may be difficult to define, and the poor conditions from which these infants come and to which they return adversely influence the outcome. Thus potential recovery in physical growth [33] and subsequent mental status [14] remain controversial. Graham *et al.* [24] stated, "We need to define more precisely the effects of severe malnutrition in infancy and early childhood, particularly reversibility or permanence. Having defined these, we need to know if it is possible to prevent or ameliorate the apparently inevitable after-effects."

Celiac disease, which causes malabsorption and growth retardation in infancy, provides a model for investigation of one form of infantile malnutrition occurring under fully controlled circumstances. These children are not exposed to intrauterine or early infantile malnutrition; they have a well defined period of malnutrition caused by a specific disease process which can be completely reversed by gluten-free diet; and the entire course of their illness and subsequent rehabilitation takes place in satisfactory environmental conditions.

The most important question is whether catch-up growth of these patients is complete or only partial. This cannot be determined in individual patients as their precise growth potential is unknown. It can only be studied in a group of patients, which is homogeneous for age and for the timing of malnutrition and rehabilitation, and for which local normal standards are available for comparison. The present study fulfills these requirements and provides evidence that children aged 1 year (±3 months) who suffer from malnutrition caused by celiac disease catch up completely in weight, height, bone age, and metacarpal cortical thickness during a dietary treatment period of 3 years.

Patients and Methods

Patients

Thirteen patients aged 9–15 months (1 year ± 3 months), who were diagnosed as having celiac disease on the basis of a gluten-dependent intestinal malabsorption syndrome with steatorrhea and mucosal atrophy, were followed for a period of at least 3 years during which time they were on a strict gluten-free diet. This group was selected as a homogeneous sample from a series of 88 celiac patients on the basis of age at presentation, adequacy of control, and duration of follow-up. It was fortuitous that all were girls, but female sex preponderance (72%) was evident in the series as a whole. The patients showed a time interval of 2–8 months from first symptom to diagnosis (mean 4.8 months), and at presentation the sample was typical in clinical features and degree of malabsorption. None showed rickets and all received supplementary vitamin D (800 IU/24 hr) during follow-up.

Measurements

At the time of diagnosis, the weight and recumbent length (single determinations by various observers), bone age according to Greulich and Pyle [25] (mean of duplicates by two observers), and metacarpal diameter and cortical thickness according to Bonnard [4] (mean of duplicates by one observer) of each patient were recorded. After the institution of dietary treatment, these observations were repeated every 3–12 months at irregular intervals which differed from patient to patient. In general, observations were made more frequently at the beginning of the follow-up period. From the age of 2 years, standing height rather than recumbent length was recorded because the former measurement was used for normal values.

Presentation of Results

The results presented graphically in Figures 1 and 2 have been derived as follows.

1. The observed values were compared with the normal range for chronologic age based on height and weight standards for Zurich children [7], bone age standards according to Greulich and Pyle corrected for Zurich children [8], and metacarpal diameter and cortical thickness standards for Zurich children [4]. The chronologic age of the child was taken to the nearest month.

2. These data were then expressed as standard scores [11]. The difference between the observed value and the normal mean for that age was calculated and expressed as a percentage of the normal standard deviation for that age (standard score). These values were plotted against time (to the nearest month), using the point of diagnosis (and the beginning of diet) as zero. In this analysis, various assumptions or approximations were necessary. The normal mean value for the age at which the observation was made was either

known (*i.e.*, quoted in tables of normal values) or was derived by interpolation between two adjacent known mean values (a linear progression between them was assumed). The standard deviation (SD) for the normal mean values was either known (*i.e.*, quoted in tables of normal values) or was derived by interpolation between two adjacent known SD values (a linear progression between them was assumed). No SD for height was available below the age of 1 year. The 1-year SD was therefore applied for two observations at 10 months and 11 months. In another patient, the last observation was made at 2 years, 11 months from zero time; the value observed at this point was approximated to 3 years. The standard score method can only be applied when values have a normal distribution. This is true for height but is only approximately true for weight [45]. At the ages under consideration, our normal values for cortical thickness, metacarpal diameter and bone age had a practically normal distribution.

3. From the calculated standard scores, the means of the standard scores at zero time and of interpolated scores for selected intersections at 6 months and at 1, 2, and 3 years from the initiation of diet were calculated together with the SD's of these means. The results are depicted graphically (Figs. 1 and 2). The use of intersections to obtain interpolated values assumes a linear progression between known points.

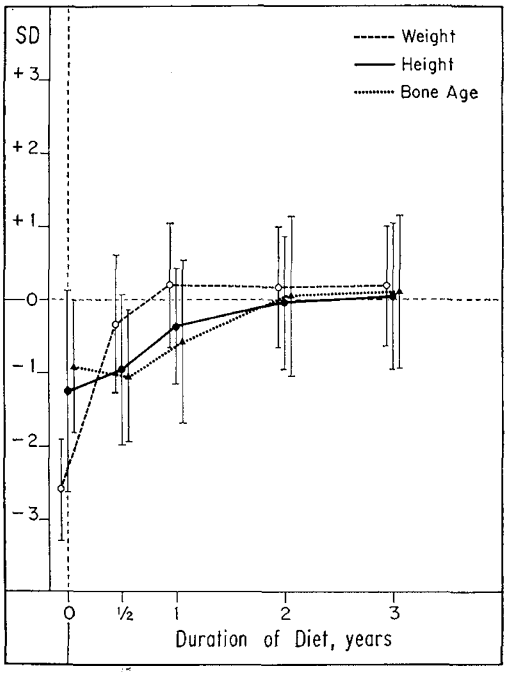

Fig. 1. Catch-up growth in patients with celiac disease who were on gluten-free diet. Mean (±1 SD) of differences from normal mean expressed as standard deviation. $n = 13$.

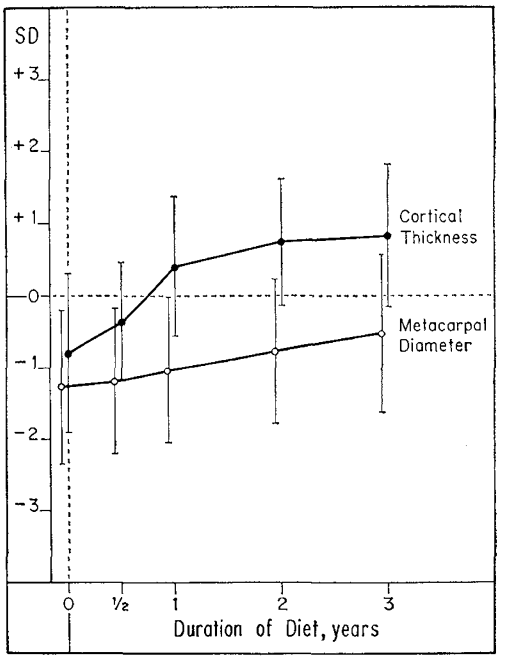

Fig. 2. Metacarpal measurements in patients with celiac disease who were on gluten-free diet. Mean (±1 SD) of differences from normal mean expressed as standard deviation. $n = 13$.

Results

Analysis of the data contained in Figures 1 and 2 shows that at zero time all variables were retarded, with standard scores significantly below normal for height ($P < 0.01$), weight ($P < 0.001$), bone age ($P < 0.01$), metacarpal cortex ($P < 0.05$), and diameter ($P < 0.001$). Weight was significantly more depressed than height ($P < 0.01$), bone age ($P < 0.001$), metacarpal cortex ($P < 0.001$), and diameter ($P < 0.001$). Height was significantly more depressed than bone age ($P < 0.05$). There were no other significant differences in the degree of retardation shown by the various indices at zero time.

When patients recover, weight catches up more quickly than the other measurements; it was not significantly below normal after 6 months of gluten-free diet, and it reached normal values after the patients had been on the diet 6 months to 1 year. Height and bone age did not reach normal levels until after 2 years of treatment, although the values were no longer significantly depressed after the patients had been on the diet for 1 year. Cortical thickness was no longer significantly depressed after 6 months of diet; it

reached normal values after 6 months to 1 year, and then showed an overshooting type of catch-up with values remaining significantly elevated at 2 years ($P < 0.05$) and 3 years ($P < 0.05$) after the onset of diet. Metacarpal diameter showed a slow steady catch-up growth and remained below normal throughout the follow-up period although the values were no longer significantly below normal after 3 years of diet.

Discussion

In these malnourished children, catch-up growth was complete for the indices measured (with the possible exception of metacarpal diameter). This conclusion is valid inasmuch as the children are a uniform population group and local normal standards are available for comparison. The advisability of using local standard percentiles for height and weight in an undernourished community has been questioned [30] as these "norms" will reflect suboptimal growth in the population and therefore fall short of full growth potential. Local figures may, however, be more appropriate than, for example, North American standards [20]. The present comparison of malnourished infants in a developed community with children whose mean growth potential is known obviates this difficulty. The methods used (standard scores derived from Zurich norms) are an improvement on our previous incomplete analyses [34, 40] which used height age, weight age, and bone age expressed as a percentage of chronologic age according to British standards [47, 48].

The use of derived morphologic ages (height age and weight age) may be criticized on several grounds. As an indication of developmental status, they confuse maturity with size [46]. Thus, reduced height age might be taken to imply retardation when the child could in fact be mature and merely below average in stature at all ages. Also, as the growth curve is linear, any given reduction in height age, for example, may correspond to a variable reduction in absolute height at different chronologic ages. Consequently, comparisons of height age between different children or in one child at different ages are liable to misinterpretation. Furthermore, valid comparisons between height age, weight age, and bone age cannot be made as these derived values do not take into account the age-dependent normal ranges for height, weight, and bone age. The measurements might wrongly seem to show different degrees of retardation when expressed as developmental years, but, in fact, show uniform retardation when the reductions from the normal mean of the measured values (height, weight, and skeletal maturation) are expressed in standard deviations.

Inasmuch as catch-up recovery is complete and bone age is not advanced in relation to height, normal future adult stature and maturity may be anticipated. For any one child, however, recovery cannot be fully assessed, as the individual's normal growth channel is unknown. A comparison of actual height with theoretical height based on mid-parent stature [16] was possible in 12 of the 13 patients. At zero time all were below the expected size (mean difference: −3.59 cm; range: 0 to −5.9 cm), and after 3 years of rehabilitation six patients were above and six below theoretical height (mean difference: −0.34 cm; range: +4.1 to −5.7 cm).

A detailed analysis of catch-up growth in eight malnourished Jamaican children has been reported by Ashworth [3]. An initial very rapid weight gain was associated with a high food intake until expected weight for height was reached. Thereafter there was an abrupt fall in food intake and catch-up weight gain proceeded more slowly, perhaps to the point of correct weight for age. The time of achieving expected weight for height averaged about 12 weeks. Once this point was reached, an increase in body fat was noted as measured by the difference between lean body mass and actual body weight. Obesity was also noted during rehabilitation by Graham *et al.* [24]. These results may be compared with our findings presented in Figure 1. The mean standard score for weight increases very rapidly during the first 6 months of rehabilitation and crosses the mean standard score for height (expected weight for height) at 3 months. No change in the slope of the weight gain curve is demonstrable until our next reference point at 6 months after onset of therapy, but thereafter the rate of catch-up weight gain clearly decreases. The mean curves indicate that after 3 months of therapy the patients were overweight for height. This was probably due to increased body fat (as noted by Ashworth [3]), but we have no other evidence to support this assumption.

The effects of malnutrition on the bones of experimental animals have been well documented [1, 13, 36, 37]. In human malnutrition, marked deficiencies in compact and trabecular bone have been reported [2, 19] as well as the cortical bone deficiency attributed to excessive endosteal resorption [18]. Very rapid and large gains in cortical bone with rehabilitation have been described [15]. In our group of celiac patients there was no significant difference in the degree of retardation in height, metacarpal diameter, and corti-

cal thickness at zero time. In a much larger series of celiac children, Bonnard and Prader [5] found that, at presentation, height was more retarded than cortical thickness and cortical thickness more than metacarpal diameter. Our results (Fig. 2) indicate an apparent failure of catch-up growth in metacarpal diameter at a time when cortical thickness had increased above normal. By subtracting metacarpal cortex from diameter, we obtained values for medullary width which, at our reference points of 0 and 6 months and of 1, 2, and 3 years from the onset of diet, had mean values of 8.48, 8.68, 7.76, 8.35 and 8.37 mm, respectively. Thus there was a tendency toward narrowing of the medullary cavity at an age when medullary width is normally progressively enlarging. Local standards for medullary width are not yet available but the results suggest that, upon recovery of the patient, his bones are slim with a thickened cortex and a constricted medullary cavity. This may be explained by continuing outer (periosteal) apposition along with a change at the inner (endosteal) surface from net resorption to net apposition. This type of cortical thickening normally occurs at puberty under the influence of sex hormones [17]; we have no explanation for similar changes which occur during catch-up growth long before puberty.

Some follow-up studies of early childhood malnutrition have suggested incomplete catch-up growth [23, 28, 31, 42, 44]. Other studies have shown body measurements of the patient upon recovery to be comparable with those of siblings [21, 26] or local population standards [9]. Satgé *et al.* [39] found incomplete recovery after 3–4 years, but most measurements were normal by puberty. Protein-calorie malnutrition of young children has a different mode of presentation in different parts of the world [12, 22, 33]. This should be taken into account when results of rehabilitation are compared.

The extent of recovery probably depends on many factors, such as the effects of adverse environment or disease before, during, and after the period of malnutrition, and the timing, degree, and duration of the malnutrition itself [10, 27, 50, 51, 52, 53].

Celiac malnutrition in our patients occurred later than the early dietary inadequacy which may lead to typical "marasmus" but earlier than the classical onset of "kwashiorkor" at the age of 1–3 years [6]. In onset it corresponds approximately to the growth retardation appearing at 6 months of age which is normally seen in rural and underdeveloped areas and which is probably caused by various adverse factors including infectious diseases, unsatisfactory child care, and malnutrition [49]. The extent of malnutrition may be judged by the body weight deficit and this has been used as a basis for classification [29]. The more severe cases of malnutrition have been shown to have a poorer potential for recovery in height, weight, and head circumference than do the less severe cases [23]. Our patients with celiac disease (with one exception) had an initial body weight which was 60–80% of the expected mean for age. This figure corresponds to that of "underweight" and "kwashiorkor" children although our patients lacked the edema characteristic of the latter condition. Two patients who had body weights 64 and 65% of the expected mean almost matched the description of "marasmus."

The commonest manifestation of protein-calorie malnutrition, however, is poor physical growth rather than the more dramatic disorders of marasmus and kwashiorkor [33], and our celiac model may therefore have more general relevance to the situation which underlies these profound disturbances. The children in our study were healthy and normally nourished up to the age of about 6 months. They then endured a period of undernutrition which lasted about 6 months, and which was followed by a 3-year period of optimal nutritional rehabilitation. Environmental conditions were good before and during the periods of malnutrition and rehabilitation. It could well be that catch-up growth would not have been so good if the environmental conditions had been poor, or if the malnutrition period had begun earlier or had continued longer or had been more severe.

This study suggests that failure of growth and maturation in infantile malnutrition should not be considered irreversible. The results of our investigation strengthen the hope that the majority of malnourished infants in underdeveloped countries are capable of at least full physical rehabilitation.

Summary

A longitudinal study of catch-up growth by malnourished infants with celiac disease indicates that recovery in weight, height, bone age, and metacarpal cortical thickness is complete during a 3-year period of rehabilitation while the patient is on a strict gluten-free diet.

Addendum

Since the preparation of this report, Rey *et al.* [38] have published an analysis of recovery in height, weight, and bone age by celiac patients on a gluten-free diet who also had complete catch-up growth.

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