Open Access Library Journal
2023, Volume 10, e10894
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Myocarditis in Under-Five Children with Community-Acquired Pneumonia Using Serum Cardiac Troponin-T and Electrocardiography

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How to cite this paper: Alao, S., Uzodimma, C. and Olowu, A. (2023) Myocarditis in Under-Five Children with Community-Acquired Pneumonia Using Serum Cardiac Troponin-T and Electrocardiography. *Open Access Library Journal*, **10**: e10894.
https://doi.org/10.4236/oalib.1110894

Received: October 18, 2023
Accepted: November 21, 2023
Published: November 24, 2023

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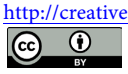

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Abstract

Community-acquired pneumonia (CAP) kills more under-five (U-5) children in Sub-Saharan Africa than in any other part of the world. Co-existing myocarditis and congestive cardiac failure (CCF) in the setting of CAP could play a crucial role in determining the disease outcome. The aim of the study was to evaluate myocarditis in U-5 children with CAP in the emergency room setting using cardiac troponin-T (cTnT) and electrocardiography (ECG). A hospital based cross-sectional study involving 76 children with CAP aged between 2 - 59 months, and their age- and sex-matched controls. Serum cTnT was measured using Roche Cobas® h232 POC system and standard electrocardiographic (ECG) tracings were obtained from participants using the APS Three Channel ECG-3B (Model- EKG-903A3) machine to evaluate for myocarditis. The mean age of subjects in this study was 19.8 ± 12.2 months. The prevalence of ECG features of myocarditis was 45%. The ECG features of myocarditis detected in the study include prolonged PR interval, reduced QRS voltages in limb leads, right axis deviation and prolonged QTc. Presence of elevated cTnT (≥50 ng/L) suggestive of myocarditis was detected in about 10% of subjects with CAP, particularly in those with CCF. The presence of elevated cTnT was a better predictor of mortality than the ECG features of myocarditis ($p = 0.029$). The prevalence of myocardial involvement in U-5 children with CAP is high and an elevated serum cTnT predicts mortality better than ECG changes in children with CAP.

Subject Areas

Paediatrics, Cardiology, Respiratory, Infections

Keywords

Cardiac Troponin-T, Myocarditis, Electrocardiography, Pneumonia

1. Introduction

Community-acquired pneumonia (CAP) refers to the pathogen-initiated acute inflammation of the lower respiratory tract and lung parenchyma which comprises of the alveoli, alveolar ducts, and the interstitial tissues [1]. Worldwide, childhood pneumonia occurs more frequently among countries in the Global South; three-quarters of all pneumonia episodes among under-five (U-5) children occur in developing countries especially in Southeast Asia and Sub-Saharan Africa [2].

Community-acquired pneumonia could impair oxygen delivery to the heart and cause hypoxia which leads to myocardial ischemia and myocardial cell death [3]. Secondly, the causative microbial agent in CAP could directly invade the myocardial tissue and result in tissue injury which is myocarditis [3].

Generally, fewer studies have investigated the cardiac impacts of CAP in children; most of the available studies were carried out in adults and in middle and high-income countries [4] [5] [6] [7] [8]. Some of the studies that investigated myocardial injury in children evaluated ECG and cardiac enzymes such as creatine kinase myocardial band (CK-MB) [3] [6]; fewer still have reported cardiac changes using the more sensitive and specific cardiac biomarker like cTnT [9] [10].

This study aims to evaluate children with CAP for myocarditis using a combination of typical ECG changes and assay of serum cardiac troponin-T (cTnT). Detection of myocarditis in children with CAP would change how clinicians manage these children. It will help clinicians to better prognosticate their patients; be more specific and where indicated, more aggressive in treatment of cases of childhood CAP associated with myocarditis.

2. Patients and Methods

A hospital-based observational cross-sectional study was conducted on 76 children with CAP aged 2 - 59 months and their age- and sex-matched controls who had no respiratory and cardiac diseases.

2.1. CAP Case Definition Criteria

1) Symptom complex of CAP, in an U-5 child presenting with cough and fever of less than 14 days duration with any of: a) age-specific increase in respiratory rate (tachypnoea) or b) lower chest wall in drawing or c) inability to feed or drink, with or without central cyanosis [11] [12] [13].

2) Radiographic confirmation of the presence of one or more of the chest radiographic features of patchy, segmental or lobar consolidation, with or without

a positive air bronchogram and with or without pleural effusion was used to confirm the diagnosis [14] [15]. The radiographic findings were confirmed by at least one radiologist.

3) Congestive cardiac failure in the children with CAP was based on presence of tender hepatomegaly (of at least three centimetres size below the right costal margin) and any two of: [16]

a) Significant tachycardia for age (>160 beats/minute in infancy, >140 beats/minute between 12 - 24 months, >120 beats/minute between 24 - 59 months). Where fever was present, a 10 beats/minute for every 1˚C rise in axillary temperature above 38.5˚C was allowed for [16]

b) Significant tachypnoea for age (>40 cycles/minute < 24 months, 30 cycles/minute in two to five years) [16]

c) Cardiomegaly (defined in < five years as apex beat located lateral to the fourth left intercostal space in the mid-clavicular line while the trachea is central) [16]

Children with known/suspected congenital or acquired heart diseases, sickle cell anaemia, features of acute kidney injury or chronic kidney disease (including abnormal electrolytes, urea and creatinine), HIV infection and severe malnutrition (weight for length/height < −3 z-score) were excluded.

Patients were made comfortable enough to have an ECG at the bed-side using the APS THREE CHANNEL ECG-3B (MODEL- EKG-903A3) machine. Where the baby was fretful or fussy, he/she was calmed. Thereafter, one millilitre of venous blood sample was collected into the lithium/heparin bottle for cTnT assay. Serum cTnT assay was determined with the Roche cobas® h232 POC system and samples were processed within 8 hours of collection as samples for this test are stable for 8 hrs at room temperature[17]. The test strip contains two monoclonal antibodies specific to cardiac troponin T (cTnT) of which one is gold-labelled, the other biotinylated. The antibodies form a sandwich complex with the cTnT in the blood. The optical system of the cobas® h232 instrument detects two lines (control and signal lines) and measures the intensity of the signal line. The integrated software converts the signal intensity to a quantitative result and shows it in the display [17]. An elevated serum cTnT value (≥50 ng/L via Roche Cobas kit) signifying myocardial injury correlates with an increased chance of respiratory failure and death [18] [19] [20].

2.2. Data Analysis

The data were collated, cleaned and entered into the Statistical Package for the Social Sciences (SPSS) software package version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) for analysis.

The main outcome variables were the serum cTnT levels and the ECG features of myocarditis. Frequency distribution tables of the variables of interest were generated. Continuous variables like age and ECG parameters were summarised with mean and standard deviation. These continuous variables were compared

between children with CAP (CAP without CCF and CAP with CCF) and their age- and sex-matched controls (no CAP) with analysis of variance (ANOVA) [21] [22].

Each group of study participants was categorised based on presence or absence of elevated cTnT and ECG features of myocarditis. Serum cTnT between the subjects and controls were compared as categorical data (elevated or not elevated) using Chi-squared test [21] [22]. Similarly, the ECG features of myocarditis between the subjects and their age- and sex-matched controls were compared as categorical variables (*i.e.* presence or absence) using the Chi squared statistics among the three groups. Where the assumptions for the use of chi-squared statistics were not fulfilled, the Fisher's exact test was used [21] [22]. The confidence level was set at 95% and a p-value less than 0.05 was considered statistically significant [22] [23].

3. Results

3.1. Sociodemographic Characteristics of the Study Population (Table 1)

The mean age was 19.8 ± 12.2 months and 56 (73.7%) were between 2 and 24 months of age. The mean age of the girls in the study, 23.4 ± 13.3 months, was significantly higher than that of boys which was 16.5 ± 10.3 months ($p = 0.013$). The male to female ratio among the study participants was 1.2:1. The social class of study participants (subjects and controls) was comparable just as the sociodemographic variables of the subjects with CAP (age, sex and social class) based on the presence of CCF were comparable between both groups of subjects ($p > 0.05$).

3.2. Clinical Characteristics of the Subjects with CAP (Table 2 and Table 3)

The proportion of subjects with CAP who presented with anaemia, central cyanosis,

Table 1. Sociodemographic characteristics of study population.

Characteristics	Controls (n = 76)	%	CAP (n = 76)	%
Age group				
2 - 24 months	56	73.7	56	73.7
25 - 59 months	20	26.3	20	26.3
Sex				
Male	42	55.3	42	55.3
Female	34	44.7	34	44.7
Social class				
High	15	19.7	11	14.5
Middle	27	35.6	24	31.6
Low	34	44.7	41	53.9

Table 2. Clinical features of subjects with CAP.

Clinical Features	CAP without CCF (62) n (%)	CAP with CCF (14) n (%)	χ^2	p-value
Cough	52 (83.9)	14 (100.0)	1.580	0.589
Fever	60 (96.8)	14 (100.0)	0.464	1.000
Anaemia	10 (20.8)	8 (57.1)	6.935	**0.017****
Cyanosis	4 (6.5)	10 (71.4)	32.087	**0.0001***
Dyspnoea	54 (87.1)	14 (100.0)	1.022	0.580
Hypoxaemia	18 (29.0)	8 (57.1)	4.010	**0.045***
Hepatomegaly	22 (35.5)	14 (100.0)	7.601	**0.007***

*$p < 0.05$, **-Fisher's exact test.

Table 3. Characteristics of CAP among subjects.

CAP characteristics	Frequency (n)	%
Radiographic		
Bronchopneumonia	72	94.7
Lobar pneumonia	4	5.3
Severity		
Severe CAP	56	73.7
Very severe CAP	20	26.3
Complications		
Congestive cardiac failure	14	63.6
Pleural effusion	6	27.3
Empyema thoracis	2	9.1

hepatomegaly and hypoxaemia was significantly higher in those with CCF compared to those without CCF ($p < 0.05$). Majority of subjects had bronchopneumonia (n = 72; 94.7%) and most presented with severe CAP. Complications were observed in about 30% (n = 22) of subjects and most presented as CCF (n = 14; 64%).

3.3. Electrocardiographic (ECG) Findings

Abnormal electrocardiographic changes were observed in 63.2% (n = 48) of subjects with community-acquired pneumonia [with or without congestive cardiac failure (CCF)] compared to 15.2% (n = 12) of matched controls ($\chi^2 = 1.569$, $p = 0.0001$). Mean heart rate, P-wave amplitude, P-wave duration and QRS duration were significantly higher in children with community-acquired pneumonia (CAP) and CCF compared with children in other groups ($p < 0.05$). The ECG features of myocarditis were found in approximately 45% (n = 34) of subjects with CAP irrespective of the CCF status. The ECG features of myocarditis (**Table 5**) detected in this study include prolonged PR interval, reduced QRS

amplitude in limb leads, right axis deviation and prolonged QTc and the proportion was significantly higher among subjects with CAP than that in the controls ($p < 0.05$). The prevalence of ECG features of myocarditis among subjects with CAP with CCF was close to twice (71.4%) that in those with CAP without CCF (38.7%).

3.4. Serum cTnT Findings in Subjects (Table 4)

There was significant difference in the proportion of subjects with elevated serum cTnT (≥50 ng/L) suggestive of myocarditis across the groups ($p = 0.006$). However, the proportion of subjects with elevated serum cTnT values suggestive of myocarditis was not significantly higher among those who had any ECG feature of myocarditis ($p > 0.05$).

3.5. Predictors of Mortality in CAP (Table 5)

Overall, case fatality in this study was 5.2% (n = 4). Evaluation of predictors of mortality in severe childhood CAP revealed that the presence of elevated cTnT suggestive of myocarditis (≥50 ng/L) was a better predictor of death in childhood CAP ($\chi^2 = 5.089$, $p = 0.029$).

4. Discussion

The high prevalence of ECG abnormalities among children with CAP in this study (63%) conforms with that reported by Kocak *et al.* [6] and Yun *et al.* [24] in Turkey and China respectively. In the study by Kocak *et al.* [6], virtually all the children with CAP manifested at least one ECG abnormality, while in the study by Yun *et al.* [24], 87% of the children with CAP had one or more ECG abnormality.

Table 4. Comparison of ECG features of myocarditis and cTnT across study groups.

	Controls (76) n (%)	CAP without CCF (62) n (%)	CAP with CCF (14) n (%)	χ^2	p-value
ECG parameters					
Sinus Tachycardia	7 (9.2)	18 (29.0)	6 (42.9)	13.056	**0.001***
Prolonged PR interval	4 (5.3)	10 (16.1)	0 (0)	5.335	**0.046***
Reduced QRS amplitude in limb leads	0 (0)	11 (17.7)	2 (14.3)	16.878	**0.002***
Right axis deviation	4 (5.3)	14 (22.6)	2 (14.3)	9.016	**0.008***
Prolonged QTc	0 (0)	14 (22.6)	2 (14.3)	21.737	**0.0001***
Serum cTnT					
<50	76 (100.0)	5.8 (93.5)	12 (85.7)	8.239	**0.006***
≥50	0 (0)	4 (6.5)	2 (14.3)		

*$p < 0.05$.

Table 5. Predictors of mortality in subjects.

Parameters	Died n = 4 n (%)	Discharged n = 72 n (%)	†χ^2	p-value
CAP status				
Without CCF	2 (50.0)	60 (83.3)	2.802	0.152
With CCF	2 (50.0)	12 (16.7)		
cTnT status				
≥50 ng/L	2 (50.0)	4 (5.6)	5.089	**0.029***
<50 ng/L	2 (50.0)	68 (94.4)		
ECG features				
Present	2 (50.0)	40 (55.6)	0.047	1.000
Absent	2 (50.0)	32 (44.4)		

*$p < 0.05$; †-Fisher's exact test.

Generally, sinus tachycardia was the commonest ECG abnormality recorded in this study (30%); a finding comparable to 41% reported by Ilten and colleagues [3] in Turkish children with CAP. It is of note that supraventricular tachycardia was not seen in any of the patients studied, this is in contrast to the report of Sadoh *et al.* [25] in Benin, Nigeria where 0.4% of the children had SVT. The study by Sadoh *et al.* [25] retrospectively reviewed ECG of 7693 children over a period of four years, a sample size that is much larger than our study. The mean amplitude of the p-wave in the subjects with CAP was significantly higher than in controls, particularly in the presence of CCF. Given that P-amplitude is representative of right atrial depolarization, this suggests a tendency towards right atrial dilatation in children with CAP.

In the current study, first degree AV block was only observed among subjects with CAP and no CCF. Interestingly, this may suggest that the occurrence of first-degree AV block is not dependent on the presence or absence of clinical CCF which itself is an indicator of disease severity in CAP. Nonetheless, studies with larger sample size are required to further elucidate this finding. The significantly higher proportion of subjects (compared with the controls) in whom reduced QRS voltages in limb leads was reported in the present study may reflect the major impact of CAP on myocardial functioning. The finding of low QRS voltages among subjects in the current study is consistent with a previous report [8].

The present study reports a significant rightward deviation of the frontal QRS axis among subjects with CAP, particularly in those without CCF. This observation is similar to reports from previous studies [3] [6] and the clockwise rotation of the frontal axis may suggest the tendency towards the occurrence of RAD across the spectrum ranges of CAP severity [26]. The current study detected a significant reduction in the mean voltages of T-waves among subjects with CAP.

However, a flat T-wave or T-wave inversion which is an ECG feature of myocarditis was not observed in any subject. Because T-wave changes tend to occur progressively, it is possible that serial ECG could have reflected progression from reduced T-amplitude to flat or inverted T-waves but serial ECG was not originally included in the scope of the current study.

A significant proportion of subjects in the index study (especially those without CCF) recorded prolonged duration of QTc compared to controls among which no such finding was observed. As a result, prolonged QTc appears to be the most sensitive ECG feature of myocarditis in CAP in the current study. This finding of superior sensitivity of prolonged QTc for detecting myocarditis is comparable to that documented by Kocak *et al.* [6] It is noteworthy that no ST segment abnormality was recorded in this study; a finding similar to that of previous studies in children. This is in keeping with previous knowledge that ST wave abnormality is more common in adults with CAP than in children [3] [4] [6] [7] [27].

Regarding serum cTnT assay, the present study reports elevated serum cTnT among subjects with CAP compared with controls; this finding is especially prominent in children with CCF compared to those without CCF. The finding of this study suggests that CCF is a significant morbidity that causes myocardial injury in CAP. Considering that about ten percent of the subjects in this study had myocardial damage sufficient enough to cause elevated cTnT, the implication is that community acquired pneumonia of intense severity occurs in children. This is in keeping with previous studies [5] [8] [24] [28] [29]. Furthermore, due to the semi-quantitative assay used in the current study, it is not feasible to obtain mean value of cTnT and allow for direct comparison with some other studies. For instance, studies by Han *et al.* [9] and Yun *et al.* [24] reported increased mean cTnT values among children with CAP compared with controls. Nevertheless, the current study and theirs [9] [24] are in agreement on occurrence of myocardial injury in patients with CAP [5] [28] [29].

The present study did not observe an association between elevated Troponin-T and ECG features of myocarditis in children with CAP. Many of the earlier studies [9] [24] did not report this important relationship in childhood CAP. The lack of association between elevated cTnT and ECG features of myocarditis in the present study indicates that the presence of ECG features suggestive of myocarditis does not necessarily suggest existence of myocardial cell damage. In other words, ECG changes occur regardless of myocardial cell death. Nevertheless, serial serum cTnT and serial ECG in future studies would help to further investigate the association between ECG-featured myocarditis and serum cTnT.

Although not part of the primary objectives of the study, elevated cTnT was found to be a predictor of mortality in children with CAP and this poor prognostic feature persists in subjects with heart failure. This observation is consistent with the reports of previous studies that evaluated the prognostic significance of elevated cTnT during infections and found it to be a poor prognostic index [5] [18] [19] [30] [31].

5. Conclusion

The current study detected ECG features of myocarditis in children with CAP including prolonged PR interval, reduced QRS amplitude in limb leads, right axis deviation (RAD) and prolonged QTc; all these features of myocarditis occurred more frequently in children with CAP with CCF than in children who had CAP without CCF. In addition, myocarditis in CAP as evidenced by elevated serum cardiac Troponin-T (≥50 ng/L) was detected in about one-tenth of the children with CAP (more in the CAP with CCF group). Although, the study did not detect association between ECG features of myocarditis and elevated serum cTnT among children with CAP, presence of elevated cTnT was a better predictor of death in severe CAP.

6. Limitation

The point-of-care machine (Roche Cobas) used for measuring serum cTnT is a semi-quantitative tool and the results generated below 100 ng/L were difficult to compare directly with mean values generated in other studies.

Conflicts of Interest

The authors declare no conflicts of interest.

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