

Central precocious puberty in children with Lennox–Gastaut syndrome: clinical characteristics and long-term outcomes of GnRH agonist treatment

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Abstract

Purpose:

Central precocious puberty (CPP) is associated with neurological disorders. Lennox–Gastaut syndrome (LGS) is a severe epileptic encephalopathy characterized by drug-resistant seizures. This study evaluated the efficacy and safety of gonadotropin-releasing hormone agonist (GnRHa) treatment in patients with LGS and coexisting CPP.

Methods:

This retrospective study included 40 patients with LGS and CPP who received GnRHa treatment for at least 1 year. Clinical and auxological data, including growth parameters, bone age, hormonal profiles, and antiseizure medication use, were assessed before and during treatment.

Results:

GnRHa treatment was initiated at a mean age of 7.71 ± 1.62 years, with an average treatment duration of 3.31 ± 1.50 years. The bone age to chronological age ratio significantly decreased from 1.27 ± 0.21 at baseline to 1.14 ± 0.17 after 27 months and 1.04 ± 0.11 at treatment completion. Height standard deviation score (SDS) decreased modestly during treatment, whereas body mass index (BMI) SDS remained stable. Peak luteinizing hormone (LH) was suppressed during treatment. Predicted adult height (PAH) showed a nonsignificant increase from 152.5 ± 11.5 cm at baseline to 155.1 ± 12.6 cm at the last follow-up. In an exploratory post hoc analysis, patients with hypoxic–ischemic encephalopathy had greater bone age (BA) advancement at diagnosis (BA/chronological age ratio, 1.44 ± 0.37 vs. 1.24 ± 0.16 ; $p = 0.049$) and a larger increase in PAH during treatment (14.5 ± 12.3 vs. 0.6 ± 8.2 cm; $p = 0.048$) than the remainder of the cohort. Menarche occurred at a mean age of 12.95 ± 1.28 years, approximately 1.80 ± 0.52 years after the end of GnRHa treatment.. Antiseizure medication use did not change significantly during the first year of treatment.

Conclusion:

GnRHa treatment was associated with sustained pubertal suppression and attenuation of skeletal maturation in patients with LGS and CPP. The greater skeletal maturation observed at diagnosis in the small HIE subgroup suggests potential heterogeneity in CPP presentation according to underlying neurological etiology and warrants confirmation in larger cohorts..

What is Known

- Children with severe neurological disorders are at increased risk of central precocious puberty, but treatment outcomes in Lennox–Gastaut syndrome remain poorly characterized.
- Evidence regarding long-term GnRH agonist treatment and neurological safety in this population is limited.

What is New:

- In 40 children with Lennox–Gastaut syndrome, GnRH agonist treatment produced sustained pubertal suppression and reduced bone-age advancement while maintaining height and BMI SDS.
- Central precocious puberty had heterogeneous structural, genetic, and idiopathic etiologies; antiseizure medication burden did not change significantly during treatment.

Introduction

The prevalence of precocious puberty (PP) has increased substantially worldwide in recent decades, with a particularly pronounced rise in South Korea [1]. PP is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys [2]. Central precocious puberty (CPP), the most common form of PP, results from the premature activation of the hypothalamic–pituitary–gonadal (HPG) axis and leads to progressive pubertal development, accelerated linear growth, and advancement of bone age (BA). If left untreated, CPP may compromise adult height potential and cause psychosocial difficulties associated with early sexual maturation. Gonadotropin-releasing hormone agonists (GnRHa) are the standard treatment for progressive CPP and effectively suppress the HPG axis and pubertal progression, thereby helping to preserve adult height potential [3].

The etiology of CPP is predominantly idiopathic, particularly in girls, although monogenic and structural or acquired central nervous system (CNS) causes have also been identified [4]. Pathogenic variants in genes involved in pubertal regulation, including *MKRN3*, *DLK1*, and *KISS1*, account for a subset of cases [5]. Among structural CNS lesions, hypothalamic hamartoma is one of the most well-established causes of CPP [6]. CPP may also occur in children with pre-existing neurological or neurodevelopmental conditions, including epilepsy, hypoxic–ischemic brain injury, hydrocephalus, chromosomal abnormalities, and various genetic syndromes, as well as in those with CNS tumors, infections, trauma, or a history of cranial irradiation [7]. Epilepsy and other underlying neurological or syndromic disorders have also been associated with premature activation of the HPG axis, although the mechanisms underlying these associations remain incompletely understood [4].

Lennox–Gastaut syndrome (LGS) is a severe developmental and epileptic encephalopathy characterized by multiple drug-resistant seizure types, including tonic seizures, cognitive or behavioral impairment, and characteristic electroencephalographic findings, such as diffuse slow spike-and-wave discharges and generalized paroxysmal fast activity [8]. The etiology of LGS is heterogeneous and includes structural and genetic causes; nonetheless, the underlying cause remains unidentified in a subset of patients. Structural etiologies include congenital brain malformations and acquired CNS insults, such as hypoxic–

ischemic injury, infection, and other forms of brain injury [9]. Given the frequent occurrence of structural brain abnormalities, genetic disorders, and severe neurological impairment in patients with LGS, findings from patients with idiopathic CPP may not be generalizable to this population.

However, little is known about the clinical characteristics and long-term treatment outcomes of CPP in patients with LGS. Most studies have evaluated the efficacy of GnRHa treatment in healthy children with idiopathic CPP, whereas few have assessed GnRHa treatment in patients with severe neurological disorders or developmental and epileptic encephalopathies. Consequently, the efficacy of GnRHa treatment in suppressing pubertal progression and its long-term effects on growth and pubertal development in patients with LGS remain unclear. Therefore, this study aimed to characterize CPP in patients with LGS and evaluate their long-term clinical outcomes following GnRHa treatment.

Methods

Study design and population

This retrospective study included 40 patients diagnosed with LGS and coexisting CPP who received GnRHa treatment for at least 1 year between the ages of 0 and 18 years, from October 2005 to September 2025. All patients were followed for at least 1 year at the Outpatient Pediatric Endocrinology Unit of Severance Children's Hospital, a tertiary center with two branches in South Korea.

Pediatric patients with diagnostic codes for both LGS and CPP were identified using the Severance Clinical Research Analysis Portal, a web-based medical data analysis platform that integrates order communication system information and anonymized electronic medical record (EMR) data. The search covered medical records from October 1, 2005, when the EMR system was implemented at our institution, to September 2025.

A total of 50 patients were screened for eligibility. Of these, two did not receive GnRHa treatment because their caregivers declined treatment. Four patients had initiated GnRHa treatment at other institutions before being transferred to our center and were excluded because pretreatment clinical data were unavailable. One patient who received growth hormone replacement therapy for growth hormone deficiency was also excluded. In addition, three patients who received GnRHa treatment for less than 1 year were excluded. Consequently, 40 patients were included in the final study population (Fig. 1).

All patients had been diagnosed with LGS by pediatric neurologists, and fulfillment of the ILAE diagnostic criteria was retrospectively confirmed by reviewing clinical and EEG records [10]. These criteria included epilepsy onset before 18 years of age; tonic seizures accompanied by at least one additional seizure type, such as atypical absence, atonic, myoclonic, focal impaired awareness, generalized tonic-clonic seizures, nonconvulsive status epilepticus, or epileptic spasms; drug-resistant epilepsy; intellectual disability; and characteristic electroencephalographic findings comprising generalized slow spike-and-wave discharges at ≤ 2.5 Hz and generalized paroxysmal fast activity at ≥ 10 Hz during sleep. For retrospective confirmation of LGS, characteristic EEG findings documented on either the most recent

EEG or an earlier EEG were considered sufficient to satisfy the EEG criterion [9]. LGS was diagnosed by pediatric neurologists based on clinical and EEG findings. Brain magnetic resonance imaging (MRI) findings were obtained from radiology reports. Underlying etiologies were classified based on a review of clinical records, neuroimaging findings, and genetic test results.

CPP was defined as the development of secondary sexual characteristics corresponding to Tanner stage 2 or higher before age 8 years in girls and 9 years in boys, advanced BA relative to chronological age, and a peak stimulated luteinizing hormone (LH) level of ≥ 5 IU/L during the luteinizing hormone-releasing hormone test [11].

Measurements

The etiologies of epilepsy were determined by reviewing medical records and brain MRI findings. Information on antiseizure medication use was collected before the diagnosis of CPP and 12 months after the initiation of GnRHa treatment. Clinical and auxological data, including Tanner stage, height, weight, body mass index (BMI), and standard deviation scores (SDS) for height, weight, and BMI calculated using the 2017 Korean National Growth Charts [12], were retrospectively reviewed at baseline and follow-up.

Pubertal development and treatment response were assessed 3 months after treatment initiation and at 6-month intervals thereafter. Pubertal development was evaluated by Tanner stage, and treatment response was assessed by measuring the serum concentrations of LH, follicle-stimulating hormone (FSH), and estradiol or testosterone. Stimulated LH was measured 30 min after GnRHa administration, and a stimulated LH level of < 2.5 IU/L was considered indicative of adequate gonadotropin suppression [13].

BA was assessed every 6 months by two pediatric endocrinologists using posteroanterior radiographs of the left hand and wrist according to the Greulich–Pyle atlas [14]. PAH was estimated using the Bayley–Pinneau method, applying the average or advanced table according to the degree of BA advancement at each assessment [15]. Long-term treatment outcomes included changes in BA advancement, growth parameters, PAH, timing of menarche, changes in the number of antiseizure medications (ASMs) as a proxy for seizure-related outcomes, and premature discontinuation of GnRHa treatment.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation for normally distributed data and as median with interquartile range for non-normally distributed data. Differences between baseline and post-treatment time points were assessed using the paired t-test or the Wilcoxon signed-rank test. Comparisons between groups were performed using the independent-samples t-test or the Mann–Whitney U test.

Effect estimates are presented with 95% confidence intervals. All statistical analyses were performed using R version 4.4.1 and SAS version 9.4 (SAS Institute Inc., Cary, NC). All p-values were two-sided, and statistical significance was defined as $p < 0.05$.

Ethical approval

This study was approved by the Institutional Review Board of Yonsei University College of Medicine (Approval No. 4-2026-0974) and was conducted according to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design and minimal risk to participants.

Results

Baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. Of the 40 patients, 33 (82.5%) were female, and the mean duration of GnRHa treatment was 3.3 ± 1.5 years. Most patients were at Tanner stage 2 at treatment initiation. All patients exhibited BA advancement relative to chronological age and had peak LH levels exceeding 5 IU/L at diagnosis.

The presumed etiologies of LGS and the ASMs used before initiation of GnRHa treatment are summarized in Table 2. Structural causes were the most common etiology of LGS, followed by idiopathic and genetic causes. Hypoxic–ischemic injury was the most common category ($n = 6$), followed by congenital cortical malformation ($n = 4$), CNS infection or autoimmune injury ($n = 4$), structural abnormalities associated with acquired hydrocephalus ($n = 3$), neoplasm ($n = 2$), and vascular injury ($n = 1$). A genetic etiology was identified in seven patients (17.5%), comprising compound heterozygous variants in *CAD*, *SCN1A*-related Dravet syndrome, *SCN2A*-related disorder, *SCN8A*-related disorder, 15q duplication syndrome, tuberous sclerosis complex, and *CDKL5* deficiency disorder ($n = 1$ each). Most patients received multiple ASMs, with sodium channel blockers being the most frequently used class.

Growth and pubertal outcomes during and after GnRHa treatment

Biochemical and auxological changes during and after GnRHa treatment are summarized in Table 3. From 3 months after treatment initiation, mean stimulated LH levels remained below 2.5 IU/L throughout follow-up, consistent with sustained suppression of the HPG axis (Fig. 2). Serum estradiol and testosterone levels also decreased after treatment initiation and remained suppressed during treatment. BA advancement progressively decreased during treatment, as reflected by reductions in both the BA/CA ratio and the BA–CA difference. By the end of treatment, the BA/CA ratio decreased from 1.27 ± 0.21 to 1.04 ± 0.11 , while the BA–CA difference decreased from 1.83 ± 0.82 to 0.31 ± 1.08 years; both changes were significant (Fig. 2). Height SDS was lower at the end of treatment than at baseline. In contrast, BMI SDS remained relatively stable throughout treatment (Table 3A).

Height velocity decreased modestly during the second year of treatment. PAH increased numerically during follow-up, although the change from baseline was not statistically significant. Final height data were available for 13 patients: the only male patient with available data achieved a final height of 182.4 cm, whereas the mean final height among the 12 female patients was 156.6 ± 6.6 cm. The mean age at menarche was 12.95 ± 1.28 years, and menarche occurred 1.80 ± 0.52 years after the end of GnRHa treatment (Table 3B).

PAH prediction error decreased over the course of treatment. Among the 13 patients with a recorded final height, PAH assessed at diagnosis significantly underestimated final height (mean error -5.4 ± 8.1 cm, $p = 0.032$), whereas PAH reassessed at the last follow-up visit had a mean prediction error of -0.2 ± 6.2 cm ($p = 0.91$). The correlation between PAH and final height was $r = 0.81$ at diagnosis and $r = 0.87$ at the last follow-up. The absolute prediction error decreased from 8.8 ± 5.9 cm to 4.9 ± 4.0 cm ($p = 0.003$) (Fig. 3).

At diagnosis, the BA/CA ratio did not differ significantly between patients with structural and nonstructural LGS etiologies (1.32 ± 0.25 vs. 1.22 ± 0.15 , $p = 0.06$). A post hoc analysis showed that patients with hypoxic–ischemic encephalopathy (HIE) ($n = 6$) had a significantly higher BA/CA ratio at diagnosis (1.44 ± 0.37 vs. 1.24 ± 0.16 , $p = 0.049$) and a significantly larger Δ PAH after treatment (14.5 ± 12.3 vs. 0.6 ± 8.2 cm, $p = 0.048$) than the remainder of the cohort.

Adverse effects, treatment discontinuation, and changes of ASM use

Among the 40 patients included in the analysis, no serious adverse events or cases of aseptic abscesses were observed. Of these, two patients discontinued treatment before completing the planned GnRHa treatment course. Both discontinued treatment because their caregivers were concerned about continued linear growth and the associated caregiving burden. Among the three patients excluded because GnRHa treatment lasted less than 1 year, one discontinued treatment after the initial injection because of a reported increase in seizure frequency. Among the 38 patients with paired ASM data, the mean number of ASMs did not change significantly from baseline to 1 year after treatment initiation (3.45 ± 1.86 vs. 3.66 ± 1.82 , respectively; Wilcoxon signed-rank $p = 0.124$). The number of ASMs increased in 13 patients (34.2%), remained unchanged in 19 (50.0%), and decreased in 6 (15.8%).

Discussion

To our knowledge, this is the first study to evaluate the long-term clinical outcomes of GnRHa treatment in patients with LGS and CPP. The etiologies of LGS were heterogeneous, with structural causes accounting for the largest proportion. GnRHa treatment was associated with sustained reductions in stimulated LH levels and attenuation of BA advancement, while PAH showed a modest, nonsignificant increase. No serious adverse events were observed during treatment among the 40 patients included in the analysis, and menarche after treatment cessation occurred at a timing consistent with that of previous cohorts with CPP. Seizures have rarely been reported in association with GnRH agonist treatment [16]. In our cohort, of 38 patients with paired ASM data, the number of ASMs did not change

significantly from baseline to 1 year after GnRHa initiation. However, seizure frequency was not assessed.

LGS is a heterogeneous developmental and epileptic encephalopathy characterized by drug-resistant seizures, cognitive and behavioral impairment, and characteristic electroencephalographic abnormalities. Its etiology is diverse, with structural causes including focal or diffuse cortical malformations and acquired brain injuries such as HIE, as well as genetic causes [10]. CNS abnormalities are also well-established causes of CPP. In a large multicenter study of 770 girls with CPP, Helvacioğlu et al. [17] reported abnormal brain MRI findings in 13.5% of patients, including previously known and newly detected CNS lesions, and found that pubertal onset before 6 years of age was associated with an increased likelihood of CNS lesions. Similarly, an Italian multicenter study reported neuroimaging abnormalities in 18.4% of girls with CPP, approximately half of which were newly identified at diagnosis [18]. The frequency of neurogenic CPP tended to be higher among girls with earlier pubertal onset. In our cohort, all four patients in whom CPP developed before 6 years of age had an underlying structural CNS abnormality, including hydrocephalus, HIE, and encephalomalacia. These findings suggest that the coexistence of LGS and CPP may not necessarily reflect a direct causal effect of LGS on pubertal activation. Rather, shared underlying etiologic factors—particularly structural CNS abnormalities and, potentially, genetic factors—may contribute both to the development of LGS and to the premature activation of the HPG axis.

GnRHa treatment effectively suppresses the HPG axis and reduces skeletal maturation. Two studies demonstrated that GnRHa treatment effectively suppressed gonadotropin production and BA advancement [19, 20]. In our cohort, mean stimulated LH levels remained below 2.5 IU/L from 3 months after treatment initiation, accompanied by attenuation of BA advancement. Although eight patients still had a BA–CA difference of more than 1 year at the end of treatment, seven had already exhibited marked BA advancement of more than 2 years at treatment initiation, suggesting that the persistent BA–CA difference at the end of treatment largely reflected greater skeletal maturation at baseline. Menarche occurred 1.80 ± 0.52 years after the end of GnRHa treatment in our cohort, compared with intervals of 1.0–1.5 years reported in previous studies [20, 21].

Linear growth during treatment should be interpreted in the context of the underlying neurological condition. In our cohort, mean height velocity was 5.07 ± 2.07 cm/year during the first year of GnRHa treatment ($n = 28$) and 4.53 ± 1.70 cm/year during the second year ($n = 18$). Children with severe neurodevelopmental disabilities may follow growth trajectories that differ substantially from those of typically developing children, reflecting the combined effects of neurological severity, impaired mobility, nutritional difficulties, and other comorbidities. Disease-specific growth charts are well established for cerebral palsy, whereas comparable references are unavailable for LGS. Studies of children with cerebral palsy have demonstrated substantial differences in growth according to the severity of motor impairment, and cerebral palsy-specific growth charts have been developed and externally validated [22]. Bruzzi et al. [23] reported that children with CPP and moderate-to-severe cerebral palsy experienced deterioration in height SDS during follow-up despite effective GnRHa treatment, whereas children with

CPP without cerebral palsy in the same study showed more favorable growth [24]. Thus, the decline in height SDS observed in our patients may not necessarily indicate inadequate control of CPP but may partly reflect the underlying severe neurological disease and its associated growth impairment.

However, PAH increased by only 2.66 ± 9.84 cm from diagnosis to the last follow-up in our cohort, a smaller gain than reported in other cohorts with idiopathic CPP [25]. In the post hoc analysis, patients with HIE had a higher BA/CA ratio at diagnosis and a larger increase in PAH than the rest of the cohort. Greater skeletal maturation at diagnosis may have contributed to the larger change in PAH. Thus, CPP in children with HIE may warrant closer follow-up. Nonetheless, the mechanism underlying the relationship between HIE and CPP remains unclear, and the small size of the HIE subgroup limits the strength of this inference.

The safety of GnRHa treatment is particularly relevant in patients with LGS because of their high seizure burden and frequent use of multiple ASMs. GnRHa has been successfully used to treat CPP in children with neurological disorders, including cerebral palsy and hypothalamic hamartoma with epilepsy [23, 26]. Nevertheless, convulsions have been reported after GnRH agonist administration, particularly in patients with pre-existing epilepsy or CNS abnormalities, and are included as a warning in drug labels. Among the 38 patients with paired ASM data, the number of ASMs did not change significantly from baseline to 1 year after treatment initiation, except for one patient who discontinued treatment because of an increased frequency of seizures. A causal relationship between GnRHa treatment and the reported increase in seizure frequency could not be established. The absence of a significant change in the number of ASMs does not establish neurological safety because of the relatively small sample size and retrospective study design.

Treatment decisions in this population should also extend beyond conventional height-related outcomes. For children with severe neurological impairment, greater final adult height may increase the physical demands of daily care and transfers, whereas excessively early menstruation may impose additional caregiving and hygiene burdens, particularly in girls with substantial functional dependence. Consequently, the goals of CPP treatment in patients with LGS may differ from those in otherwise healthy children with idiopathic CPP. Decisions regarding the initiation and duration of GnRHa treatment should therefore be individualized, considering pubertal progression, skeletal maturation, anticipated growth, neurological and functional status, and the preferences and circumstances of the patient and family.

Several limitations of this study should be acknowledged. First, an untreated control group was not included because very few patients with coexisting LGS and CPP did not receive GnRHa treatment. In addition, the sample size was relatively small, reflecting the rarity of this population within a single healthcare system. Second, owing to the retrospective design and reliance on electronic medical records, changes in seizure frequency, EEG findings, and adverse events could not be directly or systematically assessed, and changes in the number of ASMs cannot be interpreted as a direct measure of seizure control. Third, because the participants had severe and medically complex conditions that

often made routine anthropometric assessments challenging, auxological data were not consistently available at every time point, and some measurements may have been subject to error. Fourth, several subgroup and exploratory analyses, including the assessment of PAH prediction accuracy using attained final height and the HIE-related subgroup analysis, were based on very small numbers of patients (6 to 13) and were not prespecified. Therefore, further studies in larger, multicenter cohorts are needed to confirm these findings.

Conclusion

GnRHa treatment was associated with sustained reductions in stimulated LH levels and attenuation of skeletal maturation in children with LGS and CPP. The number of ASMs did not change significantly in our cohort. However, seizure frequency was not assessed, precluding any conclusions regarding neurological safety. The greater skeletal maturation at diagnosis in the HIE subgroup suggests that children with HIE and CPP may warrant closer monitoring. Given the clinical complexity of coexisting LGS and CPP, coordinated care between pediatric neurologists and endocrinologists may facilitate the integration of neurological care with the management of pubertal development and growth.

Declarations

Acknowledgments

The funders had no role in the study design, data collection, analysis, interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Yonsei University College of Medicine (Approval No. 4-2026-0974) and complied with the Declaration of Helsinki. The requirement for informed consent was waived because of the study's retrospective design and minimal risk to participants.

Consent for publication

All authors have read and approved the final manuscript and consent to its publication.

Competing interests

The authors declare no competing interests.

Author Contribution

SK conceived and designed the study, interpreted the data, and drafted the manuscript. JS conceived, designed, and conducted the study and critically revised the manuscript for important intellectual content. EJH and YKK conceived and conducted the study. KS conceived and conducted the study and analyzed and interpreted the data. HK conceived and designed the study. SJK, EBL, and KWC curated the data and prepared the figures. YC and HWC analyzed and interpreted the data.

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Tables

Table 1
Baseline characteristics of the study population

Variable	Total (n = 40)	Male (n = 7)	Female (n = 33)
Sex, n (%)	40 (100)	7 (17.5)	33 (82.5)
Age at CPP diagnosis, years	8.20 ± 1.87	9.43 ± 2.37	7.94 ± 1.68
Mid-parental height, cm	163.09 ± 6.28 (n = 38)	171.93 ± 6.66 (n = 7)	161.10 ± 4.17 (n = 31)
Tanner stage at diagnosis, n (%)			
Stage 2	29 (72.5)	7 (100)	22 (66.7)
Stage 2 to 3	8 (20.0)	0 (0)	8 (24.2)
Stage 3	3 (7.5)	0 (0)	3 (9.1)
GnRH agonist treatment, n (%)			
Leuprolide 3.75 mg	20 (50.0)	2 (28.6)	18 (54.5)
Leuprolide 11.25 mg	5 (12.5)	2 (28.6)	3 (9.1)
Triptorelin 3.75 mg	8 (20.0)	2 (28.6)	6 (18.2)
Triptorelin 11.25 mg	7 (17.5)	1 (14.3)	6 (18.2)
Bone age (BA), years	10.00 (8.75–10.50)	10.00 (9.38–10.88)	10.00 (8.75–10.25)
BA/CA ratio	1.27 ± 0.21	1.19 ± 0.13	1.29 ± 0.22
BA-CA, years	1.83 ± 0.82	1.56 ± 0.85	1.89 ± 0.82
Peak LH, IU/L	20.99 ± 15.02	17.96 ± 9.60	21.64 ± 15.97
Peak FSH, IU/L	25.17 ± 38.38	13.90 ± 14.53	27.55 ± 41.49
Estradiol (E2), pg/mL			< 8.0 (n = 26) 11.47 (10.85–14.07)
Testosterone, ng/dL		32.10 (< 2.5–383.45)	
Height, cm	121.74 ± 11.93	126.11 ± 13.51	120.81 ± 11.58
Height SDS at diagnosis	−0.70 ± 1.45	−0.85 ± 2.03	−0.67 ± 1.33
Weight, kg	25.01 ± 7.45	28.26 ± 7.60	24.32 ± 7.35
Values are mean ± standard deviation or median (interquartile range). ASM, antiseizure medication; BA, bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; SDS, standard deviation score.			

Variable	Total (n = 40)	Male (n = 7)	Female (n = 33)
Weight SDS at diagnosis	-0.62 ± 1.59	-0.40 ± 1.37	-0.67 ± 1.65
BMI, kg/m ²	16.61 ± 3.28	17.62 ± 2.80	16.40 ± 3.37
BMI SDS at diagnosis	-0.32 ± 1.78	0.08 ± 1.35	-0.40 ± 1.86
Number of ASMs at diagnosis	3.00 (2.00–5.00) (n = 39)	5.00 (3.00–5.00) (n = 7)	3.00 (2.00–4.25) (n = 32)
Treatment duration, years	3.31 ± 1.50 (n = 31)	2.66 ± 1.53 (n = 4)	3.40 ± 1.50 (n = 27)
Values are mean ± standard deviation or median (interquartile range). ASM, antiseizure medication; BA, bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; SDS, standard deviation score.			

Table 2
Etiology of LGS and number and type of anti-seizure medication before treatment

Etiology	Study population (N = 40)
Idiopathic	13 (32.5)
Genetic	7 (17.5)
Structural	20 (50.0)
Number of anti-seizure medications	
At CPP diagnosis (n = 39)	3.45 ± 1.86
One year after treatment (n = 38)	3.66 ± 1.82
Type of anti-seizure medication before GnRHa treatment*	
Valproate	21 (53.8)
GABAergic agents	21 (53.8)
Glutamatergic agents	16 (41.0)
Sodium channel blockers	26 (66.7)
SV2A ligands	13 (33.3)
Others	4 (10.3)
*Some patients received ASMs from more than one of the listed categories; therefore, percentages do not sum to 100%. One patient with resolved LGS was not receiving ASMs at the time of CPP diagnosis and was excluded from the analysis of ASM use. LGS, Lennox–Gastaut syndrome; SV2A, synaptic vesicle glycoprotein 2A.	

Table 3

Growth and pubertal outcomes during and after GnRHa treatment (A) Longitudinal hormonal and auxological parameters by treatment duration

LH, IU/L	Baseline	3 months	9 months	15 months	21 months	27 months	End of treatment [#]
	20.99 ± 15.02	1.53 ± 0.95 ^{***}	1.43 ± 0.93 ^{***}	1.25 ± 0.89 ^{***}	1.16 ± 0.84 ^{***}	1.08 ± 0.63 ^{***}	
FSH, IU/L	25.17 ± 38.38	2.05 ± 1.43 ^{***}	3.27 ± 2.60 ^{***}	3.47 ± 1.92 ^{**}	4.14 ± 2.57 ^{**}	4.43 ± 2.59 [*]	
E2, pg/mL (female, n = 33)	12.10 ± 19.60	9.02 ± 2.87	8.56 ± 1.98	8.32 ± 0.92	9.46 ± 4.10	10.24 ± 6.61	
Testosterone, ng/dL (male, n = 6)	134.42 ± 194.54	< 2.50	< 2.50	3.02 ± 1.16	< 2.50	< 2.50 (n = 2)	
BA/CA ratio	1.27 ± 0.21	1.25 ± 0.08	1.23 ± 0.21 ^{***}	1.18 ± 0.16 ^{***}	1.16 ± 0.16 ^{***}	1.14 ± 0.17 ^{***}	1.04 ± 0.11 ^{***}
BA-CA difference, years	1.83 ± 0.82	2.11 ± 0.49	1.31 ± 2.07	1.77 ± 2.00	1.55 ± 2.02	1.06 ± 1.10 ^{***}	0.31 ± 1.08 ^{***}
Height SDS	-0.70 ± 1.45	-0.40 ± 1.41 [*]	-0.75 ± 1.49	-0.35 ± 1.36	-0.73 ± 1.56 [*]	-0.74 ± 1.12 ^{**}	-1.36 ± 1.68 ^{***}
Weight SDS	-0.62 ± 1.59	-0.41 ± 1.44	-0.57 ± 1.34	-0.39 ± 1.20	-0.76 ± 1.58	-0.74 ± 1.55 [*]	-0.79 ± 1.19 [*]
BMI SDS	-0.32 ± 1.78	-0.28 ± 1.57	-0.27 ± 1.45	-0.31 ± 1.47	-0.50 ± 1.39	-0.33 ± 1.72	-0.13 ± 1.28
Values are means ± standard deviations; n decreases at later time points because of variable follow-up duration. [#] The last available measurement at or near treatment discontinuation. ^{**} p < 0.05, ^{***} p < 0.01, and ^{***} p < 0.001 vs. baseline using paired t-tests. BA, bone age; CA, chronological age; SDS, standard deviation score.							

(B) Summary growth and pubertal outcome

Outcome	Value	n
HV, year 1, cm/year	5.07 ± 2.07	28
HV, year 2, cm/year	4.53 ± 1.70	18
PAH at diagnosis, cm	151.55 ± 11.79	40
PAH at 1 year, cm	154.75 ± 13.02	23
PAH at 2 years, cm	154.07 ± 13.28	18
PAH at last follow-up, cm	155.11 ± 12.60	27
ΔPAH (final – initial), cm	2.66 ± 9.84	27
Final (near-adult) height, male, cm	182.40 (n = 1)	1
Final (near-adult) height, female, cm	156.64 ± 6.64	12
Age at menarche after treatment start, years	1.80 ± 0.52	10

Values are means ± standard deviations. Final height and age at menarche data were included only for patients who had reached both endpoints by the data cutoff. HV, height velocity; PAH, predicted adult height (Bayley–Pinneau method).

Figures

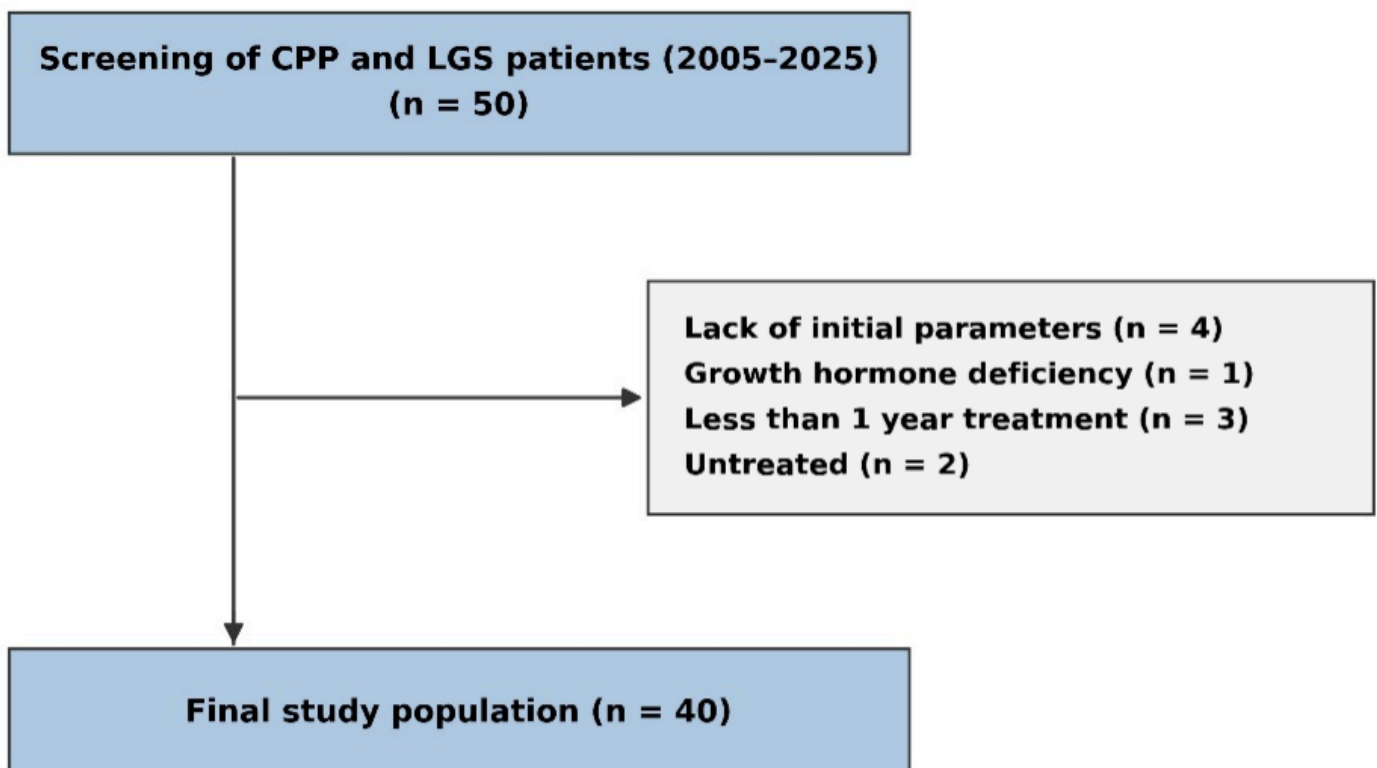


Figure 1

Flowchart of patient selection. CPP, central precocious puberty; LGS, Lennox–Gastaut syndrome

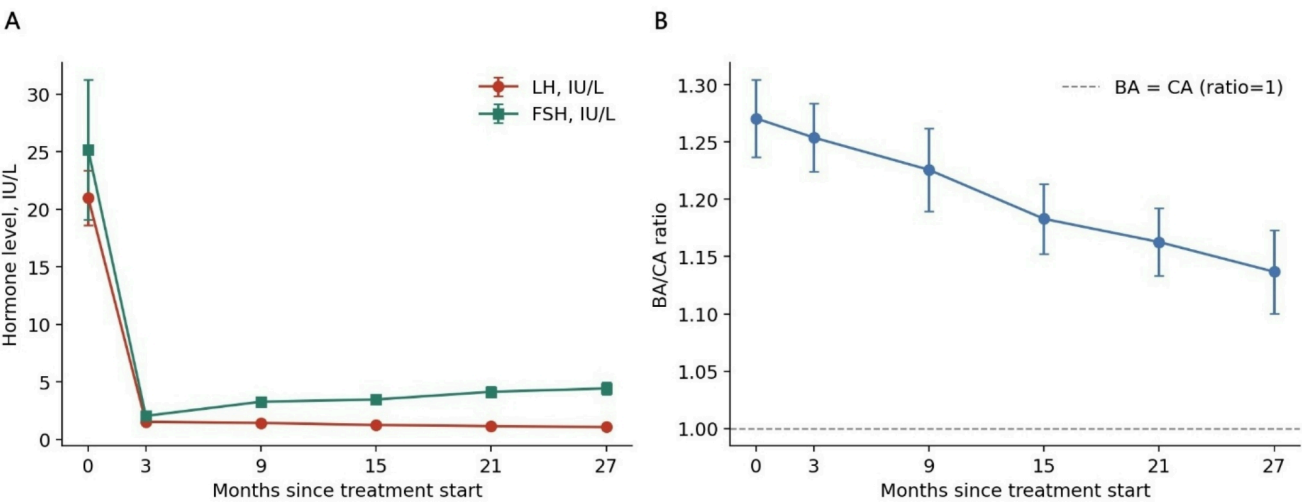


Figure 2

Hormonal and skeletal response to GnRHa treatment. (A) Changes in LH and FSH levels during GnRHa treatment. (B) Changes in the BA/CA ratio during treatment. Values are presented as mean $\pm$ SD. The dashed line indicates a BA/CA ratio of 1

BA, bone age; CA, chronological age; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist; LH, luteinizing hormone; SD, standard deviation

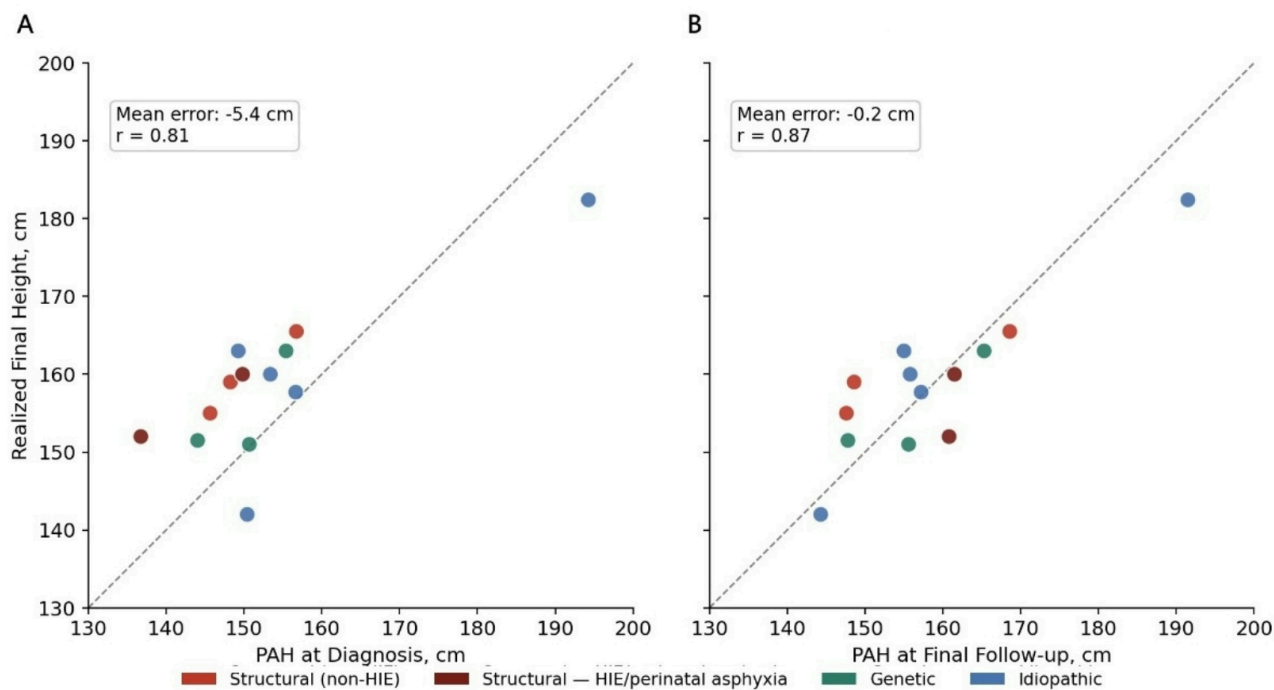


Figure 3

Predicted adult height versus attained final height by etiology. PAH, predicted adult height; HIE, hypoxic–ischemic encephalopathy

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