Original Article

Clinico-Epidemiological Study of Iraqi Children with Sanjad Sakati Syndrome

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Abstract

Background: Sanjad Sakati syndrome (SSS), also known as hypoparathyroidism–retardation–dysmorphism, is a very rare genetic disease caused by a mutation in the tubulin co-factor E gene. It is a chronic, progressive condition for which palliation is the basis of care. **Objectives:** The objective of this study is to investigate the clinico-epidemiological features of patients with SSS in a highly specialized endocrine center in Iraq. **Materials and Methods:** This is an observational retrospective study including all patients with SSS who were registered in the endocrine clinic of the Children Welfare Teaching Hospital/Medical City Complex in Baghdad, Iraq. The demographic data and information regarding history and physical examination concentrating on dysmorphic features, results of investigations, drugs used, and any comorbidities were collected and documented. **Results:** A total of 24 patients were registered and included in the study, with 14 (58.3%) males and 10 (41.7%) females, resulting in a male-to-female ratio of 1.4:1. Thirteen patients (54.2%) were diagnosed during the first year of life. Nineteen patients (79.1%) had low birth weight, and consanguinity between parents was positive in 15 patients (62.5%). All patients (100%) presented failure to thrive, dysmorphic features, and developmental delay. Nephrocalcinosis was present in 11 patients (45.8%). Comorbidities included growth hormone deficiency in 20.8%, hypothyroidism in 16.7%, and epilepsy in 8.3% of patients. One patient had intestinal pseudo-obstruction, and two patients (8.3%) died due to recurrent chest infections. **Conclusion:** In conclusion, although SSS is a rare disease, its incidence has increased in Iraq. Its management requires teamwork to improve the quality of life of affected individuals and address complications and comorbidities. Genetic counseling is also crucial for decreasing its incidence.

Keywords: Dysmorphism, growth hormone, hypoparathyroidism, hypothyroidism, intestinal pseudo-obstruction, retardation, Sanjad Sakati syndrome

Introduction

Sanjad Sakati syndrome (SSS), also known as hypoparathyroidism–retardation–dysmorphism is a very rare genetic disease first reported in Saudi Arabia in 1988 by Ahmed *et al*.[1] Bouattour *et al*. in 1990[2] also reported this syndrome, followed by David *et al.*[3] in 1992. Subsequent reports of this syndrome came from Kuwait, Oman, and Qatar.[4] The condition is referenced in the Online Mendelian Inheritance of Men database under the number 241410.[5] The tubulin co-factor E (*TBCE*) gene, located on chromosome 1q42-q43, is the cause of SSS. The *TBCE* gene encodes a molecular chaperone necessary for the heterodimerization of the two tubulin subunits alpha and beta.[6-8] SSS is usually diagnosed clinically and it is characterized by microcephaly, deep-set eyes, a depressed nasal bridge, a beaked nose, long philtrum, teeth anomalies, micrognathia, small hands and feet, severe growth retardation, and occasionally, cellular immune defects.[1,3] Patients frequently exhibit symptomatic hypocalcemia in infancy along with low serum parathyroid hormone levels. Patients with SSS have healthy cardiovascular systems, but as infants, they are at risk for developing potentially fatal pneumococcal infections.[8-10] Importantly, following treatment with growth hormone (GH), a noticeable increase in their

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height was observed.[11] Alsaffar *et al*.[12] advised routine thyroid screening for SS patients because they observed deranged thyroid status in one-third of their study participants. Short stature may develop in most SSS patients due to a combination of defects affecting GH, insulin-like growth factor 1 (IGF-1), thyroid hormone secretion, malnutrition, and recurrent infections.[11] SSS and superior mesenteric artery syndrome may share symptoms of intestinal obstruction.[13] A second case involved a Saudi infant who had an unusual combination of SSS and chronic intestinal pseudo-obstruction, which was further worsened by intestinal failure, sepsis, and early mortality.[14] Microcephaly, developmental delay, and seizures are examples of neurological signs and symptoms. Some patients had evidence of intracranial calcifications on brain imaging.[15] Patients with SSS display a variety of ocular findings including errors of refraction, strabismus, and retinal vascular tortuosity.[16] Additionally, some of them frequently have sleep breathing issues, notably obstructive sleep apnea.[17] The diagnosis of SSS may be aided by the recognition of orofacial characteristics, such as oligodontia/hypodontia, a high-arched palate, and a deep overbite.[18] The most crucial step in treating such patients is ruling out other conditions that may present similarly but require entirely different care, such as Kenny–Caffey syndrome and DiGeorge syndrome.[19] Treatment of patients with SSS poses a unique challenge for all medical professionals.[20,21] SSS is an untreatable syndrome, and the exclusive focus of treatment is on managing individually presented conditions.[22] Since growth retardation is almost always a concern among these patients, treating that deficiency is part of the primary management.[23] Other endocrinological dysfunctions, such as GH deficiency, typically do not respond to GH therapy.[4] Levothyroxine must be used to treat hypothyroidism, as with any other medical issue. Mental, neurological, and endocrine disorders may complicate the management of patients' dental care.[18] It is recommended that the parents of the affected child receive genetic counseling. In the future, pre-implantation genetic diagnosis and carrier detection will make it possible to prevent this illness.[22] SSS is a chronic, progressive condition for which palliation is the basis of care; however, most patients' lifespans are ultimately limited to less than 18 years due to recurrent infections caused by functional hyposplenism.[19] To our knowledge, this is the first study conducted in Iraq on SSS, undertaken in a highly specialized endocrinological center; it aims to study the clinico-epidemiological features of patients with this rare syndrome.

Materials and Methods

This is a statistical observational study including all patients with SSS who were registered in the endocrine clinic or admitted to the ward of the Children Welfare Teaching Hospital/Medical City Complex in Baghdad, Baghdad, Iraq, from January 1, 2023, to June 1, 2023.

The following data were collected from their records and some from the parents themselves after obtaining ethical approval from the hospital directory and the parents themselves. Age of the patients, age at presentation and diagnosis, birth weight, consanguinity between parents, positive family history, and fate of patients were among the data collected. Regarding physical signs, the following information was collected: dysmorphic features (microcephaly, deep-set eyes, thin lips, beaked nose tip, low-set ears, prominent forehead, esotropia, depressed nasal bridge, micrognathia, dental abnormalities, small hands and feet, cryptorchidism, and micropenis in males). Growth measurements including occipitofrontal circumference, weight, and height were measured at diagnosis with plotting on Center for Disease Control (CDC) growth charts (to detect failure to grow), and any developmental delay was documented after detection. The following investigations at the time of diagnosis were collected: serum (S.) calcium, S. phosphorus, S. alkaline phosphatase, and S. PTH. Abdominal ultrasound was performed for all patients initially and during follow-up looking for nephrocalcinosis. Echocardiography was performed for only five patients (who exhibited a murmur on cardiac examination), while brain computed tomography (CT) scan was conducted for eight patients (according to the opinion of the pediatric neurologist for suspected brain lesions after neurological evaluation) looking for intracranial calcification. The drugs used for the treatment in this study include calcitriol or one alpha, calcium carbonate for all patients, And thiazide, thyroxin, anticonvulsants, and GH for some patients. Concurrently, we investigated comorbidities associated with this syndrome and prognosis.

Ethical approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The aim of this study was verbally communicated to the participants, and analytical consent was obtained before any sample was taken. The researcher provided clear descriptions of the purpose and process of the survey to the patients and gave standard instructions and guidance for completing the questionnaire. A local ethics committee at the College of Medicine, University of Baghdad, Baghdad, Iraq, evaluated and approved the study protocol, participant information, and consent form, numbered 2398, on December 18, 2022.

Statistical analysis

In this study, data were entered and analyzed using Microsoft® Excel® 2019 (V16). The data were expressed as numbers followed by percentages (%).

Results

The total number of patients with SSS registered in our clinic and included in the study was 24 patients. Of these 14 (58.3%) were male and 10 (41.7%) were female with a male-to-female ratio of 1.4:1. Fourteen patients (58.4%) were below 5 years of age. The age distribution of patients is presented in Table 1.

The most important parameters of the study sample, including birth weight, failure to thrive, consanguinity, family history, and developmental history, were discussed. We observed that 19 patients (79.1%) had low birth weight. Consanguinity between parents was positive in 15 patients (62.5%). All patients (100%) exhibited failure to thrive, developmental delays, and dysmorphic features, as presented in Table 2.

The important physical findings observed during the physical examination of the study sample are listed in Table 3.

The results of the laboratory, imaging, and echo study are listed in Table 4.

Table 1: Distribution of patients according to the age at diagnosis with their gender

Age (months)/gender	Male		Female		Total	
	N	%	*N*	%	*N*	%
<1	0	0	1	100	1	4.2
1–12	8	61.5	5	38.5	13	54.2
>12	6	60	4	40	10	41.6

Table 2: Distribution of patients according to certain demographic and clinical data and their gender

Variables	Male		Female		Total	
	N	%	*N*	%	*N*	%
Birth weight						
Normal	1	20	4	80	5	20.8
Low	13	68.4	6	31.6	19	79.1
Consanguinity						
Positive	8	53.3	7	46.7	15	62.5
Negative	6	66.7	3	33.3	9	37.5
Family history						
Positive	1	25	3	75	4	16.7
Negative	13	65	7	35	20	83.3
Failure to thrive						
Positive	14	58.3	10	41.7	24	100
Negative	0	0	0	0	0	0
Developmental history						
Delayed	14	58.3	10	41.7	24	100
Normal	0	0	0	0	0	0
Dysmorphic features						
Positive	14	58,3	10	41.7	24	100
Negative	0	0	0	0	0	0

The treatment protocol of patients in the study sample, which includes the drugs needed during the observational period is shown in Table 5.

The comorbidities associated with this syndrome observed during the follow-up period are listed in Table 6.

Two patients died because of chest infections, while others had fair control with medication and regular follow-up in the endocrine clinic. However, some experienced recurrent admissions due to carpopedal spasms, seizures, and chest

Table 3: Distribution of patients according to physical findings

Physical findings	Positive		Negative	
	N	%	*N*	%
Microcephaly	24	100	0	0
Deep-set eyes	24	100	0	0
Thin lips	24	100	0	0
Beaked nose tip	24	100	0	0
Low-set ears	24	100	0	0
Prominent forehead	24	100	0	0
Esotropia	4	16.7	20	83.3
Depressed nasal bridge	24	100	0	0
Micrognathia	16	66.7	8	33.3
Dental abnormalities	18	75	6	25
Small hands and feet	24	100	0	0
Cryptorchidism/14 male	5	35.7	9	64.3
Micropenis/14 males	9	64.3	5	35.7

Table 4: Distribution of patients according to the laboratory and radiological findings

Variables	Normal		Abnormal	
	N	%	*N*	%
Low serum calcium	0	0	24	100
High serum phosphorus	0	0	24	100
High serum alkaline phosphatase	18	75	6	25
Low serum parathyroid hormone	0	0	24	100
Ultrasound/nephrocalcinosis	13	54.2	11	45.8
Echocardiography/five patients	4	80	1	20
CT of head/eight patients	5	62.5	3	37.5

Table 5: Distribution of patients according to the drugs used for the treatment of the patients and their gender

Drugs	Male		Female		Total	
	N	%	*N*	%	*N*	%
Calcitriol	10	50	10	50	20	83.3
Calcium carbonate	14	58.3	10	41.7	24	100
Thiazide	2	33.3	4	66.7	6	25
Thyroxin	2	50	2	50	4	16.7
Anticonvulsants	1	50	1	50	2	8.3
Growth hormone	4	80	1	20	5	20.8

Table 6: Distribution of patients according to associated comorbidities and complications

Comorbidities	Male		Female		Total	
	N	%	*N*	%	*N*	%
GH deficiency	4	80	1	20	5	20.8
Hypothyroidism	2	50	2	50	4	16.7
Congenital heart disease	1	100	0	0	1	4.7
Epilepsy	1	50	1	50	2	8.3
Visceral myopathy	1	100	0	0	1	4.7
Cataract	1	50	1	50	2	8.3

infections. Additionally, we report one case of recurrent admissions due to intestinal pseudo-obstruction.

Discussion

In this study, the total number of patients with SSS registered in our clinic and included in the study was 24 patients, with 14 patients (58.4%) were below 12 months of age. This is similar to the number reported in Kuwait (24 cases)[15] and higher than the number of cases reported in other countries: 15 patients in King Khalid University Hospital in Saudi Arabia between 1990 and 2015,[12] 4 cases in Sudan,[19] 3 cases in Egypt,[10] 12 cases in Oman,[17] and less than 29 Iranian cases.[24] These findings were anticipated because SSS is primarily diagnosed in children from the Middle East, particularly those of Arabian descent. However, there have also been case reports from non-Arab nations.[25]

In this study, 13 patients (54.2%) were diagnosed beyond the neonatal period, during the first year and 10 (41.6%) after that, which is similar to Sudanese cases.[19] It has been reported that most patients present within the first few weeks of birth.[8,25] This delay in the diagnosis may be due to delayed referral to the endocrine unit, considering it is a rare syndrome.

The majority of patients (79.1%) had low birth weight, which is consistent with findings from other studies.[8,18,19,26] Consanguinity between parents was positive in 15 patients (62.5%), which is lower than reported in other studies 75%,[15] 96.5%,[24] and100%.[19] This difference may be related to variations in the number of cases included in the study, as some studies are case reports. Additionally, as SSS is inherited as an autosomal recessive disease, consanguinity is an important factor. Furthermore, a positive family history was observed in 4 patients (16.7%), which is lower than other studies 100%,[4,19] which were case reports.

All our patients (100%) exhibited failure to thrive, dysmorphic features, and developmental delay, consistent with what is reported in the literature and other studies,[8,19,25] as these are typical clinical features of this syndrome.

As most of them exhibited various abnormal physical findings of SSS, only four patients (16.7%) had esotropia compared with eight patients (47%) reported in the study by Al Dhoyan *et al*.[16] Sixteen patients (66.7%) had micrognathia, and 18 (75%) of them had dental abnormalities, consistent with findings reported in other studies.[8,18]

All of the patients in our study had low calcium, high phosphorus, and low PTH, as hypoparathyroidism is one of the essential parts of this syndrome and essential for diagnosis of the syndrome. We noticed six patients had low alkaline phosphatase levels because they had already received vitamin D supplements before underdoing laboratory tests to treat hypocalcemia.

Nephrocalcinosis was present in 11 patients (45.8%) as a complication of hypoparathyroidism and its management. CT scans were performed for 8 patients only, as they had repeated fits, and intracranial calcification was found in 3 patients (12.5%) due to persistent hypocalcemia, which is lower than 29.2% in the study by Elhassanien.[15] This difference may be attributed to the fact that CT scans were performed for only some of our patients.

Apart from drug treatment for hypoparathyroidism, 6 patients (25%) use thiazide for nephrocalcinosis, 4 patients (16.7%) use thyroxin due to hypothyroidism, which is lower than reported in the study by Anteet *et al*.[12], where one-third of his cohort had abnormal thyroid function tests. Two patients (8.3%) were on anticonvulsant drugs due to epilepsy, and GH was administered for five patients (20.8%) for the treatment of short stature, but they had sub-normal GH levels without much benefit and were subsequently stopped, which differs from the study by Hafez *et al*.[10] study, where a noticeable increase in weights and heights was observed after GH treatment. One patient had GH deficiency, and all of the patients in the study by Hershkovitz *et al.*[11] had low serum levels of IGF-1.

Visceral myopathy causing chronic intestinal pseudo-obstruction was reported in one case who is still alive, whereas a previous case was reported by Pal *et al*.[14] in a Saudi child was died because of intestinal failure and sepsis.

Two (8.3%) died because of recurrent chest infections, which is the usual cause of death reported in the pieces of literature.

Conclusions

SSS is a rare disease, but its incidence has increased in Iraq due to the common practice of consanguineous marriage. Its management necessitates teamwork to improve the quality of life for affected individuals, address the treatment of complications and comorbidities, and provide genetic counseling to decrease its incidence.

Recommendation

We recommend conducting further studies to register all cases of SSS in Iraq. This will facilitate better management and the availability of genetic study for diagnosis, enhancing our scientific understanding for early detection and prevention measures.

Author contributions

Munib Ahmed Al-Zubaidi contributed to the research writing. Muneera Fadhil Ridha collected data. Hana Ali Abd-Aljabar performed statistical analysis.

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Conflicts of interest

There are no conflicts of interest.

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