British Journal of Medicine & Medical Research
4(22): 4004-4010, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Diabetic Ketoacidosis in Two Nigerian Adolescents with Homozygous Sickle Cell Anaemia

Alphonsus N. Onyiriuka[1*], Magdalene E. Odunvbun[2] and Izehiuwa G. Enato[1]

[1]Endocrine and Metabolic Unit, Department of Child Health, University of Benin Teaching Hospital, PMB 1111, Benin City, Nigeria.
[2]Haematology and Oncology Unit, Department of Child Health, University of Benin Teaching Hospital, PMB 1111, Benin City, Nigeria.

Authors' contributions

This work was carried out in collaboration between all the authors. Author ANO designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MEO and IGE managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

Case Study

Received 4th March 2014
Accepted 29th April 2014
Published 17th May 2014

ABSTRACT

In the tropics where the prevalence of sickle cell anaemia (SCA) is high, reports of concurrence of sickle cell anaemia and diabetes mellitus are rare with diabetic ketoacidosis (DKA), being rarer. In this case report, we present the cases of two Nigerian adolescents (one male and one female) with homozygous SCA who presented in DKA. Sickle cell anaemia was diagnosed eight and nine months respectively prior to their presentation with DKA. There was no history of previous multiple blood transfusions. Neither of the two cases had positive family history of diabetes mellitus. The diagnosis of DKA in each case was based on the presence of hyperglycaemia, ketonuria and acidosis. The families of these two patients were of low socio-economic status.

Conclusion: Although concurrent homozygous sickle cell anaemia and diabetic ketoacidosis is rare, it does occur in Nigerian children and adolescents.

**Corresponding author: Email: alpndiony@yahoo.com; didiruka@gmail.com;*

Keywords: Adolescents; diabetic ketoacidosis; haemoglobinopathy; Nigeria; sickle cell anaemia.

1. INTRODUCTION

In tropical countries where there is a high incidence of sickle cell anaemia (SCA), clinical experience indicates that co-existence of SCA with either type 1 or type 2 diabetes is a rare finding [1,2]. For instance, in Orissa, India, where the frequency of sickle cell gene is high (15.1%), two separate studies did not find diabetes among patients homozygous and heterozygous for sickle cell gene [3,4]. Although there are no population-based data to determine the relative prevalence of diabetes among patients with SCA in the tropics, it would appear that as a group, individuals with SCA enjoy a relative 'protection' from diabetes. The mechanisms for such protection is poorly understood. However, it has been linked to low body mass index (BMI), hypermetabolism and genetic factors [5]. On the other hand, it might be that majority of patients with SCA died early, therefore relatively small number of patients survived for the clinical manifestation of diabetes mellitus [6]. The situation in resource-limited tropical countries might be quite different from that in affluent countries, where blood transfusion are more widely used to palliate the anaemia of sickle cell disease [7]. Iron overload due to multiple transfusions can result in β-cell damage and decreased insulin production [5]. A few case reports of concurrent SCA and DM among Nigerians are available but they were not complicated by diabetic ketoacidosis (DKA) [6,8]. So far, only one case of concurrent SCA and DKA has been reported from India [9], all reflecting the rarity of the co-existence of the two clinical conditions.

The additional interest of SCA co-existing with DM is the use of HbA1C in long-term (2-3 months) monitoring of glycaemic control. Considering that the haemoglobin A1C (HbA1C) test is based on normal haemoglobin, haemoglobinopathies can affect the reliability of the test [10,11]. The physiologic basis for this unreliability include, altering the normal process of glycation of haemoglobin A to HbA1C, causing an abnormal peak on chromatography, thus making estimation of HbA1C unreliable, and the shortened lifespan (10-20 days) of red blood cells in SCA, resulting in reduction in the time for glycosylation to occur, thereby producing a falsely low HbA1C result [11]. Although sickle cell trait (HbAS) is not a disease, when an individual with HbAS co-exists with diabetes, this haemoglobin variant interferes with HbA1C measurement [12]. On the other hand, measurement of glycated serum protein (fructosamine) is unaffected by haemoglobinopathy [13], making it a useful test in assessing the glycaemic status of patients with haemoglobinopathy [9,10]. Another physiological effect observed in patients with concurrent SCA and diabetes mellitus is a primary impairment of insulin secretion [14]. This is reinforced by the study of Saad et al. [15] in which they demonstrated a lower C-peptide secretion during intravenous glucose tolerance tests.

The purpose of the present case report is to raise the alertness of clinicians to the possibility of the concurrent SCA and DKA (a rare clinical combination), thereby avoiding missed diagnosis and guiding appropriate management of cases.

2. CASE REPORTS

2.1 Case 1

A.O. is a 13 year old boy who presented at the Children Emergency Room (CHER) of University of Benin Teaching Hospital (UBTH), Benin City, Nigeria with complaints of

excessive thirst and excessive urination (both day and night) for 14 days, generalized weakness for 7 days, and fever of 3 days duration. No family history of DM. He is a known case of sickle cell anaemia (SCA), diagnosed 9 months before the above symptoms. No evidence of crises was noted. No history of ingestion acetyl salicylic acid (asprin). No previous history of blood transfusion. He was in the first year in the senior secondary school and has a good academic performance. The patient's family was of low socio-economic status.

On examination, his weight was 31kg (<5th percentile), height 140cm (<5th percentile), and BMI 15.8kg/m^2 (<5th percentile). He was pale, icteric with a body temperature of 36.8℃). He had a sickle cell habitus and was asthenic, dehydrated and conscious. He had tachycardia (120bpm), and tachypnoea (40cpm) but no flaring of alae nasae or indrawing of the chest. His blood pressure was 100/50mmHg (50th percentile for age, sex, and height). There was no tenderness in any part of the body. The liver was palpable 4cm below the right coastal margin, along the mid-clavicular line. The spleen was palpable 3cm below the left coastal margin.

In this patient with SCA, a diagnosis of DKA was made based on the presence of hyperglycaemia, ketonuria, glycosuria and acidosis Table 1. He was commenced on standard regimen for DKA, using intravenous 0.9% sodium chloride, insulin infusion at a rate 0.1Units/kg/hr. As a policy, I.V Clavulanate-potentiated amoxicillin (Augmentin) 50mg/kg/day was administered. The DKA resolved after 24 hours of commencement of treatment and he was switched to subcutaneous insulin. The blood glucose concentration ranged from 8.5-17.5mmol/L while on admission. He was subsequently discharged home after 10 days on admission on premixed insulin (70% intermediate insulin plus 30% soluble insulin) at 1Units/kg/day. He was subsequently lost to follow up.

2.2 Case 2

P. A. is a 12 year old girl who presented with a history of weight loss for 8 months, excessive urination (day and night), excessive thirst for 3 months and fever for 3 days. She was diagnosed to have SCA in a private clinic 8 months prior to presentation with above symptoms at UBTH. She had only one episode of blood transfusion. She has not attained menarche. She was neither on follow-up in the clinic nor on prophylactic medications. No evidence of crises was noted. No history of ingestion acetyl salicylic acid (asprin). The socio-economic status of the patient's family was low. There was no positive family history of DM. Her father died 11 years ago from a lymphoma.

On examination, her weight was 25kg (<5th percentile), height 134cm (<5th percentile); BMI 13.9kg/m^2 (<5th percentile). She was pale, icteric with a body temperature of 37℃. She had a sickle cell habitus and was asthenic, dehydrated but conscious. He had tachycardia 116bpm. Her respiratory rate was 28cpm and she was not respiratory distress. Her blood pressure was 90/60mmHg (<50th percentile for age, sex, and height). There was no tenderness in any part of the body. The liver was 4 cm below the right costal margin along the mid-clavicular line but no palpable spleen.

Like in the first case, a diagnosis of DKA was also made based on the presence of hyperglycaemia, ketonuria, glycosuria and acidosis Table 1. As a policy, I.V. Clavulanate-potentiated amoxicillin (Augmentin) 50mg/kg/day was administered. A treatment protocol similar to that used in case 1 above was instituted. The DKA resolved after 36 hours of commencement of treatment and she was switched to subcutaneous insulin. The blood

glucose concentration ranged from 9-18.5mmol/L while on admission. She was subsequently discharged home on the 13th day after admission on premixed insulin (70% intermediate insulin plus 30% soluble insulin) at 1.2Units/kg/day. She was subsequently lost to follow-up.

Table 1. Summary of laboratory investigation results at the time of diagnosis of diabetic ketoacidosis

Case 1		
Laboratory investigations	**Results**	**Comments**
Blood glucose value	29.3mmol/L	Hyperglycaemia
Glucose in urine	Positive(3+)	Proteinuria
Ketone bodies in urine	Positive(2+)	Ketonuria
Serum bicarbonate value	10mmol/L	Severe acidosis
Steady-state packed cell volume	20-25%	Good
Serum creatinine	1.3mg/dl	Slightly elevated
Urine protein	Negative	No proteinuria
Malaria parasite	Negative	No parasitaemia
Blood culture	No growth after 48 hrs	Sterile
Haemoglobin phenotype	SS	Sickle cell anaemia
Case 2		
Blood glucose value	21.6mmol/L	Hyperglycaemia
Glucose in urine	Positive(2+)	Glycosuria
Ketone bodies in urine	Positive(2+)	Ketonuria
Serum bicarbonate value	11mmol/L	Moderate acidosis
Steady-state packed cell volume	21-24%	Good
Serum creatinine	0.4mg/dl	Low
Urine protein	Negative	No proteinuria
Malaria parasite	Negative	No parasitaemia
Blood culture	No growth after 48 hrs	Sterile
Haemoglobin phenotype	SS	Sickle cell anaemia

3. DISCUSSION

In this case report, we present the case of two Nigerian adolescents (one female and one male) with homozygous sickle cell anaemia and concurrent diabetes mellitus who presented with diabetic ketoacidosis (DKA). In both cases, the diagnosis of SCA was based on the presence of SS haemoglobin phenotype with anaemia while the diagnosis of DKA was based on the presence of hyperglycaemia, ketonuria, glycosuria and acidosis. The diagnosis of DKA in the case reported by Mohopatra [9] was based on the similar criteria as used in the present report. The differential diagnosis of DKA include acute salicylic acid poisoning. Neither of the two patients complained of pain in any part of the body or had any evidence of sickle cell anaemia crises. In both cases, they complained of excessive urination and excessive thirst, both day and night. The additional laboratory findings of hyperglycaemia, ketonuria and acidosis made the diagnosis of vaso-occlusive crisis unlikely. The negative history of ingestion of acetyl salicylic acid (asprin) and presence of ketonuria negated the diagnosis of acute salicylic acid poisoning. The absence of a family history of DM in the two cases being reported here is not surprising. This observation is in keeping with the finding in the case reported by Mohopatra [9]. The steady state packed cell volume of 20-25% (6.7-

8.3g/dl) is relatively low but it is not surprising. It is a common clinical characteristics of patients with sickle cell anaemia in the setting where we practice.

Although our search of the literature revealed that more than three decades ago, two cases of concurrent SCA and diabetes mellitus (DM) involving Nigerian adolescents were reported; none of the two cases had diabetic ketoacidosis (DKA) at the time of initial diagnosis [6,8], representing a point of difference in relation to the present report. The rarity of concurrence of SCA and diabetes mellitus is reflected in the paucity Nigerian studies on the subject, despite the high prevalence of SCA gene among the populace. In India, in 2005, Mohopatra reported the first case of concurrent SCA and DKA [9]. The case was a known SCA patient who was diagnosed at the age of 12 years but presented at the age 17 years with abdominal pain and was initially diagnosed as having vaso-occlusive crises. She did not have a family history of DM. However, routine investigation revealed hyperglycaemia (fasting blood glucose 29.4mmol/L, 530mg/dl), ketonuria and acidosis, indicating DKA. This missed diagnosis reflect that the clinical features DKA may mimic those of vaso-occlusive crisis, suggesting the need to measure blood glucose level in all children and adolescents presenting with features of vaso-occlusive crisis. In this way, such missed diagnosis will be avoided and appropriate therapy instituted promptly.

A review of the literature revealed lack of published population-based studies that determined the relative prevalence of diabetes among patients with SCA in the tropics. However, it seems that the SCA population enjoys relative 'protection' from diabetes. Theoretical mechanisms which have been suggested to explain this observation include low body mass index (BMI), hypermetabolism and genetic factors [5]. It is well established that SCA is associated with a consistent pattern of anthropomorphic findings characterized by low lean body mass and fat mass [16]. Considering that a high BMI is a known risk factor for the development of type 2 diabetes [17], individuals with a low BMI and fat mass should enjoy a relative 'protection' from T2DM. The two patients being reported here had low body mass indices. The effect of chronic illness, anaemia, increased cardiac workload, hyperactive erythropoiesis, increased protein turnover and inflammatory and oxidative stress all contribute to the hypermetabolic state in SCA [18,19]. On the other hand, it has been postulated that the paucity of reports of cases of concurrent SCA with DM may suggest that majority of patients with SCA died early, therefore, relatively small number of patients survived for the clinical manifestation of diabetes [6]. However, this view is 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 [3]. Despite the longer survival, concurrent SCA with DM has been rarely reported from India [3,4], suggesting that other unknown factors might be responsible for the rare association of the two clinical conditions. Morrison et al. [2] postulated that genetic factors may play a role in this rare combination. They supported the hypothesis with the fact that both the β-globulin and the insulin genes are located in the short arm of chromosome 11 [15,16]. However, it is not known with certainty whether the genetic loci of insulin and β-globulin have any inhibitory effect on inheritance pattern or penetrance of the other. This is a subject for future investigation. Sheehan et al. [20] reported the occurrence of pancreatitis in a three-year old black girl with SCA following vaso-occlusive crisis. This phenomenon could lead to damage to the pancreas with subsequent fibrosis and ultimately, a decrease in insulin production, leading to development of DM. Iron overload due to multiple blood transfusions can result in islet β-cell damage and decreased insulin production [21]. However, the absence of a history of previous multiple blood transfusions in our patients excluded such possibility. In this regard, the situation in tropical

countries with limited resources might differ from that in affluent countries where blood transfusions are more widely used to palliate the anaemia in sickle cell disease [7].

The disease burden of concurrent existence of two chronic diseases needs to be considered, particularly as the families of our patients were in the low socio-economic class. The diagnosis of SCA alone has profound implications for the individual and the family, both from a medical and a financial standpoint. An additional disease burden of DM will be devastating, not only for the patient, but also to the family. The two patients described in this report have been lost to follow-up and their fate is unknown. The financial burden to their families may have been a key factor in the observed loss to follow-up. The fact that both patients were lost to follow-up, indicate a high rate of loss to follow-up in the setting where we practice. This is a common scenario and represents one of the challenges encountered in the management of chronic diseases in developing countries.

4. CONCLUSION

In conclusion, although concurrent homozygous SCA and DKA is rare, it does occur in Nigerian children and adolescents. It is, therefore, reasonable to suggest that fasting blood glucose should be determined in all patients presenting with vaso-occlusive crises to exclude concurrence DKA, thereby guiding appropriate management.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this case report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Reid HL, Photiades DP, Oli JM, Kaine W. Concurrent sickle cell disease and diabetes mellitus. Trop Geogr Med. 1988;40(3):201-204.
2. Morrison JC, Schneider JM, Kraaus AP, Kitabchi AE. The prevalence of diabetes mellitus in sickle cell hemoglobinopathies. J Clin Endocrinol Metab. 1979;48:192-195.
3. Kar BC. Sickle cell disease in India. J Assoc Physicians India. 1991;39:954-960.
4. Kar BC. Clinical profile of sickle cell trait. J Assoc Physicians India. 2002;50:1368-1371.
5. Anonymous. Therapy insight: Metabolic and endocrine disorders in sickle cell disease: Endocrine disorders in patients with sickle cell disease.
Available at: www.mediscape.org/viewarticle/568813_2. Accessed on March 25, 2014.
6. Adekile AD, Jegenda AO. Juvenile onset diabetes mellitus in a sickle cell anaemia patient. East Afr Med J. 1990;67:591-593.
7. Alayash AI, al-Quorain A. Prevalence of diabetes mellitus in individuals heterozygous and homozygous for sickle cell anemia. Clin Physiol Biochem. 1989;7:87-92.

8. Reid HL, Ene MD, Photiades DP, Famodu AA. Insulin dependent diabetes mellitus in homozygous sickle cell anaemia. Trop Geogr Med. 1990;42:172-173.
9. Mohapatra MK. Type 1 diabetes mellitus in homozygous sickle cell anaemia. J Assoc Physicians India. 2005;53:895-896.
10. Smaldone A. Glycemic control and hemoglobinopathy: When A1C may not be reliable. Diabetes Spectrum. 2008;21(1):46-49.
11. Tran H, Silva D, Petrovsky N. Case study: Potential pitfalls of using hemoglobin A1C as the sole measure of glycemic control. Clin Diabetes. 2004;22:141-143.
12. Gillery B, Hue G, Bordas-Fonfrede M, Chapelle JP, Drouin P, Levy-Marchal C, Perier C, Selam JL, Slama G, Thivolet C, Vialettis B. Hemoglobin A1C determination and hemoglobinopathies: problems and strategies. Ann Biol Clin (Paris). 2000;58:425-429.
13. Schnedl WJ, Krause R, Halwachs-Baumann G, Trinker M, Lipp RW, Krejs GJ. Evaluation of HbA1C determination methods in patients with hemoglobinopathies. Diabetes Care. 2000;23:339-344.
14. Adekile AD, Olsi SO, Oyebola DDO. Oral glucose tolerance test in children with sickle cell anaemia. East Afr Med J. 1985;62:213-217.
15. Saad STO, Braga GS, Saad MJA. Decreased C-peptide secretion in sickle cell anemia. Acta Haematol. 1989;82:81-84.
16. Barden EM, Rawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. Am J Clin Nutr. 2002;76:218-225.
17. Miller J, Silverstein JH, Rosen AL. Type 2 diabetes in the child and adolescent. In: Lifshitz F ed. Pediatric Endocrinology 5th edition, New York, Informa Healthcare Inc. 2007;1:169-182.
18. Akohoue SA, Shankar S, Milne GL, Morrow J, Chen KY, Ajayi WU, Buchowski MS. Energy expenditure, inflammation, and oxidative stress in steady state adolescents with sickle cell anemia. Pediatr Res. 2007;61:233-238.
19. Singhai A, Davies P, Wierenga KJ, Thomas P, Serjeant C. Is there energy deficiency in homozygous sickle cell disease? Am J Clin Nutr. 1997;66:386-390.
20. Sheehan AG, Machida H, Butzner JD. Acute pancreatitis in a child with sickle cell anaemia. J Natl Med Assoc. 1993;85(1):70-72.
21. Swaminathan S, Alam MG, Fonseca VA, Shah SV. The role of iron in diabetes and its complications. Diabetes Care. 2007;30(7):1926-1933.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=524&id=12&aid=4595