

Journal of Acute Disease

Review Article



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Electrocardiographic abnormalities in prevalent infections in tropical regions: A scoping review

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ABSTRACT

Cardiovascular manifestations and electrocardiographic abnormalities have been reported among some prevalent infections in tropical regions, which lead to a great amount of morbidity and mortality. The major infectious diseases include chikungunya, dengue fever, H1N1 influenza, and coronavirus disease-19 (COVID-19) in the viral category, leptospirosis, salmonellosis, scrub typhus and tuberculosis in the bacterial category, and malaria in the protozoan parasite category. All these infirmities constitute a foremost infection burden worldwide and have been linked to the various cardiac rhythm aberrancies. So we aimed to identify and compile different studies on these infections and associated acute electrocardiographic (ECG) changes. The search was made in online international libraries like PubMed, Google Scholar, and EMBASE, and 38 most relevant articles, including original research, systematic reviews, and unique case reports were selected. All of them were evaluated thoroughly and information regarding ECG was collected. Myocarditis is the predominant underlying pathology for rhythm disturbance and can be affected either due to the direct pathogenic effect or the abnormal immune system activation. ECG variabilities in some infections like chikungunya, scrub typhus, and leptospirosis are associated with longer hospital stay and poor outcome. Tropical infective diseases are associated with prominent acute cardiac rhythm abnormalities due to myocarditis, which can be identified preliminarily by ECG changes.

KEYWORDS: ECG; Chikungunya; COVID-19; Dengue; H1N1; Leptospirosis; Malaria; Salmonella; Scrub typhus; Tuberculosis

1. Introduction

Infective diseases become major hospital burden throughout the entire world, leading to an exorbitant treatment cost and mortality. Tropical infections affect approximately 2 billion individuals per year and are responsible for 200000 deaths every year[1]. The major infective agents, namely chikungunya, dengue, leptospirosis, malaria, salmonella, scrub typhus, and tuberculosis, are prevalent in more than half of the planet, and the remaining part also has sporadic reports of these infestations. Moreover, coronavirus disease-19 (COVID-19) has substantially deteriorated this ongoing trouble worldwide. The cardiovascular (CV) system entanglement in infections is one paramount cause of early hemodynamic compromise and a bleak outcome. Various researches reported acute CV involvement in 54.2% of chikungunya cases, 35% of dengue fever (dengue fever), 10%-40% of leptospirosis, 14.3% of malaria, 1%-5% of salmonellosis, 49.4% of scrub typhus, and 69.4% of tuberculosis[2-8]. Similarly, 20%-36% COVID-19 cases have CV involvement[9]. Electrocardiography (ECG) is a long-established screening tool with great sensitivity and easy reproducibility to identify CV involvement in these situations. So in this study, we aimed to compile various ECG characteristics of commonly encountered tropical infections.

2. Methodology

To identify different research articles on ECG changes in prevalent infections in tropical regions, we searched PubMed,

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How to cite this article: Jesrani G, Gupta S, Gaba S, Gupta M. Electrocardiographic abnormalities in prevalent infections in tropical regions: A scoping review. J Acute Dis 2022; 11(2): 45-51.

Article history: Received 12 February 2022; Revision 10 March 2022; Accepted 18 March 2020; Available online

doi:

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Google Scholar, and EMBASE. We used terms like "Cardiac manifestations/ECG changes in chikungunya/dengue/leptospirosis/ malaria/scrub typhus/salmonella/tuberculosis/COVID-19/H1N1" or "heart involvement/myocarditis in chikungunya/dengue/ leptospirosis/malaria/scrub typhus/salmonella/tuberculosis/ COVID-19/H1N1" and collected all relevant articles including original researches, review studies, and case series. ECG-related findings were gathered from these papers for further evaluation. Newer articles were preferred but the older ones were also added in the absence of recent studies on some particular infections. Animal experimental studies were excluded. Among similar results containing articles, recent ones were preferred and larger sample size studies were chosen over small sample size studies. With this methodology, we identified 38 articles over the past 30 years on different infections and uniformly included them in this paper (Figure 1).

3. ECG changes in chikungunya

Chikungunya is a viral disease, caused by the chikungunya virus (CHIKV), which is an RNA virus transmitted through the bite of the Adese mosquito^[2]. The disease is characterized by three clinical phases, namely acute (<3 weeks), post-acute (3-12 weeks), and chronic (>12 weeks), and fever with poly-arthralgia are commonly presenting complaints^[2]. The pathophysiological cardiac manifestations involve direct myocyte damage,

hypersensitivity reactions without obvious necrosis of the cardiac tissue[2]. Three phases in cardiac involvement have been reported, including pre-congestive or prodromal, arrhythmic phase, and the last heart failure stage[2]. The arrhythmic phase contains most ECG changes, and T wave inversion in lead II, III, aVF, V5, and V6 is the most commonly identified acute pathological change, followed by ST-segment changes^[2]. Tachycardia, deep S wave in lead V2, prominent R wave in V5, atrial fibrillation (AF), various A-V blocks, and ventricular extrasystoles are other findings in patients with CHIKV infection. In a Columbian study, including 42 patients with CHIKV infection, repolarization abnormalities (21.4%) were most commonly recognized changes, followed by first degree A-V block (19.0%), left anterior hemiblock (9.5%), U waves (9.5%), bradycardia (7.1%), left and right axis deviation (7.1%), poor R wave progression (7.1%), tachycardia (4.8%), posterior hemiblock (4.8%), ST-segment depression (4.8%), ventricular ectopic beats (2.4%), AF (2.4%), ectopic atrial tachycardia (2.4%) and inferior wall myocardial infarction (2.4%)[10]. Likewise, in a study from Venezuela including 83 cases, bradycardia (33%) was most frequently observed aberrancy, followed by non-sustained atrial tachycardia (9%), AF (6%), and ventricular tachycardia (VT) (1%)[11]. A specific diagnosis 'CHIKV-related myocarditis' has been described for the triad of fever, poly-arthralgia, and newonset arrhythmia[12]. Cardiac involvement has been associated with a worse prognosis in CHIKV disease and the mortality of these patients is 26%-48%[13].



Figure 1. The study flowchart.

4. ECG changes in dengue

Dengue fever is a result of dengue virus (DENV) infection, which is a *Flavivirus* genus member and mosquito-borne disease[14]. The disease is prevalent in more than 100 countries of the world, highly affecting south and southeast Asia[14]. Myocardial depressant factor, subclinical myocarditis, altered calcium homeostasis, autonomic tone, and coronary hypo-perfusion are some important factors in the development of cardiac impairment. Particularly ECG changes have been observed in 35%-75% of the cases and can be asymptomatic, non-specific, and transient[2].

Commonly encountered acute abnormalities include sinus bradycardia, tachycardia, T wave, ST-segment changes, A-V block, and AF[14]. A 24 hours Holter monitoring study, including 35 children demonstrated ECG changes in 29% of the cases, including sinus pause (2.9%), first (5.7%) and second degree (8.6%) A-V block, atrial (11.4%), and ventricular ectopic beats (14.3%)[15]. Likewise, in a study by Li et al. on 1782 dengue fever patients, myocarditis was observed in 11.3%, ECG demonstrated AF in 13.9%, low voltage QRS complex in 12.4%, bundle branch block (BBB) in 9.45%, ST-segment and T wave abnormality in 29.3%, ventricular premature beats in 5%, atrial premature beats in 0.08% and poor R wave progression in 0.03% of the patients[16]. There are some sporadic case reports on eccentric abnormalities like junctional bradycardia and sinus exit block[17,18]. Similarly, a report by Dhariwal et al. demonstrated a high degree of A-V block and ventricular asystole in a case of dengue fever[19]. Instead of all these abnormalities, the routine use of echocardiography is not recommended in dengue fever unless ECG is found abnormal[20]. Further, acute myocardial involvement is transient in most cases and supportive care forms the cornerstone in the management[20].

5. ECG changes in leptospirosis

Leptospirosis is an important zoonosis, caused by Leptospira species and spreads due to direct contact with pathogen or infected water sources^[4]. The disease is classified into two subcategories, namely anicteric and icteric leptospirosis. The icteric disease is considered more severe and had more cardiac involvement than the anicteric counterpart^[4]. In pathology, interstitial lymphocytic myocarditis, epicardial petechial hemorrhage, and coronary arteritis play an important role^[4]. Although affection of all the three cardiac layers has been reported, conduction system involvement is the most prominent acute complication. Minor ECG changes can be seen in up to 70% of cases due to inhibition of the Na-K ATPase pump by the leptospiral glycoprotein cell wall component^[21,22].

A prospective study by Mathew *et al.*, including 105 patients of leptospirosis, demonstrated acute ECG variabilities like sinus tachycardia in 34.2% of the patients, sinus bradycardia in 16.2%, ST-segment elevation in 13.2%, AF in 6.31%, ST-segment

depression in 5.66%, first degree A-V block in 4.76%, left BBB (LBBB) in 4.76%, incomplete right BBB (RBBB) in 4.76%, atrial and ventricular ectopic beats in 2.83%, T-wave inversions in 2.83%, junctional rhythm in 1.90%, low voltage QRS in 1.90% and abnormal QRS-T angle in 1.90% of the cases[23]. Acute QTc prolongation was observed in 3% of cases in a different study from Gujrat, India, which also demonstrated first-degree A-V block as the most common ECG abnormality (44%) in leptospirosis[24]. Opposite to this, a Brazilian study reported AF as the most common ECG abnormality (10.8%) in 157 positive cases[25]. Unfortunately, arrhythmias and repolarization abnormalities have been associated with poor prognosis in leptospirosis, and 54% mortality has been noted in cardiac involvement[21].

6. ECG changes in malaria

Malaria is a parasitic disease, caused by five species of the Plasmodium genus i.e. Plasmodium falciparum (P. falciparum), Plasmodium malariae, Plasmodium ovale, Plasmodium vivax (P. vivax), and Plasmodium knowlesi. The disease transmits through the bite of the Anopheles mosquito and P. falciparum and P. vivax are two paramount causes for most cases. Although P. falciparum is frequently presented with acute CV abnormalities due to menacing disease course, P. vivax alone or with P. falciparum has also been reported to be blamed for CV morbidity[26,27]. Like other pathogenic agents, direct cardiac injury by parasitic proteins and the release of inflammatory cytokines are two important mechanisms in pathogenesis^[5]. A study including 100 patients of severe malaria from North India demonstrated acute CV involvement in 17% of the cases and ECG changes of sinus tachycardia in 25% of the patients, non-specific ST-T changes in 8% of cases, and atrial ectopic beat in one patient[5]. Similarly, a case-control study by Sadoh et al. on Nigerian children compared ECG abnormalities in malaria with anemia (case) and malaria without anemia (control)[28]. The work depicted sinus tachycardia in all of the case subjects (100%) and 25% of the control population, ST-segment changes in 11.7% of the subjects, RBBB and left ventricular hypertrophy in 4.7%, QTc prolongation in 23.3% of the case subjects and 5% of the control individuals, and electrical alternans in one case subject. In a study from different geographic regions, 53 malaria patients were monitored for 24 hours and demonstrated supraventricular ectopic beats in 15%, ventricular ectopic in 2%, agonal rhythm (a variant of asystole) in 6%, ventricular pause in 4%, couplets in 2%, and sinus bradycardia in 2%[29]. Similar to the previous study, sinus tachycardia was observed in all study participants (100%) and 9 (17%) of them had a heart rate of more than 200/min. But an observational study from India on 27 severe malaria cases demonstrated more sinus bradycardia cases (7.4%) than tachycardia (3.7%)[30]. Moreover, Franzen et al. demonstrated that acute ECG abnormalities in severe malaria were reversible and disappeared after 9 months of followup, but the sample size was only 22[26]. The study demonstrated ST depression and T wave inversion in 22.7% of the cases, which recovered completely on follow-up.

7. ECG changes in salmonellosis

Salmonella enterica serovar typhi and paratyphi cause enteric fever with an incidence of 270/100000 persons/year and predominantly affect South and South-east Asian countries[31]. Gut is the primarily involved organ system, but cardiac manifestations have been described predominantly in the endemic regions. Persistent bacteremia leads to myocarditis and endocarditis more than pericarditis or arteritis, which is the basis of acute conduction defects[31]. In one study, ECG changes were observed up to 11.9% of the cases[32]. Prabha et al. evaluated 100 patients with enteric fever from India and found that 46% of the patients suffered from conduction defects due to myocarditis[33]. The results showed that 29% of the study population had QT prolongation, 20% had ST-T changes, 7% had any BBB. First-degree A-V block and other arrhythmias were also reported in 2% of the cases. An Egyptian study with 106 patients demonstrated T wave changes and STsegment abnormalities in 56.6% of individuals^[34]. Ventricular fibrillation was also observed in a case by Biber et al.[31]. Although ECG changes are transient, complex diversities directly correlate with the disease severity and indicate a poor prognosis[35]. Also, odd QRS complexes and left bundle branch abnormalities can lead to sudden cardiac death among these patients.

8. ECG changes in scrub typhus

Scrub typhus is an important constituent of acute febrile illness in tropical countries. The disease is acquired due to infection of bacterium Orientia tsutsugamushi of family Rickettsiaceae[36]. The transmission is through the bite of mite larvae, which forms a bite site "Eschar" due to skin necrosis. The pathogenesis includes direct myocardial invasion, endothelial and vascular damage, and abnormal immune activation[36]. The acute electrocardiographic abnormalities have been described extensively in this infection and a recent article, including 165 scrub typhus patients, ECG abnormalities were observed in 43.6% of the cases[37]. In addition, QT prolongation was observed in 19.4%, AF in 9.1%, T wave inversion in 12.7%, first degree A-V block in 3.6%, atrial premature beat in 3%, RBBB in 3%, pathological Q wave in 1.8%, poor R wave progression in 1.8%, third-degree A-V block in 0.6%, ventricular premature beat in 0.6%, LBBB in 0.6% and ST elevation in 0.6%. Thus, QT prolongation was the major aberrancy, which was more prominent in the older age group.

Similarly, a study from Thailand included 146 scrub typhuspositive patients and found new-onset ECG changes in 54.1% of the cases. Among these patients, 21.5% demonstrated sinus tachycardia, 11.3% of new-onset AF, 3.8% of supraventricular tachycardia, 3.8% of RBBB and 3.8% of non-specific ST-T changes[7]. Further, 1.3% of cases had left anterior fascicular block, premature ventricular complex, first degree A-V, and complete heart block. A study from India on 81 scrub typhus also demonstrated sinus tachycardia as the most common abnormality (46.9%)[38]. Moreover, the research stated abnormal QRS morphology in 11 (13.5%) of the cases with one patient having wide QRS tachycardia, which was unique. Opposite to the above-stated studies, Aronoff et al. studied 100 patients of scrub typhus and demonstrated relative bradycardia in 53% of the study cohort[39]. Moreover, a study from South Korea, including 233 473 scrub typhus patients demonstrated new-onset AF in 1% of the participants, which was associated with significant 3-month mortality^[40]. These changes should direct myocarditis evaluation, as a systematic review also confirmed higher mortality among these patients[41].

9. ECG changes in tuberculosis

Tuberculosis is one of the important infective diseases predominantly among developing counties. The pathogen is bacillus Mycobacterium tuberculosis, which spreads by the infected aerosol particles[42]. The pulmonary system is the primarily affected system, but the CV involvement has been documented in the literature. The pathogen affects the heart by direct spread from adjacent tissue or hematogenously, affecting the epicardium (pericarditis or pericardial effusion), myocardium (myocarditis), endocardium (endocarditis), and aorta (aortitis)[42]. Acute myocardial involvement is the predominant cause of electrical disturbance^[42]. A study of 100 pulmonary tuberculosis patients concluded sinus tachycardia (30.55%) as the most common acute rhythm abnormality, followed by P-pulmonale (12.5%), prolonged PR interval (9.72%), left axis deviation (8.33%), right axis deviation (6.94%), low voltage QRS complex (5.55%), prolonged QT interval (4.16%), sinus bradycardia (4.16%), premature ventricular beats (2.77%) and premature atrial beats (1.38%)[8]. Master et al. in 27 pulmonary tuberculosis patients also confirmed sinus tachycardia (42%) as the most common ECG finding[43]. The research further demonstrated PR prolongation (19%), T wave inversions (19%), and ST-segment changes (13%). Thus, cardiac involvement is not uncommon in tuberculosis and has been associated further with a poor outcome[42].

10. ECG changes in COVID-19 and H1N1 influenza

In the current situation, discussion on infections is incomplete without COVID-19 and H1N1 influenza appraisal. These viral diseases are relatively novel but have emerged as a significant public health problem. The common pathophysiology for viral infestation of the CV system includes extended cytokine activity leading to systemic inflammation, unvarnished myocarditis, and increased cardio-metabolic demand^[44]. Angiotensin-converting enzyme 2 receptor-mediated direct injury is particularly specific for COVID-19^[44]. Moreover, myocardial inflammation, ischemia, vasculitis, vascular thrombosis-like events serve as the basis of conduction defects and various arrhythmias are the predominate ECG findings.

In COVID-19, 17%-93% of the patient developed acute rhythm aberrancies reported by Long *et al.*[45]. Sinus tachycardia (59%) is the most common finding, followed by AF (14.3%-22%)[45,46]. Further, the reported incidence of VT or fibrillation was 1%-6%, sinus bradycardia or A-V block in 11.8%, QT prolongation in 13%, either BBB in 12%, combined ST segment and T wave changes in 41%[45]. A single cohort study including 216 COVID-19 patients, recent-onset AF was seen in 9.3%, left anterior fascicular block in 8.8%, RBBB in 6.9%, low voltage QRS complex in 5.6%, ST-segment changes in 5.6%, first degree A-V block in 5.5% and LBBB in 2.8% cases[47]. Pulmonary embolism-related ECG pattern (S1Q3T3) can be observed in 10% of the cases and atrioventricular nodal re-entry tachycardia is also reported in the context of COVID-19[45]. Moreover, conduction abnormalities have been associated with poor outcomes in COVID-19.

In H1N1 influenza, the incidence of ECG has been observed up to 28%-42.8%[48]. A study by Wang *et al.* demonstrated sinus tachycardia (13.6%), AF (13.6%), ST-segment depression (13.6%), VT (9.1%), T wave inversion (9.1%) and flattening (9.1%), ventricular premature beat (4.5%), ST-segment elevation (4.5%), P-pulmonale (4.5%) and pathological Q wave (4.5%) in H1N1 patients[49]. Further, in a study including 50 patients with H1N1, T wave inversion (16%) and ST-segment changes (12%) were the predominant acute ECG findings[48]. A mixed outcome of these abnormalities has been observed but most reports demonstrated the benign nature of such changes[48].

11. Recommendation

As observed in various studies, it is recommended that patients with chikungunya, leptospirosis, tuberculosis, and scrub typhus should be subjected to echocardiographic examination, if ECG is found abnormal as rhythm abnormalities have been associated with poor prognosis. Likewise, these patients should be evaluated with a cardiac biomarker, which can prognosticate the hospital stay and the outcome. Rhythm abnormalities are benign for COVID-19, dengue fever, malaria, and H1N1, but should not be overlooked to avoid an unfavorable outcome. In salmonellosis, rhythm aberrancies are transient, but wide QRS complexes and left bundle branch abnormalities carry adverse consequences. Further, more research is required in the field of cardiac manifestations of tuberculosis, as prospective large cohort studies on the relationship between the disease and rhythm abnormalities are scarce.

12. Conclusion

In conclusion, prevalent infections in tropical regions, have a significant association with acute cardiac conduction system abnormalities. Myocarditis has been objectified as a paramount cause of these changes, along with the direct toxic effect of the pathogen and inappropriate immune system pursuit. Among the major tropical infective agents, salmonellosis was most commonly associated with ST-segment and T wave changes, followed by leptospirosis with first-degree A-V block. Overall, COVID-19 had a maximum incidence of ECG abnormalities and sinus tachycardia was the most prevalent change. Further, dengue fever, malaria, salmonellosis, and H1N1 have a benign association with rhythm aberrancies but chikungunya, leptospirosis, scrub typhus, tuberculosis and COVID-19 demonstrated a relatively dire consequence in this milieu. Thus, infective conditions require rigorous scrutiny for CV involvement, and ECG is a worthwhile implement in this context.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

All the Authors have substantial contributions to the concept and design of the study, acquisition of data, analysis, and interpretation of data; Drafting the article, revising it critically for important intellectual content; Final approval of the version to be published. The prominent roles of each author include the following: G.J. provided the concept and design of the study, contributed to data acquisition, analysis and interpretation, review of literature and preparation of the first and final draft; S.G. (Samiksha Gupta) contributed to data acquisition, analysis, and interpretation, review of literature and modification of the draft; S.G. (Saurabh Gaba) and M.G. contributed in critical comments, data analysis, and interpretation, review of literature, modification of the draft for final publication. All the authors took responsibility to ensure the integrity of the work. The manuscript has been read and approved by all the authors, the requirements for authorship as stated have been met, and each author believes that the manuscript represents honest work.

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