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Significance of Pain in Children with Sickle Cell Anaemia and Ischaemia-induced Cardiac Injury

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Authors' contributions

This work was carried out in collaboration among all authors. Author NAC conceptualized the study and designed it, did acquisition of data, contributed to sample (ECG and cardiac troponin T) analysis and interpretation, performed statistical analysis, drafted and critically revised the manuscript and gave final approval for publication. Author UCI contributed to the study design, interpretation of data, critically revised the manuscript and gave final approval for publication. Author OHC contributed to the study design, collection of data, sample (cardiac troponin T) analysis and interpretation, critically revised the manuscript and gave final approval for publication. Author AMU contributed to the study conceptualization and design, sample (ECG) analysis and interpretation, reviewed the manuscript and gave final approval for publication. Author OFA contributed to the study design, interpretation of data, drafting of the manuscript, critically reviewed the manuscript and gave final approval for publication. Author MMM contributed to the study design, drafting of the manuscript, critically reviewed the manuscript and gave final approval for publication. The manuscript has been read and approved by all the authors who met the requirements for authorship. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the relationships between ischaemic cardiac injury (ICI) evidenced by ischaemic electrocardiogram (ECG) with raised cardiac troponin T (cTnT), pain intensity and frequency in children with sickle cell anaemia (SCA).
Study Design: Case-control.
Place and Duration of Study: Department of Paediatrics, University of Calabar Teaching Hospital over a 6-month period.
Methodology: Children with SCA aged 4 – 17 years with vaso-occlusive painful crises (VOC) were enrolled. Cases were those with ICI while controls were those without ICI. VOC was diagnosed by history and examination with Faces Pain Scale – Revised. Electrocardiography and cTnT estimation were done. Cut-off level (97.5th percentile) of cTnT was obtained from age and sex-matched healthy children with haemoglobin genotype-AA. Serum cTnT analysis was by electrochemiluminescence immunoassay. Ischaemic ECG assessment was according to World Heart Federation criteria.
Results: Fifty-six children with SCA participated among who 27(48.2%) were cases and 29(51.8%) controls. Ischaemic ECG (71.4%) and elevated cTnT (57.2%) were significantly related (*P*=.01). All cases had severe pain (*P*=.02) and accounted for >50% of those with chest pain (*P*=.25). Controls had more < 3 pain episodes per annum than cases while frequent VOC (≥3 pain episodes per annum) occurred more in the cases though the differences were not statistically significant.
Conclusion: Severe pain with frequent VOC is associated with ICI even in the absence of chest pain in children with SCA. Regular electrocardiography and cTnT measurement will identify at-risk children for adequate management.

Keywords: Pain; ischaemia; cardiac; troponin; injury.

1. INTRODUCTION

The commonest globin defect in haemoglobinopathy is symbolized by the possession of two haemoglobin S in the erythrocytes which is termed sickle cell anaemia (SCA) [1]. Highest burden of SCA is in Nigeria with prevalence of 20 per 1000 births [2]. It is characterized by acute episodic events which are usually painful [vaso-occlusive crises (VOC)] and are due to stress-induced sickling of the erythrocytes [3]. Other crises include hyper-hemolytic crisis, sequestration crisis and aplastic crisis [3]. The sickling of these erythrocytes leads to microvascular obstruction which when it occurs in the heart leads to myocardial ischaemia, reduced oxygen delivery and increase myocardial oxygen demand [4]. As the ischaemia worsens, myocardial injury sets in characterized by release of cardiac troponins T and I into the plasma [5].

Myocardial injury may be a contributing factor to the high sickle cell disease mortality rate of 50% to 90% in Africa [6,7]. Myocardial ischaemia evidenced by ischaemic electrocardiogram (ECG) changes has been shown to occur during VOC and steady state in childhood SCA [8]. Occurrence of myocardial ischaemia during steady state may be due to sickling-unsickling cycles of the erythrocytes in the coronary microvasculature [1]. However, it is the myocardial ischaemia leading to rise in serum cardiac troponin T, i.e. ischaemic cardiac injury, that is life threatening because it may cause myocardial necrosis [9]. Cardiac troponin T is a preferred biomarker because of its one global standardization [10]. Its sensitivity nears 100% within 6 to 12 hours of hospital admission while the specificity ranges from 86% to 98% [5].

Pain, a cardinal feature of VOC, is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [11]. Furthermore, VOC is defined as new onset of pain that lasts at least four hours for which there is no explanation other than vaso-occlusion and which requires therapy [12].

When children with SCA present with VOC, pain intensity can be evaluated. This acute pain is categorized into four levels: no pain (0 – 2), mild pain (4), moderate pain (6) and severe pain (8 – 10) [13]. Hicks et al. [14], reported a strong positive correlation of Faces Pain Scale – Revised (FPS-R) with visual analogue scale (r = 0.92) and colored analogue scale (r = 0.84); and concluded that FPS-R is valid for use from 4 years of age among children experiencing pain.

FPS-R has also been validated for use among children at least 4 years of age by Page et al. [15] and systematic reviews of the Paediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [16].

Adegoke et al. [17] showed that rise in serum cardiac troponin T had strong positive correlation with pain severity scores (r=0.64). This rise also significantly occurred during painful crises than in steady state (73.1% versus 11.1%; *p*=0.001) [17]. There is dearth of information on ischaemia-induced myocardial injury and pain among children with SCA. This study aimed to find relationships between pain frequency, pain intensity, pain sites and ischaemia-induced cardiac injury evidenced by ischaemic ECG with raised serum cardiac troponin T in children with SCA.

2. MATERIALS AND METHODS

Children with SCA and presenting at the Children Emergency room of University of Calabar Teaching Hospital with VOC were consecutively recruited over a 6-month period. They were not hospitalized patients before enrolment. This case-control study recruited subjects who met the inclusion criteria. Retrospectively, cases were children with SCA who developed ischaemia-induced cardiac injury (ICI) while controls were children with SCA who didn't develop ICI. Age and sex-matched apparently healthy children with genotype-AA on routine well clinic checks were enrolled in other to obtain the cut-off level (97.5^{th} percentile) of cTnT because Paediatric cTnT reference values are currently unknown to the best of our knowledge.

2.1 Inclusion Criteria

Children with SCA 4 to 17 years of age and with vaso-occlusive painful crises (bone pain) of at least 12 hours duration. Healthy children with normal electrocardiogram were introduced to obtain the 97.5^{th} percentile value of serum cTnT because to the best of our knowledge, there is no known paediatric-derived cTnT reference value.

2.2 Exclusion Criteria

Included presence of symptoms and signs of renal disease; symptoms of respiratory tract infection in the previous two weeks; severe malnutrition [Body Mass Index (BMI) <-3SD], fever, severe hypertension, severe anaemia (packed cell volume ≤15% or haemoglobin concentration ≤50g/L), cardiac disease, heart failure or shock which can cause rise of serum cardiac troponin T (cTnT); [9] intake of drugs like digoxin, frusemide, captopril or chemotherapy; presenting with non-VOC acute events, hypokalaemia, hyperkalaemia and low glomerular filtration rate-for-age-and-sex. No subject was receiving chronic blood transfusion or hydroxyurea.

Information obtained on each child's history including pain sites, painful episodes that led or did not lead to hospital admission; physical examination including degree of pain; ECG result and serum cTnT level were entered into an Interviewer-administered questionnaire. Pain assessment was with FPS-R which has facial outlines with neutral expression being the least expression and intense pain expression being the highest, on a scale of 0 – 10 [14]. Social class grouping was done as shown by Oyedeji while BMI was interpreted according to World Health Organization criteria [18,19].

2.3 Electrocardiography

This was done with a 12-lead electrocardiograph immediately after pain relief and within 15 minutes of presentation in the emergency room. A dose of intramuscular pentazocine (1mg/kg) was given for pain relief to the children with SCA. ECG was read by a Paediatric Cardiologist and interpretation followed paediatric standards [20]. Specific ischaemic ECG patterns described in the expert consensus document on universal definition of myocardial infarction (ST-segment depression, ST-segment elevation, inverted/or diphasic T-wave in ≥2 contiguous chest leads and pathological Q-wave) were noted among other abnormal ECG findings [9]. Pathologic ST-segment shifts noted were depression or elevation >1 mm in the limb leads and >2 mm in the precordial leads.

2.4 Laboratory Tests

Blood sample (4ml) was drawn from each of the children with SCA and healthy children. Capillary blood sample for packed cell volume (PCV) was also obtained from children with SCA. The blood sample from children with SCA and 3ml of blood from the healthy children were put into plain tubes, allowed to clot and centrifuged at 3000 revolutions per minute for five minutes to obtain sera. Small volume of sera of children with SCA were analyzed for potassium and creatinine. Left over 1ml of blood of the healthy children were

analyzed for haemoglobin genotype using citrate agar electrophoresis method. Subjects with normal potassium, creatinine, GFR, PCV >15%; and healthy children with genotype-AA were enrolled. The sera were stored in a refrigerator at – 20^0C for a maximum of two weeks before batch analysis for serum cTnT. Serum cTnT levels were determined by the electrochemiluminescence immunoassay method with Elecsys® 2010 Analyzer. The analyzer and its high-sensitive troponin T test kit with reference number 05092744 were manufactured by Roche Diagnostics/Hitachi High Tech. Corp. Assay limit of detection was 5ng/L. Myocardial injury is defined as serum cTnT level > 99^{th} percentile of an upper reference limit (URL) [9]. However, the URL obtained and utilized in this study was 97.5^{th} percentile of the serum cTnT of the healthy children because calculating 99^{th} percentile needs broader approach [21].

Following data and blood collection, each child with SCA was admitted in the hospital. Intravenous fluid and analgesics, among other treatment, were commenced within one hour of presentation according to our departmental policy on treatment of SCA. Upon discharge, each parent was counselled and hydroxyurea added to their routine drugs. No one died.

2.5 Statistical Analysis

Information from each questionnaire were coded, put into SPSS version 23 and analyzed therein. Proportions were presented in tables as percentages and where necessary, compared using Chi-square test and Fisher's Exact Test. Serum cTnT values showed skewed distribution hence median values were presented. Relationship between cTnT values and pain scores was assessed with Spearman rank correlation. Alpha level of 95% significance was set at < 0.05.

3. RESULTS

Fifty-six children with SCA participated in the study. Most of the subjects were less than 10 years of age (44.6%) with a male: female ratio of 1.24: 1 and the sex difference among the age groups was not statistically significant. Most of the participants were of the upper social class and the social class difference across the age groups were not statistically significant (Table 1).

3.1 Pain Characteristics

Majority of children with SCA [50 (89.3%)] had severe pain. Seventy-five percent of children with SCA had <3 painful episodes yearly that required hospitalization while 25% of them had ≥3 painful episodes yearly that also required hospitalization.

3.2 Electrocardiogram

Inverted/diphasic T-wave was seen in 32(57.1%) children with SCA. In addition, ST – segment elevation [5(8.9%)], ST-segment depression [6(10.7%)] and pathological Q-wave [2(3.6%)] were observed. All children with ST – segment abnormalities and pathological Q-wave had T-wave abnormality. Specific ischaemic ECG was seen in 71.4% of children with SCA.

Table 1. Socio-demographic characteristics of children with SCA (N=56)

	Sex [n (%)]					
Age group in years	**Male**		**Female**	**Total [n (%)]**	**Test statistics**	***P*-value**
4 – 9	14 (45.2)		11 (44.0)	25 (44.6)	χ^2 = 0.249	.88
10 – 13	10 (32.2)		7 (28.0)	17 (30.4)		
14 – 17	7 (22.6)		7 (28.0)	14 (25.0)		
Total	31 (100.0)		25 (100.0)	56 (100.0)		
	Social class group [n (%)]					
	Upper	**Middle**	**Lower**			
4 – 9	18 (43.9)	7 (58.4)	0 (0.0)	25 (44.6)	FET=7.648	.05
10 – 13	13 (31.7)	4 (33.3)	0 (0.0)	17 (30.4)		
14 – 17	10 (24.4)	1 (8.3)	3 (100.0)	14 (25.0)		
Total	41 (100.0)	12 (100.0)	3 (100.0)	56 (100.0)		

χ^2 = Chi square; FET = Fisher's Exact Test

3.3 Serum cTnT

The median (interquartile range) value of cTnT among children with SCA and healthy children were 7.85 (5.10 – 14.36) ng/L and 5.10 (5.10 – 5.10) ng/L respectively. The 97.5th percentile value of cTnT levels among the healthy children was 5.7ng/L and 57.2% of children with SCA had cTnT above this threshold. In relation to pain, serum cTnT had a significant but weak positive correlation with pain score using Spearman's Rho [$r_s(54)=0.32$, $P=0.017$].

3.4 Electrocardiogram and Serum cTnT

Twenty-seven (48.2%) children with SCA had both specific ischaemic ECG pattern and raised serum cTnT (ICI), i.e. the cases. The 29 (51.8%) without ICI, i.e. the controls, included 23.2% with only specific ischaemic ECG; 9% with only elevated cTnT and 19.6% with none of the parameters (Table 2). The relationship between specific ischaemic ECG pattern and raised serum cTnT was statistically significant ($P=0.013$).

3.5 Specific Ischaemic ECG Pattern with Raised Serum cTnT (Ischaemic Cardiac Injury), Pain Intensity and Pain Frequency

All the cases had severe pain. No one had pain score 0 to 4. The difference between cases and controls with respect to pain score was statistically significant ($P=0.024$). The occurrence of painful episodes with or without hospital admission were similar among cases and controls (Table 3).

3.6 Ischaemic Cardiac Injury and Regional Pain Sites

Most frequently occurring regional pain site was lower limb and waist (82.1%) followed by upper limb (53.6%). Chest pain was observed in 19.6% of the children with SCA however there was no statistically significant difference between cases and the controls ($p=0.253$). Furthermore, involvement of these sites was similar in cases and controls (Table 4).

Table 2. Relationship between specific ischaemic ECG pattern and raised serum cTnT level among children with SCA (N=56)

Serum cTnT level	Specific ischaemic ECG pattern [n (%)]			χ^2	*P*-value
	Present	Absent	Total		
Elevated	27 (48.2)	5 (9.0)	32 (57.2)	6.132	.01*
Not elevated	13 (23.2)	11 (19.6)	24 (42.9)		
Total	40 (71.4)	16 (28.6)	56 (100.0)		

*χ^2 = Chi square; *=Statistically significant*

Table 3. Relationship between children with SCA, pain intensity and frequency (N=56)

Variable	Children with SCA [n (%)]			Test statistic	*P*-value
	Cases	Controls	Total		
Pain intensity (score)					
Moderate pain (6)	0 (0.0)	6 (20.7)	6 (10.7)	FET=6.257	.02*
Severe pain (8 – 10)	27 (100.0)	23 (79.3)	50 (89.3)		
Annual pain episodes with hospital admission					
0 – 2	20 (74.1)	22 (75.9)	42 (75.0)	χ^2 = 0.024	.88
≥ 3	7 (25.9)	7 (24.1)	14 (25.0)		
Annual pain episodes without hospital admission					
0 – 2	6 (22.2)	8 (27.6)	14 (25.0)	χ^2 = 0.215	.64
≥ 3	21 (77.8)	21 (72.4)	42 (75.0)		

=Statistically significant; FET= Fisher's Exact Test; χ^2 = Chi square

Table 4. Relationship between children with SCA and regional pain sites (N=56)

Regional pain site	Children with SCA [n (%)]			Test statistic	*P*-value
	Cases	Controls	Total		
Lower limb and waist pain	23 (85.2)	23 (79.3)	46 (82.1)	FET = 0.329	.73
Abdominal pain	9 (33.3)	7 (24.1)	16 (28.6)	χ^2 = 0.579	.45
Lower back pain	6 (22.2)	6 (20.7)	12 (21.4)	χ^2 = 0.020	.89
Chest pain	7 (25.9)	4 (13.8)	11 (19.6)	χ^2 = 1.304	.25
Upper limb pain	17 (63.0)	13 (44.8)	30 (53.6)	χ^2 = 1.849	.17
Head and neck pain	1 (3.7)	1 (3.4)	2 (3.6)	FET = 0.003	1.00

χ^2 = Chi square; FET = Fisher's Exact Test

4. DISCUSSION

Pain intensity has been shown to correlate with serum cTnT levels in this study and all children with ischaemia-induced cardiac injury (ICI) had severe pain during VOC. Pain arises as a result of inflammatory mediators (substance P, bradykinin, prostaglandins, leukotrienes) and low pH which activate intracellular signal transduction in nociceptors (pain receptors) leading to pain perception by the individual [22]. These pain receptors are sited peripherally (Aβ fibres), e.g. in the skin & bones; and centrally (Aδ and C fibres) in the internal organs like the heart [22]. The inflammatory mediators are usually generated by dying tissues (e.g., following myocardial ischaemia) located where the pain is felt. During VOC, these dying tissues may be as a result of ischaemia. This may imply that as myocardial ischaemia and injury worsens, more mediators are released which lead to high degree of pain. Hence, elicitation of pain is a function of the amount of inflammatory mediators released in the vicinity of dying tissues [22]. Similarly, Adegoke et al. [17] showed that pain score positively correlated with serum cTnT though a third of their children with SCA had severe pain during VOC.

In addition to the heightened pain intensity, children with ICI also had previous history of painful episodes. Pain frequency was described in terms of annual pain episodes that made the child to be admitted into the hospital or be treated at home with over-the-counter analgesics without presentation to the hospital. Three or more painful crises per year was defined as severe and frequent by Nebor et al. [23] when they studied relationship between painful crises and sympatho-vagal balance. This study has shown that two-third of children with ICI had frequent painful crises without hospital admission and < 3 pain crises per annum with hospital admission. This means that these children that come to the hospital with severe pain usually have frequent VOC at home and only come to hospital when the pain treatment at home isn't working. These frequent painful crises may play a role in the genesis of cardiac injury therefore, these stated pain frequencies are clinically important factors that may help to identify children with SCA at risk of life-threatening cardiac events for intervention.

This study also observed specific ischaemic ECG pattern in majority of children with SCA. This entails that sickling-induced ischaemia occur in the myocardium during VOC. Bode-Thomas et al. [8] likewise showed that 89.5% of children with VOC had myocardial ischaemia, using general ischaemic criteria assessment. Furthermore, about half of the subjects significantly had both specific ischaemic ECG pattern and elevated serum cTnT which is ICI. This implies that erythrocyte-sickling-induced ischaemia in the myocardium during VOC can cause elevation of serum cTnT in children with SCA. Hence, myocardial ischaemia can cause myocardial injury.

Vaso-occlusive painful crises were observed most in the lower limbs and waist in this study. The reason could be that venous stasis, which usually occur in the lower limbs, [24] may be worsened during VOC when inflammatory mediators that lead to pain are slowly removed from the site of pain. This finding is similar to that by Ambe et al. [25] who showed that hand-foot syndrome was the commonest presenting feature among children with SCA.

However, there was no substantial variation in the involvement of the body regions among children with or without ICI. This implies that children with SCA can have ICI in the absence of chest pain, which is a clinically significant finding.

This is unlike in adults where angina pectoris is required in the diagnosis of ischaemic heart disease [26]. However, these children may benefit from new drugs like L-glutamine and the recently FDA approved antithrombotic Crizanlizumab [27-28].

Oral therapy with L-glutamine has been shown to reduce number of pain crises by decreasing oxidative stress and erythrocyte vascular adherence in children with SCA [27]. Similarly, Crizanlizumab reduces painful crises by reducing thrombose formation and vascular stasis caused by adherence of sickled red cells to platelets and vascular endothelium [28]. These imply reduced coronary microvascular adherence and myocardial ischaemia when both drugs are routinely ingested by children with SCA. Moreover, hydroxyurea has been shown to reduce frequency of VOC in Africa; by increasing plasma fetal haemoglobin which resists erythrocyte sickling [29]. It is now routinely prescribed to our children with SCA at 10 to 20mg/kg/day. Children with SCA in this study were treated with intravenous fluids at 2 to 3Litres/m^2 and analgesics following which they all recovered. This also shows the possible reversal nature of ICI in SCA if treatment is started early with routine fluids and analgesics especially in resource-poor settings where L-glutamine and Crizanlizumab may be unavailable.

5. CONCLUSION

Ischaemia-induced cardiac injury occurs in children with SCA who present during VOC with severe pain. Electrocardiography and serum cTnT measurement should be done in children with SCA presenting with severe pain and past history of frequent VOC. This will help in effecting possible cardiac-oriented management early in other to reduce mortality. Efforts should be made to encourage regular ingestion of hydroxyurea and other newer drugs to help reduce the frequency of pain and myocardial injury.

6. LIMITATIONS OF STUDY

Performing echocardiography in these children with ICI would have helped to confirm those that unequivocally had elevated serum cTnT. The use of 99th percentile value of serum cTnT, derived from a large pool of healthy children, as cut-off point would have clearly mapped out those who didn't have myocardial injury. Unfortunately, this value is currently unavailable. Repetition of electrocardiography, serum cTnT measurement and pain scale before discharge could have strongly supported use of intravenous fluids and analgesics as part of the treatment of ICI in SCA. The relationship between ICI, pain degree, haplotype and haemoglobin variants will need to be assessed in a larger sample size.

CONSENT

Written informed consent was obtained from each parent or guardian of the subject while verbal assent was obtained from those at least 7 years of age.

ETHICAL APPROVAL

Ethics clearance was obtained from the Health Research Ethical Committee of University of Calabar Teaching Hospital.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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