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Unexplained Precocity, AlQaysi Syndrome. A Case Report.

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Background: Precocious puberty (PP) implies the appearance of physical and hormonal signs of pubertal development at an earlier age what is considered normal. The beginning of puberty at an earlier age can have serious impact on the psychosocial wellbeing of the growing children in addition to its economic burden on the family. PP can be classified as central or peripheral depending on its etiology and many syndromes were identified for this growth disorder.
The diagnosis of PP still represents a challenge to physicians and multidisciplinary approach is a key step to find out the correct etiology and to decide about long-term therapy.

Case Report: We report a 7 year-old girl with history of prematurity presented with right sided hemihypertrophy of the body and accelerated linear growth confirmed with clinical examination and growth chart. All possible relevant laboratory and radiological tests performed to assess of her clinical condition. The diagnosis of central precocity associated with Silver-Russell Syndrome was suspected based on the clinical ground.

Conclusions: PP with hemihypertrophy should be investigated thoroughly to look for central or peripheral etiology. Despite identifying many etiologies, our patient is the first case to report with these unique features.

Keywords: Intellectual Disability, Puberty, Precocious, Musculoskeletal abnormalities.

Background:

Precocious puberty (PP) is the onset of pubertal development before the age of 8 years in girls or 9 years in boys constitutes precocious puberty. There is a lack of epidemiological studies of this condition however, Kim et al reported registered central PP in Korea from 2008 to 2014 of 37890 girls and 1220 boys and the overall incidence during the study was 122.8 per 100000

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persons (girls 262.8 and boys 7.0) [1]. In France, the national annual incidence was 2.68 (95% CI: 2.55, 2.81) per 10000 girls under the age of 9 years and 0.24 (95% CI: 0.21, 0.27) per 10000 boys under the age of 10 years from 2011-2013 [2]. A Danish study estimated the prevalence and incidence of PP in 9 year period from 1993-2001 of 670 children registered was 0.2% of girls and <0.05 of boys [3] and the annual incidence of central precocious puberty and normal variant puberty has substantially increased during the last 20 years [4].

There are numerous causes of PP can be classified as central or peripheral depending on the presence or absence of activation of the hypothalamic-pituitary –gonadal axis. Central PP is the most common form raises as a result of premature activation of the hypothalamic-pituitary axis, which can occur due to an identifiable cause as, space occupying lesion. However, the cause may be not obvious in many patients with this condition.

Peripheral PP is hypothalamic independent arises as a result of excess circulating of peripheral sex steroids due to gonadal or adrenal sex steroid secreting disorders or exogenous exposure to steroids or certain genetic mutations. Identifying the exact cause can be helpful in treatment precision on target the underling etiology.

We reported a child at age of 7-year-old girl presented with right sided unilateral PP. Despite we performed all available investigations, the case classified as central PP; we were not able to identify the cause nor the syndrome that can present in this manner. Therefore, physicians should be aware about atypical PP cases. This will encourage further research to reach the underlying cause and encourage development of new novel therapies to target exact defect.

Case Report

Our index case was a 7-year old girl of Indian in origin born of couple of non-consanguineous marriage presented to the pediatric endocrinology outpatient clinic of Zulekha Hospital in Dubai. Her mother concern about premature development of the right breast, which appeared initially as unilateral lump with intermittent mild pain and tenderness.

The mother noticed that since birth of her daughter's right side of the body more prominent than the left side with delayed gross and fine motor skills development in addition to a gradual increase of the right breast with unusual increase in her height within six to nine months.

The girl was the first child in the family and has other one sister and one brother; both have a normal growth pattern.

The parents and the school teachers observed decline in her performance and communications compared to her siblings and peers. On questioning, her mother has neither history of taking any drug nor had any disease during pregnancy.

The girl was born prematurely in Dubai at 26 weeks with weight of 980gm, head circumference 24.5cm. This required her to stay in an incubator for three months having developed respiratory distress syndrome responded successfully to two doses of Survanta, a lung surfactant followed by intermittent positive pressure ventilation (IPPV) which gradually weaned before stopped.

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The patient developed one episode of convulsion on day 11 in the incubator and managed accordingly. On day 44, fundus examination showed progressive retinal of prematurity and improved gradually.

On day 15 physical examination revealed ejection systolic murmur with bounding pulse and Echocardiography demonstrated large PDA closed on day 30. On day 57 exploratory laparotomy for high clinical suspicion of necrotizing enterocolitis.

Ultrasound and CT scan of the brain showed: both lateral ventricles are dilated with grade III intraventricular hemorrhage. Shallow cortical sulci over convexity.

Physical examination in the clinic revealed

Height: 126 cm with 75th Percentile 3 SD above mid-parental height. Figure 1.

Mild dysmorphic facies, deep nasolabial groove, Separated teeth, coarsening of the facial features, thickening of supraorbital ridge. Right side of the body obviously looks bigger than the left with right side breast enlargement (Tanner stage 3-4). Dull pink vaginal mucosa with spares of axillaries and pubic hair (stage 1-2). No midline defects or pathognomonic skin lesions such as (café au lait spot) were seen. (Photos 1-4). Her fundus exam was normal.

Investigations:

Blood tests. Table 1.

Test	Result	Reference range.
LH	2.6	0.4-4.9 IU/L
FSH	3.2	0.5-8.9 IU/L
TSH	2.69	0.60-4.84 uIU/ml
17 (OH)P	1.12	0.0-4.84 ng/ml
Estradiol	15	<50 pmol/l
Prolactin	169.7	64.0-395.0 miU/ml
Cortisol total	7.5	3.0-21 mcg/dL
Free testosterone	<0.10	0.2-1.30
GH	0.69	< or = 8.00 ng/ml
IGF-1	347.50	79.80-244.00 ng/ml.

GnRH test. Table 2.

Time	LH (U/L)	FSH (U/L)	Estradiol (pmol/L) after 24 hours in girls.
Zero	2.6	3.2	26
0.1 mg SC injection of deapptyl.			
One hour	7.5	6.9	
Two hours	20	15	54

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Karyotype: not requested for financial reasons.
Note: basic tests: ECG, other blood tests: FBC, renal and liver function, minerals, iron and vitamins were within normal ranges.
Wrist X- ray advance bone age more than 10 years and hypertrophy of right hand and bone were noted. Figure.2

Discussion

The new born infants with Russell-Silver Syndrome have many features including low birth weight with short height due to intrauterine growth retardation led to discrepancy in the size of two sides of the body, congenital hemihypertrophy.
This was first time reported in 1953 by Silver et al. There were two cases of the same above characterizes described in patients with Mosaic trisomy 18, [10]. A diploid -triploid mosaicism and 45 X / 46, XY mosaicism [11].
Russell was able to describe five children with severe intrauterine growth retardation and special facial features, triangular shaped face with a broad forehead and pointed, small chin, together with a wide, thin, 'shark-like' mouth. However these children remained small but body asymmetry was identified in two cases.
Russell and Silver emphasized different features, the composite characteristics have been identified as the Russell-Silver Syndrome. It is not accepted to separate one from each other; the Silver syndrome from the Russell syndrome on the presence of asymmetry in the newborn.
Those patients with this syndrome have normal intelligence however there may, be some delay in the early motor milestones related to decreased muscle mass relatively to large head [5].
The vast majority of affected children are born at term and are extremely light for dates with birth weights below the third centile for gestation (range 1-2 to 2.5 kg) [6].
3-M syndrome is a rare hereditary disorder characterized by severe growth retardation, distinctive facial dysmorphic features, and skeletal abnormalities [7]. The facial features described in form of triangular-in shape face with frontal bossing, depressed nasal bridge with a fleshy tip of nose mild malar hypoplasia, upturned nares, full lips and malar hypoplasia. Patients usually have large heads for their height, dolichocephalic, normal intelligence, short wide thorax, brachydactyly, clinodactyly, micromelia, and prominent heels. Both sexes are affected equally and no hormonal deficiencies are detected [8].

Mosaicism is a condition in which tissues of different genetic constitutions lie adjacent to or intermingled with each other within one individual [9]. In mosaic trisomy 18, the phenotype reported, [10]. A diploid -triploid mosaicism and 45 X / 46, XY mosaicism [11].

Neonatal Progeroid Syndrome (NPS) criteria are intrauterine and postnatal growth failure, hydrocephalic appearance, prominent scalp veins, old-looking face, absence of subcutaneous fat and neonatal teeth. Until now altogether nine cases have been reported, which were predominant

diagnosed in infant age. The NPS is in general assigned to the autosomal recessive trait and with increasing age, the outward appearance stays unchanged [12].

X-Linked short stature with skin pigmentation described with a syndrome of short stature, abnormal pigmentation of the skin and mild facial dysmorphism. The short stature and pigmentary anomalies were more marked in the males than the females [13].

Intrauterine growth retardation owing to placental insufficiency. Chronic intrauterine growth retardation leads to decrease in all growth parameters, that is, a 'perfect miniature', followed in most cases by catch up growth in the first year of life. Late intrauterine growth retardation, especially in the postmature fetus, leads to a thin, low birth weight baby with normal length and head circumference [14].

Our index patient is a unique and never described before however has some features resemble to Russel-Silver Syndrome but does not fulfil the criteria of diagnosis. The above variable conditions descriptions reported growth retardation with PP were not applied to this index case. Therefore, we consider referring this new case to the first author.

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Figure 1. Growth Chart of the patient.

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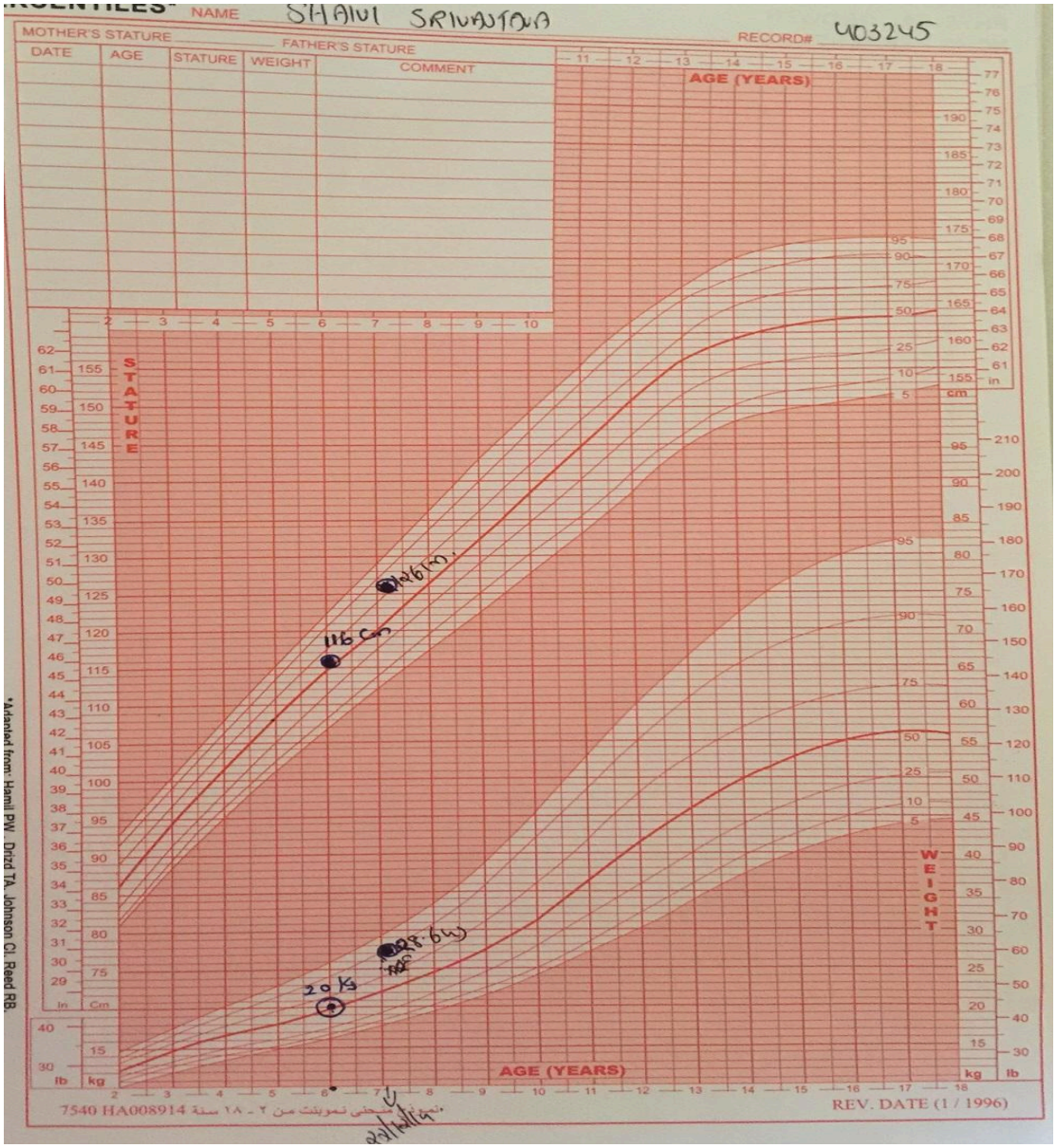

Figure 2. X-ray of both hands showed right hand is larger than the left.

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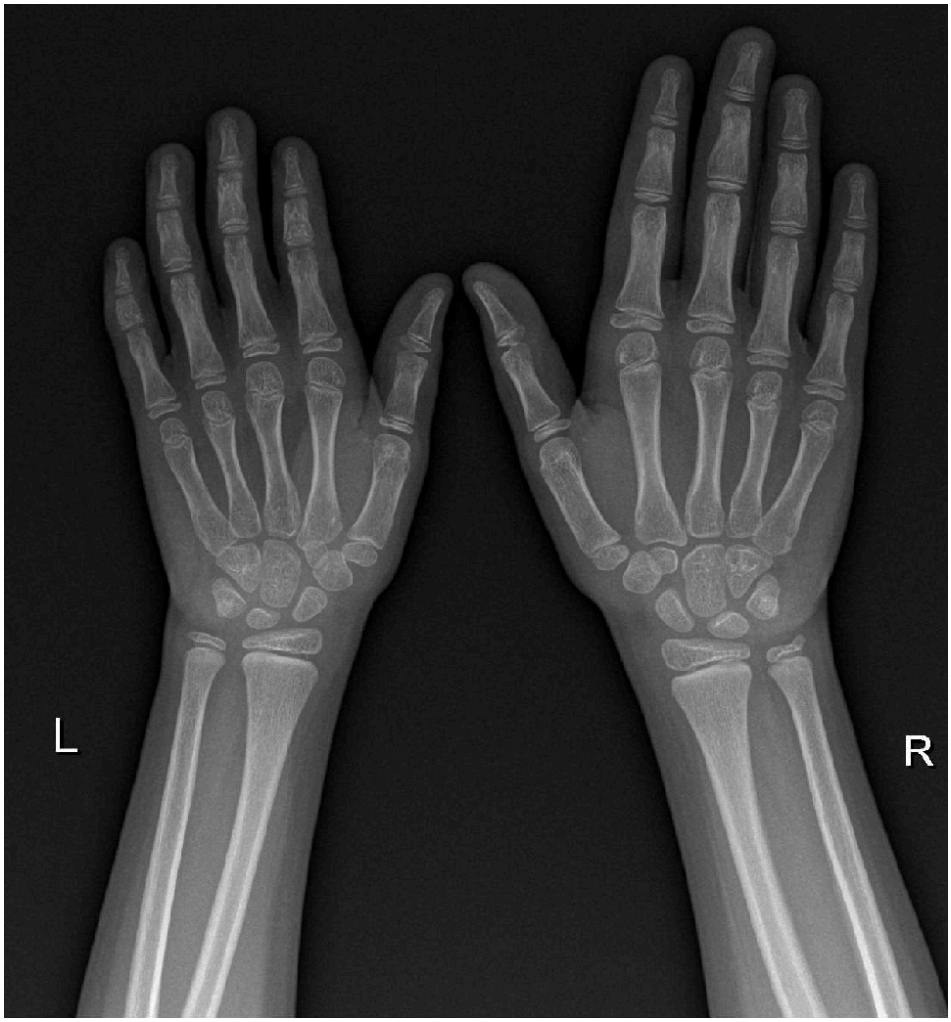

Photos 1-4.

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