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Precocious puberty in preschool children

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Abstract
Precocious puberty (PP) is the development of pubertal changes at a pathologically earlier age than the mean age for the general population. It may either occur as a result of premature activation of the Hypothalamic-Pituitary-Axis or as a result of peripheral stimulation. PP is now recognised to occur more frequently in the preschool population, and therefore we report these cases aiming to develop a better understanding of the responsible causation and underlying factors.

Keywords: precocious, puberty, preschool, hamartoma, McCune, Albright

1. Introduction
In order to establish a thorough interpretation of precocious puberty, a proper understanding of the underlying physiology of the Hypothalamic-Pituitary-Axis activation is required. The onset of normal puberty usually begins with gonadarche, which is when the hypothalamus is triggered to increase the rate and frequency of the pulsatile secretion of Gonadotropin Releasing Hormone (GnRH), thereby activating the pituitary-gonadal axis. This results in the achievement of pubertal levels of circulating gonadotropins, Follicle Stimulating Hormone (FSH) and Leutinising Hormone (LH), which are respectively responsible for the promotion of gametogenesis and production of gonadal steroids [1]. Precocious Puberty (PP) is the development of pubertal changes at an age less than 2.5-2 standard deviations (SD) below the mean age of puberty for the general population [2]. This was globally equivalent to an age younger than 8 years in females, and 9 years in males. Nowadays, confusion exists as to what may be considered a normal age for puberty and especially for females as more studies confirm that the mean age for onset of breast and pubic hair development is occurring at a younger age than what was previously considered normal [3-5]. We are reporting these patients as more cases of PP is now recognised in the preschool population that cannot be attributed to familial variation, and with an incidence of an underlying disease. We aim to stress on the accuracy for diagnosis as it is pivotal to the decision of whether institution of therapy is indicated or not, specially considering the associated psychosocial behavioural abnormalities, parental anxiety, advanced bone age and consequent reduced final height with abnormal precocious puberty [6].

2. Case Reports
Case 1
An 8-month-old female presented with bilateral stage 3 breast enlargement and stage 2 pubic and axillary hair growth according to the Tanner scale of physical development. Her mother first took notice of pubertal changes 3 months ago, and brought her in after being troubled with its progressive nature. Personal history was negative for birth asphyxia, meningitis, encephalitis, brain haemorrhage and head trauma. There was no family history of precocious puberty either. Her height was at 78cm (>97th percentile) and her weight at 9.5kg (90th percentile). Wrist x-ray showed advanced bone age of 15 months (Greulich & Pyle style). Pelvic ultrasound was unremarkable. Oestradiol levels were at 62 Pmol/L (normal values <40 Pmol/L). GnRH stimulation test was positive with basal FSH and LH values respectively at 9.5IU/L (normal values between 0.1 - 1.0 IU/L) and 0.2IU/L (normal values between 0.1 - 0.6 IU/L), with a 10-fold increase in LH value after an hour and a 3-fold increase in the FSH (LH to FSH ratio of 10:3). The diagnosis of central precocious puberty was confirmed and she was started on an IM injection of Triptorelin Acetate every 28 days.

Case 2
A 3-month-old baby boy was referred to the endocrine clinic as a case of bilateral testicular enlargement for investigation. The father was worried after noting persistent enlargement despite 3 weeks duration and so sought medical advice. Personal history was negative for birth asphyxia, meningitis, encephalitis, brain haemorrhage and head trauma. There was no family history of precocious puberty either. On examination, he was at stage 2 according to the Tanner scale for physical development. There were no other signs of puberty. His height was recorded at 55cm (>97th percentile) and weight at 5.8kg (25th percentile). Scrotal ultrasonography showed testicular volume of 6 ml on both sides with no testicular tumours or cystic lesions present. Wrist x-ray showed an advanced bone age of 8 months (Greulich & Pyle style). Testosterone levels were at 9.91nmol/L (normal values between 0.07 - 0.7 nmol/L). GnRH stimulation test confirmed the diagnosis of central precocious puberty with basal LH and FSH values respectively at 1.98IU/L (normal values between 0.1 - 1.0 IU/L) and 0.875IU/L (normal values between (0.1 - 0.6 IU/L), and an 8-fold-increase in LH and a 2-fold-increase

in FSH (LH to FSH ratio of 8:2). Central precocious puberty was diagnosed. Abdominal and brain MRI scans ruled out neoplastic etiology. He was discharged on an IM injection of Triptorelin Acetate every 4 weeks.

Case 3

An 18-month-old female infant was brought to the emergency room by her distressed mother presenting with a single episode of vaginal bleeding of moderate amount and bright brown in colour with clots. There was no history of prior bleeding, bleeding disorders or trauma. Upon examination, there was no bleeding from other orifices, general or local bruises, or signs of sexual abuse. Her genital examination was normal and the hymen was intact. Serious conflict between the parents necessitated strong reassurance over the wellbeing of their child. However, cafe au lait macules were found spread over her trunk. Her height was recorded at 72cm (<3rd percentile) and her weight at 7.87kg (<3rd percentile). Bilateral breast enlargement was noted (Tanner stage 2) without either axillary or pubic hair development. Basal gonadotropin levels were 0.2 IU/L for both FSH and LH (normal values between 0.1 - 0.6 IU/L for LH and 0.1 - 1.0 IU/L for FSH). Her oestradiol levels were at 595 Pmol/L (normal values <40 Pmol/L). Pelvic ultrasonography revealed a right ovarian cyst. Her bone age was advanced at 2 years. Skeletal survey and bone scans were performed and confirmed the presence of polyostotic fibrous dysplasia of the femur. Patient was diagnosed with McCune Albright syndrome. A full endocrine profile was carried out and ruled out other endocrinpathies. Cardiac studies were done and ruled out arrhythmia and cardiomyopathy. Upon cessation of vaginal bleeding, she was discharged on Letrozole (third generation aromatase enzyme inhibitor).

Case 4

A 4-year-old female known case of ROHHAD-NET syndrome was brought to our attention when her mother anxiously noted the development of bilateral breast enlargement (Tanner stage 2) without other signs of puberty as part of the syndromes' associated hypothalamic dysfunction. Personal history was negative for birth asphyxia, meningitis, encephalitis, brain haemorrhage and head trauma. There was no family history of precocious puberty either. Her height was recorded at 123cm (+5.2 Standard Deviation) and her weight at 36kg (+11.74 Standard Deviation), confirming an increase in her growth spurt. Wrist x-ray showed an advanced bone age of 5 years. MRI scan of the brain was normal. Her oestradiol levels were at 74.22 Pmol/L (normal values <40 Pmol/L). Her GnRH test was positive for CPP with basal FSH and LH values respectively at 7.21 IU/L (normal values between 0.1 - 1.0 IU/L) and 1.88 IU/L (normal values between 0.1 - 0.6 IU/L), and a 2-fold increase in FSH and a 6-fold increase in LH after one hour (LH to FSH ratio of 6:2). She was started on an IM injection of Triptorelin Acetate every 28 days.

Case 5

A 5-year-old female presented with 5 weeks history of bilateral breast enlargement (Tanner stage 2) with whitish vaginal discharge that distressed her mother. There was no pubic or axillary hair. Parents sought medical advice in a private hospital and were referred to endocrinology clinic for further evaluation and assessment. Reviewing her history, there were few episodes alternating between crying and laughing attacks associated with frequent agitation. Personal history was negative for birth asphyxia, meningitis, encephalitis, brain haemorrhage and head trauma. There was no family history of precocious puberty either. Upon examination, her height was recorded at 117cm (+1.32 Standard Deviation) weight at 22kg (+1.41 Standard Deviation) and head circumference at 52cm (90th percentile). Wrist x-ray showed normal bone age. Brain MRI identified a hypothalamic mass consistent with a hamartoma [fig.1] with no other CNS structural anomalies. GnRH stimulation test results showed a 60-hour LH and FSH peak respectively at 30.43 mIu/mL (normal values between 1.80 - 11.78 mIu/mL) and 15.07 mIu/mL (normal values between 3.03 - 8.08 mIu/mL). Oestradiol levels were at 36 pg/mL (normal values <21 pg/mL). CPP was confirmed. She was started on an IM injection of Triptorelin Acetate every 28 days and referred for neurosurgical consultation. Resection of the tumour was discouraged due to its nonprogressive nature with scheduled serial MRI imaging every 6 months.

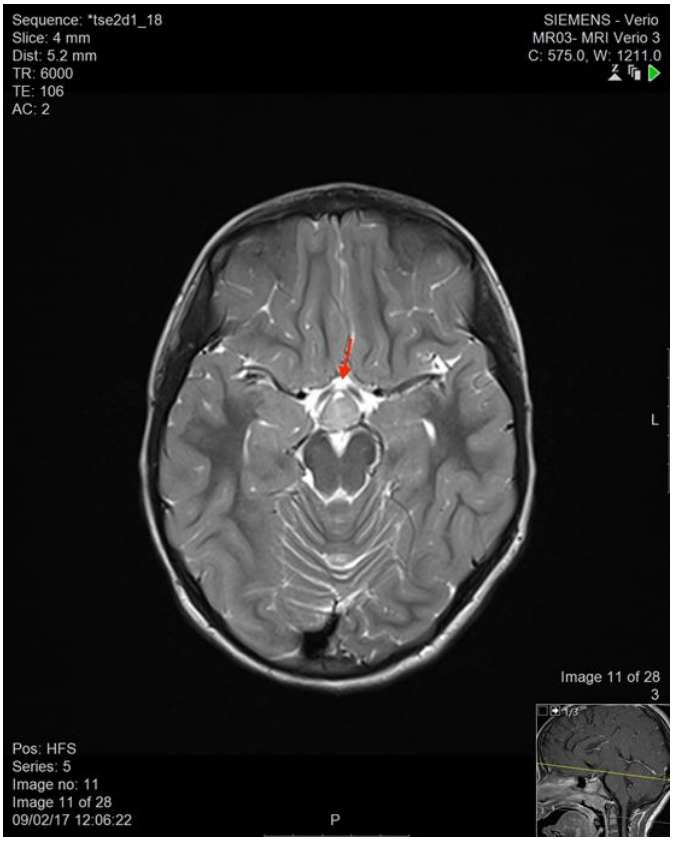

Fig 1: Hypothalamic mass in the Tuber Cinereum measuring 1.4x1.4x.1.3. The appearance of the mass was consistent with a hamartoma with normal pituitary an no other CNS structural abnormalities

3. Discussion

The two ways precocious puberty may manifest in are either gonadotropin-dependent, also known as central precocious puberty (CPP), or gonadotropin-independent, also known as peripheral precocious puberty (PPP). CPP constitutes the

premature activation of the hypothalamic-pituitary axis (HPA), either in a familial pattern, in the setting of positive family history for precocious puberty, as a result of central nervous system (CNS) pathology (hydrocephalus, meningitis, encephalitis, hypothalamic tumours etc.), or in an idiopathic manner should the above-mentioned aetiologies be ruled out. Elevated levels of basal gonadotropins as a result of hypothalamic stimulation is indicative of the integrity of the HPA, which is why the GnRH stimulation test remains the gold standard test for diagnosing CPP [7]. It is construed by interpreting pubertal FSH and LH levels in response to the administration of a synthetic GnRH. CPP is the most common cause of precocious puberty, with a frequency rate of 1 in every 5,000 to 1 in every 10,000. The majority of cases are identified more commonly in females, with a female to male ratio ranging from 3:1 to 23:1. However, more than 90% of the occurring cases in females have no identifiable neurological cause, and are considered of an idiopathic origin. Basal LH values have proven to be helpful in the initial investigation and diagnosis of CPP in females with breast development, however, is not of sufficient sensitivity to refute its presence [8]. In males, contrarily, studies have established that most cases of precocious puberty in boys are due to an underlying organic pathology, indicating additional radiological imaging to rule out neoplastic aetiology [9, 0]. Hypothalamic hamartomas (HH) are very rare, and present with a classical triad of gelastic epilepsy, CPP, and developmental delay [11]. They generally occur at an age younger than 2-4 years, further illustrating that the earlier the incidence of puberty is, the higher the likelihood of it being of an organic pathology. They are widely known to be more common in males [9, 12]. However, one study examined 15 girls with true central precocious puberty by computerised tomography, and all of the patients who were under 2 years of age were found to have a hypothalamic hamartoma. A total of 6 (33%) patients were confirmed with a pneumoencephalogram, reporting a frequent incidence in females [13]. Another study reports a case of HH in a 7-month-old child that resolved with GnRH analogue therapy, as not all cases require surgical intervention and prove a more positive outcome with medical therapy [11]. Our paper supports these contentions as we also report the incidence of a HH in a female child who as well did not require surgery. Peripheral causes of PP are always a result of an organic pathology, including ovarian or testicular tumours, congenital adrenal hyperplasia and McCune Albright Syndrome (MAS), of which the latter is the commonest. MAS is a rare disorder that is comprised of a triad of peripheral precocious puberty, polyostotic fibrous dysplasia and cafe au lait spots that are usually present during the neonatal period. The presentation on the other hand, is usually with vaginal bleeding and breast enlargement, thereby, manifesting more frequently in females. It is important to order a full hormonal profile to screen for other endocrinopathies that may accompany this syndrome, such as hypothyroidism, which occurs in 38% of the affected patients [14]. It is important to keep in mind that not all cases present with all three criteria, and only minority actually exhibit a similar classical clinical picture as our third case did. Childhood obesity has long been known to be a logical contributing factor to the development of precocious puberty due to the elevated levels of oestrogen synthesised by adipose tissue, but hasty dismissal of pubertal symptoms in obese children without taking it into the context of the full clinical picture is strongly advised against. In our fourth case, coincidence of PP with morbid obesity is reported, however the true aetiology of the PP was central in origin, as a result of a hypothalamic dysfunction. In conclusion, while a decrease in the mean age of puberty is recognised worldwide, incidence in infants is still considered very rare [11]. Three of our cases presenting with PP were under the age of 2 years, not yet significantly exposed to the environmental factors that are used to explain the earlier shift in the pubertal curve [15]. We recommend an increase in the awareness of precocious puberty in preschoolers and a higher suspicion for an underlying organic pathology warranting a thorough evaluation.

4. References

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