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Case Report

Idiopathic True Precocious Puberty in a Boy with Sickle Cell Disease: Case Report and Mini Review

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Abstract

Sickle cell disease represent a major public health problem in Saudi Arabia, In spite of the importance and relative prevalence of precocious puberty and sickle cell disease in Saudi Arabia, There is a limited data about such combination. Precocious puberty influences the psychosocial development and growth of child. In our case report we are presenting patient with sickle cell disease presented with precocious puberty rather than delay puberty. According to the best of our knowledge this the first case report describing precious puberty in a sickle cell disease patient worldwide.

Keywords: *Sickle Cell Disease; Precocious Puberty; Children*

Background

Sickle cell disease represents a major public health problem in Saudi Arabia [1]. The prevalence of sickle cell disease was highest in the Eastern region (13.4%) [1]. Endocrinopathy including growth failure and delay puberty are frequent in patient with sickle cell disease.

In our case report we are presenting patient with sickle cell disease presented with precocious puberty rather than delay puberty. According to the best of our knowledge this the first case report describing precious puberty in a sickle cell disease patient.

Case Presentation

A 7½ years Saudi boy known case of sickle cell disease, glucose-6-phosphate dehydrogenase deficiency (G6PD) and atrial septal defect secundum (ASDII) in regular follow up with hematology clinic. Patient was brought by his mother due to her concern about the development of adult body odor, progressive penile enlargement and pubic hair growth for 3 months. There was no history of meningitis, cranial irradiation, head trauma, seizures, headache, visual problem, behavioral change or medication intake apart from folic acid. No history of precocious puberty in the family.

On examination, patient looks well, not dysmorphic, his weight: 25 kg (50^{th}) percentile. The height 127.5 cm (75^{th}), Breast tanner stage I, pubic hair tanner III, The stretched penile length (SPL) was 8 cm (90^{th}) percentile, testicle size around 5 ml. There is splenomegaly 10 cm below costal margin but No palpable mass in abdominal exam. No café-au-lait spots, or bony deformity. The remaining of systemic examination was within normal limits.

Laboratory finding were consistent with true central precocious puberty: Luteinizing hormone (LH) and follicle-stimulating hormone (FSH): pre 4.8 IU/l and 3.8 IU/l respectively. Post gonadotropin releasing hormone (GnRH) (30 minutes): 42.3 IU/l and 9.9 IU/l respectively. GnRH stimulation test (60 minutes): 50.0 IU/l and 9.7 IU/l respectively. Estradiol 10 pmol/l. Testosterone (total): 12 moll/l. Dehydroepiandrosterone (DEHA) level were normal.

Other laboratory: baseline Hemoglobin (Hb): 7 - 9 g/dL. Hemoglobin electrophoresis: Hb F: 26.7%, Hb S: 71.2%, Hb A2: 2.1. Liver function test and renal function test were within normal. Thyroid function test: TSH: 0.9 mIU/l, free T4: 15 pmol/l. ACTH, cortisol Prolactin were within normal.

Tumor markers were normal. Beta HCG, LDH and alfa-feto protein all within normal.

Bone age was advanced: At chronological age of 7½ years, it was 12 - 13 years.

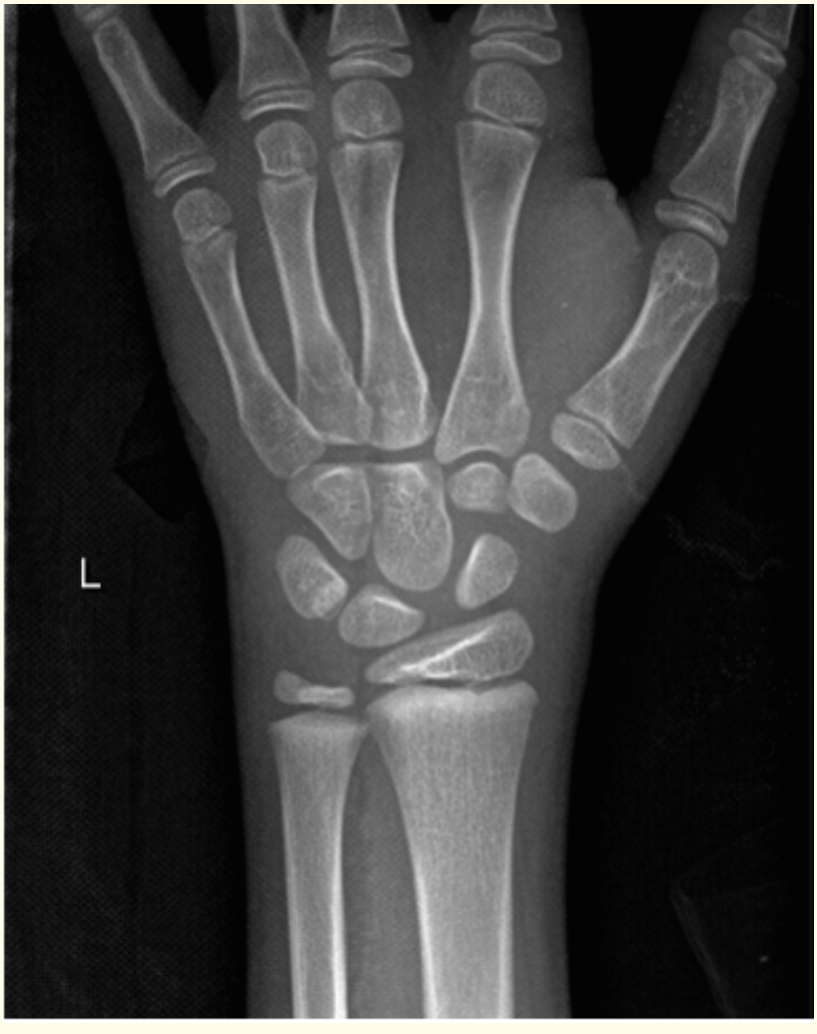

Figure 1: *Bone age about 12 - 13 yrs.*

Ultrasonography and computed tomography (CT) of abdomen and pelvis showed hepatosplenomegaly.

Brain and pituitary Magnetic resonance imaging (MRI) showed: unremarkable.

A diagnosis of Isosexual central idiopathic precocity was made by exclusion.

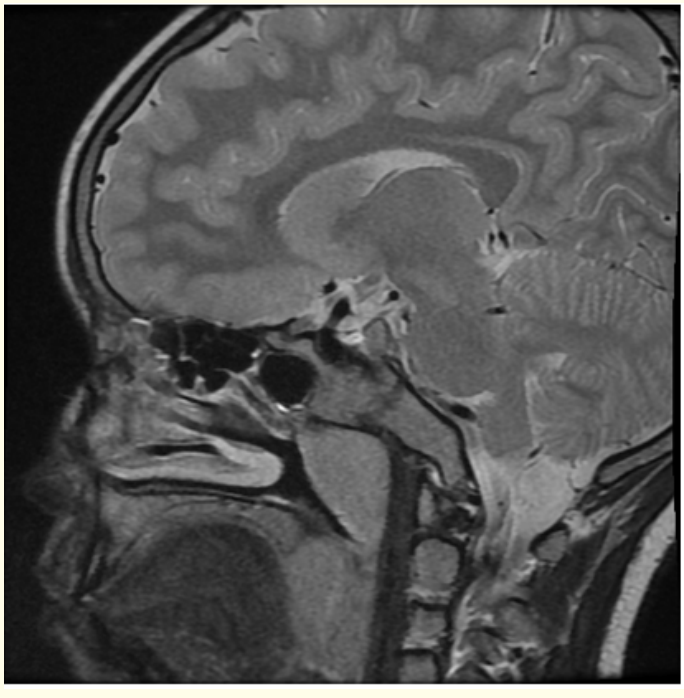

Figure 2: *MRI pituitary.*

Discussion

Hemoglobinopathies are among the most commonly inherited genetic disorders in humans. The World Health Organization (WHO) estimated that at least 5% of the world's populations are genetic carriers for hemoglobinopathies (2.3% for Sickle Cell Disease).

Sickle cell disease is an autosomal recessive hemoglobinopathy. It is caused by a single nucleotide mutation that substitutes glutamic acid for valine in the sixth position of the beta globin gene [11,12]. Penicillin prophylaxis, folate supplementation and hydroxyurea therapy have reduced morbidity and mortality related to this disease [12]. Sickle cell disease can be cured by bone marrow transplantation; however, curative treatment is costly and unavailable except for a limited number of cases [1]. Coping with this disease is a very challenging experience. Psychosocial problems are common in patients with Sickle Cell Disease (SCD) [2].

Sickle cell anemia affects almost all systems of the human body. Endocrine and metabolic disorders may be associated with this disease. Growth delay and/or failure of puberty are frequent [3-12]. Studies showed that up to 25% of boys with Sickle Cell Disease (SCD) above age of 14 had absence of testicular development and for those who had spontaneous testicular development had significantly smaller testicular volume in compare to control [7,11,13,15]. Many factors as endocrine and/or metabolic dysfunction, constitutional, hematological status (tissue hypoxia, chronic anemia, iron overload), high energy demand, genetic influence and nutritional status may play an important role in growth failure in patient with sickle cell disease [4,5,14]. In addition to that precious puberty per se as in our patient also can add to this growth problem since it may end with short stature.

Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function. It is a complex and multifactorial process that includes genetic, metabolic, environmental, ethnic, geographic, and economic factors and results in reactivation of the hypothalamic-pituitary-gonadal (HPG) axis [16,19,23]. An effective pubertal onset requires pulsatile hypothalamic secretion of GnRH stimulating the secretion of gonadotropins by the anterior pituitary gland. The classical definition of precocious puberty is the development of secondary sexual characteristics before the age of 8 years in girls and before the age of 9 years in boys [16-27].

Precocious puberty is divided into Central Precocious Puberty and Pseudo Precocious (Peripheral) puberty. Central precocious puberty (GnRH dependent) occurs because of premature activation of hypothalamic-pituitary-gonadal axis. Pseudo Precocious Puberty (GnRH independent) is caused by activity of sexual hormone independently from the activation of the gonadotropic axis [16-27].

According to recent studies, the prevalence of Central precocious puberty (CPP) is increasing and especially idiopathic CPP cases has increased [17,19,20].

Idiopathic CPP represents 90% of the cases in girls, whereas organic etiologies are more frequent (60% and up to 94%) in boys [16,17,25]. Though Ayferet., *et al*. in his study (100 male cases were evaluated) found that There was no underlying cause in 74% of the cases in boys and an organic cause was determined in only 26% [17].

Most of the organic cases had been diagnosed before the age of 7 years, whereas most of the idiopathic cases had been diagnosed after the age of 7 years [17,24,29]. Jisun Lee., *et al.* in study including 75 male cases found that puberty started after age of 8 in 93.2% of the idiopathic cases [19]. Recently, number of idiopathic cases has attributed to mutations in different genes, including KISS1, KISS1R, MKRN3, and DLK1 that cause CPP [21,22,28].

Incidence of precocious puberty is estimated to be 1 per 5000 - 10,000 individuals. In spite of the importance and relative prevalence of precocious puberty and sickle cell disease, to our knowledge, there are sparse published papers on etiology of precocious puberty in the Saudi patients and nothing regarding precocious puberty in sickle cell disease patients worldwide [31-34].

Physiologically, In response to testosterone, boys present with testicular, penile, and cricoid cartilage growth (leading to voice change), facial hair development, changes in body fat distribution, and increase in muscle mass.

Basal and post gonadotrophin hormone releasing hormone analog (GnRHa) luteinizing hormone (LH) ≥ 0.3 - 0.6 IU/L and ≥ 4 - 5 IU/L (30 - 60 min after GnRH/GnRHa administration) respectively, using modern ultrasensitive automated chemiluminescence assays, can be considered positive for central puberty initiation [30].

Bone age exceeds two standard deviations (SD), it is considered significant similar to what is found in our patient.

Therapy is indicated in children with CPP with accelerated bone age, height advancement, or psychosocial stress. Treatment goal is to halt puberty progression to a socially acceptable age, allowing the child to attain optimal height potential. GnRH agonist is the treatment of choice, with best height outcomes when initiated < 6 years age. Treatment is recommended till 11 - 12 years age.

Precocious or early puberty have also been reported in the context of a variety of pre-existing medical conditions including some diseases like adrenocorticotropic deficiency, dyspraxia and bone abnormalities, glomerulopathy with complete renal failure, also in those with chromosomal duplication and some syndromes like Russell silver syndromes 23 but not in sickle cell diseased patient.

Besides, in the last 10 years, reasons for increased reports of this condition can be attributed to better timely identification of the attributes due to improved recognition of CPP among general practitioners and an increase in parent's awareness regarding early puberty.

In Saudi Arabia study done by Khalid showed a high prevalence of poor awareness and knowledge, mainly in those areas relating to precious puberty complications [33].

Studies have shown that obesity also plays a role in the earlier onset of puberty in boys .18 our patient is neither obese nor underweight.

It's known that CNS insult may trigger early puberty; stroke is one of the complications of SCD, our patient being from eastern province with Indian haplotype having fewer strokes in comparison to African one.

Unfortunately, genetic studies to identify possible genes not done in our patient. So, diagnosis of idiopathic CPP was done after doing the standard laboratory and imaging.

Our patient started on leuprolide 3.75 mg intramuscular IM every 28 days which resulted in pubertal arrest in order to keep the epiphysis opened, our concern is that GnRH may lead to osteopenia in long term especially if used for prolonged period which may add to bony complication in sickle cell disease patient.

Conclusion

Sickle cell disease (SCD), a hereditary blood disorder, is highly prevalent in Saudi Arabia (SA); causing serious complications which decrease quality of life and cause high mortality in young adults. Growth failure and maturational delay remain significant chronic problems in children with SCD.

Precocious puberty influences the psychosocial development and growth of child. Short adult stature is one of the most serious long-term consequences of precocious puberty. Identification of a child with pathological pubertal development allows for an accurate diagnosis and application of current treatment strategies.

Additional studies are needed to investigate the mechanisms through which precocious or early puberty is triggered in patients with sickle cell disease to prevent short stature, social anxiety and child abuse.

This case report aims to raise awareness of this disease so that individuals with sickle cell disease having precocious puberty are identified and provided with appropriate care.

Competing Interests

The authors have no conflict of interests to disclose.

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