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Sanjad Sakati Syndrome: Case reports from Egypt ☆

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ABSTRACT

Background: Sanjad Sakati Syndrome (SSS) is a rare autosomal recessive congenital disorder. It is characterized by congenital hypoparathyroidism, severe prenatal and postnatal growth retardation, dysmorphic features, as well as mild to severe mental retardation. The prevalence of this syndrome is not known. Reported patients were almost exclusively from the Arabian Peninsula. The syndrome has equal distribution for both sexes and has severe and often fatal consequences. Although some of the features seen in SSS resemble DiGeorge Syndrome, Kenny-Caffey Syndrome and familial Hypoparathyroidism, lack of association with normal intelligence, cardiac lesion, lymphopenia or skeletal abnormalities makes it a distinct entity. SSS is caused by mutations in the gene-encoding tubulin-specific chaperone E (TBCE; 604934), located on chromosome 1q42.3. SSS is listed in Online Mendelian Inheritance in Man [OMIM] #241410. We report on three Egyptian cases of Sanjad-Sakati Syndrome, one case being confirmed by molecular diagnosis.

Cases: They have typical dysmorphic facial features comprised of a narrow face, deep-set eyes, a beaked nose, large floppy ears, a thin upper lip and micrognathia. The three cases showed growth retardation of variable degrees. Cardiac examination was normal in all cases. Laboratory results showed low total calcium, low ionized calcium, high serum phosphorous, normal alkaline phosphatase level, and low or normal serum parathyroid hormone which are essential for diagnosing hypoparathyroidism.

Conclusion: This diagnosis allowed for proper treatment of the patients, prevented associated comorbidities, provided a genetic counseling to their families, and enriched the genetic data concerning this syndrome on the Egyptian population being reported for the first time.

Introduction

Sanjad-Sakati Syndrome (SSS), also known as hypoparathyroid ism-retardation-dysmorphism (HRD) syndrome, is an autosomal recessive disorder that is reported almost exclusively in patients of Arab ethnicity.[1] The first report, an abstract, was by Sanjad et al.[2] SSS (HRD) is caused by mutations in the *gene-encoding tubulin-specific chaperone E (TBCE; 604934)*, located on chromosome 1q42.3.[3] SSS (HRD) is listed in Online Mendelian Inheritance in Man [OMIM] #241410.

The disorder is characterized by congenital hypoparathyroidism leading to early onset hypocalcaemic seizures, prenatal onset of extreme growth retardation, mental retardation and craniofacial dysmorphism. They have typical physical features comprised of a narrow face, deep-set eyes, a beaked nose, large floppy ears, a thin upper lip and micrognathia.[4–8]

We are reporting three Egyptian cases with SSS (HRD) from Cairo University Pediatric Hospital, genetic test was done in only one case due to lack of facilities. Up to our knowledge, these are the first reported cases of SSS (HRD) in Egypt.

Cases

Case 1

An Egyptian boy was presented to Diabetes Endocrine Metabolism Pediatric Unit (DEMPU) clinic; at the age of 9.13 years; with extreme short stature (−7.12 SDS), microcephaly, dysmorphic facies (abnormal teeth with dental caries, beaked nose, deep set eyes, retrognathia, thin lips, low set large ears, pigmented tongue)

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(Fig. 1), small hands and feet, positive signs of latent tetany, bilateral palpable pea sized testes with normal sized penis and scar of orchiopexy. He had average intelligence. He had history of cesarean section, full term, low birth weight (LBW): 1.700 kg, there is history of neonatal hypocalcaemic convulsions, bilateral undescended testes operated upon at the age of 5 years, no history of repeated infection. Systemic examination including the cardiovascular system is normal.

His lab results showed low total calcium (Ca): 7.23 mg % (normal range: 9–11 mg/dL), low ionized Ca: 0.9 mmol/l (normal range: 1.19–1.29 mmol/l), high phosphorous (PO4): 7 mg/dl (normal range: 2.4–4.5 mg /dL), normal alkaline phosphatase (ALP): 164 IU/L (normal range: 55–260 IU/L), and serum parathyroid hormone (PHT): 0.5 pmol/L (normal range: 1.2–7.2 pmol/L). Complete blood count, liver functions, renal functions, and urine analysis were within normal limits. Genetic analysis of the case revealed mutation: 12 bp (155-166del) deletion within *TBCE* gene in exon 3. The patient was treated by Vitamin D and calcium. Informed consent was obtained from the parents prior to implementing the genetic study reported here.

Case 2

A male patient first presented at the age of 2 months with generalized tonic clonic convulsions with no history of trauma or fever. Investigations done at that time revealed Ca: 5.5 mg/dl (normal range: 9–11 mg/dL), PO4: 7.9 mg/dl (normal range: 2.4–4.5 mg /dL), ALP: 142 U/L (normal range: 55 U/L–260 IU/L), PTH < 0.3 pmol/L (normal range: 1.2–7.2 pmol/L). Complete blood count, liver functions, renal functions, and urine analysis were within normal limits. The patient was diagnosed as primary hypoparathyroidism and started calcium and vitamin D therapy and convulsions were controlled.

He was full term, normal vaginal delivery, birth weight: 1.75 kg, 1st offspring of non- consanguineous marriage.

Follow up of the patient revealed severe growth retardation, height was at −6.7 SDS, weight was at −5.3 SDS and BMI was at −4.2 SDS.

The patient had typical facial dysmorphism, consisting of prominent forehead, deep set eyes, abnormal external ears, microcephaly, microphthalmos, thin upper lip, beaked small nose, micrognathism, and small hands and feet (Fig. 2). Systemic examination including the cardiovascular system was normal.

Case 3

A 2-year old boy; the first child of a non-consanguineous marriage; he was full term and had normal vaginal delivery after uncomplicated prenatal period. He was small for gestational age.

The patient had jitteriness during the first week and then he developed frank tonic convulsions at the age of 25 days that was caused by hypocalcaemia; the serum Ca level was 5 mg/dL; for which Vitamin D and calcium supplements were given. The patient discontinued therapy after 1 month.

Within the next few months the mother noticed that her son had an abnormal sound during breathing (stridor) which became more noticeable during crying. At the age of 10 months the patient developed convulsions with a serum calcium level of 6 mg/dl for which he was supplemented with calcium and Vitamin D. Lab investigations showed; Serum Ca: 8.7 mg/dl, Po4: 8.2 mg/dL, ALP: 152 U/L, and PTH level: 1.9 pmol/L.

At the age of 1 yr and 6 months the patient developed recurrent attacks of dysuria accompanied by fever and the condition was associated with loin pain. Urine analysis revealed WBCs 20–25/HPF, RBCs 6–8/HPF. Urine culture showed no growth and kidney functions were normal. CT abdomen showed bilateral renal pelvic stones and mild hydroureter and hydronephrosis.

The patient was then referred to the DEMPU clinic. On examination, at the age of 2 years; height was at −2SDS, weight was at −2 SDS. He had dysmorphic facies: microcephaly, deep-set eyes, beaked nose, thin upper lip, long philtrum, micrognathia, flappy low set ears. He had delayed motor and mental development. Cardiac examination was normal. No similar conditions in the family (Fig. 3).

Lab investigations revealed; PTH: 1.2 pmol/L (normal: 1.2–7.2 pmol/L), triiodothyronine (T3): 133 ng/dl (normal: 100–280 ng/dl), tetraiodothyronine (T4): 13.8 μg/dl (normal: 7.5–15 μg/dl), thyroid stimulating hormone (TSH): 2 μIU/ml (normal: 1.7–9 μIU/ml), the serum uric acid: 6.6 mg/dl (normal: 2–5.5 mg/dl), urinary Ca/Cr ratio: 0.06 (normal: 0.3–0.8), and uric acid/creatinine ratio: 1163 mg/g (normal: 104–593 mg/gm). Complete blood count and kidney function tests were within normal limits.

The patient received supportive treatment for his renal stones with no surgical intervention. One month later, the patient presented to the emergency department with a 5 day history of anuria; and renal function tests showed renal impairment, peritoneal dialysis was done and renal stones were surgically removed.

Discussion

Sanjad Sakati Syndrome (HRD syndrome) is a rare autosomal recessive congenital disorder with equal distribution in both sexes and the gene of the syndrome is on chromosome 1q42-q43 and has severe and often fatal consequences.[3]

It is characterized by congenital hypoparathyroidism, severe prenatal and post-natal growth retardation as well as mild to severe mental retardation. The common dysmorphic features of the syndrome are microcephaly with prominent forehead, deep- set eyes, thin lips, depressed nasal bridge with peaking of the nose, large floppy ear lobes and small hands and feet.[4–8]

Although some of the features resemble DiGeorge Syndrome, Kenny-Caffey Syndrome and familial Hypoparathyroidism, absence of association with cardiac lesion, lymphopenia or skeletal abnormalities makes it a distinct entity.[9] Ocular examination helps to differentiate the Kenny-Caffey syndrome and SSS (HRD). Nanophthalmos and corneal opacity are documented in Kenny-Caffey syndrome patients, but ocular disease is not well-described in SSS (HRD) apart from the external ophthalmic features[10]

It is commonly described in the Middle East population of Arab origin; reported patients were from Saudi Arabia, Qatar, Israeli Arab, Kuwait, Oman, Morocco and Tunisia.[2–5,7,9,11–15] The first case was described by Sanjad et al.[2] in Saudi Arabia and then they published 12 cases in 1991[4]; 6 girls and 6 boys. Symptoms had occurred in the newborn period in nine of them; all have severe hypocalcaemia associated with hyperphosphatemia and low concentration of immune-reactive parathyroid hormone. They have intrauterine growth retardation and dysmorphic facies. None of these babies suffered from congenital heart disease and cell-mediated immunity measured in five patients was normal.

Richardson and Kirk described the cases of 4 boys and 4 girls with this syndrome who were the products of 7 consanguineous marriages, 2 of the patients being brothers. In the remaining 6 families, a further 4 children had affected sibs who had died in infancy. The height, weight, and head circumference scores in all 8 children were less than -2 SD from the mean for their ages. Children had identical facies. Medullary stenosis and other skeletal defects were found in 7 of 8 children. Reduced numbers of T-cell subsets were found in 4 of 4 tested. The first one was born in UK of first cousin parents from Qatar and the other children was simply described as being from the Middle-eastern region. Although some features

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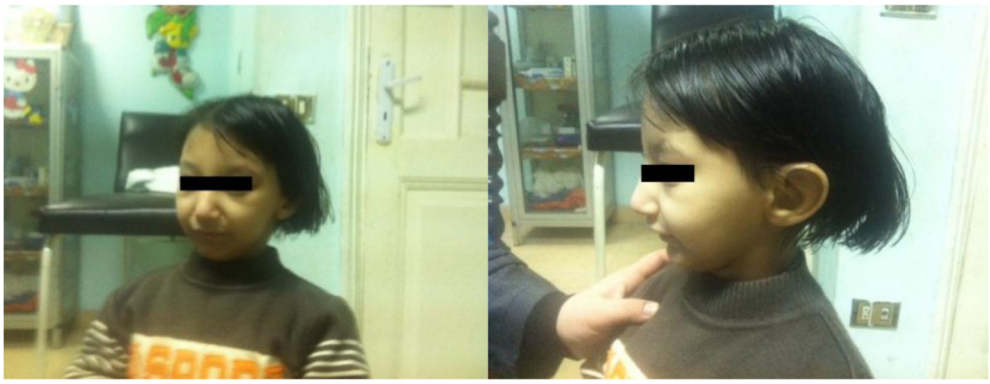

Fig. 1. Dysmorphic facies of Case 1.

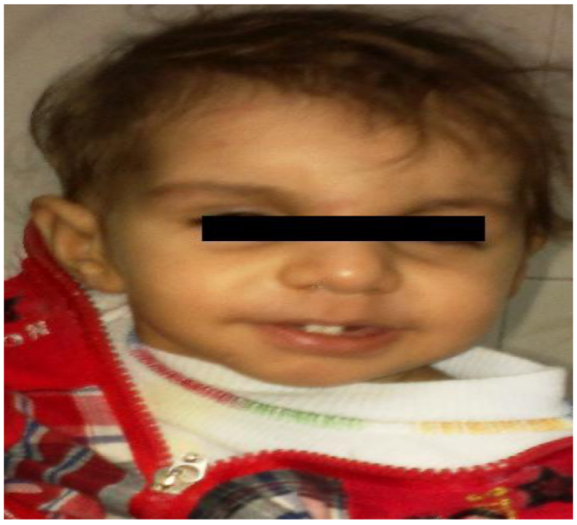

Fig. 2. Dysmorphic facies of Case 2.

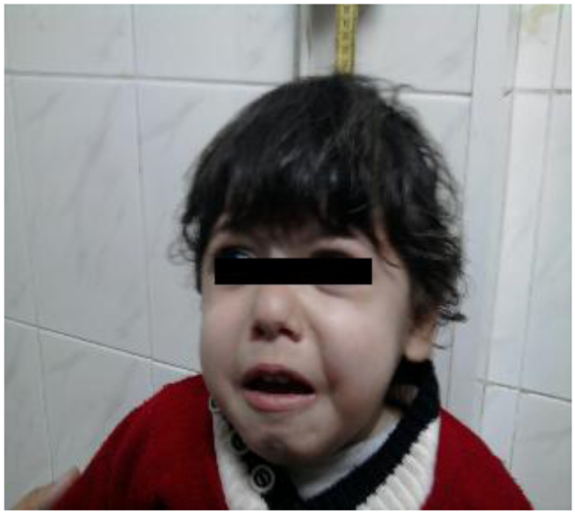

Fig. 3. Dysmorphic facies of Case 3.

suggested DiGeorge syndrome or the Kenny-Caffey syndrome, the conclusion was that it indeed represents a separate entity.[11]

Marsden et al. described an affected 5-year-old Saudi Arabian girl born of consanguineous parents. Parathyroid hormone was undetectable, although her renal response to the infused hormone was normal. Growth hormone levels remained subnormal following arginine and L-DOPA stimulation. After clonidine, the growth hormone level rose to 15 ng/ml at 120 min. Treatment with human growth hormone produced a marked increase in height and weight.[13]

Six more cases were published; 3 boys and 3 girls of Arab Bedouin origin from the Negev with the same features of the syndrome. Ethnicity and clinical features indicated that it is the same disorder as that reported from Saudi Arabia.[16] Ratbi et al. reported on the first clinical and molecular description of a Moroccan patient with SSS (HRD) and characterized the Bedouin mutation c.155-166del in the proband.[14] A recent report on a Tunisian child with SSS (HRD) who was homozygous for the 155-166del mutation provided an additional support of the common (155-166del) deletion founder effect in exon 3 of the *TBCE* gene in Arab patients. This is the same mutation detected in the first patient in our report. It is very likely that this mutation originated in the Middle East and was introduced in Egypt, Tunisia and Morocco by the Banu Hilal invaders with the spread of Islam to North-Africa in the 7th century.[15]

Parvari et al. used homozygousity and linkage disequilibrium to map the gene for this disorder to a 1-cM interval on 1q42-q43 and demonstrated that both autosomal recessive Kenny-Caffey syndrome and SSS (HRD) are caused by mutations in *TBCE* gene.[3]

Conclusion

The early recognition of the disease allowed for proper treatment of the patients, prevented associated co-morbidities, provided a genetic counseling to their families, and enriched the genetic data concerning this syndrome on the Egyptian population being reported for the first time.

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