

# Adult Height in Children With Growth Hormone Deficiency Who Are Treated With Biosynthetic Growth Hormone: The National Cooperative Growth Study Experience

Gilbert P. August, MD\*; Joanne R. Julius, MS‡; and Sandra L. Blethen, MD, PhD‡

**ABSTRACT.** *Objective.* To determine whether the height gain during puberty in children with growth hormone deficiency (GHD) who are treated with biosynthetic growth hormone (GH) is similar to that in otherwise healthy children with delayed bone ages and whether the height standard deviation score (SDS), which began to increase before puberty, continues to increase during puberty.

*Methods.* The inclusion criteria included a diagnosis of idiopathic GHD, prepubertal on enrollment in the National Cooperative Growth Study, and spontaneous onset of puberty, as defined by Tanner stage 2 breast development in girls and a testicular volume of at least 3 mL in boys. Near-adult height was judged to have been attained in the subjects who had reached a chronologic age of at least 18 years (females) or 20 years (males) or had reached at least pubertal stage 4 and a chronologic age of at least 14 years (females) or 16 years (males). These subjects constituted group 1. Group 2 was a subgroup of these subjects who met a more stringent criterion for near-adult height; in addition to meeting the above criteria, they had to have attained a bone age of at least 14 years (females) or 16 years (males).

*Results.* Group 1 consisted of 480 males and 194 females. Group 2 consisted of 153 males and 105 females. In the subjects in group 1, the Tanner pubertal stage 2 was  $14.1 \pm 1.5$  years in males and  $12.6 \pm 1.6$  years in females; the bone age at this stage was  $11.9 \pm 1.5$  years in males and  $10.6 \pm 1.5$  years in females; and the height SDS was  $-2.1 \pm 0.9$  in males and  $-2.4 \pm 0.9$  in females. The total height gained during puberty was  $22.4 \pm 7.9$  cm in males and  $17.4 \pm 6.3$  cm in females; the percentage of adult height gained during puberty was  $13.3\% \pm 4.6\%$  in males and  $11.3\% \pm 4.0\%$  in females; the near-adult height SDS was  $-1.3 \pm 1.0$  in males and  $-1.6 \pm 0.9$  in females; and the target adult height SDS was  $-0.4 \pm 0.8$  in males and  $-0.5 \pm 0.7$  in females. The growth characteristics in the subjects in group 2 were of similar magnitude. In both groups, there was a significant negative correlation between age at the onset of Tanner stage 2 and both the total height gained during puberty and the percentage of adult height gained.

*Conclusions.* The growth characteristics of these subjects were similar to those reported in normal children and in previous reports of the pubertal growth in smaller populations of children with GHD. The height SDS in-

creased in these subjects during puberty, but the target adult height SDS was not attained. This is a strong argument for early diagnosis and treatment in children with GHD to optimize prepubertal growth. *Pediatrics* 1998; 102:512-516; *idiopathic growth hormone deficiency, puberty, growth, growth hormone.*

ABBREVIATIONS. GH, growth hormone; GHD, growth hormone deficiency; SDS, standard deviation score(s); NCGS, National Cooperative Growth Study.

Many large studies have described the growth of normal children during puberty<sup>1</sup> and the initial effects of growth hormone (GH) therapy in children with growth hormone deficiency (GHD),<sup>2</sup> but there are few data from large studies on the adult height of children with GHD who are treated with GH.<sup>3-6</sup> We sought to answer two questions in this study: Is the height gain during puberty in children with GHD who are treated with GH similar to that in normal children with delayed bone ages? Does their height standard deviation score (SDS), which began to increase before puberty, continue to increase during puberty?

## METHODS

The database of the National Cooperative Growth Study (NCGS) was searched for patients who met the inclusion criteria of a diagnosis of idiopathic GHD, defined as a maximum stimulated GH level  $\leq 10$   $\mu\text{g/L}$  and no evidence of an organic cause; prepubertal on enrollment in the NCGS; spontaneous onset of puberty, defined as the appearance of Tanner stage 2 breast development in girls or a testicular volume of at least 3 mL in boys; available near-adult height; and no treatment with glucocorticoids, sex steroids, or agents to alter or delay puberty.

Near-adult height was defined by two sets of criteria. Inclusion in group 1 required either a chronologic age of at least 18 years (females) or 20 years (males) at the last visit or pubertal development of at least Tanner stage 4 and a chronologic age of at least 14 years (females) or 16 years (males). A total of 480 males and 194 females met these criteria. Inclusion in group 2 required all of the above plus a bone age of at least 14 years (females) or 16 years (males). Because bone ages for each year were not always available, we extrapolated from bone ages that had been obtained as early as 3 years before the last visit, using the assumption that the bone age had advanced 1 year for each calendar year. A total of 153 of the males and 105 of the females in group 1 met these criteria; they constituted a subgroup in whom a more stringent criterion for near-adult height was applied.

The heights of the subjects were standardized by calculating their height SDS, derived from the published standards for North American children and adults.<sup>7</sup>

## RESULTS

The growth characteristics are shown in Table 1. The mean chronologic age at the onset of Tanner pubertal stage 2 was consistent with that in children with a delayed onset of puberty. The mean bone age

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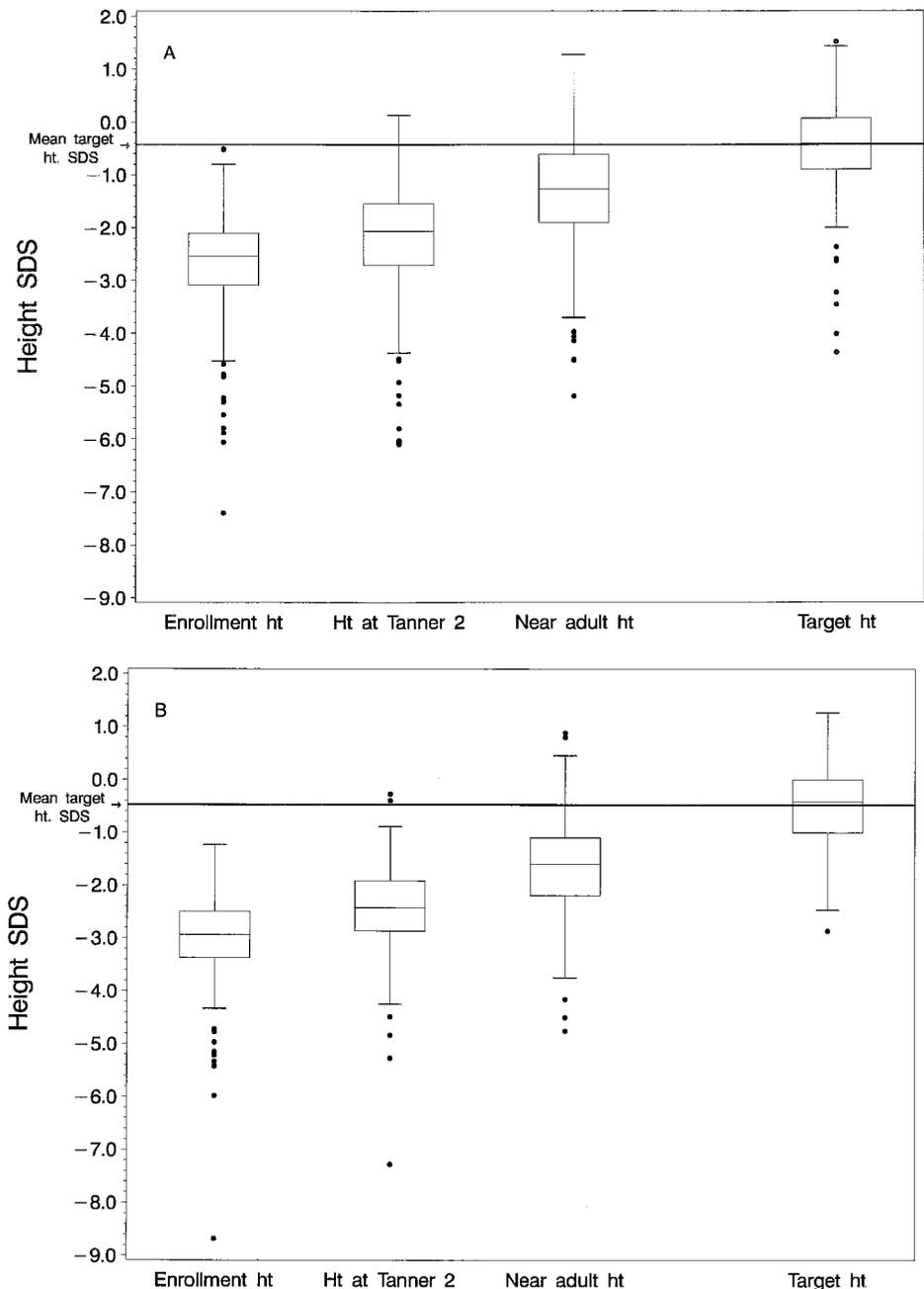
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**TABLE 1.** Characteristics of NCGS Subjects Who Have Attained Near-adult Height

	Group 1		Group 2	
	Males (n = 480)	Females (n = 194)	Males (n = 153)	Females (n = 105)
Age at NCGS enrollment (y)	12.7 ± 2.2	11.2 ± 2.1	12.0 ± 2.4*	10.9 ± 1.9
Bone age deficit (y)	2.5 ± 1.5	2.5 ± 1.2	2.3 ± 1.5	2.5 ± 1.3
Height SDS at enrollment	-2.6 ± 0.8	-3.0 ± 0.9	-2.6 ± 0.9	-3.0 ± 0.9
Age at Tanner stage 2 (y)	14.1 ± 1.5	12.6 ± 1.6	13.6 ± 1.6*	12.3 ± 1.2
Bone age at Tanner stage 2 (y)	11.9 ± 1.5	10.6 ± 1.5	11.8 ± 1.7	10.6 ± 1.7
Height SDS at Tanner stage 2	-2.1 ± 0.9	-2.4 ± 0.9	-2.0 ± 0.9	-2.5 ± 1.0
Age at near-adult height (y)	17.3 ± 1.0	15.6 ± 1.5	17.5 ± 1.1	15.8 ± 1.2
Pubertal height gain (cm)	22.4 ± 7.9	17.4 ± 6.3	24.7 ± 8.4*	19.1 ± 6.6*
Percentage of adult height gained	13.3 ± 4.6	11.3 ± 4.0	14.6 ± 4.9*	12.3 ± 4.2*
Near-adult height SDS†	-1.3 ± 1.0	-1.6 ± 0.9	-1.3 ± 1.0	-1.6 ± 1.0
Pubertal increase in height SDS	0.8 ± 0.8	0.8 ± 0.8	0.7 ± 0.8	0.9 ± 0.9
Target height SDS	-0.4 ± 0.8	-0.5 ± 0.7	-0.5 ± 0.8	-0.5 ± 0.7

\*  $P < .05$  group 1 vs group 2.

† Relative to the mean heights of normal 18-year-olds.



**Fig 1.** Effect of GH treatment and puberty on height SDS in males (A) and females (B). The lines within the boxes indicate the median, the limits of the boxes indicate the 25th and 75th percentiles, and the extensions of the boxes indicate data below the 25th percentile or above the 75th percentile, with outliers indicated as individual data points.

at this stage was within the range at which puberty is expected in normal children. Some of the deficit in height SDS had been decreased after GH treatment that was initiated before the onset of puberty. The decrease in the deficit in height SDS during puberty was significant ( $P < .0001$ ) by the time the subjects had reached near-adult height. The target genetic height SDS, however, was not attained (Fig 1).

The age at the onset of Tanner pubertal stage 2 and, therefore, the start of puberty, affected the total height and the percentage of final adult height that was gained during puberty (Figs 2 and 3). There was a significant negative correlation between age at the onset of puberty and subsequent height gain during

puberty, but there was no such correlation between age at the onset of puberty and near-adult height (data not shown).

## DISCUSSION

The growth characteristics of the subjects in this study during puberty are very similar to those of normal children with delayed bone ages and delayed puberty. These growth characteristics also are similar to those reported in earlier studies.<sup>3-6</sup> We and others followed the subjects only to near-adult height rather than to final adult height, and it is likely that the final adult heights of these subjects are slightly greater than the heights reported here. It also should be

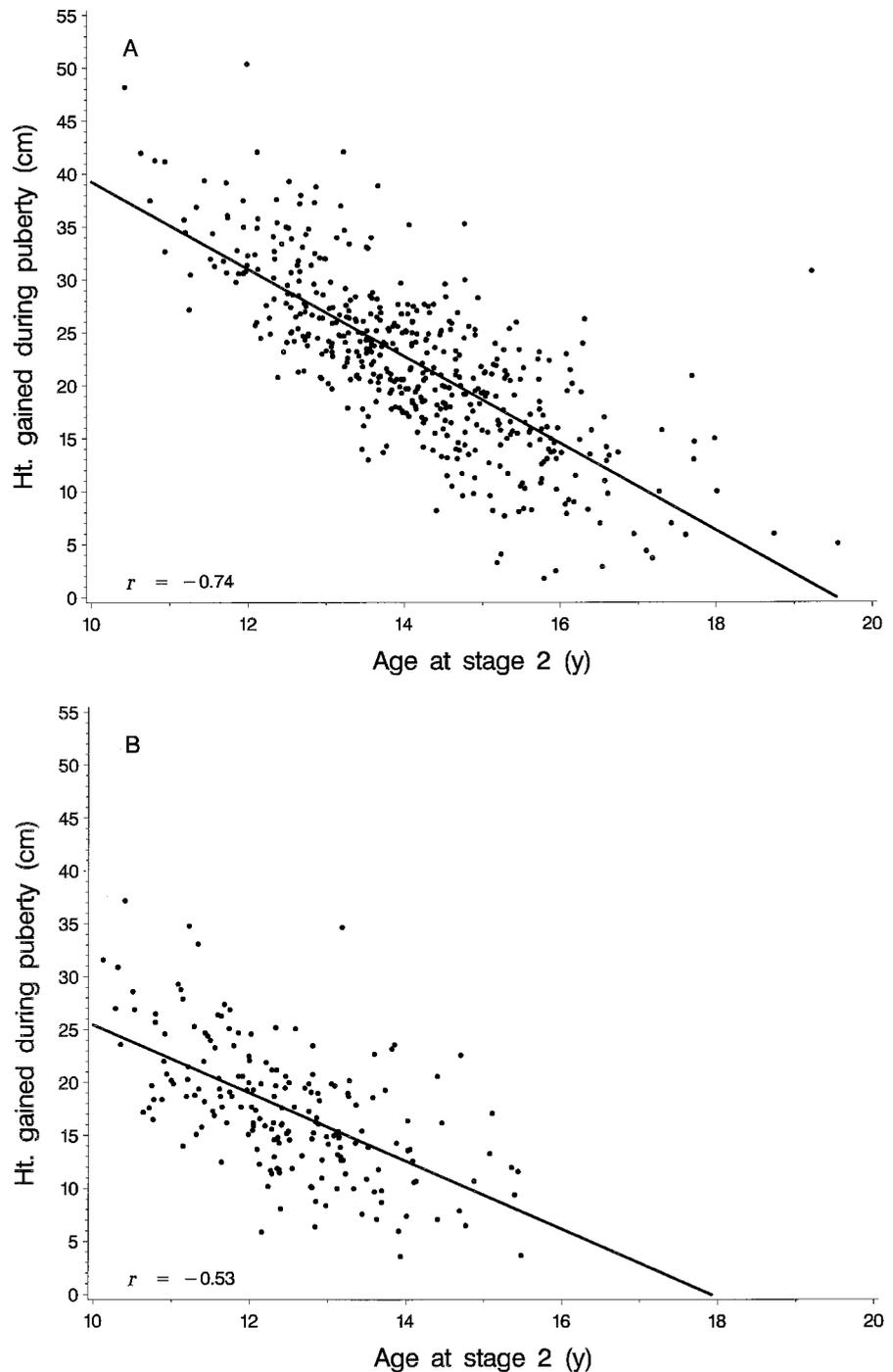


Fig 2. Effect of age at the onset of puberty (Tanner stage 2) on height gained in males (A) and females (B).

noted that the onset of puberty was recorded as the date of the first visit at which physical evidence of puberty was observed. Because in many instances puberty had actually begun before this date, the amount of pubertal growth that we observed could be less than what actually occurred.

The percentage of adult height gained during puberty in our subjects compared favorably with that in otherwise healthy children with delayed bone ages.<sup>8</sup> Otherwise healthy boys with a delayed bone age of 12 years would be expected to gain 15.5% of their adult height during puberty; the males in group 1 in our study gained 13.3% of their adult height during

puberty and those in group 2 gained 14.6% of it. The corresponding values in females are a gain of 10.4% expected in those with a delayed bone age of 10.5 years and actual gains of 11.3% in group 1 and 12.3% in group 2.

The total height gained during puberty in our subjects was also similar to that expected in otherwise healthy children with delayed puberty.<sup>9</sup> In addition, the total height gained during puberty and the percentage of adult height that was gained during puberty in our subjects were negatively correlated with the age at the onset of Tanner pubertal stage 2. This is in agreement with the

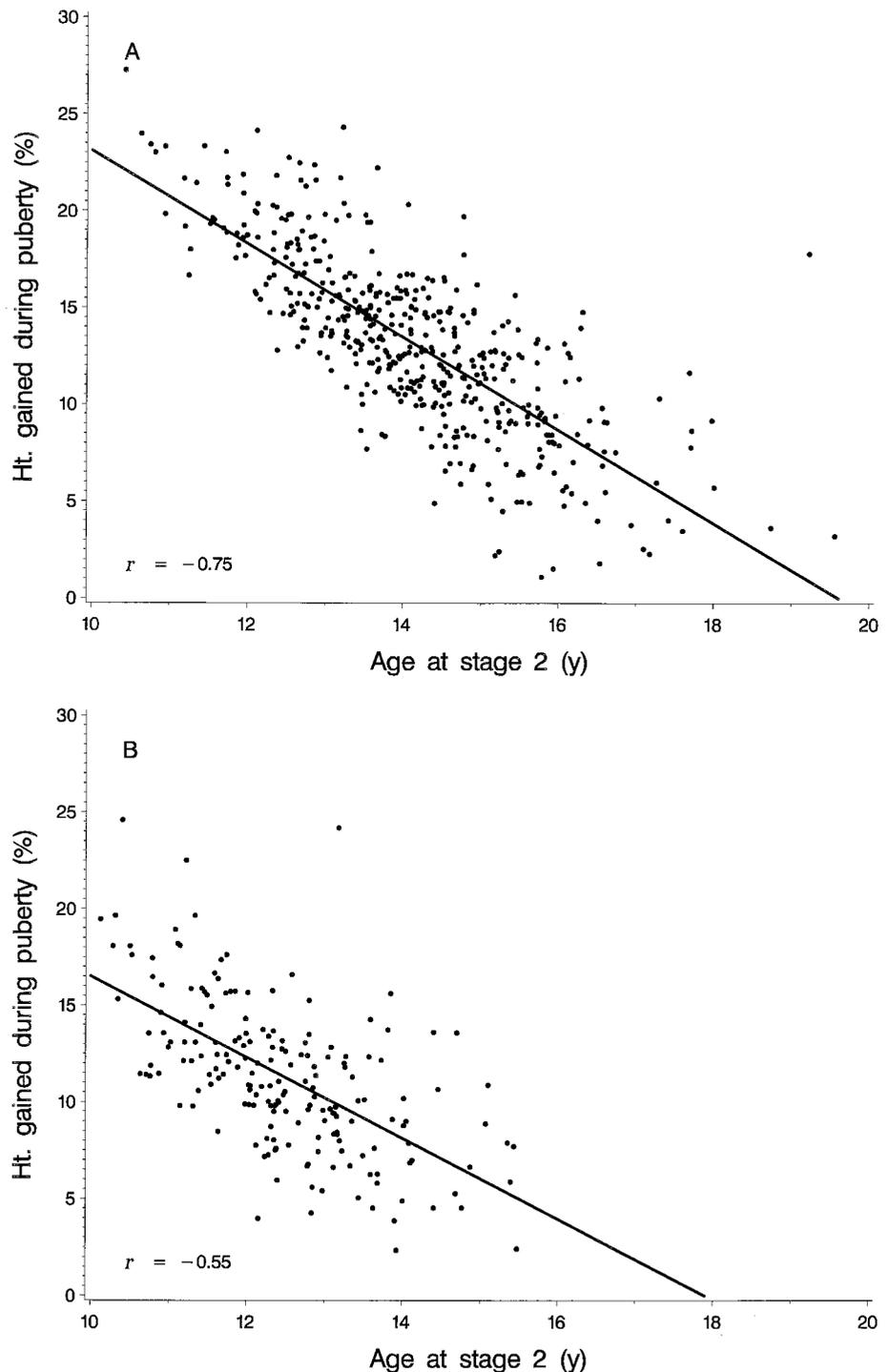


Fig 3. Effect of age at the onset of puberty on the percentage of adult height gained in males (A) and females (B).

**TABLE 2.** Characteristics of Subjects in Similar Studies\*

	Ranke et al		Blethen et al	
	Males (n = 66)	Females (n = 64)	Males (n = 72)	Females (n = 49)
Age at enrollment (y)	10.5 (5.3, 13.1)	9.9 (4.3, 11.6)	11.3 ± 2.1	10.1 ± 2.8
Height SDS	-2.7 (-3.5, -1.7)	-2.9 (-4.8, -1.8)	-3.0 ± 1.2	-3.4 ± 1.0
Age at Tanner stage 2 (y)	13.8 (12.1, 15.4)	12.9 (11.2, 14.1)	14.0 ± 1.9	12.6 ± 2.2
Height SDS at Tanner stage 2	-1.6 (-2.6, -0.4)	-1.4 (-3.0, -0.4)	-1.9 ± 1.2	-1.9 ± 1.5
Adult height SDS	-1.3 (-2.8, 0.2)	-1.2 (-3.6, 0.2)	-0.7 ± 1.3	-0.7 ± 1.1
Target height SDS	-0.4 (-1.8, 0.6)	-0.7 (-2.1, 0.8)	-0.3 ± 0.8	-0.2 ± 0.8

\* Values are median (10th, 90th percentiles) (Ranke et al<sup>3</sup>) and mean ± SD (Blethen et al<sup>4</sup>).

results of similar, but smaller, studies in children with GHD.<sup>3-6</sup>

The results of our study show that the height SDS progressively increases in patients with idiopathic GHD who are treated with GH throughout puberty. This is in agreement with the results from a similar, but smaller, study in European children<sup>3</sup> and with the results from controlled clinical trials of recombinant DNA-derived GH.<sup>4</sup> The results of these studies are presented in Table 2. The gains in height SDS during puberty have been substantial, ranging from 0.4 SDS in the European study<sup>3</sup> to 0.8 SDS in our study and to 1.2 SDS in the clinical trials.<sup>4</sup> However, in none of these studies has this gain been sufficient to bring the mean final height to the target genetic height. This disparity between the mean final height and the target genetic height may result primarily from an insufficient increase in the child's height SDS before the onset of puberty. This cause for the disparity is suggested by the strong positive correlation between final height and height at the onset of puberty.<sup>10</sup>

There is interplay among several factors that influence growth during puberty. As we and others have shown, there is a negative correlation between age at the onset of puberty and total height gained during puberty. There is also a negative correlation between age at the onset of puberty and the duration of puberty.<sup>11</sup> This means that although younger children may be shorter when they start puberty, they still may attain a normal final height because of their longer duration of puberty and greater height gain during puberty.

If the final heights of children with GHD are to be optimized, then it is important that the diagnosis be made and treatment be initiated as early as possible to afford these children the opportunity to make up

much of their height deficit before puberty. The percentage of adult height that is gained during puberty may be biologically limited.

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