Case study

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

Key Words

Anemia; Diabetes Mellitus; Ketosis; Sickle cell

Running title

Sickle Cell Toddler with ketosis

Abbreviations

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

Ms_AJPR_58338ABSTRACT

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 hypogonadism are common endocrine dysfunctions with 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 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 toddler who just turned 16 months old recording the youngest patient diagnosed with such rare combination. 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 high prevalence rates among people with African, Mediterranean and Indian background (1). 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 (2).

SCA is considered as a chronic disabling condition with multi-system involvement attributing to several factors including chronic anemia, iron overload, high energy demand, and malnourishment as well as due to the accompanied frequent sequestrations resulting in microvasculature damage and tissue hypoxia (2). Certainly, the endocrine

disorders are one of the most challenging complications of the disease to include in common growth delay, osteopenia and hypogonadism with low frequency of other endocrine dysfunctions comprising impaired glucose tolerance (3). 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 (4). However, it should be noted that the concurrent combination of SCA with DM is very rare and only few cases have been reported so far around the world (5).

Despite uncommonness of the association, concurrent diagnosis of SCA and DM possesses both diagnostic and therapeutic dilemmas for caring clinicians (6-7). 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 from development of DM (8).

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 potentially raised claims concerning allegedly protective mechanisms against development of DM in patients suffering from SCA will be discussed, together with briefly highlighting some of the encountered clinical challenges of such rare association.

2. Case Report

A-16 month old male Libyan toddler product of consequent marriage has been diagnosed with SCA at age of 15 months following an admission for anemia evaluation. Shortly after that the child was brought by his mother to Emergency Department with concerns of frequent changing nappies (polyuria) and excessive thirst with frequent asking for water (polydipsia) for 2 weeks. The child also had 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 was pale 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: 90/55mmHG and T: 37 C.). Abdominal examination revealed mild distention with generalized tenderness. Other systemic examinations findings including joints were unremarkable. His lab investigations as show in Table 1

revealed high blood sugar (995 mg/dl), urine positive for sugar and ketones, acidotic blood gas (Ph 7), low HCO3 (12 mEq/L) and low Hb (7 g/dl), but with normal Glycated Hb (HbA1c) (6%). Initial impression was vaso-occlusive crisis on background of his SCA; however, in presence of other parameters (hyperglycemia, ketonuria, glycosuria and acidosis), a diagnosis of diabetic ketoacidosis (DKA) was made, as previously described (6), despite normal HbA1C. He received a bolus of 0.9% normal saline at 20ml/kg over one hour and subsequently slowly rehydrated. Regular insulin was also started after the second hour at rate of 0.01unit/kg/hour. Patient made full recovery and discharged from ICU after 48hrs without any complications**.** Upon discharge the child was commenced on multiple dose regimen of insulin before referred to the relevant specialties.

3. DISCUSSION

To our knowledge, this is the first Libyan case study describing such rare concurrent diagnosis of DM on background of SCA, and the fourth global report to present with DKA. More interestingly, described toddler in the current report is the youngest patient among few reported cases worldwide.

Searching accumulating literature for relevant published studies on co-existence of SCA and DM, it can be asserted that the association remains rare and much rarer is ketosis at presentation (5). Certainly, in only three published reports, DKA was the initial presentation at time of diagnosis. The first case study was described by Mohapatra in 2005 involving an Indian girl aged 17 years (8). The girl, who is known case of sickle cell anemia since 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 diabetes mellitus on background of SCD was made (8). Nine years later the association has been described again in a report dated 2014 on two Nigerian adolescents aged 12 and 13 years with SCA who presented in DKA (6).The third report was published more recently in 2019 when the condition was defined in a another Nigerian child aged 9 years with sickle cell anemia, who presented with features of mesenteric crisis and DKA (5). 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 rare combination.

To date there is no yet clear explanation for rarity of co-existence of the two disease entities. One potential claim owing to less longevity, as it has been suggested that SCA patients usually die early because of the disease complications, and thereby a relatively small number of patients might survive for the clinical manifestation of diabetes (8). However, in a recent Hospital based cross sectional study conducted in Odisha India for investigating prevalence of DM among SCA affected patients (9), it has been shown that patients can survive to an average age of (47.6 ± 13.6) years. That finding together with age of the child in the current report might contradict the longevity theory but rather supporting there may be a genetic or epigenetic protective effect of SCA towards the development of DM, as previously suggested (10).

An additional potential protective factor could be attributed to body mass index (BMI) (5). Certainly, in a Hospital based study, prevalence of diabetes among SCA patient has been shown to be lower than in general public and more interestingly the BMI was found lower in the affected patients as compared to their controls (9). Thus, it seems that the association between co-existence of diabetes mellitus and SCA needs meticulous exploration and further studies are required to delineate such mysterious relation.

Despite prevalence of the combined diagnosis of SCA and DM is very negligible, it can be quite challenging for the health providers in terms of establishing diagnosis and delivering proper management especially when present acutely with ketosis (6). 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 (7). Of note, serum fructosamine can be reliably used as an alternative measure of glycaemic status in such patients (11). 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 (8), and thereby a high clinical suspicion and routine measuring blood sugar in SCA patients seem key points for reaching right diagnosis.

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

might precipitate cerebral edema (5). Thus, careful assessment of the fluid status at presentation together with recommending a slow correction policy of IV fluid appear essential to avoid such complication at the same time reliving the crisis.

4. CONCLUSIONS

This report outlines the first Libyan case study with 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 factors. Measuring of blood sugar routinely in patients with SCA seems essential and should be implemented to reaching diagnosis. Further studies are required now to properly guide about diagnosis 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