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Radiology Approach of Precocious Puberty: A Review on Different Available Imaging Modalities

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Abstract

Diagnosis and management of precocious puberty are challenging. The two main classes of precocious puberty are Central Precocious Puberty (CPP) and Peripheral Precocious Puberty (PPP), which should be differentiated from normal pubertal variants. Radiology plays an essential role in the diagnosis and management of precocious puberty. We reviewed available studies in the case of different radiology modalities to find the role of these methods in precocious puberty assessment. We found that bone age assessment can be the initial step in the diagnosis of precocious puberty; however, a normal bone age cannot rule out precocious puberty in a deterministic manner. The use of pelvic ultrasound can further help the approach to precocious puberty. Moreover, suspected female and male cases of congenital adrenal hyperplasia should be evaluated with adrenal sonography. Testis and mammary ultrasound assessments are usually conducted in asymmetrical changes. Still, breast ultrasound staging may be helpful in even the diagnosis of precocious puberty. Brain magnetic resonance imaging is another modality used in CPP cases. The role of artificial intelligence is a neglected part, which is partly covered by BoneXpert software. Future studies should focus on scoring methods based on bone age as well as breast and pelvic (ovary and uterus) ultrasound assessments in diagnosing female precocious puberty cases and distinguishing the patients from normal pubertal variants.

Key Words: Bone age, Boy, Girl, Imaging, Precocious puberty, Radiology.

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1- INTRODUCTION

Puberty is termed as the condition of becoming mature. The hallmark of the condition is changes in sex hormones and the development of secondary sexual characteristics. It can be pointed out that the changes during puberty are not confined to gonads and different structural changes of the body shape, but also the process has intellectual, emotional, and social effects (1, 2). The physiologic changes during puberty, normally, start between 8 to 13 years old in females and 9 to 14 years old in males (3).

However, it should be considered that part of the puberty process starts in the uterus and within the first few months of a newborn life, hypothalamus-pituitary-gonadal axis has a transient activation that is called "mini-puberty". This axis is deactivated until pubertal maturation, as mentioned above (4, 5).

Many factors affect the time of puberty, such as race. Puberty happens earlier in Black cases compared to Caucasian and Hispanic (6). Nutrition is another affecting factor, and 25% of the variation in puberty time can be explained by nutritional factors (7). Furthermore, it is proposed that 50 to 75 percent of the pubertal timing differences are described by genetic factors (8). Other factors like physical activity, and environmental exposures also affect the puberty process (9, 10).

There are some timing disorders in puberty, including delayed or precocious puberty. The definition of these terms has always been challenging as the trend of puberty onset time has been declining in the recent centuries (11). Delayed puberty is defined as the absence of breast development after the age of 13 or a lapse of more than four years between the physical signs of thelarche and menarche. The definition is different in boys and is characterized by the lack of size increase in testes after the age of 14 years old (12).

Preconscious puberty is also defined as the presence of tanner 2 stage of secondary sexual characteristics before the age of nine years in boys and eight years in girls (13). The definition in African-American and Hispanic cases is different and cases with less than seven years and six months of age are considered precocious puberty patients (14). Although delayed puberty usually has harmful psychosocial effects, the problem with precocious puberty is both physical and psychological (15). The management of precocious puberty is also a challenge. Here, we review the radiological approach to precocious puberty.

2- MATERIALS AND METHODS

A thorough search was conducted from inception until December 2022. The used keywords included precocious puberty, central precocious puberty, peripheral precocious puberty, boys, girls, male, female, bone age, ultrasonography, and magnetic resonance imaging of the head, breast sonography, pelvic sonography, and testis sonography. PubMed, Scopus, and ISI web of science databases were searched using these keywords. Moreover, Google scholar was also reviewed for available information. Besides, the references of the included studies were hand-searched for relevant studies. All the studies were included and their abstracts and titles were reviewed for related studies. The full texts of the included studies after the title and abstract screening were also evaluated. The studies were also assessed in case of quality using Joanna Briggs's quality checklist according to the type of study. Those who had good quality according to the checklist were included and reviewed with different subtitles. We tried to find the gap of knowledge in this approach. We also provided related images of the referred cases to our outpatient and inpatient settings in Mashhad University of Medical Sciences.

3-RESULTS AND DISCUSSION

3-1. Etiology of precocious puberty

There are two main types of precocious puberty, including Central Precocious Puberty (CPP) and Peripheral Precocious Puberty (PPP). CPP, also called GnRH dependent, is usually idiopathic but can have a variety of causes, such as CNS malignancies or injuries, genetic or familial causes, syndromes, and environmental factors (16). CNS tumors that affect the hypothalamus-pituitary-gonadal axis, like tuber cinereum hamartomas, optic glioma, ependymoma, astrocytoma, arachnoid cysts, and pineal tumors are usually responsible for CPP. Other CNS problems like septo-optic dysplasia and hydrocephalus are also other causes of CPP. Injuries to the CNS can be caused due to irradiation, trauma, bleeding, or infection that can potentially cause CPP (16-18). Different gene mutations have been described related to CPP, including Delta-like non canonical Notch ligand 1 (DLK1), kisspeptin (KISS1), kisspeptin receptor (KISS1R), and Makorin Ring Finger Protein 3 (MKRN3) genes. MKRN3 mutation is also related to Prader-Willi Syndrome, and a rare part of patients with this syndrome suffer from CPP (19).

Moreover, heterozygote deletion of MKRN3 is also linked to CPP without Prader-Willi Syndrome (20). Other genetic syndromes are reported to be associated with CPP, including Sturge-Weber syndrome, neurofibromatosis type 1, and tuberous sclerosis (16). Furthermore, familial CPP constitutes 27.5% of all CPP cases (21).

Other terms for PPP are Pseudo precocious puberty or GnRH-independent precocious puberty. This type of precocious puberty is not due to the pulsatile secretion of GnRH from the hypothalamus. Instead, it is the inappropriate presence of sex steroids that cause precocious puberty. Several causes have been proposed for PPP, including Gonadal tumors, Adrenal tumors, congenital adrenal hyperplasia, McCune-Albright syndrome, Van Wyk and Grumbach syndrome, testotoxicosis, and the use of exogenous sex steroids (16). The most common etiology of PPP in girls is the ovarian follicular cyst. PPP is also the most prevalent endocrinologic manifestation of McCune-Albright syndrome. The condition is characterized by the triad of café-au lait skin lesions, fibrous dysplasia of bone, and PPP. Usually, girls with this problem can reach the age of puberty and present with PPP; however, with a slightly lower frequency, boys with McCune-Albright syndrome present PPP, too (22, 23). Hypothyroidism usually is associated with delayed puberty; however, rarely some subjects may develop PPP. Testotoxicosis is a term assigned for an autosomal dominant genetic disorder of male cases, which is characterized by symmetrical testis enlargement. It is the activation mutation in luteinizing hormone (LH) receptors that causes autonomous testosterone production in Leydig cells (24).

3-2. Epidemiology of precocious puberty

The epidemiology of preconsciousness among different communities varies at different times. Moreover, there is a female predominance in the incidence of CPP. A Danish study was conducted in this regard between 1998 and 2017. They reported that the mean annual incidence of CPP, during that 20-year period, was 92 per 100,000 for girls and 9 per 100,000 cases for boys, which is ten times higher in girls. They also reported that the disease incidence revealed a six-fold increase in girls and a 15-fold increase in boys during this time (25).

Kim et al. also conducted a study from 2008 to 2014 in Korea. They reported the total incidence of CPP as 122.8 per 100,000 persons, which was 262.8 per 100,000 cases in girls and 7.0 per 100,000 cases in boys (26). Another study in

France reported an incidence of 26.8 per 100,000 for girls and 2.4 per 100,000 for boys from 2011 to 2013. They also noted that the incidence varies between different parts of the country; however, they could not address the reason behind this fact (27).

Still, the epidemiology work-up of precocious puberty lacks large sample studies, and the number of studies is limited. In the case of the epidemiology of PPP, further studies are needed, and there is a gap of knowledge for this issue. CPP is more prevalent in female cases; however, PPP is higher in males compared to females (28, 29). The researchers are advised to conduct more epidemiologic studies to gain better results.

3-3. Pubertal variants

There are four different types of pubertal variants, including premature adrenarche, premature thelarche, isolated premature menarche, and nonprogressive or intermittently progressive precocious puberty (30). Premature thelarche (PT) is regarded as isolated breast maturation in Tanner stage 2 or 3 before the age of 7 or 8 and typically within the first 2 or 3 years of females' life (31). This condition is not potentially pathologic, and usually progresses over time; however, in some cases may progress to CPP. The bone age in these cases may be normal or advanced. Although advanced bone age may be due to a pathologic cause, there are cases with advanced bone age and no pathologic finding. With this regard, premature thelarche cases should be followed; and in case of accelerated presence of physical examination findings or rapid bone growth, they should be followed for further treatment requirements. The main problem with these cases is the development of short stature, and should be avoided (32-34).

Premature Adrenarche (PA) is regarded as pubic hair growth, in the absence of breast enlargement in girls and testis or phallus enlargement in boys. The condition is defined in girls less than eight years, and boys less than nine years of (34, 35). It is about nine folds higher in females compared to males. Advanced bone age is typical in PA cases and is not usually associated with pathologic conditions (36). Moreover, the final height in PA cases is within the normal height according to the height of their parents (37, 38). It is proposed that there may be some clue in the internal genitalia sonography of girls with PA. Aydin et al. (39) reported that PA girls had significantly higher endometrial volume and thickness. Uçar et al. (40) also proposed that PA female cases have notably higher bone age-adjusted uterine length.

Isolated Premature Menarche is the presence of an episode of vaginal bleeding without any other sign of secondary sexual development. The condition may happen in other cyclic episodes; however, there will be no progression in other signs of puberty. However, it can be an alarm about precocious puberty; and with this regard, a follow-up is needed (41). It is reported that the adult height of these cases will be within the mid parental target height (42).

In nonprogressive or intermittently progressive precocious puberty, the puberty signs (gonadarche and pubarche) do not progress or regress after a while. These cases should be followed in 3 to 6 months to find the possible progression to precocious puberty, and prevent short stature (43).

3-4. Radiological Management of precocious puberty

3-4-1. Bone age

Bone age is a valuable method and is not confined to the pediatric endocrinology service; and other specialists like orthodontics and pediatric orthopedics use this method, too. Two popular methods are Tanner-Whitehouse 2 (TW2) and

Greulich-Pyle (GP) (44, 45). The prerequisite for both of these two methods is a left-hand and wrist dorsal-plantar X-ray. The GP method is based on an atlas review. The images were gathered from upper-middle-class Caucasian children in Cleveland, Ohio, United States. TW2 model is a numeric scoring method that is based on three different ways, including assessment of the radius-ulna-short bones (RUS), which includes 13 long or short bones, 7 carpal bones, and a combination of 7 and 13 bones methods. The TW2 method is based on radiographs of average socioeconomic class children in the United Kingdom, collected between the 1950s and 1960s. This method of scoring was updated in 2001 and named TW3 (46). Gilsanz-Ratib (GR) is another atlas-based method like GP. Both GP and GR use left hand and wrist radiographs. However, the GR method is newer and provides digital images with higher qualities. The GR atlas was developed according to a two-decade bunch of hand and wrist images of European-derived children in 2005 (47). A superiority of the GR method compared to the GP method is that the GR method can discriminate anomalies related to individual variations in bone morphology (48). Still, physicians should get more familiar with the GR method, and further studies are required to establish its accuracy in different populations.

In a non-routine manner, ultrasonography and magnetic resonance imaging may be used for bone age assessment. The lack of ionizing radiation is the benefit of these methods. Sonography is achieved in different windows, including front, back and side. It is an easy, accessible, and time-saving modality, and poses nearly low costs to the patients. However, it is operator dependent and needs further standardized scoring methods (49).

Magnetic resonance imaging (MRI) is another radiation-free modality for bone age assessment; however, this method is not widely used. MRI is expensive and not available in all parts of this earth globe. Moreover, this method takes time and is not suitable for young age children due to the widespread movements and lack of cooperation in this regard. Furthermore, developing a reliable assessment method is another critical point (50, 51).

Artificial intelligence also has helped bone age assessment methods. Programmed algorithms are trained using machine learning methods. BoneXpert is a clearly-known software developed in this regard. The software was developed by Visiana Company in 2009, using plain radiographs of the hand and wrist to replace radiologists in bone age rating. The accuracy of this software has been addressed in different populations (52, 53). The accuracy of the software was increased to a root mean square error of 0.63 years relative to a single rater in the third version of trained BoneXpert, which is suitable to replace a radiologist in this regard (54, 55).

Bone age assessment is the first and essential imaging in every suspected case of precocious puberty. When the bone age is within the two standard deviations of the chronological age, it can be normal (56). However, in the early stages of CPP, patients may present normal bone age, while fat girls with pseudo thelarche can have advanced bone age (57, 58). With this regard, bone age follow-up should be considered for all suspected cases of precocious puberty (59). **Fig. 1** shows bone age assessment images according to the Gilsanz-Ratib atlas-based method.

3-4-2. Magnetic resonance imaging of the head

Magnetic resonance Imaging (MRI) of the head is a modality, which is used to assess the presence of central nervous System (CNS) lesions in CPP cases (60). The lesions detected in CNS MRI may be present in the hypothalamic-pituitary axis

or can be in other parts of the brain (61). Mostly seen lesions include hypothalamic hamartoma, meningomyelocele, encephalitis, glioma, pinealoma, astrocytoma, neonatal encephalopathy, hydrocephalus, and neurofibromatosis type one (62, 63).

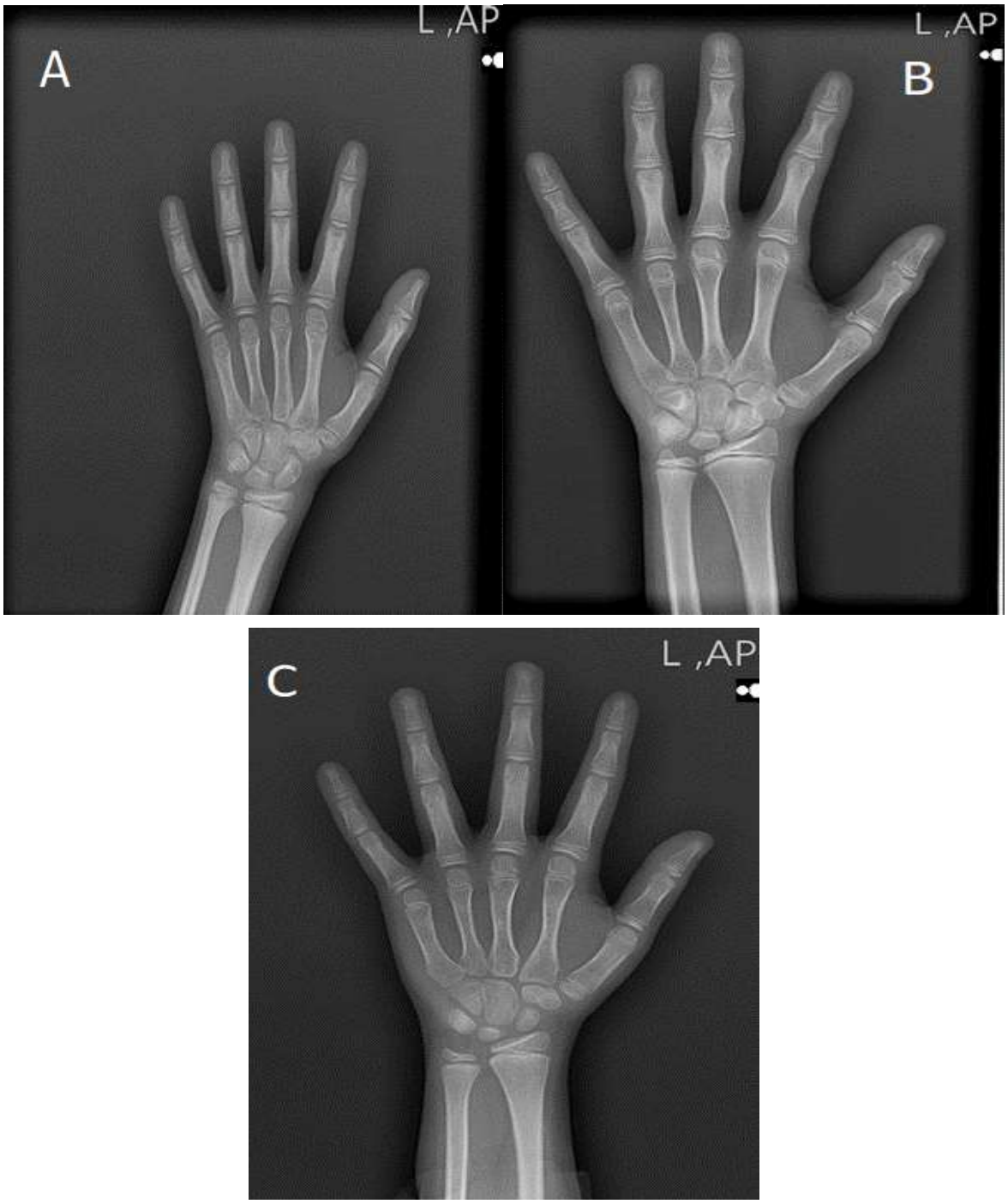

Fig. 1: Left hand radiograph bone age assessment according to the V. Gilsanz /O. Ratib Hand Bone Age atlas (A). In a 9-year-old girl with equal chronological age and bone age; (B). In a 15-year-old boy with delayed bone age (Bone age ≈ 14 years old); (C). In a 7-year-old girl with accelerated bone age (Bone age ≈ 7.5-8 years old).

There is no consensus regarding the age of Brain MRI in CPP cases. Some believe that it should be considered in every CPP case aged six years or less (64, 65). However, what happens if CNS lesions are present even in cases higher than six years old? With this regard, sellar magnetic resonance imaging protocols without contrast enhancement have been developed (66). Still, there is a need for MRI protocol development and its indication in these cases.

Moreover, it is proposed that in 90% of the girls with CPP, unlike boys, the condition is idiopathic (67). Therefore, CNS lesions have higher rates in male CPP cases compared to females (68). However, this is even controversial, and a recent study in China proposed that 83.7% of the CPP male cases had no CNS lesions and were idiopathic (69). However, in an older study by Sanctis et al. (70), the reported rate of idiopathic CPP in boys was 60 percent, which was far lower than that reported in the study by Wang et al. (69). Vurallı et al. (71) reported the prevalence of CNS pathologic findings to be 21.7% in boys and 6.2% in girls, which again confirm the higher rate of CNS lesion in male CPP patients.

There are few studies on the case with CNS pathologies related to CPP in males. Part of this lack of attention may be due to the lower rate of CPP in boys compared to girls. Several studies have reported that while 90% of precocious puberty cases in girls are CPP, only 60% of male precocious puberty cases are detected as CPP. Still, these studies are old and are usually limited to one ethnicity (72-76).

Thus, researchers should be advised to conduct more extensive multi-ethnicity studies to solve the present controversies. The gender and age distributions in relation to the presence and absence of lesions are effective in the modification of the diagnosis approach.

3-5. Pelvic ultrasound vs. gold standard

The role of pelvic sonography is of note in diagnosing CPP, PPP, and even pubertal variants. The gold standard method in the diagnosis of CPP and ruling out of the condition from PPP is gonadotropin-releasing hormone (GnRH) stimulation test (77). However, the test is not accessible in all laboratory settings and is not an easy assessment method. Moreover, it is time and money consuming (78). High pubertal levels of gonadotropins can be indicative of CPP; however, in PPP, the level of gonadotropins is low, and the level of sex steroids is high. However, ruling out pubertal variants is challenging. PT patients may have prepubertal and pubertal levels of gonadotropins (79). The LH/FSH ratio may be helpful, as it is often lower in CPP (80). In the case of PA, the presence of any other androgenic site should be investigated, and the GnRH test is not indicated (81).

Unlike the GnRH test, sonography is easy and accessible and poses a less financial burden. However, the accuracy of the test is operator-dependent. Different sonography parameters can be helpful in the diagnosis of precocious puberty. Rakhshankhah et al. (82) proposed a sensitivity of 75.27% and specificity of 75.56% for uterine volume at a cut-off of 1.40 ml in detecting CPP. They also proposed a cut-off of 13.5 mm for the transverse diameter of the uterine with a specificity of 71.11% and sensitivity of 72.04%. The suggested cut-off for the fundus/cervix ratio was also 0.98 with a sensitivity of 78.49% and specificity of 70%. Wen et al. (83) also reported that the best marker for CPP in girls is uterine length. The best-proposed cut-off was 2.45 cm with a sensitivity and specificity of 84.21% and 88%. They also reported that endometrial thickness of 0.26 cm or higher had a sensitivity of 76.92% and a specificity of 100% for CPP diagnosis (83).

De Vries et al. (59) proposed a cutoff value of 2.0 mL for ovarian volume with a sensitivity of 88.8% and specificity of 89.4%. They also suggested a cutoff value of 3.4 cm for uterine length with 80.2% sensitivity and 57.8% specificity. Khoroushi et al. (84) also proposed a cut-off of 1.35 cc for ovarian volume with 86% sensitivity and 80% specificity. The proposed cut-off in their study regarding the uterus volume was 1.65 cc with 86.0% sensitivity and 74.0% specificity. The best cut-off for uterus length was also 37.5 mm with 80.0% sensitivity and 94.0% specificity.

However, Lee et al. (85) could not find reliable pelvic sonography parameters in the case of CPP diagnosis. The uterine length of 4.09 showed a sensitivity and specificity of 33.33% and 79.79%, respectively. The maximum ovarian volume also had a sensitivity of 85.0% and specificity of 26.09% at the cut-off of 3.5 ml. The specificity and sensitivity of uterine/cervix ratio at the cut-off of 1.45 were 68.0% and 45.1%, respectively. The most valuable marker in Lee et al.'s (85) study was uterine volume, which showed a sensitivity of 64.18% and a specificity of 71.79% at the cutoff value of 3.30 ml. The diagnostic value of pelvic sonography was higher in the study by Binay et al (86). They presented 93.1% sensitivity and 86.6% specificity for a cut-off value of 3.0 cm. Moreover, they reported a cut-off of 1.3 mL with a sensitivity of 72.7% and specificity of 90.0%.

The role of pelvic ultrasound study in differentiating CPP cases from PT patients has also been investigated. Badouraki et al. (87) proposed that uterine length is a valuable marker in differentiating CPP cases from PT patients. The reported cut-off was 3.19 cm with a sensitivity of 85.7% and specificity of 82.4% for 6 ≤ years-old cases. Moreover, the reported cut-off for >6 to 8 years-old patients was 3.83 cm with a sensitivity and specificity of 91.7% and 90.9%, respectively.

Variations in the proposed diagnostic values and cut-offs may be due to different factors, including inter-operator differences, ethnicity variations, and even the use of varying sonography devices (88). Further studies are needed to find the best sonography index for the diagnosis of CPP. If this be possible, the approach to precocious puberty would be more straightforward without any time or money burden. However, it may be used as a screening method to rule out the cases that do not need further assessment with the GnRH stimulation test.

Another advantage of pelvic sonography is the detection of possible masses and tumors. Although these tumors are uncommon and may present with a palpable mass in the abdominal examination, there may be some cases with no evident finding in the physical exam. These tumors usually pose pathologic changes like electrolyte imbalance, hypertension, abnormal virilization or feminization, and precocious puberty (89). There may be ovarian tumors, including germ-cell and granulosa-cell tumors in the ovary (90).

Vaginal malignancies are also common among gynecologic malignancies of children, especially among those aged ≤ 4 years old (91). These tumors may present with vaginal bleeding that mimics premature menarche (92). Sarcomas (especially embryonal rhabdomyosarcomas) and Germ-cell tumors (mainly yolk sac) are of note among vaginal malignancies (91, 93).

When pelvic sonography is accompanied by abdominal sonography, it can provide a view of the adrenal gland to assess the presence of adrenocortical tumors (94). The most common presentation of these tumors is PPP, which occurs in 50 to 84.2% of the involved cases (95, 96).

Sonography also may provide some clues for congenital adrenal hyperplasia, including increased size (adrenal limb width >4 mm), abnormal echogenicity, or lobulated/cerebriform surface (**Fig. 2**).

A retrospective assessment reported that the modality has 92% sensitivity and 100% specificity in this regard (97). **Fig. 3** shows the measurement methods for ovarian or uterus volume and size evaluation.

3-6. Breast ultrasound

Breast evaluation is primarily conducted during the examination of every female precocious puberty case. With this regard, a score is assigned according to the five-scale Tanner staging. Sonography is also helpful in breast development grading, as it can evaluate the presence of fibroglandular tissue. Moreover, this modality can also assess the possible masses in the breast (98). García et al. (99) developed a five-scale sonography scoring that corresponded to the Tanner scale. Bruni et al. also reported another five-scale sonography scoring. However, this scale may need further improvement.

Calcaterra et al. (100) reported that breast volume $\geq$ 0.85 cm^3 can detect rapidly progressive CPP from non/slowly progressive or transient CPP with 66.0% sensitivity and 61.7% specificity. Moreover, they reported that ultrasound scoring according to the García scale was associated with rapidly progressive CPP. Youn et al. (98) also tried to differentiate precocious puberty cases from premature thelarche; however, they proposed that the ability of sonography is limited for this reason. Studies are limited in this field, and there is a need for further investigations on o the value of breast sonography in precocious puberty. Still the modality is helpful with breast masses that should be suspected, especially in unilateral breast enlargement (101). **Fig. 4** shows breast ultrasound images in premature thelarche.

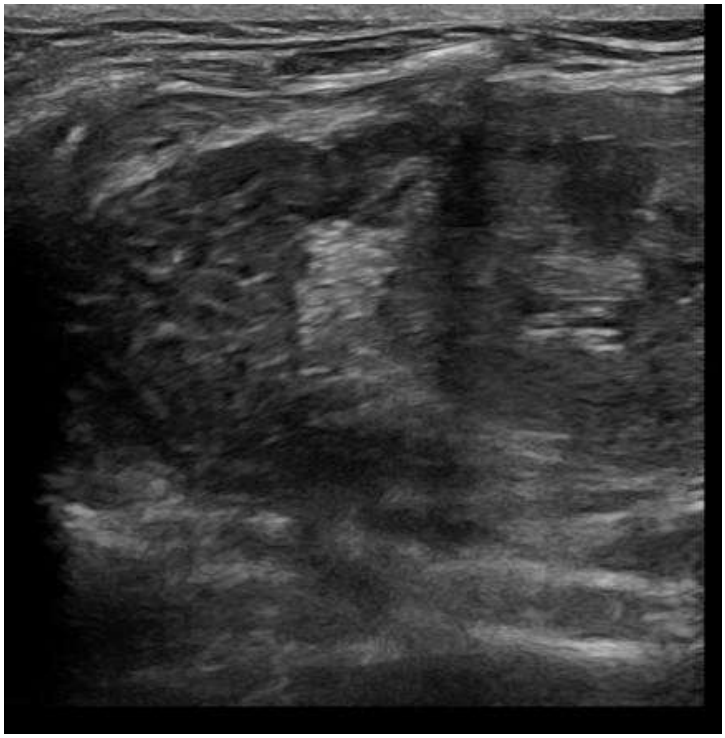

Fig. 2: Cerebriform appearance of adrenal gland in congenital adrenal hyperplasia (CAH) in a 2-month-old infant

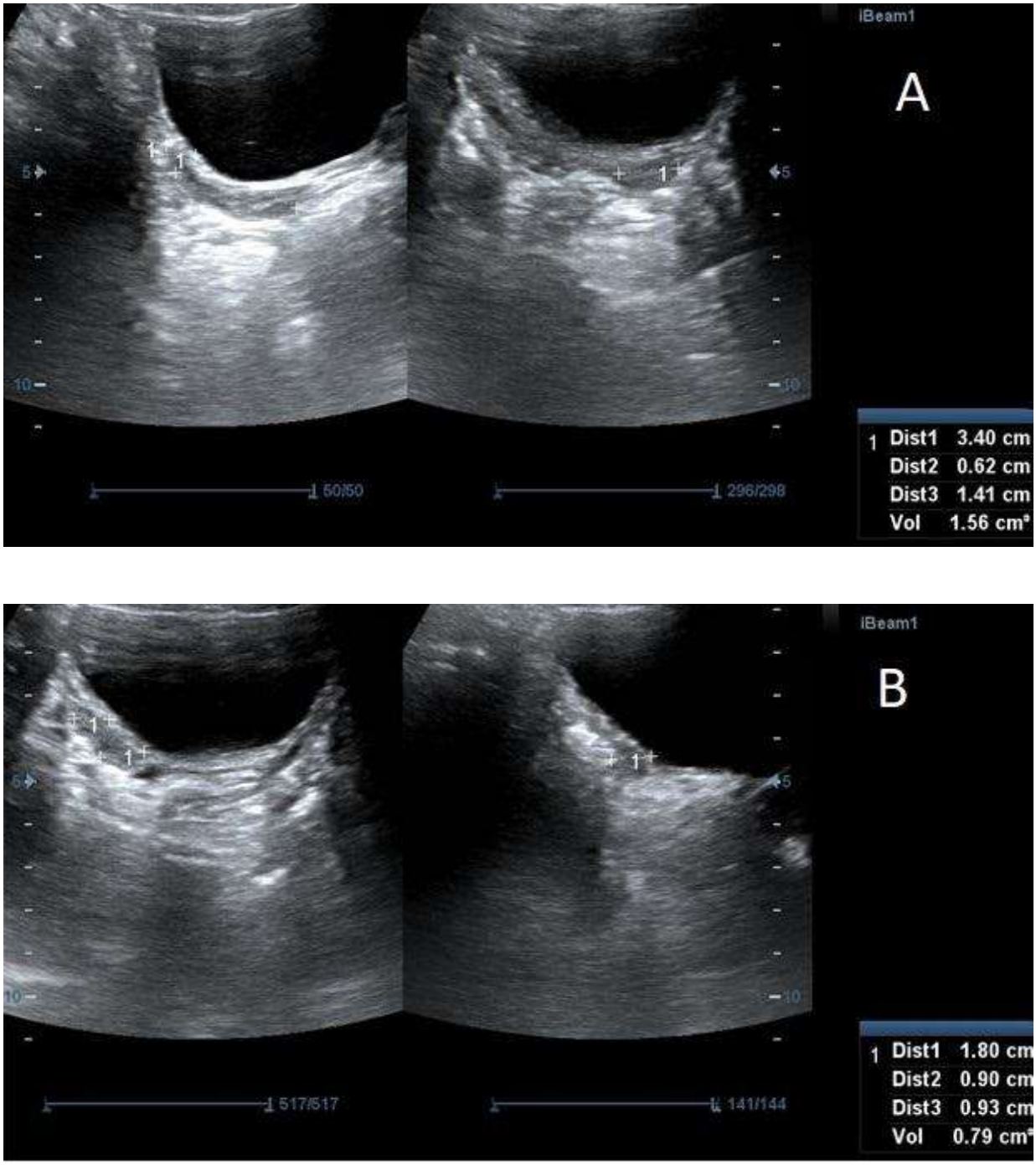

Fig. 3: Method of uterus diameters and volume measurement in a 7-year-old girl with bilateral breast enlargement; AP diameter and uterus volume are lower than the highest cut off reported in the literature; fundus to cervix is 1:1; (A).

Method of ovarian volume measurement in the same patient; the volume is 0.79 cc lower than puberty cut off, and pelvic sonography in this girl showed that we can consider thelarche as pubertal variant and follow up pelvic sonography can help for size change diagnosis in uterus and ovaries (B).

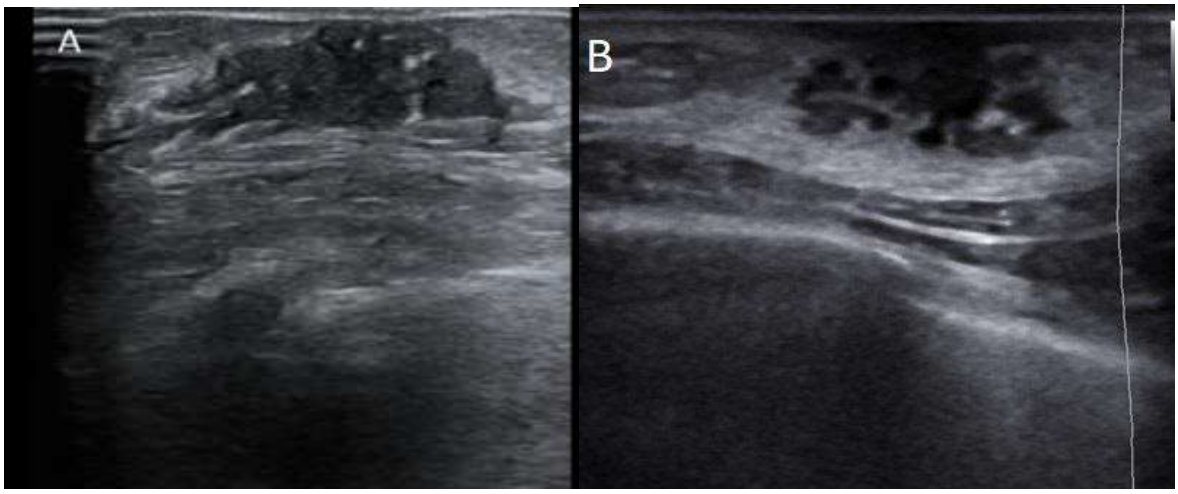

Fig. 4: Breast ultrasonography revealed premature thelarche as a pubertal variant; (A). Tanner stage 3 in a 4.5-year-old girl; (B). Tanner stage 2 in a 5-year-old girl

3-7. Testis ultrasound

Central precocious puberty is presented by normal symmetric enlargement of the testes in boys. Sonography study is significant in asymmetric changes of the testes. Leydig cell tumor, hCG-secreting testicular tumors, and testicular adrenal rests tumor (TART) are among the tumors that can cause unilateral testis enlargement (102, 103).

3-8. Scantly used modalities

Some modalities are needed in some exceptional cases. For example, as McCune-Albright Syndrome cases are prone to fibrous dysplasia lesions, a positron emission Tomography (PET) scan is needed in these patients (104).

3-9. Providing an approach

Although confirmation of precocious puberty is based on the GnRH stimulation test, radiology plays a vital role in the diagnosis and management of precocious puberty cases. The main concern in the case of precocious puberty is the development of short stature during adulthood time. With this regard, the timely diagnosis of precocious puberty can result in appropriate GnRH agonist treatment in these cases (68). Fahmy et al. (105) recently proposed a radiologic approach to precocious puberty, with a bone age assessment. The bone age assessment can be suggested for all suspected cases of precocious puberty. An accelerated bone age is usually indicative of precocious puberty; however, it should be considered that the bone age may be normal at the initial diagnosis of precocious puberty. It is proposed that the initial sign of puberty in girls is breast development and usually, bone aging accompanies breast maturation. However, testis enlargement is often the first manifestation of puberty in boys, and bone aging may show a delay after this initial symptom (106). With this regard, follow-up of suspicious cases with even normal bone age is important. Moreover, pubertal variants usually present normal bone age, but some cases may have advanced bone age (36, 107, 108). With this regard, two rarely found challenges are the diagnosis of precocious puberty with normal bone age at the very initial steps and the differentiation of precocious puberty from pubertal variants with accelerated bone age.

Sonography of the internal genitalia and breast can also be helpful in diagnosing precocious puberty. However, the number

of studies found in the literature is not enough to conclude. Different volumetric assessments of the uterine and ovary can be helpful in precocious puberty diagnosis. Researchers should focus on finding parameters that can be used in the screening of cases. Moreover, the proposal of scoring systems can be helpful, too. In fact, all efforts should be made to reduce the number of cases that need a GnRH stimulation test, as the test is expensive and not available in all settings. Karaoglan et al. (109) proposed a scoring to differentiate precocious puberty from premature thelarche. Their model used age of onset (6.5 years), bone age /chronological age ratio (≥ 1.1), uterine length (32 mm), estradiol (12 pg/ml), and ovarian volume (1.09 cm^3). They proposed that the sensitivity and specificity of this scoring in differentiating the two entities were 89.6% and 87.4%, respectively.

Although many of the CPP cases are idiopathic, brain MRI may be indicated in all CPP cases to rule out CNS pathologic causes; however, not for all age groups. Moreover, CPP cases should be followed regarding bone age and possibly using a pelvic ultrasound. Female PPP cases should undergo pelvic and adrenal sonography. Male PPP cases also should have a laboratory workup (102, 103).

Testicular sonography in boys and breast sonography in girls should be done in the presence of asymmetry. There may be other uses for breast sonography in case of precocious puberty diagnosis and follow-up; but still, the literature has insufficient data in this regard (16).

4- CONCLUSION

Imaging modalities play a fundamental role in the management of precocious puberty cases. Sonography is a handful and accessible modality with this regard. Uterus and ovarian sonography can be used as a helpful modality in case of diagnosis of CPP in girls; however, it suffers from low sensitivity and specificity. Future research should focus on improving the accuracy of this modality. Moreover, inclusion of imaging findings including bone age and sonography findings along with some clinical and laboratory findings may provide a scoring for easier diagnosis of precocious puberty. In this case, the high costs of diagnosis through GnRH stimulation tests will be reduced.

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