

1 **Case study**

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

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26 **Keywords**

27 Anemia; Diabetes Mellitus; Ketosis;Sickle cell; **Toddler**

28 **Running title**

29 Sickle Cell Toddler with ketosis

30 **Abbreviations**

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

33 **Ms_AJPR_58338**

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35 **Ethical issue**

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

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50 **ABSTRACT**

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

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74 **1. INTRODUCTION**

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

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82 SCA is considered as a chronic disabling condition with multi-systeminvolvement. This is
83 attributed to several factors including chronic anemia, iron overload, high energy
84 demand, and malnourishment as well as due to the accompanied frequent
85 sequestrationsresulting in microvasculature damage andtissue hypoxia[3]. Of note, the
86 endocrine disorders are one of the most challengingcomplications of the disease,and that
87 includesgrowthdelay, osteopenia and hypogonadism with a lower frequency of other
88 endocrine dysfunctions comprisingimpaired glucose tolerance [4]. Interestingly, a part of
89 the disease sequels, there is an association between SCA and diabetes mellitus (DM)type
90 1 that is well documented in the literature[5-6]. However, it should be noted that the
91 concurrent combination of SCA with DM is very rare, and only a few cases have been
92 reported so far around the world[6].

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

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

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99 In this report, we will present the first Libyan case study of co-existence of SCA and type
100 1 DM in a toddler who presented with ketosis. Further, some of the proposed theories
101 concerning allegedly protective mechanisms against the development of DM in patients
102 suffering from SCA will be discussed, together with briefly highlighting some of the
103 encountered clinical challenges of such rare association.

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119 2. Case Report

120 A-16-month-old male Libyan toddler of Mediterranean origin and product of consequent
121 marriage has been diagnosed with SCA at the age of 15 months following admission for
122 anemia evaluation. Shortly after that, the child was brought by his mother to the
123 Emergency Department with concerns of frequent changing nappies (polyuria) and
124 excessive thirst with frequent asking for water (polydipsia) for 2 weeks. The child also
125 had a history of rapid breathing and excessive crying that worsened overnight before day
126 of the admission. There was no family history of SCA or DM, and all family members,
127 including siblings, were completely healthy. On examination, the child was pale (but not
128 icteric), irritable, excessively crying, severely dehydrated, and distressed (respiratory rate
129 of 70 cycle/min) with maintained other vital signs (heart rate: 155 beat/min; BP:
130 90/55 mmHg and T: 37°C.). Abdominal examination revealed mild distention with
131 generalized tenderness. Other systemic examination findings, including joints, were
132 unremarkable. His lab investigations as shown in Table 1 revealed high blood sugar (995
133 mg/dl), urine positive for sugar and ketones, acidotic blood gas (pH 7), low HCO₃⁻
134 (12 mEq/L) and low Hb (7 g/dl), but with normal Glycated Hb (HbA_{1c}) (6%). Initial
135 impression was a vaso-occlusive crisis on the background of his SCA; however, in the
136 presence of other parameters (hyperglycemia, ketonuria, glycosuria and acidosis), a
137 diagnosis of diabetic ketoacidosis (DKA) was made, as previously described [6], despite
138 normal HbA_{1c}. He received a bolus of 0.9% normal saline at 20 ml/kg over one hour and
139 subsequently slowly rehydrated. Regular insulin was also started after the second hour at a
140 rate of 0.01 unit/kg/hour. The patient made full recovery and discharged from ICU after
141 48 hrs without any complications. Upon discharge, the child was commenced on a
142 multiple-dose regimen of insulin before referred to the relevant specialities. The child

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

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147 3. DISCUSSION

148 SCA, a common genetic blood disorder, is caused by homozygosity for the sickle gene
149 resulting in recurrent hemolytic crisis, tissue ischemia and multi-organ dysfunctions [4].

150 The management primarily involves symptomatic treatments of the acute crises and
151 preventing the long term complications [6].

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

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159 Searching the accumulating literature for the relevant published studies on co-existence of
160 SCA and DM, it can be asserted that the association remains rare and much rarer is ketosis
161 at presentation [6]. Certainly, in only three published reports, DKA was the initial
162 presentation at the time of diagnosis. The first case study was described by Mohapatra in
163 2005, involving an Indian girl aged 17 years [9]. The girl, who is known case of sickle
164 cell anemia since the age of 12 years, was admitted with the complaints of weight loss for

165 5 months; fever, and abdominal pain. Sickling crisis was the preliminary clinical
166 impression before a diagnosis of type 1 DM on the background of SCD was made[9].
167 Nine years later, the association has been described again in a report dated 2014 on two
168 Nigerian adolescents aged 12 and 13 years with SCA who presented with DKA[7]. The
169 third report was published more recently in 2019 when the condition was defined in
170 another Nigerian child aged 9 years with sickle cell anemia, who presented with features
171 of mesenteric crisis and DKA[6]. Hereby, we present the first national report and the
172 fourth worldwide on a toddler who just turned 16 months old recording the youngest
173 patient diagnosed with such a rare combination.

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

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

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

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

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

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216 4. CONCLUSIONS

217 This report outlines the first Libyan case study with a concurrent diagnosis of SCA and
218 DM, and the fourth global report to present with DKA. The association remains rare, and
219 much rarer is ketosis at presentation with no satisfactory explanations. Potentially short
220 lifespan, low BMI and genetic role, however, have been suggested as leading factors
221 in the allegedly protective mechanisms against development of DM in patients suffering
222 from SCA. Measuring blood sugar routinely in patients with SCA seems essential and
223 should be implemented to ease in reaching diagnosis. Further studies are required now to
224 properly guide diagnosis and management of such rare association.

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

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

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UNDER PEER REVIEW