Review

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Prevalence of cranial MRI findings in girls with central precocious puberty: a systematic review and meta-analysis

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Abstract

Background: Some pediatric endocrinologists recommend that girls with central precocious puberty (CPP) have cranial magnetic resonance imaging (MRI) performed only if they are younger than 6 years of age. However, no practice guidelines exist. The objective of this review was to assess the frequency of intracranial lesions in girls with CPP.

Content: We searched six electronic databases (PubMed, Cochrane, Web of Science, SCOPUS, ProQuest, and Dissertation & Theses) from 1990 through December 2015. We included studies on girls with CPP and MRI data. Case reports, case series, studies from the same author/group with the same patient population, and studies with conditions predisposing to CPP were excluded. Two physicians independently reviewed the search results and extracted data. A random-effects model was used to obtain pooled prevalence of positive MRI's across studies. Heterogeneity among studies was evaluated with the Q-statistic. Publication bias was assessed with funnel plots and Egger's test. Pooled prevalence was computed by age group. A linear regression assessed the relationship between intracranial lesion prevalence and healthcare availability. We included 15 studies with a total of 1853 girls <8 year old evaluated for CPP.

Summary: The pooled prevalence from all studies was 0.09 [95% confidence interval (CI) 0.06–0.12]. There was a significant heterogeneity, indicating the appropriateness of a random effects model in computing pooled prevalence. In

the few studies stratified by age group, pooled prevalence was 25% in girls <6 years vs. 3% in girls 6–8 of age.

Outlook: Our results support that the benefit of routine MRIs in girls with CPP older than 6 years of age without any neurological concerns is not clear-cut.

Keywords: central precocious puberty (CPP) and magnetic resonance imaging (MRI); CPP and neuroimaging; precocious puberty work-up; precocious puberty and neuroimaging.

Introduction

Precocious puberty (PP) has been defined by the development of secondary sexual characteristics before the age of 9 years in boys and 8 years in girls [1–6]. If PP occurs due to the activation of the hypothalamic-pituitary gonadal axis, it is termed as central precocious puberty (CPP). CPP can be idiopathic due to genetic mutations or is associated with central nervous system (CNS) abnormalities, such as hamartomas or brain tumors. CPP can be treated with gonadotropin (GnRH) agonists in order to prevent short final adult height and psychological effects on the child [1, 6].

The definition of PP is based on studies from the 1960s [2]. The age at which girls are considered to have PP has been questioned, as several studies have shown that normal girls have been entering puberty earlier for the past two decades [7–14]. In 1997, a large epidemiologic US study with >17,000 girls indicated that breast and pubic hair development were occurring significantly earlier than in the past [15]. Following this study, a letter published in the journal *Lancet* by a group of pediatric endocrinologists proposed revising the guidelines for the age at which PP should be investigated [16]. The Pediatric Endocrine Society issued recommendations in 1999 for PP, lowering the age threshold from 8 to 7 years for White girls and to 6 years for Black girls [17]. However, 8 years continues to be a commonly-used threshold for the definition of PP [18–23].

Once CPP is confirmed with laboratory testing, CNS imaging is considered to rule out the presence of CNS abnormalities. The prevalence of CNS abnormalities in boys is

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reported to be as high as 40–75% [20, 24]. Therefore, it is recommended that all boys with PP have brain magnetic resonance imaging (MRI). However, the prevalence of CNS abnormalities in girls is much lower, varying between 0% and 27% among different studies and decreases with increasing age [21–23]. Because some of these prevalence rates include incidental lesions, the prevalence of brain tumors and other progressive pathologies is even smaller [23]. Based on these data and in light of discussions regarding the decreasing age of normal puberty, it is hard to justify routine brain MRI in all girls presenting with puberty before age 8. It has been suggested that girls with CPP should have a brain MRI performed routinely only if they are younger than 6 years of age [1]. However, cranial MRI continues to be performed routinely in many centers for all the girls presenting with breast development before the age of 8 due to the risk of finding an occult intracranial lesion.

Brain MRIs are expensive and potentially harmful due to administration of contrast agents as well as IV sedation which is often needed in young children [25]. Other considerations are increased anxiety in children, and in parents, and the possibility of finding an incidental lesion which is not related to CPP but increases the need for follow-up imaging studies and follow-up visits, as well as healthcare cost.

Objective of the study

The aim of this study was to perform a meta-analysis of the prevalence of intracranial lesions detected with brain MRI in girls with CPP. The secondary aim was to stratify this data by age groups to better understand the risk of finding an intracranial lesion in girls with CPP who are older than 6 years of age. We also tested the relationship between the availability of healthcare measured by physician density according to geographic locale and the risk of finding of an intracranial lesion in girls presenting with CPP.

Materials and methods

The prevalence of intracranial lesions detected with cranial MRI in girls with CPP

Definition of central precocious puberty

PP secondary to the activation of the hypothalamic-pituitary-gonadal axis is termed as CPP. Several hormone measurements have been used to confirm the diagnosis of CPP. The use of a GnRH stimulation test is the most common

confirmatory test and a stimulated luteinizing hormone (LH) > 5 or LH/follicle-stimulating hormone (FSH) > 0.66 is considered pubertal by many endocrinologists [4, 26]. With the increasing sensitivity of LH assay, a basal LH level is now used in many centers. An LH level > 0.2–0.3 (depending on the assay) is consistent with CPP [27, 28].

Search strategy for systematic review

In December 2015, PubMed, Cochrane, Web of Science, SCOPUS, ProQuest, and Dissertation and Theses were searched in cooperation with a specialized reference librarian to identify potentially relevant articles (Supplemental Material, Appendix 1). References of key articles were also screened to identify potentially eligible articles. A final literature review was conducted in February 2017 to include the most recent publications but no additional studies meeting our criteria were found.

Eligibility criteria

We included original studies with a study population including girls diagnosed with CPP using the definition of PP as development of secondary sexual characteristics before age 8 which included MRI data, regardless of the original question of the study. Studies published after 1990 were evaluated for inclusion because MRI became the preferred method of imaging to screen CNS lesions in the early 1990s. Inclusion of articles was not restricted to those written in English. A few of the included studies either did not specify which girls had MRI vs. computed tomography (CT), or used CT for selected girls in whom MRI was contraindicated. All case reports and case series, studies from the same author/group which might potentially include the same patient population, and studies with patients who were previously known to have CNS lesions or conditions known to increase the risk of CPP were excluded. Articles with a subset of patients meeting the criteria were included if data were extractable.

Data screening and extraction

After a de-duplication process (Supplemental Material, Appendix 2), all identified articles were first screened by title only to exclude clearly irrelevant articles [29]. The remaining articles were then screened by abstracts and full texts as needed. Finally, selected article's full texts were reviewed in detail before inclusion in the meta-analysis (Table 1). Two different authors (SO, HA) performed

Table 1: Study characteristics.

Author	Year	Country	Diagnostic criteria	Imaging modality	Years of enrollment	n	Group
Kao	1992	US	Not specified	MRI	1987–1991	14	Rad
Bridges	1994	UK	GnRH stim test	MRI	1975–1990	85	Endo
Cisternino	2000	Italy	GnRH stim test	CT or MRI	1988–1988	274	Endo
Bajpai	2002	India	Baseline LH, FSH/GnRH stim test	MRI ^a	1990–2000	77	Endo
Ng	2003	UK	GnRH stim test	MRI	1990–2001	67	Endo
Chalumea	2003	France ^b	^b	CT or MRI ^c	^b	443	Endo
Grunt	2004	US	Baseline LH, FSH	MRI	1987–1996	75	Endo & Rad
Lee	2009	Taiwan	GnRH stim test	MRI	1985–2007	179	Endo
Jaruratanasirikul	2010	Taiwan	Baseline LH, FSH	MRI	1995–2009	68	Endo
Jakubowska	2011	Poland	GnRH stim test	MRI	1999–2009	36	Endo & Rad
Mogensen	2012	Denmark	GnRH stim test	MRI	1993–2009	104	Endo & Rad
Shiva	2012	Iran	Baseline LH, FSH	MRI	2007–2009	38	Endo
Atta	2013	Pakistan	GnRH stim test	MRI	2009–2011	26	Endo
Pedicelli	2014	Italy	GnRH stim test	MRI	1990–2012	167	Endo
Kim	2016	Korea	Not specified	MRI	2005–2015	200	Endo

^aFive patients had CT. ^bMulticenter study, varies based on the center. ^cThirty-nine patients did not have imaging but were followed for >2 years and did not have any health concerns. Endo, endocrinology; Rad, radiology.

both the screening of the title, abstracts and the review in detail. Cross-checking was conducted for consistency. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for reporting [30].

The following data were extracted from selected studies using a pre-designed extraction form: (1) general information, including authors, publication year, country; (2) total number of girls who had an MRI during evaluation of CPP; (3) total number of girls found to have CNS lesions; (4) age range of patients; (5) characteristics of reported brain lesions. We attempted to contact authors of the articles included in the meta-analysis via e-mail to gather unpublished data, especially regarding the age information in order to analyze data based on age groups of <6 and 6–8, and <7 and 7–8.

A detailed review of these articles revealed that certain lesions were classified as incidental by some groups while classified as pathologic by others. In order to sort this out, all brain lesions reported in these 15 articles were listed and re-grouped. A Rathke's cleft cyst, empty sella, pituitary microadenoma and isolated stalk thickening were the lesions for which there was no clear consensus on the relationship with CPP [31–33]. We re-ran the meta-analysis after placing these lesions in “questionable relationship with CPP” category (Table 2).

Bias assessment

A visual inspection of funnel plots was supplemented with Egger's test of symmetry to assess bias.

Statistical analysis

All analyses were performed using the METAN procedure in STATA [34]. The prevalence of positive MRIs and an exact binomial 95% confidence interval [35] was computed for each study. A composite or pooled estimate of the prevalence for all studies combined was computed and it represents the weighted average of the prevalence from individual studies, weighted by the sample size and variability of each study. Studies with greater sample sizes contributed more to the estimate than smaller studies. The precision of the pooled estimate (i.e. a 95% confidence interval) was a function also, in part, of the population size of each study.

In the absence of any consensus in the literature for the prevalence of positive MRI findings in these children (which is in fact the motivation for our meta-analysis), we used the standard null hypothesis that the prevalence is zero. Rejecting this hypothesis would lead to the conclusion that MRI's do yield positive findings in a portion of children. We used the confidence interval of the pooled proportion as a test of this hypothesis. If the lower limit of the 95% confidence interval is above zero, we will conclude that it is statistically significant.

The Q-statistic was used to test for heterogeneity among studies in prevalence and sample size [36]. In the presence of significant heterogeneity, a random effects model [37] was used with a continuity correction to handle zero proportions (prevalence). A random effects model assumes that studies are sampled from a larger population or different populations with different prevalences. The variance of the pooled prevalence under this model is a function of both within and among-study variability,

Table 2: Characteristics of MRI findings in the study population.

Pathological findings (n = 142)	Questionable relationship with CPP (n = 42)	Incidental findings (n = 50)
Agenesis of corpus callosum (1) Arachnoid cyst (12) Astrocytoma (15) Craniopharyngeoma (4) Glioma (4) Hypothalamic teratoma (1) Hypothalamic tumor (1) Hypothalamic hamartoma (68) Hydrocephalus (10) Meningitis (1) Neurofibromatosis (1) Neurotuberculosis (4) Periventricular leukomalacia (1) Intracranial hypertension (1) Pontine tumor (1) Pinealoma (1) Pituitary hypoplasia (6) Suprasellar tumor (1) History of radiotherapy (1) 4th ventricular tumor (1) Unknown (7)	Empty Sella (13) Pituitary microadenoma (22) Rathke's cleft cyst (4) Isolated stalk thickening (3)	Absence of bright spot (2) Arnold Chiari Malformation (2) Cavum vergae cyst (1) Choroid plexus cyst (2) Cyst of pars intermedia (4) Dilated Virchow spaces (1) Enlarged cisterna magna (1) Gliosis (2) Hypomyelination in trigonal region (1) Increase in pituitary volume (21) Lipoma of the lamina quadrigemina (1) Pineal cyst (4) Pituitary stalk deviation (5) Pseudocyst of the sphenoid bone (1) Spinal fluid-like area in the posterior wall (1) Vascular malformation (1)

Incidental lesions from Mogensen et al.'s paper was not extractable and was not included in this table. Tumors are in bold.

resulting in a larger (more conservative) standard error and a wider confidence interval for the pooled prevalence than under a fixed effects model. The confidence interval is used to determine statistical significance, i.e. if the 95% confidence interval for the pooled estimate of prevalence is above 0, we will conclude that the estimated percentage of positive findings was significantly more than zero.

Sub-group analysis of the prevalence of CNS lesions in different age groups

The pooled prevalence of intracranial lesions stratified by age groups <6 vs. 6–8, and <7 vs. 7–8 was reported descriptively, due to the small number of studies where such stratification could be performed.

Additionally, the percentage of tumors was calculated to understand the incidence of lesions that will require intervention when found during MRI imaging of the brain in girls with CPP.

Relationship between the prevalence of CNS lesions and availability of healthcare

Data describing physician density (MD/1000 population) was gathered from a World Health Organization (WHO)

report conducted in 2008–2014 [38]. We used a linear regression to assess the relationship between physician density and the prevalence of CNS abnormalities in girls presented with CPP.

This research is not related to either human or animal use.

Results

The prevalence of intracranial lesions detected with cranial MRIs in girls with CPP

Search results

Our initial literature search in December 2015 identified 2818 articles, and 1392 unique articles remained after de-duplication. We excluded 1264 articles after screening by titles including case reports/series, articles studied patient population with underlying conditions known to predispose to PP, articles which studied only boys and those with clearly irrelevant topics leaving 128 articles. Two additional articles were identified via screening citation lists of selected articles. Among these, 130 articles, 96 articles were excluded after screening by abstracts and full texts as needed due to not having any imaging data

Figure 1: A flow diagram illustrating the process by which articles were included or excluded in the study.

($n=94$), reporting data only with CT imaging ($n=1$) and boys only ($n=1$). We reviewed a total of 34 articles full-text for inclusion. Fifteen articles were included in this meta-analysis. No further articles were identified by final literature review in March 2017 (Figure 1).

Study characteristics

The study characteristics are shown in Table 1. Included studies were published between 1990 and 2015. There were data from a total of 1853 patients extracted from 15 articles.

Meta-analysis

There was a significant heterogeneity (variability) in the prevalence of positive MRI and sample size among the studies (Q -statistic = 57.0, $df=14$, $p<0.01$). Therefore, a random effects model was used to pool the prevalence estimates. The estimated proportion of positive MRIs across all studies was 0.09 (95% CI 0.06–0.12), which was statistically significant at the 5% level (Figure 2).

When all findings were re-examined and the lesions with questionable relationship with CPP excluded, there was still significant heterogeneity in the prevalence

Figure 2: Forest plot of the proportion of the girls <8 with positive MRI findings.

among the studies ($\chi^2 = 60.7$, $df = 14$, $p < 0.01$). The pooled random-effects estimate for the proportion of positive MRI's decreased to 0.07 (95% CI 0.05–0.10). This was significantly greater than zero ($z = 8.4$, $p < 0.01$).

Risk of bias

Egger's test showed no significant asymmetry or presence of small-study bias when all intracranial lesions were included in the analysis and after intracranial lesions with questionable relationships with CPP were excluded ($p = 0.37$ and $p = 0.15$, respectively).

Funnel plots are graphs used to assess the presence of bias in the selection of studies for publication [39]. The effect size (in this case, proportion of positive MRI's) for each study is plotted on the x-axis and its sample size on the y-axis. If there is no publication bias, and all studies came from the same population with a common effect size, effect size is solely a function of sample size and large studies should be more likely to report large effect sizes (producing significant results) than smaller studies.

This results in an inverted funnel-shaped plot (with the point at the top) symmetrical about the mean effect size. The absence of this shape signifies that effect sizes are independent of sample size, which is evidence of publication bias because publication bias will inflate the number of large effect sizes among smaller studies.

The funnel plot conforms to the basic inverted funnel shape, indicating the absence of bias, with the exception of missing points in the lower left. This indicates a potential bias for smaller studies with small prevalence not included, leading to a slight over-estimation of pooled prevalence. The bias introduced by this would be small, as small studies contribute little weight to the pooled estimate (Supplemental Material, Appendix 3).

Sub-group analysis of the prevalence of intracranial lesions in different age groups

We were not able to obtain any unpublished data after making multiple attempts to reach to the authors. The age data were extractable from only five of the articles. When data

Table 3: Subgroup analysis.

Author	<6 years old, n	Positive MRI, n	%	[95% Confidence interval]	6–8 years old, n	Positive MRI, n	%	[95% Confidence interval]
Bajpai	30	9	0.3	0.15–0.49	47	7	0.15	0.06–0.28
Chalumea	108	29	0.27	0.19–0.36	335	6	0.02	0.01–0.04
Pedicelli	35	6	0.17	0.07–0.34	132	0	0	0–0.03
Overall			0.25	0.19–0.32			0.03	0.00–0.1
	<7 years old, n				7–8 years old, n			
Cisternino	125	14	0.11	0.06–0.18	149	12	0.08	0.0–0.14
Chalumea	202	31	0.15	0.11–0.21	241	4	0.02	0.00–0.04
Grunt	42	7	0.17	0.07–0.31	33	2	0.06	0.01–0.2
Pedicelli	103	6	0.06	0.02–0.12	64	0	0	0.00–0.06
Overall			0.12	0.07–0.17			0.03	0.00–0.08

were divided based on <6 and 6–8 age groups, there were 173 girls who were <6 years old, and 514 girls who were 6–8 years of age. The pooled prevalence of intracranial lesions was 0.25 (0.19–0.32) in girls <6 years old, and 0.03 (0.03–0.1) in girls 6–8 years old. When data were stratified into <7 and 7–8 age groups, there was a total of 472 girls <7 years old and 487 girls 7–8 years old. The pooled prevalence of intracranial lesions was 12% (0.07–0.17) in girls <7 years old and 3% (0.0–0.8) in girls 7–8 years old (Table 3).

In this patient pool of 1853 patients, the incidence of tumors was found to be 1.6%. These tumors were astrocytomas, gliomas, craniopharyngiomas, suprasellar tumors, hypothalamic tumors, pontine tumor, pinealoma and 4th ventricular tumor (Table 2).

Relationship between the prevalence of CNS lesions and availability of healthcare

We hypothesized that patients in countries with limited access to healthcare would be less likely to seek medical care for signs of early puberty unless they also experienced other health concerns such as headache, weakness or visual abnormalities. Therefore, when they seek medical care with early signs of puberty, it would be more likely that they would have an intracranial lesion compared to their counterparts in developed countries. This might also explain some of the heterogeneity in our study. We found a non-significant trend of highly variable data points with this direction ($R^2 = 0.17$, $p = 0.12$) (Figure 3).

*WHO Global Health Observatory (GHO) data/Country statistics [38].

Figure 3: Physician density vs. prevalence of intracranial lesions.

Discussion

We performed a systematic review and meta-analysis of the prevalence of patients who were found to have intracranial lesions using MRI during the work-up for PP. The overall prevalence of CNS lesions was found to be 9% (95% CI 0.06–0.12) when all the patients less than 8 years old with CPP were included in the analysis. This decreased to 7% when data were re-analyzed after examining all the brain lesions and eliminating those whose relationships with CPP were not clear. The biggest single group of abnormal findings was the hypothalamic hamartoma. Studies have found that hypothalamic hamartoma is almost exclusively found in girls with CPP diagnosed at less than 6 years of age. Moreover, finding a hamartoma supports the diagnosis of CPP but would not require any treatment other than standard GnRH agonist therapy. The incidence of tumors which would require intervention was found to be 1.6%.

A subgroup analysis revealed a higher overall prevalence of intracranial lesions in girls who were <6 years of age as compared to 6–8 years of age. A similar trend continued to be observed in <7 vs. 7–8 years old group as seen in previous studies [18, 23]. We found a slight non-significant trend toward higher prevalence of intracranial lesions in girls with CPP in countries with limited access to healthcare, which might be explained by delayed medical evaluation in the setting of limited availability.

The age cut-off for female PP derives from studies published in 1960s and data based on the children evaluated prior to that [2]. There has been a great controversy over the past three decades regarding the trend of decreasing age of puberty. Many studies, most of which were included in this meta-analysis, show that the incidence of brain lesions in girls older than 6 years of age with CPP is low [17, 18, 40] and authors suggest performing cranial MRI in selected cases only. On the other hand, there are many other studies claiming the opposite [41, 42].

Following the publication of the US study in 1999 proposing a cut-off of 7 years for evaluation of PP [17], Chalumeau et al. examined whether this approach would miss important CNS lesions. In 197 girls with CPP, 11 (6%) had an intracranial lesion. The prevalence of intracranial lesions was 19% in girls with onset under age 6, and 2% in patients between the ages of 6 and 8. Based on the data from this study, the authors developed an algorithm to identify girls at a lower risk and reported that age <6 years or estradiol >45th percentile identified all girls with organic brain lesions and they applied this algorithm to a larger group of patients from multiple centers in Europe [43]. In this larger population, they found a very similar prevalence of organic brain lesions. Only 2% of girls with

CPP had an organic lesion in the age group 6–8, but for the group with puberty onset before age 6, the prevalence was 29%. In 2000, Cisternino et al. reported a rate of 8.7% in 274 girls, with a neoplasm rate of 2% [44].

In 2006, Stanhope et al. published an editorial and stated that it would be unfortunate to miss the diagnosis of early and treatable intracranial tumors and he suggested that newer age limits for the diagnosis of PP should be used with caution. In 2007, a consensus paper on the use of GnRH analogs in children was published in *Pediatrics*, stating that the likelihood of finding an organic brain lesion decreases by age and stated “Girls with CPP at <6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6 and 8 years of age require head MRI. Girls with neurologic findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination”.

Our study supports the decreasing trend of the prevalence of intracranial lesions by age and the idea that there are few girls with CPP older than 6 years of age with intracranial lesions. We agree with Kaplowitz who recently published a review article describing the low prevalence of intracranial lesions requiring intervention in the 6–8 year age group. He suggested that cranial MRI should be performed only in selected cases in this age group while notifying parents of the low likelihood of finding an intracranial tumor [45].

To the best of our knowledge, this is the first meta-analysis providing an overall estimate of the prevalence of intracranial lesions in girls with CPP. These data are important to describe the overall prevalence especially in the setting of a wide range of estimates. There is a high heterogeneity among studies possibly due to the wide age range, differences in quality of imaging techniques and variability between the features of patients included from each center. Also, the variability of cut-off for baseline LH level or LH/FSH ratio following a GnRH stimulation test differs in different centers, as well as assay quality. Even though we tried to ensure that all patients were diagnosed with CPP based on the same criteria, it was not possible to guarantee a homogenous group of patients. It was unfortunate not to be able to gather further data to analyze and understand better the differences between different age groups. One of the studies was conducted by a radiology group, which is subject to selection bias.

MRIs are expensive. A cranial MRI typically costs about \$1000–\$5000, depending on the patient’s geographical location. The cost is not limited to the procedure but also includes the charge for the neuroradiologist interpreting the study, the charge for sedation when needed, and the charge due to follow-up MRIs and subspecialty visits in

the case of an incidental finding. MRIs do not expose the child to ionizing radiation; however, there is a potential harm from the radiocontrast agents used during MRI imaging. The US Food and Drug Administration (FDA) is currently investigating the risk of brain deposits caused by gadolinium-based contrast agents used for MRI. They published a statement in 2015 and urged all the health-care professionals' to re-assess the need for MRI [19]. The concerns for unnecessary MRIs are not limited to long-term side effects and cost, but include parental and patient anxiety. When an incidental finding is detected, there is a need for additional MRIs and sub-specialist visits to monitor incidental lesions which increase the degree of patient and parental anxiety, also resulting in missed school and work days.

There is little debate that all girls with CPP with onset before age 6, and any girl with clinical findings indicating the possibility of an intracranial lesion need brain imaging. However, a majority of girls referred to pediatric endocrinologists and diagnosed with CPP are in the 6–8 age group and have no CNS-related symptoms. Our study showed the decreasing trend of the prevalence of intracranial lesions by age and supports the idea that there are few girls who are older than 6 years of age will be found to have an intracranial lesion.

Conclusions

Our results support that the benefit of routine MRIs in girls with CPP older than 6 years of age without any neurological concerns is not clear-cut. Intracranial pathology requiring intervention is a rare finding in girls with CPP older than 6 years. We should balance the potential risks and cost of healthcare against the likelihood of detecting an intracranial lesion requiring intervention at an earlier age than it would otherwise present.

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References

1. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009;123:e752–62.
2. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.
3. Wheeler MD, Styne DM. Diagnosis and management of precocious puberty. *Pediatr Clin North Am* 1990;37:1255–69.
4. Brito VN, Latronico AC, Arnhold IJ, Mendonça BB. Update on the etiology, diagnosis and therapeutic management of sexual precocity. *Arq Bras Endocrinol Metab* 2008;52:18–31.
5. Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002;56:129–48.
6. Klein KO. Precocious puberty: who has it? Who should be treated? *J Clin Endocrinol Metab* 1999;84:411–4.
7. Sun SS, Schubert CM, Chumlea WC, Roche AF, Kulin HE, et al. National estimates of the timing of sexual maturation and racial differences among US children. *Pediatrics* 2002;110:911–91.
8. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen puberty study. *Pediatrics* 2009;123:e932–9.
9. Danubio ME, De Simone M, Vecchi F, Amicone E, Altobelli E, et al. Age at menarche and age of onset of pubertal characteristics in 6–14-year-old girls from the Province of L'Aquila (Abruzzo, Italy). *Am J Hum Biol* 2004;16:470–8.
10. Lindgren G. Pubertal stages 1980 of Stockholm school children. *Acta Paediatr* 1996;85:1365–7.
11. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, et al. Continuing positive secular growth change in The Netherlands 1955–1997. *Pediatr Res* 2000;47:316–23.
12. Huen KF, Leung SS, Lau JT, Cheung AY, Leung NK, et al. Secular trend in the sexual maturation of southern Chinese girls. *Acta Paediatr* 1997;86:1121–4.
13. Rosenfeld RL, Bachrach LK, Chernausk SD, Gertner JM, Gottschalk M, et al. Current age of onset of puberty. *Pediatrics* 2000;106:622–3.
14. Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE, Juul A. Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. *Pediatrics* 2005;116:1323–8.
15. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics* 1997;99:505–12.
16. Elders MJ, Scott CR, Frindik JP, Kemp SF. Clinical work-up for precocious puberty. *Lancet* 1997;350:457–8.
17. Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. *Pediatrics* 1999;104(Pt 1):936–41.

18. Pedicelli S, Alessio P, Scirè G, Cappa M, Cianfarani S. Routine screening by brain magnetic resonance imaging is not indicated in every girl with onset of puberty between the ages of 6 and 8 years. *J Clin Endocrinol Metab* 2014;99:4455–61.
19. Bizzarri C, Spadoni GL, Bottaro G, Montanari G, Giannone G, et al. The response to gonadotropin releasing hormone (GnRH) stimulation test does not predict the progression to true precocious puberty in girls with onset of premature thelarche in the first three years of life. *J Clin Endocrinol Metab* 2014;99:433–9.
20. DeSanctis V, Corrias A, Rizzo V, Bertelloni S, Urso L, et al. Etiology of central precocious puberty in males: the results of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab* 2000;13:687–93.
21. Atta I, Laghari TM, Khan YN, Lone SW, Ibrahim M, et al. Precocious puberty in children. *J Coll Physicians Surg Pak* 2015;25:124–8.
22. Bridges NA, Christopher JA, Hindmarsh PC, Brook CG. Sexual precocity: sex incidence and aetiology. *Arch Dis Child* 1994;70:116–8.
23. Chalumeau M, Chemaitilly W, Trivin C, Adan L, Breart G, et al. Central precocious puberty in girls: an evidence-based diagnosis tree to predict central nervous system abnormalities. *Pediatrics* 2002;109:61–7.
24. Choi KH, Chung SJ, Kang MJ, Yoon JY, Lee JE, et al. Boys with precocious or early puberty: incidence of pathological brain magnetic resonance imaging findings and factors related to newly developed brain lesions. *Ann Pediatr Endocrinol Metab* 2013;18:183–90.
25. FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) (Issued on 7-27-2015).
26. Oerter KE, Uriarte MM, Rose SR, Barnes KM, Cutler GB Jr. Gonadotropin secretory dynamics during puberty in normal girls and boys. *J Clin Endocrinol Metab* 1990;71:1251–8.
27. Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. *Pediatrics* 2009;123:e1059–63.
28. Neely EK, Wilson DM, Lee PA, Stene M, Hintz RL. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. *J Pediatr* 1995;127:47–52.
29. Mateen FJ, Oh J, Tergas AI, Bhayani NH, Kamdar BB. Titles versus titles and abstracts for initial screening of articles for systematic reviews. *Clinical Epidemiol* 2013;5:89–95.
30. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *J Am Med Assoc* 2015;313:1657–65.
31. Bosnjak J, Budisic M, Azman D, Strineka M, Crnjakovic M, et al. Pineal gland cysts-an overview. *Acta Clin Croat* 2009;48:355–8.
32. Motta S, Decimi V, Pincelli AI, Fraschini D, Grimaldi M, et al. Precocious puberty and empty sella syndrome in a girl cured of acute lymphoblastic leukemia. *J Pediatr Endocrinol Metab* 2011;24:1067–9.
33. Acharya SV, Gopal RA, Menon PS, Bandgar TR, Shah NS. Precocious puberty due to rathke cleft cyst in a child. *Endocr Pract* 2009;15:134–7.
34. STATA/MP (Version 14.0 for Windows). College Station, TX, USA: StataCorp.
35. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;17:857–72. Cochran 1954.
36. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
37. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
38. World Health Organization. WHO information for physician density. Available at: <http://www.who.int/gho/countries/en/>.
39. Light RJ, Pillemer DB. Summing up: the science of reviewing research. Cambridge, MA: Harvard University Press, 1984:x+191pp.
40. de Muinich Keizer SM, Mul D. Trends in pubertal development in Europe. *Hum Reprod Update* 2001;7:287–91.
41. Ng SM, Kumar Y, Cody D, Smith CS, Didi M. Cranial MRI scans are indicated in all girls with central precocious puberty. *Arch Dis Child* 2003;88:414–8; discussion 414–8.
42. Mogensen SS, Aksglaede L, Mouritsen A, Sørensen K, Main KM, et al. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. *PLoS One* 2012;7:e29829.
43. Chalumeau M, Hadjiathanasiou CG, Ng SM, Cassio A, Mul D, et al. Selecting girls with precocious puberty for brain imaging: validation of European evidence-based diagnosis rule. *J Pediatr* 2003;143:445–50.
44. Cisternino M, Arrigo T, Pasquino AM, Tinelli C, Antoniazzi F, et al. Etiology and age incidence of precocious puberty in girls: a multicentric study. *J Pediatr Endocrinol Metab* 2000;13:695–701.
45. Kaplowitz PB. Do 6–8 year old girls with central precocious puberty need routine brain imaging? *Int J Pediatr Endocrinol* 2016;2016:9.

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