Case study

Concurrent Sickle Cell Anemia and Diabetes Mellitus with ketosis in a Libyan Toddler:First National Report and Youngest Case Study

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Abbreviations

Body Mass Index (BMI); Diabetic Ketoacidosis (DKA); Diabetes mellitus (DM);Glycated Hb (HbA1c), Hemoglobin (Hb);

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Ethical issue

As per the local Ethics Committee of the Institute (Benghazi Children's Hospital), written consent is being taken from the parents/care givers of all admitted children to include all procedures the child might undertake, treatments shall be given, storing patient's data and publishing it if worth considering. Verbal consent from the parents of our child was also obtained and all are agreed to share their child's data and publishing it.

ABSTRACT

Sickle cell Anemia (SCA) is a common inherited haemoglobinopathy resulting from a single-point mutation on the β-globin subunit of hemoglobin.It is a chronic condition with multi-system involvement.Growth delay, osteopenia and hypogonadismare common endocrine dysfunctions with a lower frequency of impaired glucose tolerance. However, there is an association between SCA and diabetes mellitus (DM), though it is very rare.Certainly, there are only a few published reports worldwide outlined this uncommon combination. In this report, we will present the first Libyan case study of co-existence of the two diseases in a-16-month-old male toddler recording the youngest patient diagnosed with such a rare combination.The child, who was diagnosed earlier with SCA, brought with concerns of frequent changing nappies (polyuria) and excessive thirst (polydipsia) for 2 weeks that worsened recently. On admission, the toddler was distressed, lethargic and his lab parameters showed hyperglycemia, ketonuria, glycosuria and acidosis, a diagnosis of diabetic ketoacidosis (DKA) on the background of SCAtherefore was made. Further observations are warranted to properly guide about the diagnosis and management of such rare cases.

1. INTRODUCTION

Sickle cell Anemia (SCA) is one of the most common inherited haemoglobinopathy with highprevalence rates among people with African (almost 1.5 % of population in Sub-Saharan Africa),Mediterraneanand Indianorigin[1-2]. The underlying pathology is due to a single-point mutation on the β-globin subunit of hemoglobin (Hb) determining polymerization of the mutant HbS and resulting in sickling of erythrocytes upon exposure to low oxygen tension[3].

SCA is considered as a chronic disabling condition with multi-systeminvolvement.This is attributed to several factors including chronic anemia, iron overload, high energy demand, and malnourishment as well as due to the accompanied frequent sequestrationsresulting in microvasculature damage andtissue hypoxia[3]. Of note, the endocrine disorders are one of the most challengingcomplications of the disease,and that includesgrowthdelay, osteopenia and hypogonadism with a lower frequency of other endocrine dysfunctions comprisingimpaired glucose tolerance [4]. Interestingly, a part of the disease sequels, there is an association between SCA and diabetes mellitus (DM)type 1 that is well documented in the literature[5-6]. However, it should be noted that the concurrent combination of SCA with DM is very rare, and only a few cases have been reported so far around the world[6].

Despitethe uncommonness of the association, concurrent diagnosis of SCA and DM possesses both diagnostic and therapeutic dilemmasfor caring clinicians [7-8]. An

additional interest is that there is no yet clear explanation of why patients suffering from SCA are, at least to some extent, partially protected fromthe development of DM [9].

In this report, we will present the first Libyan case study of co-existence of SCA and type 1 DM in a toddler who presented with ketosis. Further, some of the proposed theories concerning allegedly protective mechanisms against the development of DM in patients suffering from SCAwill be discussed,together with briefly highlighting some of the encountered clinical challengesof such rare association.

2. Case Report

A-16-month-old male Libyan toddler of Mediterranean origin and product of consequent marriagehas been diagnosed with SCAat the age of 15 months following admission for anemia evaluation. Shortly after that, the child was brought by his mother to the Emergency Departmentwith concerns of frequent changing nappies (polyuria) and excessive thirst with frequentasking for water (polydipsia) for 2 weeks. The child also had a history of rapid breathing and excessive crying that worsened overnight before day of the admission. There was no family history of SCA or DM, and all family members, including siblings, were completely healthy. On examination, the child waspale(but not icteric),irritable, excessively crying, severely dehydrated, and distressed (respiratory rate of 70 cycle/min) with maintained other vital signs (heart rate: 155beat/min; BP: 90/55mmHgand T: 37C.). Abdominal examination revealed mild distention with generalized tenderness. Other systemic examinations findings,including joints,were unremarkable. His lab investigations as shownin Table 1revealed high blood sugar (995 mg/dl), urine positive for sugar and ketones, acidotic blood gas (Ph 7), low HCO3 (12mEq/L) and low Hb (7 g/dl), but with normal Glycated Hb (HbA1c)(6%). Initial impression was a vaso-occlusive crisis on the background of his SCA; however, in the presence of other parameters (hyperglycemia, ketonuria, glycosuria and acidosis), a diagnosis of diabetic ketoacidosis (DKA) was made, as previously described [6], despite normalHbA1C. He received a bolus of 0.9% normal saline at 20ml/kg over one hour and subsequently slowly rehydrated. Regularinsulin was also started after the second hour at a rate of 0.01unit/kg/hour. The patient made full recovery and discharged from ICU after 48hrs without any complications**.**Upon discharge, the child was commenced on a multiple-dose regimen of insulin before referred to the relevant specialities. The child

was progressing well when seen in the initial follow ups, though the long terms prognosis of such cases remains obscure.

3. DISCUSSION

SCA, a common genetic blood disorder, is caused by homozygosity for the sickle gene resulting in recurrent hemolytic crisis, tissue ischemia and multi-organ dysfunctions [4]. The management primarily involves symptomatic treatments of the acute crises and preventing the long term complications [6].

Apart of the disease's sequels and complications, there is an association with DM [5]. Hereby, and to our knowledge, we report the first Libyan case study describing such rareconcurrent diagnosis of DMon the background of SCA, and the fourth global case study to present with DKA. More interestingly,the described toddler in the current report is the youngest patient among the few reported cases worldwide.

Searchingthe accumulating literature for the relevant published studies onco-existence of SCAandDM, it can be asserted that the association remains rare and much rarer is ketosis at presentation[6]. Certainly, in only three published reports, DKA was the initial presentation at the time of diagnosis. The first case study was described by Mohapatra in 2005, involving an Indian girl aged 17 years[9]. The girl, who is known case of sickle cell anemia since the age of 12 years, was admitted with the complaints of weight loss for

5 months; fever, and abdominal pain. Sickling crisis was the preliminary clinical impression before a diagnosis of type 1 DM on the background of SCD was made[9]. Nine years later, the association has been described again in a report dated 2014 ontwo Nigerian adolescents aged 12 and 13 years with SCA who presented withDKA[7].The third report was published more recently in 2019 when the condition was defined in another Nigerian child aged 9 years with sickle cell anemia, who presented with features of mesenteric crisis and DKA[6].Hereby, we present the first national report and the fourth worldwide on a toddler who just turned 16 months old recording the youngest patient diagnosed with such a rare combination.

To date, there is no yet clear explanation for the rarity ofco-existence of the two disease entities. One potential claim owing to less longevity,as it has been suggested that SCApatients usually die earlybecause of the disease complications, and thereby a relatively small number of patients might survive for the clinical manifestation of diabetes[9].However, in a recent Hospital-based cross-sectional study conducted in Odisha India for investigating the prevalence of DM among SCA affected patients [10], it has been shown that patients can survive to an average age of (47.6 ± 13.6) years. That finding together with the age of the child in the current reportmight contradict the longevity theorybutrather supporting there may be a genetic or epigenetic protective effect of SCA towards the development ofDM, as previously suggested[11].

An additional potential protective factor could be attributed to bodymass index (BMI)[6]. Certainly, in a Hospital-based study, the prevalence of diabetes among SCA patient has been shown to be lower than in general public, and more interestingly the BMIwas found lower in the affected patients as compared to their controls [10]. Thus, it seems that the association between co-existence of diabetes mellitus and SCA needs meticulous exploration, andfurther studies are required to delineate such mysterious relation.

Despiteawidespread scarcity of the combination (SCA and DM), it can be quite challenging for the health providersin terms of establishing a diagnosis and delivering proper management especially when patients present acutely with ketosis [7]. Certainly, Glycated Hb(HbA1c),a frequently used marker to screen for and monitor disorders of glucose metabolism, is considered unreliable lab marker for monitoring blood sugar level in patients with haemoglobinopathies including SCA[8].Of note,serum fructosamine can be reliably used as an alternative measure of glycaemic status in such patients [12]. Further, there is an overlap in terms of the clinical presentation of sickling crisis and DKA since abdominal pain, and respiratory distress are predominant clinical features in both conditions [9], and thereby a high clinical suspicion and routine measurement ofblood sugar in SCA patients seem key pointsfor reaching a right diagnosis.

Furthermore, the duration of dehydration correction carries an additional obstacle in managing the sickling crisis in the affected patients,particularly when it co-exists with DKA. Indeed, extra fluid is recommended for relieving the crisis at the same time over

hydration might precipitate cerebral edema [6]. Thus, careful assessment of the fluid status at presentation together with recommending a slow correction policy of IV fluid appear essential to avoid such complications at the same time reliving the crisis.

4. CONCLUSIONS

This report outlines the first Libyan case study with a concurrent diagnosis of SCA and DM, and the fourth global report to present with DKA.The association remains rare, and much rarer is ketosis at presentation with no satisfactory explanations. Potentially short lifespan, low BMI and genetic role, however, have been suggested as leading factorsin the allegedly protective mechanisms against development of DM in patients suffering from SCA.Measuringblood sugar routinely in patients with SCA seems essential and should be implemented toease inreachingdiagnosis. Further studies are required now to properly guidediagnosis and management of such rare association.

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Table 1 shows lab parameters of a toddler with sickle cell anemia who presented with ketosis before concurrent sickle cell anemia with diabetes mellitus diagnosis was made.

Laboratory investigation	Result	Comment
Blood glucose level	995mg/dl	hyperglycemia
Glucose in urine	Positive(3+)	glycoseuria
Ketones in urine	Positive(2+)	Ketonuria
pH	7	Acidosis
Serum bicarbonate	12	Acidosis
HB1AC	6%	Normal
HB	7gm/dl	Anemia