Sanjad-Sakati Syndrome: A Rare Autosomal Recessive Disorder of Congenital Hypoparathyroidism-Microcephaly-Mental Retardation-Seizures-Growth Retardation and Dysmorphism

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Abstract

Three families with seven patients (three males and four females) represented by repeated attacks of seizures and hospitalized in Taef Children Hospital. These patients were seen over a period of 9 months. All patients shared most of the typical dysmorphic features of Sanjad-Sakati syndrome as microcephaly, deep set eyes, beaked nose, micrognathia, abnormal ear malformations, short stature and small hands and feet. In addition to the previous features, hypoparathyroidism was diagnosed by laboratory investigations and showed low calcium concentration, high phosphorus level and low immuno-reactive parathyroid hormone level. All the patients had normal karyotype. Accurate and proper clinical examination was of great importance to differentiate this syndrome from another similar syndrome known as Kenny-Caffey syndrome which has the same homozygous deletion in TBCE gene. We recommended molecular study for all the patients and their parents which confirms the diagnosis and gives great help in genetic counseling.

Key Words: Seizures – Hypoparathyroidism – Dysmorphism.

Introduction

CONGENITAL hypoparathyroidism in association with growth and mental retardation, seizures and dysmorphic features has been reported from the Middle East in children of consanguineous parents, was first described by Sanjad et al. [1], known as Sanjad-Sakati syndrome or Middle-East syndrome or Richardson-Kirk syndrome [2].

Sanjad-Sakati syndrome (SSS) is a rare autosomal recessive disorder, characterized by congenital hypoparathyroidism as associated with severe prenatal and postnatal growth retardation with dysmorphic features. Facial anomalies in this syndrome include: Beaked nose, deep seated eyes or enophthalmous, depressed nasal bridge, long philtrum, micrognathia or retrognathia, thin lips and ear abnormalities. Microcephaly with various degrees of mental retardation ranging from mild to severe degree. Short stature, small hands and feet are very frequency signs. Seizures (any type) are one of the most cardinal signs of this syndrome and may be the main cause of death. In addition to the previous signs, abnormal phosphorus/calcium metabolism is a frequent sign, while cellular immune deficit is an occasional sign [3].

In this study, three families with children of Sanjad-Sakati syndrome (SSS) (7 cases and they have 6 relatives died with the same syndrome), represented with severe hypocalcemic tetany or convulsions and by clinical examination they fit with the features of Sanjad-Sakati syndrome.

All patients were symptomatic in the newborn period. Their hypocalcemia was associated with hyperphosphatemia and very low concentrations of immune-reactive parathyroid hormone. Cell-mediated immunity measured in only five patients and it was normal. There were no chromosomal abnormalities in all patients. All patients had severe intra-uterine and postnatal growth retardation. Four patients have died, the remaining patients were on treatment in the form of vitamin D and calcium in addition to symptomatic anticonvulsant drugs, but there was no change in growth pattern.

The purpose of this study is to elicit early clinical diagnosis of this rare autosomal recessive disorder, with early medical intervention to prevent the high morbidity and mortality rate of this syndrome. Molecular study is very important as there is a known gene locus in the Middle East area, which helps much in further prenatal diagnosis through amniocentesis molecular study in further pregnancy.
Patients and Methods

This study includes three families with seven children (three males and four females) were referred to Taef Hospital with severe hypocalcaemic tetany or convulsions. They were seen over a period of 9 months. All patients were fit clinically for the criteria of Sanjad-Sakati syndrome. The 1st family had two male sibs patient and they had other male sib and male cousin of the same condition, both died at 11 and 5 years old respectively.

The 2nd family had 3 female cousins and one female sib died at the age of 2 months. The 3rd family had a female and her male 2nd cousin patients (she had 2 female sibs died at age of 2 months and 5 years respectively, as well as, her female cousin died at age of 2 years, all had the same criteria of Sanjad-Sakati syndrome. A full explanation of the study had been provided to the studied cases’ parents and written consent had been obtained.

Four each case the following was conducted:

- Three-generation pedigree analysis including consanguinity, similar conditions and other affected members in the family.
- Detailed full clinical examination including history taking, physical examination with special emphasis on dysmorphic features. Measurements of the patients were taken and estimated through international growth curves.
- Cytogenetic study for each patient with analysis of chromosomal study.
- Laboratory investigations including serum calcium, phosphorus and quantitative estimation of radio-immune assay of parathyroid hormone.
- Other investigations as EEG, MRI, complete eye evaluation, cell-mediated immunity tests and complete ENT evaluation in some but not all patients.

Results

Cases:

Family 1:

Two affected male sibs complaining of repeated attacks of hypocalcaemic convulsions, having other male sib and male cousin complaining of the same condition, both died at 11 and 5 years old respectively. This family showed positive consanguinity as shown in Fig. (1) for all affected patients. Their hypocalcemia was associated with hyperphosphatemia and very low concentration of immune-reactive parathyroid hormone indicating hypoparathyroidism. None of both male sibs had congenital heart disease. Cell-mediated immunity was measured and showed normal values. There were no chromosomal abnormalities. Both affected male sibs shared several dysmorphic features including deep seated eyes, beaked nose and depressed nasal bridge. Difficulties for feeding, growth retardation, microcephaly, short stature, micrognathia, thin lips, low set ears with thick ear lobule and small hands and feet. Mental retardation was found in both affected sibs. Both patients were on treatment of vitamin D and calcium supplements with no change in their growth pattern. The previous dysmorphic criteria of both sibs in addition to hypoparathyroidism with growth retardation coincided with Sanjad-Sakati syndrome (SSS).

Family 2:

Three affected female cousins and female sib died at age of 2 months had the same condition but not diagnosed and died from convulsions. One affected female was an outcome of a consanguineous marriage Fig. (2). The affected female sought medical advice in Taef Children Hospital complaining of convulsions associated with dehydration. She was hospitalized and received fluid infusions. Investigations showed low calcium concentration, high phosphorus level associated with low concentrations of immune-reactive parathyroid hormone. EEG showed generalized hypersrrhythmia. Full clinical examination including history taking showed other similar affected female sib and other affected family members. Dysmorphic features including deep seated eyes, microcephaly, growth retardation, small hands and feet, thin lips, micrognathia, low set malformed ears and beaked nasal tip. Cytogenetic study was done and showed no chromosomal abnormalities. After one week the patient discharged and put on vitamin D and calcium supplements regime and advised for regular check up. This female patient was fit with the criteria of this rare autosomal recessive syndrome.

Family 3:

An affected female and her male second cousin. She had 2 female sibs died at the age of 2 months and 5 years respectively as well as a female cousin died at age of 2 years. All of them had the same condition. This family showed +ve consanguinity for all affected patients Fig. (3). This female patient was hospitalized in Taef Children Hospital complaining of repeated attacks of convulsions associated with chest infections. Investigations showed anemia, leucocytosis, low serum calcium and high level of phosphorus. After these results, further investigations were done and showed very low
concentrations of immune-reactive parathyroid hormone. Full clinical examination of the patient showed growth retardation, microcephaly, short stature, deep seated eyes, low set malformed ears, micrognathia, thin upper lip, depressed nasal bridge and small hands and feet Fig. (4). Later, cytogenetic study was done and showed normal female karyotyping.

Fig. (1): Pedigree analysis of family (1) showed two affected male sibs. They had other male sib and male cousin both died at 11 and 5 years respectively. Both had the same condition. Pedigree analysis of this family showed +ve consanguinity for all affected patients.

Fig. (2): Pedigree analysis of family (2) showed three affected female cousins and one female sib died at age of 2 months. She had the same condition but was not diagnosed and died from convulsions. One affected female was an outcome of consanguineous marriage.
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Fig. (3): Pedigree analysis of family (3) showed an affected female and her male 2nd cousin. She had 2 female sibs who died at age of 2 months and 5 years respectively as well as female cousin who died at age of 2 years. All of them had the same condition. Pedigree analysis of this family showed +ve consanguinity for all affected patients.

Fig. (4): Affected female patient with dysmorphic features of Sanjad-Sakati syndrome as deep set eyes, thin lips, low set and malformed ears, micrognathia, microcephaly, growth retardation and small hands and feet.

All the patients of these 3 families shared common specific dysmorphic features of Sanjad-Sakati syndrome. Also, all of them showed microcephaly, growth retardation, mental retardation with signs of congenital hypoparathyroidism in the form of low immune-reactive parathyroid hormone, low calcium level and high level of phosphorus. All the patients showed normal karyotyping excluding any chromosomal abnormalities. In further step, we recommended molecular study for all the patients and their parents as the gene locus is nearly known for this rare autosomal recessive syndrome especially in the middle east which help much in genetic counseling for these families.

Discussion

Sanjad-Sakati syndrome is a rare autosomal recessive disorder characterized by congenital hypoparathyroidism, mental retardation, growth retardation, microcephaly, seizures and specific dysmorphic features mainly facial anomalies with especial emphasis of ophthalmic manifestations which help much to distinguish from other disorders as Kenny-Caffey syndrome [4].
In this study, all the affected patients in these 3 different families showed most of the dysmorphic features of Sanjad-Sakati syndrome. Clinically, it was important to be differentiated from other middle-east syndrome sharing the same locus of Sanjad-Sakati syndrome known as Kenny-Caffey.

Khan et al. [8] described a syndrome resembling Sanjad-Sakati syndrome and has the same homozygous deletion in TBCE (155-166del) in Saudi Arabian patients, known as Kenny-Caffey syndrome [6]. Both syndromes sharing the same gene locus, but clinically, Kenny-Caffey has different clinical features. It is characterized by normal intelligence, late closure of anterior fontanel, macrocephaly and postnatal (rather than prenatal) growth retardation. Ophthalmologic features differ among both syndromes. In Sanjad-Sakati syndrome, ocular findings include errors of refraction, deep seated eyes, strabismus and retinal vascular tortuosity [7]. While, in Kenny-Caffey syndrome, anophthalmous and corneal opacity have been documented in this syndrome patients, but ocular disease has not been documented in Sanjad-Sakati syndrome apart from the external ophthalmic features [8].

In this study, we recommend molecular study as further step for all patients and their parents as the gene locus is nearly known for this rare autosomal recessive disorder especially in Saudi Arabia (Middle East) which help much genetic counseling for these families. Hellani et al. [8] found that in Saudi Arabia, the disease of Sanjad-Sakati is caused by deletion of 12bp (155-166nt) in the tubulin-specific chaperone E gene. Also, Courtens et al. [9] supported the previous finding as they found that, Sanjad-Sakati disorder had been mapped to the long arm of chromosome 1 (1q42-q43) and mutations in the gene coding for tubulin-specific chaperone E (TBCE) had been identified as the cause of the disease. Mutations in the same gene were also reported in patients with autosomal recessive Kanny-Caffey syndrome. This finding, combined with the clinical similarity between the two syndromes, suggests that the two conditions are not only allelic, but are also caused by the same ancestral mutation [10]. Kelly et al. [11] and Parvari et al. [6] demonstrated that both autosomal recessive Sanjad-Sakati syndrome and the Kenny-Caffey syndrome maps to the same region of Sanjad-Sakati syndrome and suggested that these were likely to be allelic disorders, if not the same condition. So, in our study, it was of great importance, to do proper clinical examination in order to differentiate between both syndromes.

It was not surprising during study of these 3 families to observe that, more than affected sibs were diagnosed, as Al Tawil et al. [12] reported female triplets with the clinical and biochemical manifestations of Sanjad-Sakati syndrome. They were born at 35 weeks gestation after assisted pregnancy (in vitro fertilization). Consanguinity plays a role, as their parents were first cousins and also from Middle East (Saudi Arabia). This indicates that, although it is a rare syndrome, consanguinity is these areas of Middle East especially in Saudi Arabia, will increase its rate of appearance.

Conclusion and Recommendation:

In conclusion of this study, proper and accurate clinical examination of this rare syndrome with especial emphasis on dysmorphic features to differentiate from another similar autosomal recessive disorder "Kenny-Caffey syndrome" is of great importance for accurate diagnosis. Our recommendation as a further step is if possible to do molecular study for TBCE gene, which confirm our clinical evaluation and help much in genetic counseling for these families with affected members.

References

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