SPECTRUM OF PHENOTYPIC PRESENTATION OF SANJAD SYNDROME_ JORDANIAN CASE SERIES:

Basma .Sarir ,1 ,2 Najat .Jerby 2, D.Majali,1 R.Aledwan1,H.ALawneh 1.
1Department of Pediatrics, queen Rania AL Abdulla Hospital, Amman, Jordan.
2 Department of pediatrics, Sabratah teaching hospital , Sabratah , Libya
Correspondence toH.ALAWNEH:H.Alawneh@yahoo.com,B.SARIR:srir.basma.1980@gmail.com).

Abstract:

The syndrome of hypoparathyroidism associated with growth retardation, developmental delay, and dysmorphism (HRD) is autosomal recessive, congenital disorder with severe, often fatal consequences. It is presumed to be caused by homozygous inheritance of a single recessive mutation from a common ancestor. Since the syndrome is very rare, with all parents of affected individuals being consanguineous. (2) All affected persons had homozygous deletion of 12 bp (155–166del) in exon 3at 1q42-43 of the TBCE gene. All of the parents were heterozygous carriers of this mutation. (3)

Aim: We aimed to clarify the clinical spectrum of HDR.we also wanted to focus on uncommon, serious complications of HDR.to increase awareness of sanjad syndrome among pediatricians.

Method:We reviewed the Hospital records for the Period 2000–2016,we studied fifteen patients sequently (eight boys, seven girls) from 10 Jordanian families.

Result: All our patients were presented with severe hypocalcaemic tetany or convulsions to our pediatric endocrinology clinic. All patients shared several dismorphic features including deep set eyes, microcephaly, thin lips, beaked nose tip, micrognathia, and depressed nasal bridge, and Mental retardation of varying degree was found in all patients (1).

Conclusion: Most of them were symptomatic in the newborn period. Their hypocalcaemia was associated with hyperphosphataemia and very low concentrations of immunoreactive parathyroid hormone. Two of the babies suffered from simple congenital cardiac disease (small ASD), while one patient had pulmonary hypertension.All had severe intrauterine and postnatal growth retardation. Two patients have died. The remaining thirteen patients are on treatments with 1-α vitamin D_3/calciumsupplements with no change in their growth pattern. (1)

Introduction:

Sanjad Sakati syndrome has been reported in areas of the Middle East and has a high prevalence among Arabs. Since it may be confused with other syndromes that can present with hypocalcaemia And dysmorphic features, genetic testing allows Sanjad Sakati to be excluded in any child

presenting with hypocalcaemia anddeep-set eyes. Theavailability of genetic testing enables accurate diagnosis Of affected children, discovery of carriers and prospective counseling as well as prenatal diagnosis of Sanjad Sakati syndrome. (HRD) is an autosomal recessive disorder that was first described in 1988. It is Characterized by congenital hypoparathyroidism, growth and mental retardation with distinct phenotypic features. It is linked to the TBCE gene on chromosome 1q42-43 which encodes for the tubulinspecific chaperone E protein. (5)

The presenting compliant in most of the patients was hypocalcaemic seizure, generalized type, usually detected in the first days or weeks of life. The age at diagnosis of ranged from 1st week of life to 12 years. HDR syndrome it is not uncommon in the Gulf area, especially Saudi Arabia. The incidence in Saudi Arabia varies from 1:40,000 to 1:100,000 live births. Male to female ratio was equal. (6

Some authors consider it a variant of Kenny- caffey syndrome type 1. (6).This case series reports 15 patientswith Sanjad Sakati syndrome from 10families in Jordan, 4of them were first degree parent. (5

Case Series:

We reviewed the Hospital records for thePeriod 2000–2016, we
Have 15 casesof HDR. Information was extractedfrom the medical records and personalinterview.All the patients first presentedduring the neonatal period, at around2–3 weeks of age, with hypocalcaemicseizures (7). They were low birth weight.
All 15 patients had measurements taken of their calcium, phosphorus andparathyroid hormone (PTH) levels; 3 had brain imaging and 2 had skeletal survey, 2 patients had Dexa scan, 2 patients had bone age,and 5 patients had an ophthalmologicalAssessment. All of the patients werediagnosed biochemically to have hypoparathyroidismby the low levelsof PTH, hypocalcaemia and elevatedphosphorus levels (Table 1). All ofthe patients were put on 1-α vitamin D_3/and calcium supplements. 4patientsDevelopedmild bilateralmedullary renal nephrocalcinosis as a complication of the treatment.One patient had refractory hyperphosphataemia.One patient had recurrent hospitalAdmissions for chronic constipation and intestinal pseudo-obstruction.One patient had recurrent pneumonia with pulmonary hypertension. And2 patients died at hospital in July2015, March2016 respectively. One died post sever chest infection, in ICU .Other patient died one month post operative for visceral myopathy.

Phenotypic features:

All the patients had severe failure tothrive, microcephaly, delayed motormilestones, mental retardation andlearning difficulties. All of them hadteeth abnormalities such as delayedteething, dental caries or abnormalteeth. They had distinct dysmorphicfeatures including: deep-set eyes, micrognathia,depressed nasal bridge,microphthalmia, prominent foreheadand small hands and feet.

Family history:

Parental consanguinity was reported in 7 families out of 10 families. The parents of 4 caseswere first cousins. Three patients hada positive family history of the same condition, all of them were siblings.

Imaging results:

Three patients underwent brain imaging:2 cases showed normal brain imaging, 1case had Chiari malformation type 1. Skeletalsurvey was normal in 2patients. Boneage was assessed for 2 patients and wasdelayed in both.DEXA scan was done for 2 pateints, 1 case had osteopenia, Z score -2.4, and other case had osteoporosis, Z score -5.1.Echocardiography was assessed for 5patients, 3 cases had normal Echocardiographical study, 1 case had small ASD, and PDA, 1 case had mitral valve prolapse with pulmonary hypertension.

Renal ultrasonography was requested for all 15 patients, 4 cases had bilateral mild medullary nephrocalcinosis, while rest of cases had normal results.

DENTAL ASSESSMENT:

Most of our cases have micrognathic mandible, hypoplastic maxilla, thinupper lip; High archedpalate,microdontia,and enamel hypoplasia defects.

Ophthalmological assessment:

It was done for 7patients and it showed abnormalretinal vessels dilatation and tortuosityin 1case, retinal hemorrhage in 1 case, myopia in 3cases, and hypermetropia in the 3patients.

Genetic testing:

We did not do genetic testing for our patients, they were diagnosed clinically, supporting with laboratory finding.

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 special emphasis of ophthalmic manifestations which help much to distinguish from other disorders as Kenny-Caffey syndrome(4).This condition is associated with metabolic and septic complications starting in the neonatal period. Chronic intestinal pseudo obstruction owing to visceral myopathy is a rare disabling condition. We report a rare concurrence of Sanjad-Sakati syndrome and chronic intestinal pseudo obstruction in a Jordanian male child,10 years of age .he complicated by intestinal failure due to visceral myopathy,bacterial and

fungal sepsis, and early mortality in one month post operative.

Also, he was suffering from sever malnutrion, although he was on TBN.As well he tried on NG feeding which was failed.

Pseudo-obstruction syndromes result in features suggestive of mechanical obstruction and bowel dilatation in the absence of any demonstrable obstruction or mucosal disease. The syndrome may affect any region of the gut. Less severe variants without bowel dilatation are diagnosed by measurement of gastrointestinal transit and pressure profiles. The aims of treatment are restoration of nutrition and hydration, symptom relief, normalization of intestinal propulsion with prokinetics, and suppression of bacterial overgrowth. Surgery plays a limited role, adjunctive to medical treatment, facilitating enteral nutrition and decompression by means of jejunostomy. Infrequently, resection of localized disease or intestinal transplantation is indicated. The roles of intestinal pacemakers (interstitial cells of Cajal) and genetic mutations in the etiology of pseudo-obstruction, as well as the cost-benefit ratio of transplantation for pseudo-obstruction, will be clarified in the future

Conclusion and Recommendation:

In conclusion of this study, proper and accurate clinical examination of this rare syndrome with special emphasis on dysmorphic features to differentiate from another similar autosomal recessive disorder "Kenny-Caffey syndrome" is of great importance for accurate diagnosis(8).The treatment of patients with Sanjad Sakati syndrome is a challenge for most physicians especially in controlling their
High phosphate levels and the adverse effects of therapy include generalized calcifications, as seen in one of our patients (9).

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:

1. Sanjad S, Sakati N, Abu-Osba Y. Congenital hypoparathyroidism
With dysmorphic features: a new syndrome. Pediatric Research, 1988, 23:71A.

2. Sanjad SA et al. A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features. Archivesof Disease in Childhood, 1991, 66(11):193–196. Naguib KK et al. Sanjad–Sakati syndrome

3. Naguib KK et al. Sanjad–Sakati syndrome/Kenny–Caffey syndrome type 1: a study of 21 cases in Kuwait. Eastern MediterraneanHealth Journal, 2009, 15(2):345–352.

4. Hershkovitz E et al.Hypoparathyroidism-retardation-Dysmorphism (HRD) syndrome—a review. Journal of Pediatric Endocrinologyand Metabolism, 2004, 17 (12):1583–1590.

5. Hershkovitz E et al. The new syndrome of congenital hypoparathyroidism associated with dysmorphism, growth retardation, and developmental delay—a report of six patients. IsrealJournal of Medical Sciences, 1995, 31(5):326–327.

6. KHAN A.O., AL-ASSIRI A. and AL-MESFER S.: Ophthalmic features of hypoparathyroidism-retardation-dysmorphism. JAAPOS, 11 (3): 288-290, 2007.

7-PARVARI R., HERSHKOVITZ E., GROSSMAN N. and LOEYS B.: Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nature Genet, 32: 448-452, 2002.

8-MARSDEN D., NYHAN W.L. and SAKATI N.O.: Syndrome of hypoparathyroidism, growth retardation and multiple minor anomalies. Am. J. Med. Genet, 52: 334- 338, 1994.

9-HELLANI A., AQUEEL A., JAROUDI K., OZAND P. and COSKUN S.: "Pregnancy after preimplantation gentic diagnosis for Sanjad-Sakati syndrome". Prenat. Diagn., 24 (4): 302-306, 2004.