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Clinical Research Article

Central Precocious Puberty in Italian Boys: Data From a Large Nationwide Cohort

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Abstract

Context: There are only a few nationwide studies on boys with central precocious puberty (CPP) and the last Italian study is a case series of 45 boys that dates back to 2000.

Objective: We aimed to evaluate the causes of CPP in boys diagnosed during the last 2 decades in Italy and the relative frequency of forms with associated central nervous system (CNS) abnormalities on magnetic resonance imaging (MRI) compared to idiopathic ones.

Methods: We performed a national multicenter retrospective study collecting data from 193 otherwise normal healthy boys with a diagnosis of CPP. Based on MRI findings, the patients were divided into: Group 1, no CNS abnormalities; Group 2, mild abnormalities (incidental findings) unrelated to CPP; and Group 3, causal pathological CNS abnormalities.

Results: The MRI findings show normal findings in 86%, mild abnormalities (incidental findings) in 8.3%, and causal pathological CNS abnormalities in 5.7% of the cases. In Group 3, we found a higher proportion of patients with chronological age at diagnosis < 7 years ($P = .00001$) and body mass index greater than +2 SDS ($P < .01$). Gonadotropin-releasing hormone analogue therapy was started in 183/193 subjects. The final height appeared in the range of the target height in all groups and in 9 patients in whom the therapy was not started.

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Conclusion: In our study on a large nationwide cohort of boys referred for precocious puberty signs, the percentage of forms associated with CNS abnormalities was one of the lowest reported in the literature.

Key Words: central precocious puberty, boys, magnetic resonance imaging

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; CNS, central nervous system; CPP, central precocious puberty; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; MRI, magnetic resonance imaging; PP, precocious puberty; PPP, peripheral precocious puberty; SDS, standard deviation score.

Based on the activation of the hypothalamic-pituitary-gonadal (HPG) axis, precocious puberty (PP) can be classified as gonadotropin-dependent or central precocious puberty (CPP), or as gonadotropin-independent or peripheral precocious puberty (PPP). PPP can also be dependent on ectopic human chorionic gonadotropin (hCG) secretion. CPP in boys is defined as testicular enlargement (Tanner stage G2) before the age of 9 years. CPP may be secondary to an identifiable underlying central nervous system (CNS) disorder, may be associated with genetic disorder, or it may be idiopathic (without relevant CNS lesions) (1-3).

A few epidemiological studies, usually from small case series, indicate a lower prevalence of CPP in male compared with female individuals. In a population-based cohort study using Danish National Patient Registry (1998–2017) a mean annual incidence rate of 0.9 per 10 000 boys and 9.2 per 10 000 girls has been reported (4-6). However, an underestimation in boys may be due to the greater difficulty of their clinical assessment, which requires an evaluation of the testicular volume carried out by experienced physicians. Historical data underline the greater frequency of organic CPP in male compared to female individuals (73%-94% in male vs 8%-33% in female subjects) (7, 8) suggesting the need for magnetic resonance imaging (MRI) of the brain in every boy with CPP. Furthermore, much of the older data regarding male CPP included cases of secondary CPP due to untreated virilizing congenital adrenal hyperplasia, a condition which has nearly disappeared due to newborn screening programs.

More recent studies, however, report a more variable prevalence of organic forms, probably due to the diversity both in the study design and in the patient selection criteria with the possibility of selection bias (Table 1). Many studies include patients with signs of early pubertal development in follow-up for lesions or syndromes known to be associated with CPP and boys without other conditions (9-11, 13, 14).

Furthermore, recent studies from the United States, Europe, and Korea report an increased frequency of CPP in boys during the last few decades, analogous to what has already been observed in girls, but confirmatory data are still insufficient (5, 6, 17-19). Finally, there are only a few nationwide studies and, more specifically, the last Italian study is a case series of 45 boys with CPP that dates back to 2000 (9).

Therefore, we performed a national multicenter retrospective study collecting clinical data of boys with CPP diagnosed between January 1, 2001, and December 31, 2020, from 15 Italian centers of pediatric endocrinology. The primary aim of this study was the evaluation of the causes of CPP (excluding genetic causes) in male patients diagnosed during the last 2 decades in Italy and the relative frequency of forms with associated CNS abnormalities compared with idiopathic forms of CPP. Secondary aims were to evaluate the incidence rates of boys presenting different forms of CPP over time, the clinical characteristics at diagnosis and during follow-up in patients with idiopathic CPP compared to forms with associated CNS abnormalities, and the outcomes of gonadotropin-releasing hormone (GnRH) analogue treatment.

Materials and Methods

Patients and Study Design

We retrospectively collected data of boys with a diagnosis of CPP between 1 January 1, 2001, and December 31, 2020, from 15 centers of pediatric endocrinology (6 centers in the North, 4 in the Center, and 5 in the South of Italy) belonging to the Italian Society of Paediatric Endocrinology and Diabetology (ISPED).

These patients were selected with specific and homogeneous criteria, as they were in good health, with no neurological signs or symptoms and were referred only for clinical signs of early pubertal development. The diagnosis of CPP was confirmed at each center based on the clinical guideline for an increase in the testicular volume greater than or equal to 4 mL (gonadarche) before the age of 9 years, with an increased height velocity, an advancement of bone age (BA) ≥ 1 year compared to chronological age (CA), a baseline luteinizing hormone (LH) > 0.3 IU/L, and/or LH > 5 IU/L after a GnRH stimulation test (1, 18, 20, 21).

Inclusion criteria were (i) the onset of gonadarche before 9 years of age in otherwise normal healthy boys; (ii) the execution of brain MRI with a detailed examination of the hypothalamic-pituitary area at diagnosis; and (iii) in subjects who underwent GnRH treatment, good treatment compliance documented by clinical and hormonal parameters as well as the BA assessment.

Exclusion criteria were (i) chronic medical conditions already under follow-up at the centers participating in the study and known to be associated with CPP (also including CNS lesions and/or syndromes); (ii) congenital adrenal hyperplasia; (iii) other forms of PPP and isolated premature adrenarche (defined as premature pubic/axillary hair development, normal growth rate, and normal BA after exclusion of serious adrenal disorders) (6).

Figure 1 shows the flowchart of participant enrollment in the study.

Patients were divided into 3 groups based on the MRI findings:

1. Group 1, no CNS abnormalities or minor intracranial alterations not involving the hypothalamic-pituitary region
2. Group 2, mild abnormalities of the hypothalamic-pituitary region, considered incidental findings unrelated to CPP; incidental findings were defined as lesions of the pituitary region discovered fortuitously by imaging for reasons unrelated to pituitary disease (22)
3. Group 3, pathological CNS abnormalities known to be associated with CPP

Since there are rather controversial data in the literature (3, 20, 22, 23), the patients were allocated into the different

Table 1. Summary of main studies reporting prevalence of organic forms of CPP in males

Author	Study design	Diagnostic criteria	Country	Number of cases	Percentage of organic forms
De Sanctis, 2000 (9)	Retrospective multicentric	CA < 9 yrs TV > 3 mL	Italy	45	46%
Chemaitilly, 2001 (10)	Retrospective monocentric	CA < 9 yrs M & F	France	26	77%
Alikasifoglu, 2015 (11)	Retrospective monocentric	CA < 9 yrs TV > 4 mL	Turkey	100	26%
Yoon, 2017 (12)	Retrospective monocentric	CA < 10 yrs M & F	South Korea	138	7%
Topor, 2018 (13)	Retrospective monocentric	CA < 9 yrs TV > 3 mL	USA	50	64%
Lee, 2018 (14)	Retrospective monocentric	CA < 9 yrs TV > 4 mL	South Corea	71	38%
Wang, 2020 (15)	Retrospective monocentric	CA < 9 yrs TV > 4 mL	China	129	16%
Ziqin, 2021 (16)	Retrospective monocentric	CA < 9 yrs CPP & PPP	China	62	21%

Abbreviations: CA, chronological age; F, female; M, male; TV testicular volume;;.

groups through a process of collaboration between clinicians and neuroradiologists. The retrospective nature of the study did not allow us to centralize the MRI reports, but an expert pediatric neuroradiologist was available at each center. In selected cases, the multidisciplinary approach was extended to the pediatric oncologist. In all cases with pathological CNS abnormalities, in the majority of cases with incidental findings (excluding empty sella), and in patients with pineal cysts, a neuroradiological follow-up was performed (2 or more MRI scans during the follow-up).

To evaluate the possible increase in the frequency of CPP diagnosis over the years, all cases were further divided into 4 groups according to the following referral periods: 2001–2005, 2006–2010, 2011–2015, and 2016–2020. Within each referral period the boys were subdivided based on age at diagnosis $<$ or ≥ 7 years

We analyzed 5 groups of variables related to demographics, the visit before GnRH analogue therapy, characteristics of therapy, the visit after 1 year of therapy, and at the end of therapy.

Methods

The variables collected at the visit before CPP diagnosis included auxological data, age at the onset of pubertal signs, ethnicity, family history for PP, brain MRI findings, and hormone evaluation at baseline and after GnRH stimulation tests.

During the follow-up, height SDS, body mass index (BMI) SDS, and testicular volume were evaluated retrospectively 1 year after the start of the therapy, at the end of the therapy, 1 year after the suspension of the therapy, and at the final follow-up visit.

Body weight was measured with a digital body weight scale, while height was measured in a standing position with a Harpenden stadiometer by experts in auxological evaluation. The BMI was calculated according to the formula: weight (kg)/height (m^2). Height, weight, and BMI were expressed as a standard deviation score (SDS) according to Italian standards (24).

Pubertal development was assessed according to Marshall and Tanner's genital stage (25) and a Prader orchidometer was used to measure testicular volume.

The BA was evaluated in each center by experienced physicians using the Greulich and Pyle method (26).

All boys with a diagnosis of CPP underwent a brain MRI with pre- and post-gadolinium-enhanced T1- and T2-weighted images in axial, coronal, and sagittal sections. The brain MRI with a detailed examination of the hypothalamic-pituitary area was evaluated at individual sites by radiologists trained in pediatric investigations.

All centers used semiautomated chemiluminescence methods for hormonal measurements; the commercial system and kits used differed among the centers (27, 28).

The conventional GnRH test was performed by intravenous administration of 50 to 100 μg of drug, with samples taken at 0, 30, and 60 minutes.

Statistical Analysis

The characteristics of the patients enrolled in the study were reported in summary tables both for the overall sample of patients and for the cohorts.

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Data distribution was normal, so parametric statistics were used. Descriptive statistics for the continuous variables were expressed as mean ± SD, minimum values, and maximum values; the discrete or nominal variables were described and summarized by percentage relative frequencies. A sample size of 193 subjects allowed us to estimate a CPP prevalence of 6% assuming a precision level of 3.5% (half-width) using the binomial distribution. The prevalence of CPP was calculated as a point estimate and 95% CI using the binomial distribution. The trend of the frequency of CPP diagnosis over the years was estimated using the generalized additive mixed model (29) The analysis was performed using the R program. A Student *t* test was used to compare the different characteristics of continuous variables. A one-way ANOVA was used to compare differences in proportions for categorical variables. A Chi-square test

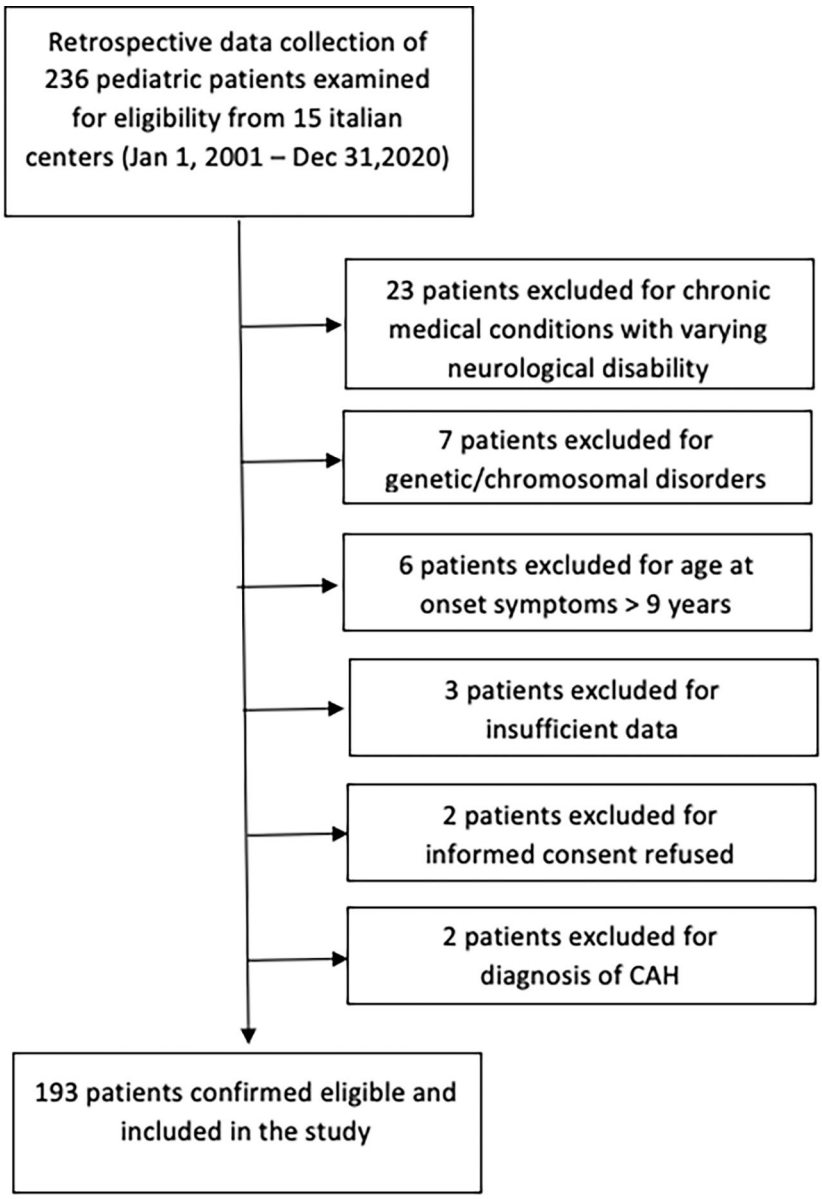

Figure 1. Design of the study and overview of recruitment of male patients with CPP.

for trend was used to compare numbers and incidence between groups categorized by years.

A probability value less than 0.05 was considered statistically significant.

Ethical Approval

The study was promoted by the Italian Society of Pediatric Endocrinology and Diabetology and was approved by the ethics committee of the coordinating center of Bologna (No. 570/2020/Oss/AOUBo), and subsequently by the remaining centers. Informed consent was obtained from all participants included in the study.

Results

Figure 2 shows the frequency and the etiology of CPP according to the referral periods. The number of cases increased during the last 2 decades and most of these cases were found to be idiopathic. Considering the trend of observed and estimated change over time during the study period, the estimated percent change between the start and end time points was 30% (95CL, 2.9%-10%). The 95% CI shows that the percent change is not statistically significant (Supplementary Fig. S1) (30). An increase in CPP diagnoses was observed only in Group 1 patients with age at referral ≥ 7 years (2001–2005, 8.9%; 2006–2010, 20.9%; 2011–2015, 27.5%; 2016–2020, 30.5%). The frequency of diagnoses remained stable over time in all groups of patients with age at referral < 7 years and in patients in groups 2 and 3 with age at referral ≥ 7 years.

MRI Findings

Table 2 shows the distribution of MRI findings at diagnosis in the study population.

Normal MRI findings (Group 1) were found in 167/193 boys (86%). Mild anomalies evaluated as incidental findings

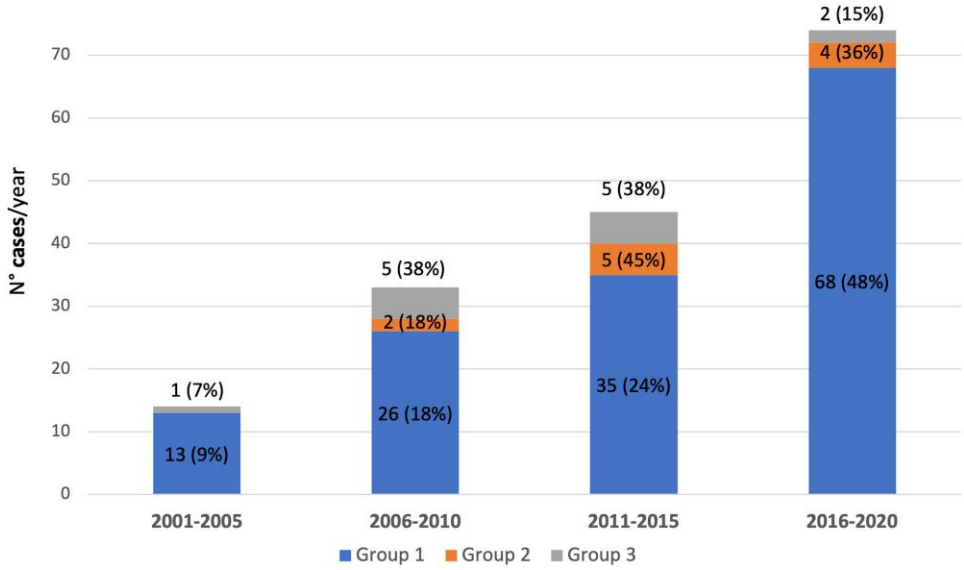

Figure 2. Frequency and etiology of CPP cases divided according to the referral periods: 2001–2005, 2006–2010, 2011–2015, and 2016–2020.

Table 2. MRI findings at diagnosis in males with CPP

Findings	Number of Patients
GROUP 1 (NORMAL)	167 (total)
No relevant findings	156
Pineal gland cyst	4
Variation of perivascular spaces	2
Cyst of septum pellucidum	2
Arnold Chiari I	1
Arachnoid cyst pericerebellar region	1
Lipoma of the lamina quadrigemina	1
GROUP 2 (INCIDENTAL FINDINGS)	15 (total)
Empty sella	6
Pituitary hypoplasia	2
Lipoma of interpeduncular cistern	2
MRI suggestive of microadenoma	2
Cyst of pituitary pars intermedia	1
Ectopic neurohypophysis	1
Cavum vergae cyst	1
GROUP 3 (PATHOLOGICAL)	11 (total)
Hypothalamic hamartoma	5
Optic glioma	3
Germinoma non-hCG secreting	1
Pilocytic astrocytoma	1
Craniopharyngioma	1

Abbreviations: CPP, central precocious puberty; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging.

(Group 2) were observed in 15/193 boys (8.3%). An organic form of CPP due to CNS pathological findings (Group 3) was seen in 11/193 boys (5.7%).

The MRI finding of pineal cyst was considered when there was a unilocular cyst within the pineal gland, mainly characterized by a signal intensity similar to cerebrospinal fluid with a thin, smooth rim of contrast enhancement, seen in most cases and calcifications, encountered in 25% of cases. Our cases were isolated, asymptomatic forms with a diameter less than or equal to 5 mm, which were considered normal variants and included in Group 1 of minor intracranial alterations not involving the hypothalamic-pituitary region (31).

The MRI finding of pituitary microadenoma was considered when there was an intraglandular focal area of delayed enhancement on the dynamic contrast-enhanced MR images during the injection of the contrast medium. Although the pathophysiological relationship with CPP is uncertain, after a multidisciplinary approach, the boys with pituitary microadenoma were included in Group 2 of the incidental findings in the hypothalamic-pituitary region. (20, 22)

Furthermore, the age at diagnosis and the hormonal data both in the subjects with pineal cyst and pituitary microadenoma were similar to those of the subjects in Group 1 with normal MRI findings (data not shown) and the neuroradiological follow-up showed absolute stability of the lesion in all cases.

In the Group 3 subjects, with the exclusion of cases of hypothalamic hamartoma, a histological diagnosis was made after biopsy or surgery and the diagnostic and therapeutic approach was also agreed upon with the pediatric oncologist.

All cases of hamartoma underwent serial MRI checks (2 to 4, at 12-18 months apart) and showed no tendency toward enlargement of the lesion.

Clinical and Endocrine Features at Diagnosis

Table 3 shows auxological data and hormonal results subdivided according to MRI findings at the time of diagnosis.

Groups 1 and 2 did not differ significantly in any of the parameters. In Group 3 the percentage of subjects with CA at diagnosis < 7 years was significantly higher than in the other 2 groups (5/11 cases in Group 3 vs 7/167 cases in Group 1 and 0/15 cases in Group 2; X^2 21.8, $P < .00001$). In subjects with hamartoma, this percentage reached 60% (3/5 cases).

Within Group 3, cases with hypothalamic hamartoma showed—in comparison with cases with other pathological findings—a lower age at diagnosis (6.8 ± 3.5 vs 8.05 ± 1.8 years) and a lower age at onset of symptoms (5.4 ± 3.5 vs 7.4 ± 1.6 years), while testicular volume (9.2 ± 3.3 vs 8.0 ± 4.6 mL) and

Table 3. Auxological data and hormonal results in males with CPP divided according to MRI findings at the time of diagnosis

Parameter	Group 1 N°167, mean ± SD (range)		Group 2 N° 15, mean ± SD (range)		Group 3 N° 11, mean ± SD (range)	
Age at diagnosis, years	N° 167	8.9 ± 1.1(4–11)	N° 15	9.4 ± 0.7 (8.4–10.6)	N° 11	7.5 ± 2.8 (1.1–10.4)*
Age at onset symptoms, years	160	8.2 ± 0.8	15	8.5 ± 0.4	11	6.5 ± 2.8*
Height SDS	158	0.8 ± 1.2	12	0.9 ± 1.4	10	1.3 ± 1.7
BMI SDS	158	0.7 ± 1.9	12	0.9 ± 0.8	10	1.3 ± 1.1
BA/CA ratio	153	1.2 ± 0.1	13	1.2 ± 0.2	9	1.4 ± 1.2 (0.9–2.8)
Testicular Volume, ml	167	6.9 ± 3.1	15	7.4 ± 3.4	11	8.6 ± 3.8
Basal LH, IU/L	167	1.5 ± 1.7	15	1.5 ± 1.4	11	3.7 ± 3.6*
Peak LH at GnRH test, IU/L	167	15.3 ± 0.3	15	16 ± 6.8	11	16.1 ± 6.4
Basal LH > 0.3 IU/L (%)	167	76.7%	15	91.6%	11	100%
Peak LH > 5 IU/L (%)	167	91.4%	15	100%	11	100%
Pubertal testosterone levels (%)	150	71.0%	12	75.0%	9	100%

*$P < .05$ vs groups 1 and 2.

baseline LH value were higher (5.8 ± 4.0 vs 1.5 ± 1.2). The difference was significant only for the LH value ($P < .05$).

The percentage of BMI at diagnosis greater than +2 SDS was significantly higher in the subjects of Group 3 than in the other groups (3/10 −30% vs 8/158 −5.1% and 0/15 cases; $P < .01$).

Overall, 27/193 boys were adopted at CA of 4.9 ± 2.1 years; 26/27 cases belonged to Group 1 and 1/27 to Group 3 (hypothalamic hamartoma). In some cases, there could be a potential discrepancy between declared and real chronological age.

Data regarding family history of PP were available in 129 subjects. A positive family history was found only in Group 1 (22/116 cases, equal to 19%). The retrospective nature of the study did not allow us to evaluate the maternal vs paternal inheritance nor to perform genetic analysis in this group of subjects.

Ten subjects with a mean CA at diagnosis of 9.3 ± 0.6 years (9 belonging to Group 1 and 1 to Group 3), with a mean BA of 9.0 ± 0.7 and a mean target height (TH) of 172.6 ± 3.2 cm, did not start the therapy by the will of the families and/or the child. The case belonging to Group 3 with a hypothalamic hamartoma was referred at a CA of 9 years, already with a testicular volume of 15 mL and a BA of 13.5 years. Therefore, in agreement with the family, it was decided not to start the treatment.

A total of 183/193 subjects started GnRH analogue therapy at a mean CA of 8.8 ± 1.2 years. In Group 3, the CA at the start of therapy was significantly lower than in the other groups (7.4 ± 6.5 years, $P < .05$). The mean duration of therapy was 2.7 ± 1.1 years. Monthly formulations were used in 97.2% and quarterly in 2.8% of cases. There were only 10 transient mild adverse events (headache, local pain).

Clinical and Endocrine Features During Follow-Up

Table 4 shows height SDS, BMI SDS, and testicular volume in the 3 groups at diagnosis, after 1 year of therapy, and at the end of therapy. The parameters at diagnosis in the subjects who did not complete follow-up and in the subjects that completed the follow-up were not significantly different (Supplementary Table S1) (30).

Figure 3 shows the final heights (FH) with the respective target heights (TH) in the 3 groups of patients undergoing GnRH analogue therapy and in 9 patients of the group in which the therapy was not started. The FH appeared to be in the range of the TH in all groups. None of the subjects who did not undergo therapy achieved a FH ≥ TH. The mean TH in the subjects with available FH and in the subjects without available FH was not significantly different (Supplementary Table S2) (30).

Discussion

In our large study population of otherwise normal healthy boys referred for PP signs, the percentage of organic forms due to causative brain lesions was 5.7%, one of the lowest reported in the literature. In accordance with all the previous studies, our patients with organic forms showed a significantly lower CA at diagnosis than those with idiopathic forms. Therefore, we observed an increase over time in the number of diagnoses of CPP, particularly with regard to the idiopathic forms.

Compared with historical studies (7, 8), more recent studies published in the last 2 decades already report a lower but more variable prevalence of organic forms (10-16). This variability is attributable to many factors, such as different study design, the low number of cases linked to the monocentric character, and, above all, the different criteria for selecting the patients and the methods of defining the incidental findings.

Our results were consistent with those obtained in a Chinese and a Korean study in which selection criteria very similar to ours were applied (12, 15). Wang et al (15) reported that 16.3% of their cases had sellar abnormalities, of which only 1 was pathogenic, and Yoon et al (12) reported that 7% of the CPP boys with MRI findings were all classifiable as incidental findings. Considering the same results obtained in populations of different ethnicities, we can probably rule out the influence of environmental factors and suggest that this picture should be typical of male CPP itself.

In agreement with Wang et al (15), syndromic forms or medical conditions with psychomotor delay, chromosomal abnormalities, and/or autism were also excluded; according to a recent study, they are more frequently associated with CPP and seem to be more commonly represented in males (32).

Table 4. Height, BMI, and testicular volume in the 3 groups of male patients with CPP at diagnosis, after 1 year of therapy, and at the end of therapy

	Height (SDS)						BMI (SDS)						Testicular volume (mL)					
	N°	At diagnosis	N°	After 1 yr of therapy	N°	End of therapy	N°	At diagnosis	N°	After 1 yr of therapy	N°	End of therapy	N°	At diagnosis	N°	After 1 yr of therapy	N°	End of therapy
Group 1	158	0.8 ± 1.2	126	0.8 ± 1.5	96	0.6 ± 1.5	158	0.7 ± 1.9	122	0.7 ± 1.7	95	0.6 ± 2.1	167	6.9 ± 3.1	133	6.1 ± 1.4	100	6.8 ± 3.5
Group 2	12	0.9 ± 1.2	8	1 ± 0.9	6	1 ± 0.6	12	0.9 ± 0.8	8	1.1 ± 1.1	6	0.7 ± 1.1	15	7.4 ± 3.4	8	8.3 ± 1.4	6	9.1 ± 2.5
Group 3	10	1.3 ± 1.7	6	1.2 ± 1.3	4	1.3 ± 0.3	10	1.3 ± 1.1	6	1.5 ± 0.9	4	1.8 ± 0.5	11	8.6 ± 3.8	6	8.1 ± 9.2	4	9.5 ± 5.7

In other studies (9, 10, 13, 14), the enrollment of patients already being followed for CNS lesions and/or syndromes such as neurofibromatosis typically associated with CPP introduces an evident selection bias by increasing the overall number of organic forms with CNS abnormalities.

The spectrum of MR lesions reported in the literature is wide and their classification into CNS abnormalities related to CPP, incidental findings or normal variants is uncertain (3, 11, 12, 14, 15, 20, 22, 33-35). In particular, the clinical significance of pituitary microadenoma appears controversial. In fact, considering that it is a histological diagnosis, its relationship with the MR image may be uncertain. Our inclusion of pituitary microadenoma in the group of incidental findings took into account the similarity of clinical and hormonal behavior to that of subjects with normal MRI findings and neuroradiological follow-up. Its inclusion is also in agreement with the conclusions of recent studies on pediatric populations selected with criteria similar to ours (20, 23). As regards the isolated and asymptomatic forms of pineal cysts, these are included by some authors in the normal variants (20, 34) and by others in the incidental findings (22, 29). According to large MR studies the reported prevalence in the population of normal young adults is 2% to 2.5%, similar to that found in our study population (31). Empty sella is classified as incidental findings in all recent studies concerning pediatric patients with CPP (20, 23, 32). Its reported prevalence in the general population is between 8% and 35%, while among adults, the frequency of empty sella found during routine autopsy varies between 5.5% and 12% (22). Finally, both pineal cyst and empty sella have been found in other pediatric conditions (ie, idiopathic short stature) suggesting that they are not specific for CPP (29, 36)

In accordance with all the previous studies, our patients with CNS pathological findings show a significantly lower CA at diagnosis than those with idiopathic forms. In studies that do not use our selection criteria, it is hypothesized that this aspect depends on the follow-up of patients already followed for syndromic forms of CPP (8-11). The presence of similar results in our study and other studies that use the same selection criteria seems to demonstrate that the phenomenon is an intrinsic characteristic of organic forms with associated CNS abnormalities. Unfortunately, from a diagnostic point of view, this parameter does not show a sensitivity of 100%, and 6/11 of our cases with causative brain lesions showed a CA at diagnosis greater than 7 years. Therefore, in the current state of knowledge, while emphasizing the importance of early CA at diagnosis as a discriminating criterion for performing an MRI, it cannot be applied to all cases and thus limits the number of investigations to be performed in male patients with CPP.

The increase over time in the number of diagnoses of CPP, with particular regard to the idiopathic forms, is a finding common to many studies (6, 11-15). In particular, in the Danish study that took into consideration the data from a population registry, a 15-fold increase in CPP incidence in boys with Danish origin (from 0.1 per 10 000 to 2.1 per 10 000) was reported (6) Among the possible influencing factors, better awareness of CPP among local pediatricians, better access to specialized care, and/or parents' increased knowledge obtained through media are taken into consideration from time to time. The increase over time found in our study only in patients with idiopathic "early" CPP with age at referral ≥ 7 years could lead us to hypothesize the influence of a better

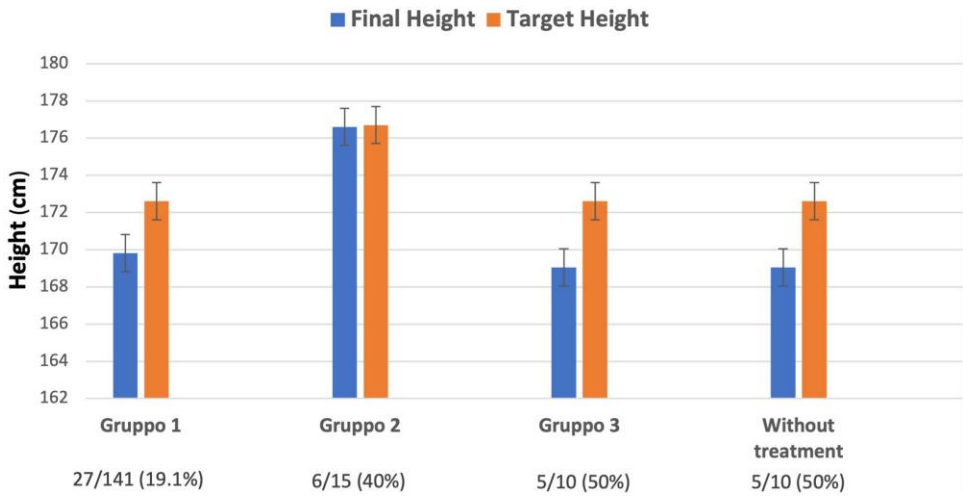

Figure 3. Final heights and target heights in the 3 groups of subjects diagnosed with CPP who underwent GnRH analogue therapy and in a group of subjects diagnosed with CPP who did not start therapy.

awareness among the local pediatricians of these less severe forms of CPP. However, only in an American study is the comparison with a critical potential confounder reported, that is, the overall patient volume which increased in the same referral periods. Therefore, the authors conclude that the increase is only apparent and not real (13). Our data on the trend of observed and estimated change over time appear to be in line with the conclusions of this study.

Other factors, such as the effects of endocrine-disruptor chemicals, improved nutritional supplements, and higher adiposity, are also hypothesized to explain the increase in diagnoses. The Copenhagen Puberty Study, in a population of 1528 Danish boys aged 5.8 to 19.9 years, reported the effect of increased adiposity on the earlier onset of puberty (19). Other studies report a higher BMI in males with idiopathic forms of CPP (11, 14, 15). The results of our study were consistent with the results of Topor et al (13) and do not seem to confirm these data. In fact, both at diagnosis and during follow-up in Groups 1 and 2, most patients show BMI values within +2 SD. Only in subjects with organic forms, we observed higher average BMI values, which could, however, be related to the organic pathology itself and might not represent a characteristic of CPP in males.

The presence of a positive family history of PP only in boys with idiopathic CPP confirms the influence of genetic factors reported in various recent studies, especially in boys with CPP (3, 37-40). The search for genetic variants is beyond the scope of the current study, but our results confirm the usefulness of performing a genetic analysis before proceeding with further diagnostic tests (3). In fact, Bessa et al demonstrated a high frequency of MKRN3 mutations in a cohort of 20 boys with CPP, previously classified as idiopathic, suggesting the importance of genetic analysis in this group (38).

Our results regarding follow-up and therapeutic outcome have limited value, in particular because prolonged follow-up is available in few subjects, especially in groups 2 and 3. On the other hand, there is a scarce amount of data in the literature regarding a cohort of boys with CPP selected with homogeneous criteria similar to ours. In accordance with the results of the study by Mul et al (41), our patients reach, on average, a FH that is not significantly different from the TH, but the results of the 2 studies are only partially comparable due to their different study design and enrollment of patients. The strengths of our study are its considerable size—the largest national series of Italian boys with CPP examined in the last 2 decades—and the homogeneous diagnostic approach used in the pediatric endocrinology centers participating in the study.

The limitations are the retrospective nature of the study, the unavailability of the total number of boys referred and evaluated over the same period, including those who did not meet criteria for CPP, and the non-centralization of the MRI and BA reports. Radiological investigations were in all cases evaluated only by expert pediatric personnel.

In conclusion, in the data we obtained from a large nationwide cohort of otherwise normal healthy boys referred for PP signs, the percentage of organic forms due to causative brain lesions is lower compared with previous literature data. Based on current knowledge, it is still not possible to have a safety marker predictive of organic forms of CPP that would establish a limit for MRI examination in the idiopathic ones.

Disclosures

The authors have nothing to disclose.

Data Availability

All data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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