Original Article

Growth failure starts from early infancy in children with short stature at age 6

Masahiro Noda¹, ², Naoko Sato¹, ³, and Toshiaki Tanaka¹

¹Tanaka Growth Clinic, Tokyo, Japan
²Showa General Hospital, Tokyo, Japan
³National Center for Child Health and Development, Tokyo, Japan

Abstract. We compared the growth of 183 children with short stature (≤ 2SD) and 73 children of normal height at age six who were visiting the Tanaka Growth Clinic. We classified these short children as suffering from either idiopathic short stature (ISS, n = 119), GH deficiency (GHD, n = 33) or small-for-gestational-age short stature (SGASS, n = 31) on the basis of subsequent test results and other factors. We also conducted a retrospective study of changes in their height, wt and nutritional intake over time. The mean changes in height SD score from birth to 6 yr were –0.24 SD in normal height children with a normal birth length and +2.27 SD in normal height children with a low birth length. In short children, these changes were –1.93 SD for children with ISS, –2.41 SD for those with GHD and +0.58 for those with SGASS. The mean changes from birth to 6 mo were –0.84 SD, –1.03 SD and +0.38 SD in children with ISS, GHD and SGASS, respectively. The mean change in height SD score from birth to age 1 yr was –1.07 SD, –1.44 SD and +0.35 SD, respectively. The decrease in height SD score from birth to 6 mo accounted for 43.5% of the decrease in height SD score from birth to 6 yr in children with ISS and it accounted for 42.6% of the decrease in children with GHD. Only 19% of short children bottle-fed well, and 53% fed poorly, as opposed to 56% and 16% of normal height children who fed well and poorly, respectively. Post weaning, only 22% of short children ate well, and 56% fed poorly, as opposed to 53% and 17% of normal height children who fed well and poorly, respectively. These findings demonstrated that growth failure started from early infancy in ISS and GHD children. It was suggested that poor nutritional intake in infancy and early childhood was a partial cause of short stature at age 6.

Key words: short stature at age 6, poor nutritional intake, GH deficiency (GHD), SGA short stature, idiopathic short stature

Introduction

Karlberg’s model divides the growth process in children into infancy, childhood, and puberty (ICP), with the major roles in each of these three stages influenced by nutrition, growth hormones and sex hormones, respectively (1).

In clinical practice, the importance of nutrition in infancy and early childhood may
be seen in the fact that a higher proportion of children with short stature and no underlying disease seem to be poor eaters. Few studies, however, have addressed in detail nutritional intake in the growth process of infancy and early childhood as a separate factor for short stature.

The aim of the present study was to investigate the cause of short stature at age 6. We classified children with short stature who were ≤ 2 SD below the mean height at age 6 as suffering from either GH deficiency (GHD), short stature born small-for-gestational-age (SGASS) or idiopathic short stature (ISS) and carried out a retrospective study of their nutritional intake and growth process in infancy and early childhood compared with 6-yr-old children of normal height.

**Subjects and Methods**

The study subjects comprised 183 children with short stature (109 boys, 74 girls) who were ≤ 2 SD below the mean height at age 6 and had been examined at the Tanaka Growth Clinic because of their short stature and 73 children of normal height (50 boys, 23 girls) who were ≥ 1 SD below the mean height at age 6. We obtained comprehensive agreement to participate in this study from the parents at the subjects’ first visits to the Clinic. The former children are referred to as short children and the latter are referred to as normal height children hereafter. One doctor took a medical and dietary history at presentation. In the initial examination, the mothers were asked whether they had breastfed or bottle fed their children or had used a mixture of both, and in the latter two cases, they were asked whether their children had bottle-fed poorly, normally, or well. No information on nutrition was received for 37 of the children of short stature at age 6. The mothers were also asked whether their children had eaten poorly, normally or well after weaning. No information on postweaning eating was received for 42 children with short stature at age 6. The mothers were further asked whether their children had been poor eaters as 1–2-yr-old toddlers.

The mean values within each group were compared by using a sign test, and the $t$-test was used for comparisons between two groups. Comparisons between three groups were made by one-way analysis of variance and the James-Howell test, with $p<0.05$ regarded as significant. Proportions were compared by using a $\chi^2$ test.

Table 1 shows clinical parameters and attributes at birth and age 6 for both groups. The mean birth length of short children was significantly lower than that of normal height.
children, but there was no significant difference in mean birth wt.

The mean heights of the fathers and mothers of the short children were significantly lower. The target height tended to be higher for normal height children and was significantly higher for girls, although for boys, the difference was not significant. The height standard deviations for parental height were calculated by using the standard values for 17 yr and 6 mo in 1980; the values for both parents of the short children were significantly lower than the mean values. There was no significant difference from the mean for fathers of normal height children, but their mothers were significantly shorter. The same tendency was also evident for mean birth wt.

In their subsequent courses, 119 of the short children were diagnosed as having ISS, 33 were diagnosed as having GHD, and 31 were diagnosed as having SGASS. Table 2 shows the clinical characteristics in three groups of short children.

GHD was defined as a peak GH ≤ 6 ng/ml in two or more secretion stimulation tests, and SGASS was defined as having been born as SGA and failing to catch up to normal height by age 2 while displaying a normal response in GH stimulation tests.

The mean SD scores for birth length of short children were −0.48 for children with ISS, −0.20 for those with GHD and −3.23 for those with SGASS. Children with SGASS were significantly smaller than those with ISS or GHD, but there was no significant difference between those with ISS and GHD. The same tendency was also evident for mean birth wt.

The mean height SD scores at age 6 were −2.41 for children with ISS, −2.60 for those with GHD and −2.65 for those with SGASS. The children with ISS were significantly taller than those with GHD and SGASS, but there was no significant difference between children with GHD and those with SGASS. The mean percent overweight at age 6 was significantly lower in children with SGASS than in children with ISS or GHD.

The mother’s height tended to be lower in children with ISS, but the differences among the three groups were not significant. The mean father’s height was significantly lower for children with ISS than for children with GHD.

| Table 2 Clinical characteristics for the three groups of short children |
|----------------------------------|------------------|------------------|------------------|
|                                  | ISS              | GHD              | SGASS            |
| Boy/girl                         | 75 / 44          | 19 / 14          | 15 / 16          |
| Gestational age (wk)             | 38.7 ± 1.9       | 39.1 ± 1.0       | 36.7 ± 4.8       |
| Birth length (cm)                | 47.8 ± 2.2       | 48.3 ± 1.9       | 41.9 ± 6.1       |
| Birth weight (g)                 | 2785 ± 443       | 2964 ± 310       | 1920 ± 794       |
| Birth length SDS (SD)            | −0.48 ± 1.03     | −0.20 ± 0.89     | −3.23 ± 2.94     |
| Height at age 6 (cm)             | 102.9 ± 2.6      | 100.8 ± 2.6      | 101.1 ± 2.1      |
| Height SDS at age 6 (SD)         | −2.41 ± 0.36     | −2.60 ± 0.52     | −2.65 ± 0.48     |
| Weight at age 6 (kg)             | 15.9 ± 1.4       | 15.4 ± 1.5       | 14.7 ± 1.2       |
| % overweight at age 6 (%)        | −2.4 ± 7.8       | −1.7 ± 7.4       | −6.2 ± 7.0       |
| Father’s height (cm)             | 165.6 ± 4.6      | 167.8 ± 4.6      | 166.7 ± 6.5      |
| Father’s height SDS (SD)         | −0.86 ± 0.87     | −0.47 ± 0.82     | −0.66 ± 1.17     |
| Mother’s height (cm)             | 153.3 ± 4.5      | 153.8 ± 3.9      | 154.8 ± 5.0      |
| Mother’s height SDS (SD)         | −0.93 ± 0.90     | −0.81 ± 0.79     | −0.62 ± 0.99     |
| Mid-parents height SDS (SD)      | −0.90 ± 0.61     | −0.64 ± 0.45     | −0.67 ± 0.79     |
**Results**

**Comparison of changes in mean height SD score for short children and normal height children**

Normal height children were divided into those born with a low birth length and those born with a normal birth length, while short children were divided into those with ISS, GHD or SGASS. Figure 1 shows the changes in the mean height SD scores for the different groups.

There was no significant difference in the changes exhibited by the children with ISS and GHD. A comparison was therefore made between the 152 children in these two groups (ISS + GHD) and the 64 children of normal height at age 6 who had been born with a normal birth length (Table 3).

The mean height SD score at birth was significantly lower for children with ISS + GHD, and growth in length from birth to 6 mo was also significantly lower in this group. As a result, the height SD score was significantly lower for children with ISS + GHD. Growth in length from birth to age 1 was also significantly lower for children with ISS + GHD, at 20.5 ± 3.4 cm vs. 25.0 ± 2.8 cm for normal height children with a normal birth length. The height SD score at age 1 was also significantly lower for children with ISS + GHD. The change in height SD score from birth to age 1 was also significantly lower for children with ISS + GHD.

Although there were no significant differences in the growth in length and in the change in height SD score from age 1 to age 3, the growth in height from age 3 to age 6 was significantly lower for children with ISS + GHD. As a result, the mean height SD score at age 6 yr for children with ISS + GHD was more than 2 SD lower than that for normal height children with a normal birth length. The mean decrease in height SD score from birth to 6 yr was significantly greater in ISS + GHD (−2.03 SD) than that in normal height children with a normal birth length (−0.24 SD).

With respect to changes in wt, although there was no significant difference in birth wt between the two groups, children with ISS + GHD gained significantly less during all the periods, from birth to 6 mo, from 6 mo to age 1 yr, from age 1 to 3 yr and from age 3 to 6 yr, than in normal height children with a normal birth length; as a result, the wt at 6 mo and age 1, 3 and 6 were significantly lower in this group.

We then compared changes in mean height SD scores for children with SGASS and the 9
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There were no significant differences in mean length at birth and height SD score between the two groups. Although both groups showed catch-up growth from birth to 6 mo, growth in length from birth to 6 mo was significantly lower in children with SGASS than in normal height children with a low birth length. As a result, the height SD score at 6 mo was significantly lower in this group. Growth in length from birth to age 1 was also significantly lower for children with SGASS, with the mean being 23.7 cm vs. 27.4 cm for normal height children with a low birth length. The height SD score at age 1 was also significantly lower for children with SGASS (−2.88 SD vs. −1.06 SD). Both groups showed catch-up growth of approximately 0.4 SD from age 1 to 3 yr. From age 3 to age 6, the mean height SD score for normal height children with a low birth length increased, but it decreased for children with SGASS.

From birth to 6 yr, the height SD score increased by 2.27 SD on average in children of normal height at age 6 with a low birth length, while it increased by 0.58 SD in children with SGASS. Children with SGASS gained less wt during all the periods than normal height children with a low birth length.

### Changes in height SD score for short children (Fig. 1)

The mean changes in height SD score (ΔHtSD) from birth to 6 yr were −1.93 SD for children with ISS, −2.41 SD for those with GHD and +0.58 for those with SGASS, and the changes from birth to 6 mo were −0.84 SD, −1.03 SD and +0.38 SD, respectively. The mean ΔHtSD scores from birth to age 1 were −1.07 SD, −1.44 SD and

| Table 3 Comparison of children with ISS+GHD and normal height children with a normal birth length |
|-----------------------------------------------|
| ISS+GHD | Normal height children with normal birth length | Significance |
|--------|-----------------------------------------------|---------------|
| At birth to 6 mo | | | |
| Δheight (cm) | 15.7 ± 2.8 | 18.0 ± 3.6 | p < 0.0001 |
| Δheight SDS (SD) | −0.88 ± 1.11 | −0.07 ± 1.31 | p < 0.0001 |
| Δweight (kg) | 4.1 ± 0.78 | 4.9 ± 0.84 | p < 0.0001 |
| 6 m to 1 yr | | | |
| Δheight (cm) | 4.8 ± 3.3 | 7.1 ± 2.6 | p < 0.0001 |
| Δheight SDS (SD) | −0.22 ± 0.69 | −0.40 ± 0.70 | NS |
| Δweight (kg) | 0.9 ± 0.6 | 1.5 ± 0.7 | p < 0.0001 |
| 1 yr to 3 yr | | | |
| Δheight (cm) | 18.0 ± 4.8 | 19.2 ± 2.6 | NS |
| Δheight SDS (SD) | −0.39 ± 1.18 | −0.08 ± 0.60 | NS |
| Δweight (kg) | 3.8 ± 1.7 | 4.5 ± 0.9 | p < 0.05 |
| 3 yr to 6 yr | | | |
| Δheight (cm) | 16.1 ± 4.5 | 20.7 ± 4.4 | p < 0.0001 |
| Δheight SDS (SD) | −0.49 ± 1.00 | 0.11 ± 0.95 | p < 0.0005 |
| Δweight (kg) | 4.1 ± 1.8 | 6.1 ± 1.5 | p < 0.0001 |
| At birth to 6 yr | | | |
| Δheight (cm) | 54.5 ± 3.3 | 64.6 ± 3.2 | p < 0.0001 |
| Δheight SDS (SD) | −2.03 ± 1.06 | −0.24 ± 0.95 | p < 0.0001 |
| Δweight (kg) | 13.0 ± 1.4 | 16.8 ± 1.8 | p < 0.0001 |

NS: not significant.
+0.35 SD, respectively. The ΔHtSD score was significantly higher for children with SGASS than for those with ISS and GHD (p < 0.05). From age 1 to age 3, ΔHtSD was also significantly higher for children with SGASS (+0.44 SD), who were still catching up, than those with ISS (–0.42 SD) and GHD (–0.24 SD). From age 3 to age 6, there tended to be a greater decrease in height SD score in children with GHD (–0.73 SD) compared with those with ISS (–0.42 SD) and SGASS (–0.20 SD), although this difference was not significant.

The decrease in height SD score from birth to 6 mo accounted for 43.5% of the decrease in height SD score from birth to 6 yr in children with ISS, and it accounted for 60.0% of the decrease in children with GHD. The decrease in height SD score from birth to 1 yr accounted for 55.1% of the decrease in height SD score from birth to 6 yr in children with ISS, and it accounted for 21.6% of the decrease in height SD score from birth to 6 yr in children with ISS, and it accounted for 30.4% of the decrease in children with GHD.

**Wt gain in short children (Fig. 2)**

Although there was no significant difference among the three groups of short children in wt gain from birth to age 1, age 1 to age 3 and age 3 to age 6, wt gain by short children was significantly lower than that by normal height children during these periods (birth to age 1, 5.0 ± 0.8 kg vs. 6.3 ± 0.8 kg; age 1 to age 3, 3.8 ± 1.7 kg vs. 4.5 ± 0.9 kg; age 3 to age 6, 4.1 ± 1.8 kg vs. 6.1 ± 1.6 kg).

| Table 4 Comparison of children with SGASS and normal height children with a low birth length |
|---------------------------------------------------------------|
| SGASS | Normal height children with low birth length | Significance |
| At birth to 6 mo | | |
| Δheight (cm) | 17.1 ± 3.3 | 18.8 ± 2.8 | p < 0.05 |
| Δheight SDS (SD) | 0.38 ± 1.38 | 1.84 ± 2.13 | p < 0.05 |
| Δweight (kg) | 3.7 ± 1.1 | 4.5 ± 0.5 | p < 0.05 |
| 6 mo to 1 yr | | |
| Δheight (cm) | 6.7 ± 4.4 | 8.4 ± 2.6 | NS |
| Δheight SDS (SD) | –0.03 ± 1.33 | 0.22 ± 0.53 | NS |
| Δweight (kg) | 1.2 ± 1.0 | 2.0 ± 0.7 | NS |
| 1 yr to 3 yr | | |
| Δheight (cm) | 18.1 ± 3.3 | 20.0 ± 3.0 | NS |
| Δheight SDS (SD) | 0.44 ± 1.02 | 0.42 ± 0.75 | NS |
| Δweight (kg) | 3.7 ± 0.7 | 4.5 ± 1.0 | p < 0.01 |
| 3 yr to 6 yr | | |
| Δheight (cm) | 17.4 ± 2.2 | 21.1 ± 1.7 | p < 0.0001 |
| Δheight SDS (SD) | –0.20 ± 0.47 | 0.29 ± 0.31 | p < 0.01 |
| Δweight (kg) | 4.2 ± 0.8 | 6.5 ± 2.3 | p < 0.0001 |
| At birth to 6 yr | | |
| Δheight (cm) | 59.2 ± 6.4 | 69.2 ± 2.6 | p < 0.0001 |
| Δheight SDS (SD) | 0.58 ± 2.98 | 2.27 ± 0.92 | NS |
| Δweight (kg) | 12.8 ± 1.1 | 17.6 ± 2.5 | p < 0.0001 |

NS: not significant.
Nutritional intake

The proportions of short children and those of normal height children who were solely breastfed were 32% and 35%, respectively, while 46% of short children and 51% of normal height children were partly bottle-fed. In addition, 22% of short children and 14% of normal height children were solely bottle-fed, with no significant differences between the two. Figure 3 shows the rates of poor, normal and good bottle-feeding among those who were partly or solely bottle-fed.

Only 19% of short children bottle-fed well, and 53% fed poorly, as opposed to 56% and 16% of normal height children who fed well and poorly, respectively. Significantly fewer short children bottle-fed well, and significantly more were poor feeders. Among short children, 37% of those with ISS, 32% of those with GHD and 37% of those with SGASS were solely breastfed, with no significant differences among these groups. For those who were partly or solely bottle-fed, 45% of those with ISS, 59% of those with GHD and 50% of those with SGASS were described by their mothers as poor feeders.

Figure 4 shows the same figures for postweaning eating. Only 22% of short children ate well, and 56% fed poorly, as opposed to 53%
and 17% of normal height children who fed well and poorly, respectively. Significantly fewer short children ate well, and significantly more were poor eaters. A high proportion of short children overall were also described by their mothers as having poor postweaning food intake; the proportions were 52% for children with ISS, 71% for children with GHD and 50% for children with SGASS, with the figure for children with GHD being particularly high. This tendency remained true for the subsequent early childhood, with 34% of those with ISS, 52% of those with GHD and 29% of those with SGASS described as poor eaters.

**Discussion**

Usually, Japanese children grow by approximately 25 cm from birth to one yr old. The annual growth rate of this period is the maximum in terms of human growth. Therefore, it makes sense that the growth from birth to one yr affects the height during childhood. The height increase in the period from birth to 6 mo, in particular, accounts for approximately 70 to 75% of the height increase from birth to one yr.

Tanaka et al. (2) reported that the height SD score in short children decreased by approximately 1 SD from birth to one yr and that it subsequently decreased slowly until 6 yr. Our findings were comparable to Tanaka’s report, but we demonstrated that the greater decrease in height SD score was from birth to 6 mo. The rapid growth during the first 6 mo of life was significantly lower for children with ISS and GHD compared with normal height children with a normal birth length. Subsequent growth also remained slow, and the mean height SD score continued to decline with significantly lower wt gain. The height SD scores in children with ISS and GHD decrease approximately 2 SD from birth to 6 yr. Approximately 40% of the decrease in height SDS occurred during the first 6 mo of life, and approximately 55 to 60% of the decrease occurred from birth to one yr. Since the normal height children at 6 yr did not show a significant change in height SD score from birth to one yr, the growth from birth to 6 mo or one yr of life seems critical for subsequent growth.

The mean height SD score decreased further in all groups of short children after age 3. The decrease in height SD score from 3 to 6 yr of age was the greatest children with GHD, although the difference between children with GHD and those with ISS was not significant. According to Karlsberg’s infancy-childhood-puberty model, the childhood phase starts around 3 to 4 yr of age, and GH is the important factor for growth in this phase. GH secretion decreases in children with GHD, and this probably contributed to the difference in height and wt gain between children with GHD and those with ISS after age 3, as described previously (2).

While the height SD score rapidly decreased in children with ISS/GHD, those with SGASS tended to catch up by age 3; however, after age 3 they failed to reach a normal height, and the height SD score decreased, having peaked at age 3. In general, children with SGA who catch up exhibit a rapid rise in height SD score from birth till 6 mo and catch up to normal height by age 2 yr (3). In this study, children with SGASS exhibited significantly poorer growth in both height and wt at 6 mo of age compared with normal height children with a low birth length, as the latter group had caught up to ≥−1 SD by 6 mo of age. These findings suggest that SGA children who had a low height SD score and poor wt gain at 6 mo of age, could be predicted to be of short stature at age 6, since children who were SGA tended to catch up by 6 mo after birth. Although normal height children with a low birth length showed catch-up growth above −1 SD of the height SD score at 6 mo of age, children with SGASS with little improvement in height SD score at 6 mo of age tended not to improve subsequently and to ultimately develop short stature.

According to Karlsberg’s infancy-childhood-puberty model, the important factor during the infancy phase is nutrition. Socha et al. studied
1138 healthy infants and compared biochemical test data at 6 mo after birth in those fed high-protein formula, low-protein formula and breast milk. Branched-chain amino acid, IGF-1 and urine C peptide/Cr were highest in those children fed high-protein formula, and both bottle-fed groups exhibited markedly higher branched-chain amino acid, C peptide and urea levels compared with solely breastfed infants. IGF-1 is also reportedly correlated with growth until 6 mo after birth (4). Yasunaga investigated factors related to the dietary and developmental environments of children. In a study evaluating the growth of 409 boys and 903 girls who underwent regular health checkups at 4 mo and 18 mo, Yasunaga found that factors negatively affecting changes in height SD score included being solely breastfed at 4 mo and being a poor eater at 18 mo in boys and being solely breastfed in girls (5).

Our study showed that physical changes in short children started in early infancy. Since nutrition is an important factor for infant growth, poor nutritional intake was suggested as the backdrop for this early growth failure, and we think that the dietary history information obtained from the mothers partially confirmed a nutritional problem in short children.

In our investigation of nutritional intake, we found that a high proportion overall of short children had been poor bottle-feeders and also poor eaters after weaning, and that this tendency was particularly pronounced for children with GHD. This suggested that GH may have an effect on the appetite center. In clinical practice, the administration of GH to children with GHD or SGASS usually increases their appetite, and this may be due to the action of GH on appetite. In fact, it is well known that patients treated with GH eat more, and there have been numerous reports of improved eating behavior and food intake due to GH treatment, including improved eating behavior in patients with Turner syndrome or Silver-Russell syndrome (6) and increased food intake in SGA children (7).

It is unclear whether the effect of GH on appetite is the result of its acting directly on the central nervous system, indirectly via peripheral tissues or both, but the presence of GH receptors in the central nervous system in the choroid plexus, hippocampus, hypothalamus and spinal cord has already been demonstrated. A rise in GH levels in the cerebrospinal fluid of patients with acromegaly or children with GHD undergoing GH treatment (8, 9), the neuroprotective action and cellular synthesis of GH/IGF1 after head trauma (10–12) and the ability of GH and IGF1 to cross the blood-brain barrier and act on the central nervous system have also been demonstrated. The fact that intraventricular administration of GH increases levels of β-endorphin, a hormone that increases food intake, and that the β-endorphin levels in the cerebrospinal fluid increase in GHD patients who undergo treatment with GH also suggest that GH may act on the central nervous system to increase appetite. This suggests that insufficient GH itself might account for the particularly noticeable tendency of children with GHD to be poor eaters. A higher proportion of short children were poor eaters compared with normal height children, and their parental height was also shorter. This suggests the existence of genetic factors that might contribute to appetite. Among children of short stature, parental height tended to be particularly short for children with ISS, with the mean height SD score for parents of ISS children being significantly lower than that for parents of children with GHD. A lack of GH is believed to be one cause of the decline in appetite seen in GHD, whereas in children with ISS, the decline in appetite may be caused by genetic factors.

Intervention to correct poor nutritional intake during infancy and early childhood is no easy task. As described above, however, the results of this study suggest that one of the main causes of short stature at age 6 might be poor nutritional intake in infancy and that this change begins in early infancy. For this reason,
timely measures for dealing with infants with low growth rates due to poor nutritional intake by increasing nutritional and protein intake must be considered, including not persisting with breastfeeding alone but also supplementing with formula from the early stages of infancy.

**Conclusion**

Growth failure starts from early infancy in children with short stature at age 6, so it might be possible to improve body height in these children by ensuring they get proper nutrition.

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