Association of Hypoparathyroidism-Retardation-Dysmorphism Syndrome (HRD) with Down syndrome

Abstract
Hypoparathyroidism-Retardation-Dysmorphism (HRD) syndrome, also known as Sanjad Sakati Syndrome (SSS), is a rare autosomal recessive genetic condition seen in offspring of consanguineous parents of Middle Eastern origin. HRD consists of hypoparathyroidism leading to hypocalcemia and hyperphosphatemia, growth retardation, and characteristic dysmorphic features. This case presents a Saudi baby girl who was born to a first-degree consanguineous parent who previously had an affected baby with HRD. The patient's facial features were suspicious of both HRD and Down syndrome. She was found to have complete atrioventricular septal defect on Echocardiogram which is the most common cardiac defect in Down syndrome. In addition, she developed hypocalcemia and hyperphosphatemia secondary to hypoparathyroidism. Surprisingly, Chromosomal analysis revealed Trisomy 21. The overall scenario of this case suggests a unique association of Hypoparathyroidism-Retardation-Dysmorphism syndrome (HRD) with Down syndrome.

Keywords: Dysmorphism; Hypoparathyroidism; Hypocalcemia; Sanjad sakati syndrome; Growth retardation; Down syndrome; Newborn; Saudi

Case Presentation
A Saudi baby girl was born by spontaneous vaginal delivery at 40 weeks of gestation to a 44-year-old gravida 6, para 6 mother who had uneventful pregnancy. Her Apgar score was seven and nine at one and five minutes, respectively. The baby was born to first-degree consanguineous parents. There was a family history of Hypoparathyroidism-Retardation-Dysmorphism syndrome (HRD) affecting the patient’s brother. She was referred to our hospital at the age of 6 hours for Endocrinology evaluation. Her birth weight was 2500g, length was 45cm, and the head circumference was 30 cm. All growth parameters were below the 5th percentile. Her vital signs, including blood pressure, pulse rate, respiratory rate, body temperature, and O2 saturation on room air were 61/41(45) mmHg, 145/min, 40/min, 36.9°C and 96%, respectively. The patient was conscious, active, but hypotonic. She was not cyanosed nor on respiratory distress. There were dysmorphic features including: small deep-set eyes, upward-slanting palpebral fissures, beaked nose, thin lips with a long philtrum, micrognathia, small hands and feet, Single transverse palmar crease, and wide space between the first and second toes. Cardiovascular examination revealed a single first heart sound and a split-second heart sound, with a grade 3/6 ejection systolic murmur audible at the upper left sternal border. The rest of the physical examination was normal. Investigations showed hypocalcemia: 6.4 mg/dl (N= 8.5-10), hyperphosphatemia: 7.9 mg/dl (N = 2.5-4.9), and low parathyroid hormone (PTH): 1.37 (N= 15-65). Alkaline phosphatase was 114 U/l(N=46-116), and Magnesium 2.1mg/dl (N= 1.8-2.4). Complete
blood count (CBC) revealed leukocytosis of 25,000, neutrophilia, and shift to the left. Blood culture showed no growth. Chest X-ray, Skeletal survey, Cranial, renal and abdominal ultrasound were all normal. Echocardiogram showed: complete atrioventricular canal (balanced type), and moderate atrioventricular valve regurgitation. Karyotyping showed trisomy 21. In the 3rd day of life, the patient underwent septic workup and was started on Ampicillin and Gentamycin as she developed Tachypnea with respiratory rate of 73 breath/min, respiratory distress, and desaturation to 90% on room air. The patient then showed improvement in the 4th day. After echocardiogram, she was started on Captopril and on Furosemide 1mg/kg/dose twice per day. She was seen by Endocrinologist and advised to start her on calcium carbonate 50 mg/kg/day divided every 8 hours and alphacalcidol (one-alpha) 0.2 microgram (2 drops) orally once daily. Throughout hospital stay, she showed low calcium level. Neither tetany nor seizures were developed. In the 8th day of life, she developed sudden cardiac arrest and died after Cardiopulmonary Resuscitation.

Discussion

This case presents a patient who is an outcome of consanguineous marriage that was previously resulted in a baby born with HRD. The patient had dysmorphic features that are consistent with HRD syndrome (microcephaly, small deep-set eyes, beaked nose, thin lips with a long philtrum, micrognathia, and small hands and feet) [1]. Upward slanted palpebral fissures, single transverse palmar creases, wide gap between the first and second toes, and hypotonia are strongly suggesting the possibility of Down syndrome [7]. Complete atrioventricular septal defect, which affects approximately 3% of all patients who have congenital heart disease, tends to be associated with down syndrome [8]. Neonatal hypoparathyroidism is relatively common, and occurring usually as a transient condition associated with well-defined risk factors such as prematurity, perinatal asphyxia, and maternal diabetes [3]. Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome and Kenny-Caffey syndrome are both causing permanent hypoparathyroidism. Children with Kenny-Caffey syndrome have normal intelligence, thickening of the long bones, medullary stenosis (thin marrow cavities), postnatal growth retardation, and retinal calcifications, congenital cataracts [9]. DiGeorge syndrome is also one of the congenital hypoparathyroidism characterized by absence of thymus gland and cardiac anomalies including tetralogy of Fallot, pulmonary atresia, and ventricular septal defect [10]. Regarding our patient; The family history of HRD, craniofacial features, microcephaly, intrauterine growth retardation, and hypoparathyroidism strongly suggests HRD. Molecular genetic studies of the patient were scheduled to be carried out as a supported diagnostic procedure, but the sudden death of the baby prevented any further testing. Trisomy 21 in karyotyping result reveals this unique association of both HRD and DS.

References