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Original Article

Age at menarche and near final height after treatment with gonadotropin-releasing hormone agonist alone or combined with growth hormone in Korean girls with central precocious puberty

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Abstract. The use of a GnRH agonist (GnRHa) in central precocious puberty (CPP) is known to slow puberty progression, subsequently prevent early menarche, and attenuate the height loss caused by advanced skeletal maturation. But enhancing the final height has been so controversial that an additional approach has been used. We investigated the menarcheal age and near final height (NFH) in girls with CPP treated with GnRHa (N = 61) or GnRHa combined GH (N = 24). GnRHa was started at 8.1 ± 0.7 yr and administered for 2.1 ± 1.0 years. GH was used for 2.1 ± 1.1 yr in subjects with a short predicted adult height (PAH). Menarche occurred at 11.6 ± 0.8 yr of age, which was 15.7 ± 6.4 mo after GnRHa discontinuation. PAH increased significantly from 152.0 ± 7.2 cm to 158.8 ± 5.6 cm during treatment, and the NFH (159.7 ± 4.8 cm) was taller than the midparental height (157.8 ± 3.4 cm). The combined treatment group showed a greater height increment during treatment. Younger age, taller height at the start of treatment, taller parental height and longer duration of treatment were the factors influencing NFH. In conclusion, GnRHa treatment in girls with CPP could improve NFH and delay menarche close to the general population. If GnRHa combined with GH is used in girls with CPP and a short midparental height, it would improve the NFH to a value similar to that in the general population.

Key words: GnRH, precocious puberty, menarche, height, GH

Introduction

Central precocious puberty (CPP) in girls is defined as breast development before 8 yr old due to precocious activation of the hypothalamic-pituitary-gonadal axis, and the most common form is idiopathic, which is usually treated with a GnRH agonist (GnRHa). GnRHa selectively decreases gonadotropin secretion and subsequently lowers sex steroids to a prepubertal level (1). The aims of the treatment

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are to slow down the progression of secondary sex characteristics, subsequently prevent early menarche and attenuate height loss caused by advanced skeletal maturation.

In a review of GnRHa therapy, it was reported that efficient suppression of gonadal steroid hormones can delay menarche until an appropriate age and developmental stage agreed to by the family and physician. But enhancing the final height has been so controversial that an additional approach has been used. In this approach, GH is used to promote growth velocity during the slow phase of growth during GnRHa treatment, and aromatase inhibitors are administered to try to delay estrogen-induced closure of the growth plate. This "belt and braces" approach may be beneficial in some cases, but there has been no controlled trials of its efficacy with respect to adult height (AH) (2).

A report from the Health Insurance Review and Assessment Service revealed an average 44.4% annual increase in CPP diagnosis and a 4.5-fold increase in patients treated with drug therapy during the period of 2006–2010 (3). However, there are few reports about the age at menarche or final AH after long-term GnRHa treatment in Korea (4, 5). This might be caused by difficulty in continuous follow-up after the end of treatment.

The aim of our study was to evaluate the age at menarche after the discontinuation of GnRHa and the statural growth outcomes in girls with CPP who were treated with GnRHa with or without GH.

Materials and Methods

Subjects

We retrospectively analyzed the medical records of 85 idiopathic CPP girls who were treated with GnRHa at the Pediatric Endocrinology Clinic of Chungbuk National University Hospital, South Korea, from 2002 to 2012 and attained near final height (NFH) after menarche. Among the patients, 24 were treated additionally with GH.

The diagnostic criteria for idiopathic CPP were age at breast development of less than 8 yr old, peak level of LH above 5 IU/L during a standard intravenous GnRH stimulation test, bone age (BA) advancement and no evidence of a hypothalamic-pituitary lesion confirmed by magnetic resonance imaging performed based on clinical judgment.

Methods

All the patients were treated with GnRHa at a dose of 75–150 μg/kg according to body weight (1.875 mg for < 20 kg, 2.5 mg for 20–30 kg, and 3.75 mg for > 30 kg) every 4 wk until 11.5–12 yr of BA, and 24 patients received additional GH at a dose of 0.6–1.0 IU/kg in 5–7 divided doses weekly (0.7 ± 0.1 IU/kg/wk). For those whose predicted adult height (PAH) was below the fifth percentile at the start of GnRHa, GH treatment was combined with GnRHa if the parents wanted. After the initiation of GnRHa treatment, the patients were regularly observed for height, weight, and sex maturation rate every 3 mo, and a left-hand radiogram was taken every 6 months for the evaluation of BA. An LH level < 3 IU/L 30–60 minutes after GnRHa injection was considered to indicate adequate suppression at 6 mo of treatment. BA was assessed by the Greulich-Pyle method (6) by the same observer. Height (H) was expressed as a standard deviation score (SDS, HSDS) according to chronologic age (CA) and BA, respectively, which was calculated using the Korean children and adolescents growth standard (7). PAH was calculated using the Bayley-Pinneau method (8). Midparental height (MPH) was defined as the average of the parental heights minus 6.5 cm. NFH was calculated as the PAH at the last follow-up visit after menarche with a BA over 13.5 yr. To evaluate height increment, the gain in PAH (ΔPAH) was expressed for; between the end of treatment and the start of treatment, between the last follow-up and the start of treatment and between the last follow-up and the end of

Table 1. Auxological data of the subjects with central precocious puberty (N = 85)

	At start of Tx	At end of Tx	At last FU visit	*P*-values[§]		
				Ts vs Te	Te vs Lf	Ts vs Lf
CA (yr)	8.1 ± 0.7	10.3 ± 0.7	12.5 ± 1.0	0.000	0.000	0.000
BA (yr)	10.5 ± 1.1	11.5 ± 0.7	14.5 ± 1.0	0.000	0.000	0.000
ΔBA-CA (yr)	2.4 ± 0.9	1.3 ± 0.9	2.0 ± 0.9	0.000	0.000	0.000
P-value*	0.000	0.000	0.000			
H (cm)	129.9 ± 7.2	143.0 ± 5.8	156.1 ± 5.1	0.000	0.000	0.000
MPH (cm)		157.8 ± 3.4				
PAH (cm)	152.0 ± 7.2	158.8 ± 5.6	159.7 ± 4.8	0.000	0.003	0.000
P-value†	0.000	0.134	0.001			
HSDS for CA	0.7 ± 1.0	0.7 ± 0.8	0.7 ± 0.9	0.859	0.265	0.308
HSDS for BA	–1.5 ± 0.9	–0.6 ± 0.8	–0.4 ± 0.9	0.000	0.000	0.000
P-value‡	0.000	0.000	0.000			

Values are presented as the mean ± standard deviation. *, *P*-value by paired *t*-test between CA and BA at each point; †, *P*-value by paired *t*-test between MPH and PAH at each point; ‡, *P*-value by paired *t*-test between HSDS for CA and HSDS for BA at each point; §, *P*-value by paired *t*-test between each point; CA, chronologic age; BA, bone age; H, height; MPH, midparental height; PAH, predicted adult height; SDS, standard deviation score; Tx, treatment; FU, follow-up; Ts, at start of Tx; Te, at end of Tx; Lf, at last follow-up.

treatment.

For the comparison of auxological differences and growth-promoting effects, the subjects were classified into two groups, treated with GnRHa only (N = 61) and treated with GnRHa plus GH (N = 24).

The study protocol was approved by the institutional review board of Chungbuk National University Hospital (IRB No. 2015-020-001). The need for informed consent was waived by the IRB.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, USA). All data are expressed as the mean ± standard deviation. The paired t-test was applied to compare the data within groups; the Student's *t* test and ANOVA were used to compare means between groups; and the Tukey method was used as a post hoc analysis. Multiple linear regression analysis was used to examine the association of multiple clinical factors with NFH. A *P*-value of less than 0.05 was considered statistically significant.

Results

Comparison of clinical and auxological characteristics of subjects at the start and end of treatment and at NFH (Table 1)

At the beginning of GnRHa therapy, BA was significantly more advanced than CA (by 2.4 ± 0.9 yr). The patients were treated with GnRHa for 2.1 ± 1.0 yr, and those treated with GH were treated for 2.1 ± 1.1 yr. At the end of the treatment, BA was still larger than CA by 1.3 ± 0.9 yr. At the last follow-up after menarche, BA was still more advanced than CA (by 2.0 ± 0.9 yr). The difference between BA and CA was significantly decreased during the treatment period, but the difference again increased after treatment until the NFH was reached at the last follow-up point. Nevertheless, BA advancement significantly decreased from the start of treatment to the last follow-up visit at which point the NFH had been reached.

Height significantly increased during treatment and after treatment until the NFH was reached. Compared with the MPH (157.8 ± 3.4 cm), the PAH at the start of treatment (152.0 ± 7.2 cm, P = 000) was significantly shorter, but the PAH at the end of treatment (158.8 ± 5.6 cm, P = 0.134) was not statistically different, and the NFH at the last follow-up visit (159.7 ± 4.8 cm, P = 0.001) was significantly taller than the MPH. PAH increased significantly during and after treatment until the NFH was reached. The HSDS for CA during treatment did not differ from that at the last follow-up, but the HSDS adjusted for BA increased significantly during treatment and continued to increase until the last follow-up point after treatment. Menarche occurred at 11.6 ± 0.8 yr of age, which was 15.7 ± 6.4 mo after the end of GnRHa treatment (data not shown in the Table).

Comparison of auxological characteristics during treatment and at last follow-up according to the types of treatment (Table 2)

At the start of treatment, the CA and BA were not different between the two groups, but MPH, height, and PAH were significantly shorter and HSDS adjusted for both CA and BA was significantly lower in the combined GnRHa plus GH treatment group. That is, the two groups were totally different groups at the start of GnRHa therapy. But at the end of GnRHa treatment and at the last follow-up point, at which point the NFH had been reached, all the parameters including height, HSDS for CA and BA and PAH were not statistically different. GnRHa has been used longer in combined GnRHa plus GH treatment group without statistical significance. The age at menarche and the time from the end of GnRHa treatment were not different between the two groups. Compared with the group that was treated only with GnRHa, the combined GnRHa plus GH treatment group showed a significantly greater PAH increment during the treatment period and from the start of treatment until the NFH was reached.

Although the HSDS for BA was significantly different between the two groups at the start of therapy, it became insignificant after therapy and at the last follow-up point. Both groups showed a significant increase in HSDS for BA from the start of therapy right up until the last follow-up point. Likewise, PAH was significantly different between the two groups at the start of therapy, but the difference was insignificant after therapy and at the last follow-up point (Fig. 1). The PAH was significantly shorter than the MPH at the start of treatment, but there was no difference between them at the end of treatment, and the NFH was significantly taller than the MPH in both groups (Fig. 2).

Effect of auxological factors at the start of treatment on NFH (Table 3)

Multiple linear regression analysis was performed to find the factors influencing NFH. To exclude the confounding factor of GH treatment, the subjects treated with GnRHa only were used for this analysis. Younger CA, taller height at the start of treatment, taller MPH and longer duration of GnRHa treatment were significantly related to NFH. But the PAH at the start of treatment and the difference between BA and CA did not appear to be associated with NFH.

Discussion

In this study, the PAH of the CPP subjects was significantly shorter than the MPH at the start of GnRHa treatment, but at the end of therapy, the PAH was the same as the MPH, and the NFH at the last follow-up was even higher than the MPH. The subjects treated with the combined GnRHa plus GH therapy showed shorter height, lower HSDS for CA and BA and shorter MPHs and PAHs at the start of treatment, but their NFHs were the same as those of the subjects treated with GnRHa only. Menarche occurred at 11.6 ± 0.8 yr of age, which was 15.7 ± 6.4 mo after the end of GnRHa treatment. The

Table 2. Auxological data of the subjects with central precocious puberty (N = 85) divided into two groups by type of treatment

	GnRHa alone (N = 61)	GnRHa + GH (N = 24)	*P*-value
At the start of GnRHa treatment			
CA (yr)	8.2 ± 0.8	7.9 ± 0.7	0.085
BA (yr)	10.5 ± 1.1	10.4 ± 1.3	0.732
H (cm)	131.3 ± 7.2	126.2 ± 8.0	0.003
MPH (cm)	158.4 ± 3.4	156.3 ± 3.2	0.001
HSDS for CA	0.9 ± 1.0	0.3 ± 1.3	0.008
HSDS for BA	–1.3 ± 0.9	–2.1 ± 1.1	0.001
PAH (cm)	153.7 ± 7.4	147.7 ± 8.0	0.000
At the end of GnRHa treatment			
CA (yr)	10.2 ± 0.7	10.4±0.7	0.364
BA (yr)	11.5 ± 0.7	11.7±0.8	0.201
H (cm)	143.0 ± 5.6	142.8±6.4	0.894
HSDS (CA)	0.8 ± 0.8	0.5±1.0	0.229
HSDS (BA)	–0.5 ± 0.8*	–0.7 ± 0.8*	0.234
PAH (cm)	159.2 ± 5.7†	157.7 ± 5.4†	0.277
At menarche			
CA (yr)	11.5 ± 0.8	11.8 ± 0.7	0.151
after Tx end (mo)	15.3 ± 6.6	16.8 ± 6.3	0.333
Duration of treatment			
GnRHa (yr)	2.0 ± 1.0	2.5 ± 0.9	0.059
GH (yr)	–	2.1 ± 1.1	–
At the last follow-up			
CA (yr)	12.5 ± 1.0	12.6 ± 1.0	0.568
BA (yr)	14.5 ± 1.0	14.4 ± 1.0	0.573
H (cm)	156.4 ± 5.2	155.3 ± 4.8	0.402
HSDS for CA	0.8 ± 1.0	0.4 ± 1.0	0.157
HSDS for BA	–0.3 ± 0.9*	–0.5 ± 1.0*	0.505
PAH (= NFH, cm)	160.0 ± 4.9†	159.1 ± 4.9†	0.412
Assessment of height increment			
ΔPAH (Te~Ts)	5.4 ± 5.0	10.0 ± 5.7	0.000
ΔPAH (Lf~Ts)	6.3 ± 5.3	11.4 ± 5.8	0.000
ΔPAH (Lf~Te)	0.8 ± 3.0	1.3 ± 3.1	0.460

Values are presented as the mean±standard deviation. *, P<0.001 vs. at the start of GnRHa treatment; †, P<0.001 vs. at the start of GnRHa treatment; ‡, P-value by Student's t-test between groups; CA, chronologic age; BA, bone age; H, height; HSDS, height standard deviation score; MPH, midparental height; PAH, predicted adult height; SDS, standard deviation score; Tx, treatment; NFH, near final height; Ts, at start of Tx; Te, at end of Tx; Lf, at last follow-up.

factors positively influencing NFH were younger CA, taller height at the start of treatment, taller MPH, and longer duration of GnRHa treatment.

In comparison with the 50th percentile female height (160.7 cm) of the Korean growth chart in 2007, the average MPH of our subjects (157.8 ± 3.4 cm) was shorter, but the NFH (159.7 ± 4.8 cm) was the same (7). The average AH of Korean females has increased in recent years, with the values in 1985, 1998 and 2007 being 157.6 cm, 160.0 cm and 160.7 cm, respectively. Taking this secular trend into consideration, the MPH of our subjects was no different from the AH in 1985 (9, 10).

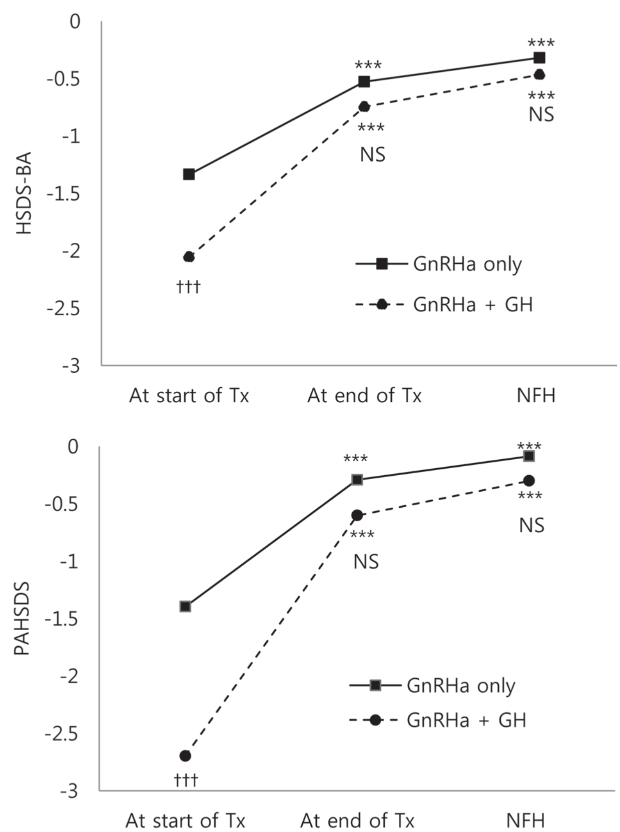

Fig. 1. Changes in height standard deviation score for bone age (HSDS-BA) and predicted adult height (PAH). At the start of therapy, the HSDS-BA (upper panel) and PAHSDS (lower panel) were significantly different between the GnRHa group (■) and combined GnRHa plus GH group (●), but the differences became insignificant during treatment and at near final height (NFH). HSDS-BA and PAHSDS in each group increased significantly during treatment and at NFH. Tx, treatment; ** $P < 0.001$, vs. start of treatment; ††† $P < 0.001$, NS, not significant between two groups at each point.

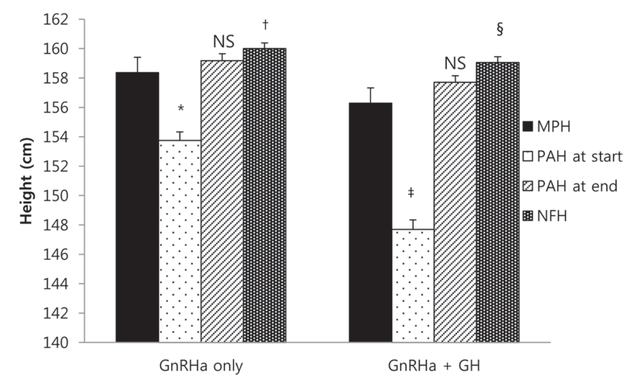

Fig. 2. Comparison of midparental height (MPH) with predicted adult height (PAH) and near final height (NFH). Compared with the MPH, both groups showed shorter PAHs at the start of treatment, but there was no difference at the end of treatment; NFH was significantly taller than MPH. Data are shown the mean ± SE. * $P < 0.001$; † $P < 0.01$ vs. MPH; ‡ $P < 0.001$; § $P < 0.05$ vs. MPH. NS, not significant vs. MPH.

Because no randomized controlled studies have evaluated the effect of GnRHa on final height compared with untreated controls, most studies compare PAH before treatment with the final height attained or historical data from untreated patients. Although the use of BA for the prediction of AH is unreliable when skeletal maturation is advanced, the use of the Bayley-Pinneau tables for average children appears to be the preferred methodology for height prediction (11). Our study also used this method. Carel *et al.* (12) reported that final AH was improved by 4.8 ± 5.8 cm compared with the PAH before treatment and by 8.3 cm compared with a historical group. They also pointed out that continuing GnRHa treatment beyond 11 yr of age in girls did not improve AH and could actually decrease it. Another study suggested that 12–12.5 years was the appropriate BA at which to stop treatment to achieve the maximum AH (13). Like these two studies, we discontinued GnRHa at 10.3 ± 0.7 yr, at which point the BA was 11.5 ± 0.7 yr. Klein *et al.* (14) reported that GnRHa treatment improves the final height of children with rapidly progressing precocious puberty, but not sufficiently enough to reach the target height. In the study of Pasquino *et al.* (15), their AH of the untreated group was an average of 5.4 cm shorter than that of the treated group and 4.1 cm shorter than the target height. A few long-term studies are available on final height in Korean girls with CPP. Kwon

Table 3. Multiple linear regression analysis between growth parameters and near final height

	Near final height			
	β	SE (β)	T	*P*-value
CA at Tx start	–3.233	1.433	–2.256	0.028
Height at Tx start	0.661	0.181	3.659	0.001
MPH	0.320	0.103	3.089	0.003
PAH at Tx start	0.097	0.143	0.679	0.500
ΔBA-CA at start	–2.032	1.107	–1.835	0.072
GnRHa Tx duration	2.044	0.480	4.263	0.000

SE, standard error; CA, chronological age; BA, bone age; Tx, treatment; MPH, midparental height; PAH, predicted adult height; △, difference; GnRHa, gonadotropin-releasing hormone analog.

et al. (16) reported that the PAH increased by approximately 5 cm in 2 yr and approximately 6–7 cm in 3 yr after treatment. Another study (4) showed that NFH increased by approximately 5.1 cm in 71 CPP patients who started treatment at 8.5 yr of age. Contrary to these two studies, real AH was measured in one report in which 59 girls with CPP and a PAH of 156.6 cm at the start of GnRHa treatment achieved an AH of 160.4 cm (5). But the starting age of GnRHa treatment in that study was 8.7 yr of age, a somewhat older age. Our study showed that NFH increased 6.3 cm from the initial PAH at 8.2 ± 0.8 yr as a result of treatment with GnRHa only.

Several studies have demonstrated that the final AH differs depending on the onset of CPP treatment (17–19). Final AH was found to be similar to the PAH at discontinuation of treatment and higher than the MPH in a group under 6 yr of age. In a group between 6 and 8 yr of age, the final AH was similar to the MPH but shorter than the PAH at discontinuation of treatment. In a group between 8 and 10 yr of age, final AH was shorter than MPH as well as the PAH at discontinuation of treatment (18). A recent study evaluated a group of patients between 16 and 32 yr of age who had previously received GnRHa treatment, and it found no difference in AH between subjects who had begun receiving treatment at approximately 8 yr of age and other subjects who had not received any treatment (19). Overall, previous reports suggest that earlier treatment showed a good result as far as AH is concerned. Therefore, GnRHa treatment is needed to increase the AH in CPP patients, at least in those under 8 yr of age.

Although we did not randomize the subjects, the combined GnRHa plus GH therapy was used for low PAH-SDS subjects (–2.7 ± 1.1 SDS). Their NFH increased 11.4 cm from the PAH at the start of therapy. In spite of the shorter MPH in this group, the NFH was similar to that of the GnRHa-only group. Another report of combined GnRHa plus GH treatment in Korean girls with CPP, which was performed for an average 1.9 years, showed an increase in PAH of 4.7 cm after treatment to improve AH, which is not so different from the result for their GnRHa-only group of 3.8 cm (5). Also, in a Chinese study, both GnRHa alone and combined GnRHa plus GH therapy for an average of 1.1 yr were able to improve the NFH in girls with CPP (3.9 cm vs. 4.7 cm) to a similar extent (20). The height gain in our study was greater than those in the previous reports in Korea and China. But our subjects were different from those in these two reports in many aspects; that is, our subjects had shorter MPHs, were more than 1 yr younger at the start of treatment, had shorter PAHs at the start of treatment and had longer duration of GH therapy.

Factors leading to a greater final height were reported to be less delay in the onset of treatment, longer duration of treatment and younger CA and BA at the onset of treatment (14). Other Korean reports suggested that younger CA at the start of therapy and taller MPH are factors (4, 5). Our results also showed the two factors noted above, as well as taller height at the start of therapy and longer duration of GnRHa use. We performed an analysis after excluding combined GnRHa plus GH treatment group.

The age at menarche after the discontinuation of GnRHa and the duration from menarche to the end of GnRHa treatment were similar to those in two Korean reports (4, 5). The BAs at menarche were 12.6 and 12.8 yr in these previous reports, respectively, both of which are similar to the average age of 12.6 yr at menarche among normal Korean girls (21). In one controlled study, the average age at menarche in a GnRHa-treated group was 12 yr, which represented a significant delay when compared with the age of 9.6 yr in the study's untreated group (19).

The limitation of our study was that the subjects were not randomized for GnRHa only or combined GnRHa plus GH therapy. This might have resulted in bias in selection of subjects. But the combined GnRHa plus GH group had shorter heights, lower HSDS adjusted for CA and BA and shorter PAHs and MPHs, although there was no difference in CA and BA. Therefore, the two groups were different at the start in terms of many height parameters, but they were not different after treatment.

In conclusion, GnRHa treatment could improve NFH in girls with CPP to at least a level similar to the MPH and could delay menarche so that it occurred close to the time it occurs in the general population. Combined GnRHa plus GH therapy, if used in CPP subjects with a short MPH, can improve NFH to a level similar to the average AH of the general population.

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