

## **Association of Type - 1 Diabetes Mellitus and Sickle Cell Disease in Children: Case Series from Saudi Arabia**

### **ABSTRACT:**

This case series aims to highlight a unique coexistence of two important diseases in children, sickle cell anemia and diabetes mellitus, which are relatively common in Saudi Arabia. Coexistence of the two diseases in the same patient is very rare, with only few cases reported in the literature. This is the first time to report more than 2 patients with this combination from one center. The involved 4 children are originally from the Southern and Eastern regions of Saudi Arabia representing both the African and Arab-Indian sickle gene haplotypes. The coexistence of the two diseases is not related to the sickle cell disease severity. It also can affect homo- and heterozygous forms of sickle cell disease at any age during childhood from infancy through adolescence. In sickle cell disease patients, Type-1 Diabetes can first present insidiously or as Diabetic Ketoacidosis. No clear explanation to the rarity of this combination is known so far. Diabetes mellitus should be considered in the differential diagnosis of cases with sickle cell disease experiencing abdominal pain, dehydration and acidosis. Further evaluation and comprehensive guidelines tailored for management of this condition are recommended.

**Keywords:** Sickle Cell Disease, Type-1Diabetes, Diabetic Ketoacidosis, Saudi Children

## 1. INTRODUCTION

Sickle Cell Disease (SCD) is an autosomal recessive disorder characterized by production of abnormal hemoglobin S. Sickle Cell Disease in Saudi Arabia was first reported in the Eastern Province in the 1960's [1]. The prevalence of SCD in Saudi Arabia varies significantly in different parts of the country, with the highest prevalence is in the Eastern Province, followed by the Southwestern Provinces [2]. In the Eastern Province, the sickle hemoglobin gene is usually associated with the Arab-Indian (AI) haplotype; in Southwestern Province patients the Benin haplotype predominates [3]. Clinical and hematological variability exist in SCD in Saudi Arabia with two major phenotypes: a mild phenotype and a severe phenotype [2].

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both [4]. According to the latest report by the International Diabetes Federation, Saudi Arabia is listed as third among the top 10 countries with the highest prevalence rates of Diabetes (3.6 million cases of Diabetes). Over the last 3 decades, the incidence rate of type - 1 DM (T1D) is growing in Saudi Arabia, and the prevalence of T1D in Saudi Arabian children and adolescents is 109.5 per 100,000 [5].

Studies have shown that concurrent Sickle Cell Anemia with Diabetes Mellitus is very rare [6][7][8]. However, a few cases of combined presentation of both diseases have previously been reported in the literature [9][10][11][12][13][14][15][16][17][18].

During the period from 2010 – 2020, Pediatrics' registry at King Fahd Military Medical Complex (KFMMC), Dhahran, Saudi Arabia, included 340 patients with SCD and 99 with T1D. From this registry we

report this case series of four children with combined SCD and T1D. The patients belong to two different ancestries with the Arab-Indian and African gene haplotypes. Up to our knowledge, no such number of cases (4) has been reported from a single centre in the literature till date.

## **2. CASE REPORTS**

### **2.1 Case 1**

A 10 – year – old boy from the Southern Province; Saudi Arabia, was diagnosed as SCD in the first year of his life. He experienced frequent vaso-occlusive crisis for which he has received Hydroxyurea with a very good response. He received blood transfusion once. His parents are cousins and both of them are Sickle Cell carriers. They have another son with SCD and two daughters, both are carriers. His uncle has Insulin Dependent Diabetes Mellitus (IDDM).

A year ago, he was hospitalized complaining of: polyuria, polydipsia and weight loss for one month and dizziness for one week. On examination he was mildly dehydrated, HR: 104, BP: 112/63, RR: 22/m, Temp.: 37 and SO<sub>2</sub>: 99%. Weight: 27kg (5<sup>th</sup> PC), height: 137 cm (50<sup>th</sup> PC) .The rest of examination was otherwise unremarkable.

His investigations showed: Urine: sugar 4+ and ketones: 4+. Random blood sugar: 26 mmol/L. Capillary blood gases: PH: 7.32, PCO<sub>2</sub>: 24, HCO<sub>3</sub>: 13.4. The diagnosis of Diabetic Ketoacidosis was made.

CBC: HB: 8.9 gm/dl, WBCs: 9.6 x 10<sup>3</sup>/ul, Platelets: 193 x 10<sup>3</sup>/ul. HB electro-phoresis: HBS: 67.8%, HBA: 10.8%, HBF: 18.4%, HBA<sub>2</sub>: 3%. Liver functions: Total bilirubin: 39 umol/L (direct: 7 ) , AST: 47U/L, ALT: 34 U/L, LDH: 536U/L. Kidney function is unremarkable.

GAD 65: +ve > 2000 IU /ml (N: <10), ICA: +ve 1: 160 (N: <1:10), IAA: Normal (<0.4). Thyroid antibodies: negative, and TFT are normal.

He was started on IV fluids and insulin, stayed for 4 days in hospital and then discharged on insulin: Lantus 12 U and Novo Rapid: 5,6,6 U. He's been doing well since then.

## 2.2 Case 2

In 2011, a 16 month old girl from Al –Hassa , Eastern Province, Saudi Arabia presented with history of polyuria and polydipsia for 2 weeks, and fever, cough, irritability and runny nose for 3 days. She was not known to have any illness before this presentation. Her pregnancy, delivery and neonatal period were uneventful. She was breastfed with normal growth and development. She had been immunized up to her age. Her parents are unrelated and both of them are Sickle Cell carriers. She has 2 brothers: one is Sickle Cell carrier and the other is normal. On examination, she was drowsy, with rapid deep breathing and severe dehydration. Heart rate: 134, RR: 26/m. Temperature: 38.4, Weight: 9Kg (5th PC), Height: 73 cm (25th PC), HC: 47cm. Apart from inflamed tonsils, systemic examination was unremarkable. Initial investigations showed: CBC: RBCs:  $4.7 \times 10^6$ /ul, HB: 9.07gm/dl, MCV: 61FL, WBCs:  $15.4 \times 10^3$ /ul, Platelets:  $513 \times 10^3$ /ul. HB electrophoresis: HBS: 56.8%, HBF: 33.3%, HBA: 7.1%, HBA2: 2.8%. Diagnosis of Sickle Cell Alpha Thalassemia was made and confirmed by family studies and DNA analysis.

Random Blood Sugar: 55 mmol/L, Blood gases: pH: 7.0, HCO<sub>3</sub>: 6.5 and urine ketones +++. The diagnosis of Sickle Cell Disease with severe Diabetic Keto- Acidosis was made. She was admitted to PICU and received hydration therapy, insulin and antibiotics. After 36 hours her blood gases showed: pH: 7.39, HCO<sub>3</sub>: 24 and urine ketones were negative.

Further investigations showed: ICA: 1:80 (Titer < 1:10), C-peptide: <0.14 (N: 0.22-1.09). T1D was confirmed and she was discharged on insulin (Lispro and Lantus).

### 2.3 Case 3

A 15- year- old girl was diagnosed as Sickle Beta Thalassemia in the first year of life. Her parents were Sickle and Beta Thalassemia carriers and her 3 siblings (2 brothers and one sister) are all Sickle Cell carriers.

Her pregnancy, delivery and neonatal history are unremarkable. Her nutrition, growth, and development are normal. Her Sickle Cell Disease course was complicated with vaso-occlusive and sequestration crisis and acute chest syndrome. On examination: she is well built, pale and slightly jaundiced. Growth parameters and pubertal staging are within average. Systemic examination is otherwise unremarkable. CBC: HB: 8.6 gm/dl, RBCs:  $4.1 \times 10^6$ /ul, , WBCs:  $16.8 \times 10^6$ /ul, , ANC:  $2.6 \times 10^3$ /ul, Reticulocytes: 10.3%, MCV: 63FL, MCH: 20pg, Platelets:  $477 \times 10^3$ /ul. HB electrophoresis: HBA: 4.8%, HBA2: 6.9%, HBS: 71.7%, HBF: 16.6%. Liver and kidney functions are within range. She has been commenced on Hydroxyurea at the age of 10 with good response. At the age of 14 she had an episode of painful crisis when she was discovered accidentally to be diabetic with random blood glucose level of 22 mmol/L. She never had symptoms or signs of Diabetes. The blood and urine tests were repeated and the diagnosis of IDDM was confirmed. She has been commenced on Insulin therapy. Currently, she is receiving: Aspart 6 units TDS and Lantus 10 units at bed time.

### 2.4 Case 4

A 4 ½ year old girl was diagnosed with SCD at the age of 8 months when she had dactylitis, followed by frequent vaso-occlusive crisis. She also had 3 episodes of sequestration crisis with drop of HB to 3-5 gm/dL, blood transfusions and ultimately splenectomy at the age of 3. In addition she suffered from 3

episodes of acute chest syndrome and has been started on hydroxyurea. At the age of 3 ½ she experienced polyuria and polydipsia and weight loss with blood sugar of 280m mmol/L, She has been on insulin therapy since then with good blood sugar control and no DKA episodes.

Both her parents are Sickle Cell carriers and she has a normal younger brother. On examination: well, HT 98 cm, WT 14.4 kg, no goiter, systemic examination is unremarkable.

LAB :- thyroid normal, celiac negative , HBA1c 5.2 % , CBC : RBCs:  $2.7 \times 10^6$ /ul, HB: 8.1 gm/dL, Retics: 16.9%, MCV: 85FL, MCH: 30pg, WBC:  $12.36 \times 10^3$ /ul, Platelets:  $5916 \times 10^3$ /ul. HB electrophoresis ( post-transfusion): HBS: 54.2%, HBA: 37.7%, HBA2: 2.8% and HBF: 5%. SBR: 36.2 (conjugated: 7), AST: 64.4U/L, ALT: 33U/L, LDH: 644U/L, kidney functions are normal; Fructosamine: 5.30, HBA1c:6.5%, C-peptide: P. Currently, she is receiving Hydroxyurea and Insulin (Novo-rapid and Lantus) with good blood sugar control.

### 3. DISCUSSION

In this report we present four children with combined SCD and IDDM for the first time in the literature. It is also the first presentation of IDDM with different Sickle Cell Disease genotypes: homozygous Sickle Cell Anemia, HBS-beta Thalassemia and HBS Alpha-thalassemia. Our patients belong to two different ancestries representing both the Arab-Indian and the African haplotypes of SCD. These 4 children represent 1.1% of 340 children with SCD, and 4% of 99 children with T1D registered in our center. This prevalence is quite high compared with previous studies. In a review study of 100 African-American patients with Diabetes, only one patient was confirmed to have sickle cell anemia [6]. In another study on pregnant black patients with Sickle Cell Anemia, there was no single case of Diabetes. Similarly, studies from India and Nigeria failed to detect a single case of HbSS-diabetic [10]. Data from children and adolescents with Diabetes aged less than 30 years from 443 centers in Germany and Austria included 72,926 patients recorded in the database between January 1990 and July 2015. Out of this huge number of diabetic patients, there were only 12 patients with SCD [19].

There is no definitive explanation for the infrequent association of these two common diseases and it seems that the SCA population enjoys relative “protection” from Diabetes [20][21].

Theoretical mechanisms which have been suggested to explain this observation include low body mass index (BMI), hyper metabolism and genetic factors [5]. Both insulin and b-globins genes coexist in the short arm of chromosome 11, but there is no known inhibitory effect on the inheritance pattern or penetrance of the other [10]. It has also been postulated that the paucity of reports of cases of this combination may suggest that the majority of patients with SCA died early, therefore, relatively a small number of patients survived for the clinical manifestation of Diabetes [22]. However, this is not a plausible explanation in our era of recent medical advances: data show that mortality rate from SCD is decreasing and mean lifespan is constantly increasing [9][23]. This view is also challenged by the knowledge that, in India and Saudi Arabia where SCA with the Asian haplotype which is less severe and associated with a longer survival than the African haplotype, the co-existence of the two conditions is still rare. A significant proportion of patients with Asian haplotype survive beyond 30 years of age [10]. Other unknown factors might be responsible for the rare association of the two clinical conditions.

The occurrence of T1D in children with SCD could be secondary to pancreatic damage due to micro-infarctions, immune mediated mechanism or iron overload resulting from multiple blood transfusions. Micro-infarctions in the pancreas may lead to hypo perfusion and destruction of the islets, resulting in reduced insulin secretion [19]. Sheehan et al (1993) reported the occurrence of pancreatitis in a three-year-old black girl with SCA following a vaso-occlusive crisis. This phenomenon could lead to damage to the pancreas with subsequent fibrosis and ultimately, a decrease in insulin production, leading to the development of DM [24]. It is also well known that Diabetes Mellitus is a common manifestation of iron overload in patients with chronic red cell transfusions and subsequent secondary hemochromatosis [25][26]. Shoar et al (2005) reported a child with SCD and T1D based on positive auto-antibodies [9]. All our patients have positive auto antibodies, and none of them received multiple transfusions.

The diagnosis of IDDM in a SCD patient can be challenging, eg, abdominal pain occurs in both SCD ( vaso-occlusive crisis) and DM (DKA), so checking blood sugar and blood gases are important in these situations.

Four cases of combined homozygous Sickle Cell Anemia and T1D presenting with DKA have been reported earlier [11][13][14][15]. In this case report, we present two patients with homozygous SCA and concurrent DM who presented with DKA. The 1<sup>st</sup> is a baby girl from the Eastern Region of Saudi Arabia (Arab- Indian haplotype) with a mild form of SCD which was unmasked by DKA at the age of 16 months. The baby also had an alpha thalassemia trait that could have participated to the mild phenotype of this baby [2]. The alpha thalassemia carrier state could not protect against developing T1D. The 2<sup>nd</sup> is a school boy from the Southern region of Saudi Arabia (African haplotype) with a severe form since the 1<sup>st</sup> year of his life that presented also with DKA as the 1<sup>st</sup> presentation of DM at the age of 10 years. The diagnosis of T1D was confirmed by the detection of ICA antibodies in both cases.

Type 1 Diabetes can also present typically with polyuria, polydipsia and weight loss coupled with glucosuria and hyperglycemia in patients with SCA [7][9][10][12][17]. Typical laboratory confirmation of T1D is usually by detection of T1D auto antibodies as in the case of Shoar et al (2013). Their patient had significant signs and symptoms of hemochromatosis secondary to multiple blood transfusions and they could not eliminate the possibility that this contributed to his Diabetes [9]. Two of our patients from the Southern Region of Saudi Arabia (one is SS and the other S/B thalassemia) presented with these typical symptoms of T1DM. Both also had positive T1D specific auto-antibodies with no such contributing factors as they had no significant history of blood transfusion. For glycemic control assessment in diabetic patients with SCD, HBA1c lacks accuracy and serum Fructosamine is not standardized and has not yet been validated [18].

Treatment of DKA in children with SCD can be difficult. VOC treatment mandates well hydration of patients with SCD, and if they have DKA, hydration should be careful to avoid cerebral edema.

It can be given over 24 hours instead of 48 hours as the treatment of DKA protocol mandates (14). Follow up of these patients is extremely important as both diseases can be complicated by vasculopathy on the long term resulting in retinopathy, nephropathy and neuropathy [<sup>10</sup>].

#### **4. CONCLUSION**

This report of 4 children with combined SCD and T1D from a single center is the first in the literature. T1D can affect children with severe as well as mild SCD from the Southern and Eastern regions of Saudi Arabia (both African and Arab-Indian haplotypes). Patients with homo- and heterozygous forms of SCD may also suffer from T1D at any age during childhood. T1D can first present insidiously or as DKA in children with SCD. Further evaluation and comprehensive guidelines tailored for management of this rare condition are recommended.

#### **CONSENT**

As per institution policy, written informed consent was obtained from the patients for publication of this case reports and preserved by the author (s).

#### **ETHICAL APPROVAL**

Ethical approval from respective Institutional Review Board (IRB Protocol No. AFHER-IRB-2022-012), Eastern Region, Kingdom of Saudi Arabia, was obtained for publication of this case series.

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