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Revisiting acute myocarditis in children to save lives

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Abbreviations: CMR: Cardiovascular Magnetic Resonance; CRP: C-Reactive Protein; DAD: Diffuse Alveolar Damage; DCM: Dilated Cardiomyopathy; DILD: Diffuse Interstitial Lung Disease; EF: Ejection Fraction; ICU: Intensive Care Unit; IVIG: Intravenous Immunoglobulin; LV: Left Ventricle; SF: Shortening Fraction; SUDC: Sudden Unexpected Death in Childhood; US: Ultrasound

Abstract

Background: A case of sudden unexpected death of an 11-year-old child with tonsillitis illustrates acute myocarditis and the difficulty in diagnosing it.

Aims: Consider myocarditis among acute pediatric conditions, suggesting this disease should be included in the differential diagnosis for children who are toxemic critically ill, particularly when they have respiratory symptoms.

Methods: A critical review of studies published from 1987 to 2018 was conducted. Relevant studies addressed children with deterioration of a condition initially considered benign and discussed clinical aspects suggesting various pathologies such that the presence of myocarditis was "masked." Papers on myocarditis and sudden death in children were selected by searching electronic databases (Pubmed, Scielo, Semantic Scholar, Google Scholar, Springer Link, Science Direct, NCBI, Research Gate, and others). Articles on immunology, pathology, pneumology and radiology were also included that addressed medical reasoning and might assist in early diagnosis.

Results: Many cases of myocarditis remain undiagnosed due to nonspecific symptoms. Therefore, the true prevalence is unknown. The literature reports a high prevalence of histologically proven myocarditis on post-mortem examination in pediatric cases of sudden death based on the presence of a lymphocytic infiltrate necrosis of myocytes.

Conclusion: Early diagnosis and treatment of myocarditis might save children who would otherwise die or develop chronic dilated cardiomyopathy. Information presented in this review may assist in better recognition of this life-threatening disease.

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Introduction

The high incidence of pediatric emergencies presenting with respiratory symptoms and the wide variety of childhood illnesses, including gastroenteritis and fevers without an obvious source, might mask a possible diagnosis of acute myocarditis. Since children with this condition may also be asymptomatic or exhibit a variety of nonspecific symptoms, the true incidence of the myocarditis in childhood remains unknown. Despite its frequently benign nature and self-limited course, acute myocarditis may cause rapid clinical deterioration and even lead to sudden unexpected death. The mortality may be as high 75% in children under 1 year of age with disease due to Coxsackie B virus, while it is less than 25% among older children with acute myocarditis [1]. Due to many variables associated with the condition and its often nonspecific characteristics, the diagnosis of acute myocarditis poses a challenge to pediatricians. In fact, while many of the vast variety of pediatric diseases can be definitively diagnosed clinically, myocarditis can sometimes only be confirmed by a post-mortem examination.

The true number of children affected by viral myocarditis, the most common etiology of the disease, is certainly higher than the numbers reported in studies. Most affected children survive the disease in its relatively benign form and, in general, children with myocarditis present with any of the broad range of pediatric complaints, such as gastroenteritis or respiratory illness.

However, some children indeed die from this condition. In this review, we include an illustrative case of an 11-year-old boy being treated for tonsillitis who died within a short period of time. Myocarditis was diagnosed only on post-mortem examination. This demonstrates that the disease may be responsible for some cases for Sudden Unexpected Death in Childhood (SUDC). Unless autopsy is performed to ascertain the exact cause of death, the true incidence of myocarditis in this respect is unknown. So while autopsy should be considered a diagnostic method in SUDC, it is seldom performed currently [2].

The fact that common and seemingly nonlethal pathogens may cause myocarditis suggests there might be some underlying immunodeficiency favoring infection of the myocardium. This possibility requires further research, including post-mortem examinations of cases of SUDC to understand why children with a seemingly benign, nonlife-threatening infection die. Immunodeficiency syndromes might involve innate immunity, such as phagocyte dysfunction or complement system abnormalities, which can be associated with overwhelming infections. Or there could be defects of adaptive immunity, such as deficient immunoglobulin production or abnormal T cell function, which are associated with recurrent infections of the mucous membranes [3,4]. The immune response is the main barrier to disseminated infections with a high mortality rate [5,6]. If innate immunity mechanisms do not completely effect the defense acts, it will be necessary to add adaptive immunity for a quickly efficient response in infectious and no infectious diseases. In cases of severe failure defense (immunodeficiency), this could favor life-threatening diseases as fulminant myocarditis. The latter may appear suddenly following a nonspecific viral infection, with rapid progression to severe heart failure, cardiogenic shock, and potentially fatal arrhythmias [7].

An urgent need is the identification of new markers that might be highly specific and sensitive for the early diagnosis of myocarditis. Immunohistochemical detection of inflammatory cells (T and B lymphocytes, macrophages or HLA- Human Leucocyte Antigen) in cardiac tissue increase the sensitivity for the diagnosis of myocarditis when histological diagnosis is in conclusive by Dallas criteria. This is the context within which the Lake Louise criteria were formulated in 2009, improving diagnostic efficiency through the use of contrast-enhanced Cardiovascular Magnetic Resonance imaging (CMR) [8].

Echocardiography is a relevant diagnostic tool to help with clinical decision-making, especially for the emergency care of children with myocarditis and severe cardiac dysfunction (Figure 1). As an example, FAST (Focused Assessment with Sonography in Trauma) has proved helpful in critical situations, e.g., cardiac tamponade, with the help of US-guided regional anesthesia [9,10]. Therefore, using focused US examination or functional echocardiography in pediatric emergency departments might improve diagnosis and treatment of critically ill patients (Figure 2). For this purpose, US training programs for pediatric emergency providers need to be implemented (Video 1) [9,10].

In the pediatric emergency care setting, thinking of acute myocarditis in the differential diagnosis is crucial. Early therapeutic action, if appropriate, includes administration of intravenous immunoglobulin (IVIG) at the onset of symptoms, as is routinely done in many centers [11]. This may reduce the mortality rate [12] as well as progression of the disease to its chronic form of Dilated Cardiomyopathy (DCM). Myocarditis is the most frequent cause of DCM in childhood. The first European registry of cardiomyopathy (January 2018), which included 3,208 adult patients in 18 countries, reported that hypertrophic cardiomyopathy and DCM were the most frequent subtypes of cardiomyopathy. Study for pediatric patients clinically suspected or biopsy-proven myocarditis is still ongoing (until December 2018 and ended in 2019). Echocardiography and Electrocardiography were performed in 95,1%, almost of all patients. Magnetic resonance imaging in 71,6%, genetic testing in 35,7% and endomyocardial biopsy in 10,7% of the patients [13].

In the present study, we introduce a new expression "Hermetical heart" to denote a unified understanding of the plurality of conditions affecting the cardiovascular system in acute myocardial diseases. The heart is acutely and but often silently affected in myocarditis, which is why clinicians must be alert to the possibility of this disease, especially in the emergency care setting.

***Note*:** Hermetic (adj.)–1630s "dealing with occult science or alchemy," from Latin *hermeticus*, from Greek *Hermes*, god of science and art (among other things), who was identified by Neoplatonists, mystics, and alchemists with the Egyptian god Thoth as *Hermes Trismegistos*, "Thrice-Great Hermes," who supposedly invented the process of making a glass tube airtight (a process in alchemy) using a secret seal. Hence, "completely sealed" (c.1600, implied in *hermetically*)–Online Etymology Dictionary.

Clinical case

The clinical case reported here, which has been published elsewhere [14], is an illustration of the problem of unrecognized acute myocarditis. An 11-year-old boy had been seen by his primary care physician complaining of a sore throat. He was given antibiotics for a clinical diagnosis of tonsillitis, although no specific tests were done. The following day, he collapsed at home. He was taken to the emergency room but did not respond to cardiopulmonary resuscitation and was pronounced

dead. There was no family history of heart disease or sudden death. At autopsy, gross findings included purulent exudate on the tonsils and an enlarged heart. On microscopy, there was no fibrosis or myocardial hypertrophy, corroborating that this was an acute cardiac condition characterized by a predominantly lymphocytic infiltrate and areas of necrosis. Laboratory analysis included bacterial culture of swabs; blood cultures; C-Reactive Protein (CRP); meningococcal and pneumococcal screening; toxicology testing for alcohol and drugs; and serology for Mycoplasma pneumoniae, cytomegalovirus, Epstein-Barr virus, parvovirus, rubella, chlamydia and Toxoplasma gondii. All of those tests were negative, as were Gram stain and culture of the cerebrospinal fluid. Adenovirus DNA was detected in the blood, myocardium, and tonsils but not in the lung. The post-mortem diagnosis was adenovirus myocarditis.

Aim

Myocarditis should be considered in the differential diagnosis for children with acute illnesses that appear to progress. Unexplained heart failure often sets in silently. Initially, myocardial dysfunction is attended primarily by respiratory symptoms rather than symptoms suggestive of cardiac disease [15,16]. Wheezing and crackles on chest auscultation are often found in pulmonary diseases, such as asthma and bronchiolitis or respiratory infections, but they might also be clues to acute myocarditis with heart failure [15,16].

Materials and methods

The present study consisted of a review of published articles on myocarditis and SUDC, including those specific to related fields such as immunology, pathology, pulmonology, and radiology, that were published between 1987 and 2018. The sources considered to be included addressed the complexity inherent in making the diagnosis of acute myocarditis in children with a rapidly deteriorating condition, such as sudden death, and its immune and autoimmune pathophysiology. The following search terms were used both in English and Portuguese: myocarditis, diagnosis, children, immunology, sudden death, and childhood. Titles and abstracts of all publications obtained from an electronic search and references of such studies were screened by the authors. Duplicate studies were excluded. The following databases were searched: PubMed, Scielo, Semantic Scholar, Google Scholar, Springer Link, Science Direct, NCBI, Research Gate, J-Stage, AHC Media, ESC, British Medical Journal, SCCALP.org, MDedge, BMC Journals, AAP.org, AHA Journals, SUDC.org, Heart Views, and UFRGS (Federal University of Rio Grande do Sul). The electronic search identified a total of 528 studies on myocarditis, of which 233 were initially selected based on titles and abstracts. We excluded 197, including 177 that did not meet the eligibility criteria and another 20 duplicate publications, leaving 36 studies for review (Figure 3).

Clinical signs and heart failure physiology

Prodromal symptoms, including fever, muscle pain and complaints associated with nonspecific respiratory infections or gastroenteritis, may precede cardiovascular symptoms. However, the clinical manifestations of myocarditis can be extremely variable, ranging from a complete lack of symptoms to fulminant disease resulting in sudden death. The probable causes of SUDC in the absence of a previous history of heart disease are ventricular arrhythmias and atrioventricular block secondary to inflammation involving the cardiac conduction system (Figure 4) [17,18]. Signs of heart failure, including tachycardia, a gallop rhythm with a third heart sound, and crackles and inspiratory wheezing in the lungs, may be present. Muffled heart sounds suggest systolic dysfunction or pericardial effusion, that is, myopericarditis. Hypotension indicates increased severity of the disease, which may result in frank cardiogenic shock. Such patients should be managed in the Intensive Care Unit (ICU) and may require procedures such as extracorporeal membrane oxygenation [19].

Children with myocarditis usually exhibit progressive dyspnea. Impaired ventricular contractility leads to increased diastolic ventricular pressure and diastolic ventricular volume, in turn increasing left atrial and pulmonary venous pressure, resulting in pulmonary congestion. When the heart's compensatory mechanisms are exhausted, the elevated pulmonary venous pressure and left ventricular diastolic and systolic dysfunction lead to inadequate cardiac output, ultimately progressing to cardiogenic shock. Fever and anemia, which increase the heart rate, might be sources of additional stress to the heart [1]. Diastolic ventricular filling is impaired both by tachycardia and by the reduction of the end-systolic volume because of the impaired contractility. Patients appear pale due to poor peripheral perfusion, and they might also complain of abdominal pain because of mesenteric ischemia. Chest pain might develop because of impaired coronary perfusion or associated pericarditis or pleurisy. More rarely, an enlarged liver and fluid retention may occur when the right ventricle is affected.

Fulminant myocarditis is characterized by a short viral prodromal period and rapid deterioration of myocardial function, resulting in cardiogenic shock. Among children who survive the fulminant disease but progress to the chronic phase with DCM, approximately 40% will undergo heart transplantation or die within 5 years of diagnosis [12].

Diagnosis and treatment of acute myocarditis

Diagnosis of acute myocarditis is based on clinical manifestations together with findings on noninvasive tests. These may include chest radiographs, which may show cardiomegaly or signs of pulmonary venous congestion; echocardiography, which is essential both for diagnosis and follow up; electrocardiography; magnetic resonance imaging using the Lake Louise criteria; measurement of enzymes indicating myocardial injury such as troponin and CKMB; and CRP levels. This full set of tests is recommended to increase the odds of a correct diagnosis. Myocardial scintigraphy is also currently being used. This evaluates the presence of the myocardium swelling and necrosis. In cases of positive myocardial scintigraphy, biopsy could be indicated.

Invasive tests, such as intracardiac or endomyocardial biopsy, held to be the gold standard for the diagnosis of myocarditis at many specialized centers around the world, are still a source of debate among specialists [20,21]. Some consider that these procedures lack adequate sensitivity because of a particular biopsy sample may lack adequate histologic evidence. In addition, there is a high risk of complications resulting from perforation. Post-mortem diagnosis is made based on the Dallas criteria, with cardiac tissue histology demonstrating a lymphocytic infiltrate and myocyte necrosis [21].

Since viral infections are the leading cause of myocarditis, assessment for viral DNA is performed. Approximately 51 adenovirus serotypes and more than 60 different types of enteroviruses, including Coxsackie A (23 serotypes) and B (6 serotypes) viruses, have already been identified, with Coxsackie B considered

the most common cause of myocarditis [1]. Adenoviruses and enteroviruses have also been associated with myocarditis. The number of cases reports of myocarditis in childhood increased in the 2009 Influenza A (H1N1) pandemic . More recently, the prevalence of myocarditis linked to Parvovirus 19 (PB19) and to Human Herpesvirus-6 (HHV6) have been increased.

Isolation of viruses from myocardial tissue on post-mortem examination poses a considerable challenge. New molecular techniques with high sensitivity and specificity, such as immunochemical methods for viral detection, may yield an etiologic diagnosis. Several studies have shown how difficult is to isolate the etiologic agent from patients who have died from myocarditis. The exact agent is not identified in approximately 50% of cases, even though the infection is virus-mediated.

The Lake Louise criteria [8], formulated in 2009, describe findings on contrast-enhanced CMR that increase the sensitivity and specificity for the diagnosis of myocarditis. These findings indicate focal or global myocardial edema, hyperemia and capillary leak, and fibrosis or necrosis seen as late gadolinium enhancement.

According to the literature, administration of immunosuppressant agents, such as azathioprine and cyclosporine, combined with steroids for treatment of acute myocarditis among children is controversial. Beta-blockers, diuretics and inotropes are used if heart failure occurs. High-dose IVIG might yield better results in early stage of this disease. It is for this reason that early diagnosis is urged in the hope that such treatment will reduce mortality and stop progression to chronic cardiomyopathy.

Since 1990, the routine protocols at two children's hospitals in Boston and Los Angeles in the United States include high-dose IVIG for suspected cases of acute myocarditis [22,23], an approach subsequently adopted at pediatric hospitals worldwide. Several studies found a more satisfactory response to this treatment among children (better outcomes in myocarditis secondary to Kawasaki disease) compared with adults. One study reported effective responses in acute viral myocarditis to combinations of high-dose IVIG and steroids, such as methylprednisolone [23].

Post-mortem studies

Some post-mortem studies are discussed, along with an antemortem study of critically ill children admitted to an ICU in Cairo, Egypt.

1. In 8 cases of sudden infant death associated with histologically diagnosed myocarditis or pericarditis, viral genomes identified at autopsy included adenoviruses, cytomegalovirus, and enteroviruses found in myocardium, liver and muscle samples. This study points to the possible participation of these pathogens in the sudden death of infants under 1-year-old [24].

2. Among 1516 autopsies of children aged 0–18 years who died from various causes over 10 years at a specialized center in the United Kingdom [25], 1.8% (28 cases) had histologically proven myocarditis. An observation to this study, in which, was not a choice of SUDC cases primarily as a sample and therefore the use of Dallas criteria to ensure a histological myocardial diagnosis.

In this study, among 28 cases of myocarditis, 17 presented as sudden death, of them 10 had no apparent prodrome or life-threatening symptoms. Of the 11 deaths that were not sudden, 6 children had respiratory complaints, 3 had gastrointestinal symptoms, 1 abdominal pain, and 1 fever in association with a nonspecific viral illness. In this group, 7 children were admitted to the hospital with worsening of respiratory symptoms, being 3 treated initially as pneumonia before hospitalization.

Prodromal symptoms, including fever, respiratory, and gastrointestinal symptoms, occurred in approximately 80% of these 28 children with histologically proven myocarditis.

3. In 32 cases of child deaths at a pediatric hospital in Australia in which myocarditis was histologically proven, 16 had myocarditis as the only single significant finding, while the other 16 had myocarditis in association with other conditions, such as bronchopneumonia. This study demonstrated the variety in the presentation of myocarditis in childhood and adolescence, indicating that myocarditis may or may not be associated with other potential causes of death [26].

4. In a Cairo pediatric ICU [27], 63 critically ill children admitted with respiratory failure were studied, excluding children with congenital or acquired heart disease or previous heart failure. Respiratory diseases were diagnosed in 41 cases (65%) upon admission. Myocarditis was suspected in 16 children on the basis of abnormal cardiac enzymes, echocardiogram and electrocardiogram, of whom 10 had an admission diagnosis of respiratory infection 2 of encephalitis, and 4 of other conditions. These 16 were given IVIG for 48 hours. The mortality rate was 50%, that is, 8 children with suspected myocarditis survived.

Myocarditis and pulmonary radiological patterns

Radiology studies are relevant for the present review, as they indicate wide variability in the interpretation of chest radiographs [28].

Increased lung opacification suggests a heterogeneous group of pulmonary diseases known as Diffuse Interstitial Lung Disease (DILD). One of the causes of diffuse lung opacification is pulmonary edema, which is classified as hydrostatic (due to elevation of the pulmonary venous pressure and its occurrence during heart failure) or nonhydrostatic (due to increased capillary permeability, usually caused by Diffuse Alveolar Damage (DAD) and its occurrence with sepsis) [29].

Pulmonary edema and interstitial pneumonia exhibit the same radiologic pattern characterized by increased lung opacification, which may hinder the differentiation between myocarditis with pump failure and interstitial lung disease, such as mycoplasma pneumonia. Increased lung opacification might present as ground-glass opacities with preserved vascular markings, or as parenchymal consolidation, which obscures vessels. Such criteria for differentiation notwithstanding, these findings are considered to be nonspecific and might represent several different alveolar, interstitial, or mixed diseases. Pulmonary edema is the most common cause of diffuse acute lung disorders presenting with ground-glass opacities or consolidation patterns.

For the assessment of interstitial edema due to pulmonary venous congestion, which is suggestive of myocarditis, chest radiographs might not suffice as a single imaging modality due to the poor definition of the pulmonary vessels and their calibers, peribronchial thickening, and the fact that cardiomegaly might be either present or absent.

When there is a discrepancy between the clinical history and inconclusive radiologic findings, high-resolution tomography, echocardiography, and electrocardiography should be

performed. Laboratory tests, including measurement of cardiac enzyme levels, are useful for diagnosis, even though the results may be not be immediately available, a hindrance when the disease is rapidly progressing.

Infections are always at the top of the differential diagnosis for acute pulmonary disease. The presence of centrilobular nodules together with the "tree-in-bud" pattern (due to accumulation of secretions in the bronchioles) seen on tomography is a radiologic finding useful to confirm an infectious pulmonary disease, discarding diseases related to pulmonary venous congestion. Increasing the diagnosis problem, pulmonary edema can also be confused with findings in several noninfectious DILD.

Therefore, myocarditis should be included in the differential diagnosis, because it can also present with rapidly progressive respiratory symptoms since a chest radiograph, in general does not enables differentiation among the various possible diagnoses [28].

For pediatricians who daily face several acute breathing scenarios in emergency rooms, the diagnosis of acute myocarditis should be included in their medical rationality.

Variability and agreement of radiological diagnoses

Icaza published a study in which chest radiographs of 60 children aged up to 5 years old with acute respiratory symptoms with apparent lung involvement were reviewed by a pediatric emergency physician, a pediatric pulmonologist, and a radiologist [30]. Considerable inter-rater variation was apparent and may be inherent to the interpretation of radiologic findings. Variability index occurs considerably in results, not only, in radiology as in several medical areas when a medical board discuss about scenarios with inconclusive diagnoses.

Such variability is compounded by the fact that radiologic interpretation in the acute setting is often made by physicians with different levels of experience and training. This is especially true in Brazilian emergency departments, where radiologists are not always available. According to Icaza, diagnostic errors are due to lack of knowledge or inappropriate conclusions, which may result from interpretive associations based on incorrect initial hypotheses [30]. Making the wrong diagnosis clearly impacts treatment. For decades, we have been dealing with the over prescription of antibiotics. In the case of acute lower airway disorders, the main challenge is to distinguish bacterial pneumonia from other diseases that do not require antibiotics. Errors are actually more frequent in apparently simple cases compared with the most difficult ones, which demand consultation with others to make a correct diagnosis. To overcome the subjective nature of image interpretation and thus improve inter-rater agreement, requiring double interpretation of all images might help. However, non subjective factors also interfere with interpretation, such as overlapping structures on two-dimensional radiographs, a child's small size, poor technical quality, and an inadequate inspiration. Icaza concluded that error and variability are intrinsic parts of the diagnostic process [30].

Understanding the immune and autoimmune process in myocarditis

Experiments conducted in mice showed that myocarditis was due to an immune process triggered by the local action of cytokines, whereby macrophages, mast cells, CD4 and CD8 T cells, B lymphocytes, and killer cells were all activated, resulting in necrosis of myocytes and interstitial edema of the affected heart tissue, with a consequent deleterious effect on the heart's pumping function. This immune reaction, occurring in response to viral infection, promotes the release of interleukin 1ß and tumor necrosis factor alpha (TNT alpha), which might contribute to reduction or suppression of myocardial contractility. The result is cardiac dysfunction that occurs in acute myocarditis and the possible development of chronic myocarditis, according to several studies.

Inoculation of Coxsackie B3 virus into sensitized mice induced acute heart inflammation, the intensity of which depended on the pathogenic properties of the virus and genetic aspects of the host. Low viral replication levels were indicative of clinical improvement of the induced myocarditis and no progression to the chronic stage. Some mice developed an acute form of disease and others the chronic form, while a third group exhibited resistance to the development of myocarditis at all.

Coxsackie B3 viral replication inside the myocytes caused immediate damage, leading to cell death. The host's immune defense acts to control virus replication, but the repair response, with collagen deposition and fibrosis, causes further myocardial injury.

Some authors have detected an initial antigen-antibody reaction that triggers an autoimmune response with production of autoantibodies. It is believed that the pathogenesis of the disease is directly related to successive immune responses. Both recurrent viral attacks and the host's immune and inflammatory responses influence the extent of the myocardial damage. Virus-infected defense cells, such as lymphocytes and killer cells, become unable to regenerate. If viral peptides remain on the myocyte cell membrane surface, even after viral replication has ended, they may be subject to cross-reactions through mechanisms not yet fully elucidated. According to one hypothesis, necrotic cardiomyocytes release intracellular components, which behave as antigens, triggering an autoimmune response against the own cardiac tissue via production of low-affinity IgM autoantibodies.

In laboratory experiments with rats, an autoimmune response developed a few hours after the induction of acute myocarditis by inoculation with Coxsackie B3 virus.

Investigators still do not have a clear idea of the determinants of complete recovery and cure or of progressive structural damage and cardiac dysfunction. The mouse study suggests that immune dysregulation subsequent to viral infection may have a role in the pathogenesis of myocarditis in humans and to its progression to chronic DCM [31].

Results and discussion

For patients who die, the surveyed literature recommends diagnostic confirmation of acute myocarditis by post-mortem examination according to the Dallas criteria, that is, the presence of a predominantly lymphocytic infiltrate and areas of fibrosis or myocyte necrosis, which are pathognomonic of the disease. However, some studies note that the specificity and sensitivity of the Dallas criteria have not been fully established. Nevertheless, the Dallas criteria [22] remain the more widely accepted criteria worldwide for the post-mortem diagnosis of myocarditis. The Lake Louise criteria [8] can help diagnose myocarditis antemortem if CMR is performed.

According to the research reviewed in the present study, viruses are the most common cause of myocarditis in children,

with adenoviruses and enteroviruses at the top of the list [11,14]. Echoviruses, parvoviruses (PB19), cytomegalovirus, human herpesviruses (HHV6), Epstein-Barr virus, influenza viruses, human immunodeficiency virus, hepatitis C virus, rubella virus, respiratory syncytial virus, and coinfections with more than one virus have also been described. Other possible etiologies include bacteria, fungi, adverse drug effects and hypersensitivity reactions, and insect and animal bites. Kawasaki disease, hypereosonophilic syndrome, and inflammatory bowel conditions, such as celiac disease, have also been mentioned as causes of myocarditis.

In this review, it was not found articles directly related to acute myocarditis in childhood with specific radiological disorders such as pulmonary venous congestion presence on pneumology articles. References of pulmonary disorders and serious evolution of myocarditis in childhood occurred in post-mortem studies.

Lack of autopsies influences statistical data on the cause of death

Several studies reported a dramatic decline in performing autopsies for patients admitted to the hospital who died due to disease in Brazilian general and university hospitals, especially since 2000. This situation was described in two studies, one conducted in 2009 at Clinical Hospital of Federal University of Minas Gerais and the other at the Fluminense Federal University in 2011 [32,33], which reported a reduction from 23,321 autopsies of adults and children in the period from 1966 to 1998 to 492 from 1999 to 2009.

It is believed that one of the reasons for this decline is the lack of publicly available information on the vital role autopsies play in advancing and improving medicine. As a rule, in cases of sudden death by natural causes, it is extremely painful for family members to make such a decision; thus, they usually refuse consent.

As related above, the not consent by relatives in countries where this procedure requires an authorization is common, due to the moment of suffering that the parents of child are living. In these cases, endomyocardial biopsy constitutes an alternative tool for post-mortem cardiac tissue study. The procedure can be discussed with relatives in order to enable the enlightenment of the causa mortis in SUDC cases when autopsies were not authorized. The post-mortem biopsy from the cardiac muscle can allow the diagnosis of myocarditis, mainly in cases related to mitochondrial and energetic metabolic diseases.

Conclusion

Among the pediatric population, sudden death is commonly associated with myocarditis [34]. An understanding of the onset and development of disease and of studies targeting it are crucial because cardiovascular diseases are considered the most common causes of death worldwide, even more than those caused by cancer. According to data provided by the *American Heart Association* in 2017, the number of annual deaths due to cardiovascular diseases, without reference to particular age ranges, might increase from 17.3 million in 2013 to 23.6 million in 2030 [35].

A multidisciplinary conference "Understanding SUDC Medical Conference" [36] was held in New York City in May 2017. Lecturers and investigators in cardiology, epidemiology, genetics, neurology, and forensic pathology analyzed the results of studies on sudden death in children [36,37]. This fact confirms that this condition is a troublesome medical problem that requires further investigation.

While acute myocarditis may be associated with significant morbidity and mortality, the available data on its prevalence are limited and inconclusive, since a definitive diagnosis of myocarditis in childhood is usually only possible by histologic analysis of the myocardium, obtained either by biopsy or post-mortem [38,39]. More commonly, it is a presumptive diagnosis [22,38].

When critically ill children, particularly those with severe respiratory symptoms, are deteriorating clinically and not responding to treatment, physicians should consider myocarditis as a possible diagnosis.

This review contributes to discussions on the creation of a protocol for pediatric emergencies, including a broader range of diagnostic tests, such as functional echocardiography (Video 1), which is crucial for diagnosis and follow-up of myocarditis, as well as consideration of administration of IVIG if myocarditis is suspected, focusing on save lives.

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The authors may also like to acknowledge (anonymously) the pediatric patient on whom this review was motivated. Unfortunately, this child died as a result of undiagnosed myocarditis within three days.

Figures

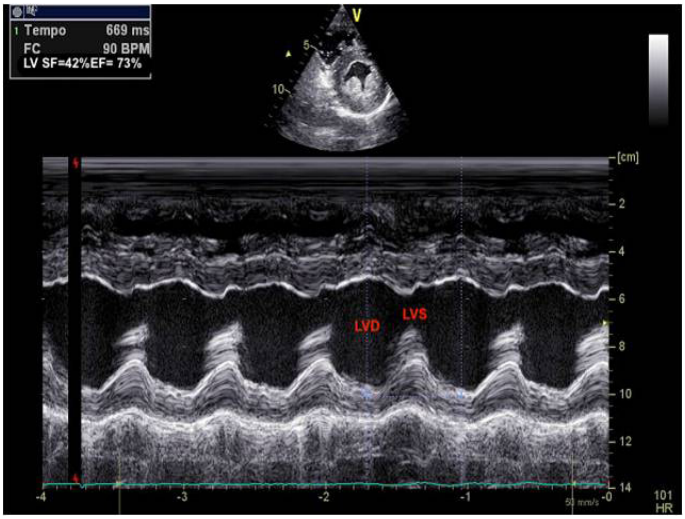

Figure 1: Transthoracic echocardiogram at the transverse plane of ventricles (short ventricular axis) showing maximum and minimum diameters of the Left Ventricle (LV) and calculation of the Ejection Fraction (EF) and Shortening Fraction (SF) of the LV in a healthy individual. The equations used for calculation by the Teichholz method are EF (%) = maximum diastolic diameter of LV^3–maximum systolic diameter of LV^3/maximum diastolic diameter of LV^3 X 100 (normal EF: >55%). SF = maximum diastolic diameter of LV–maximum systolic diameter of LV/maximum diastolic diameter of LV X 100 (normal SF: >28%).

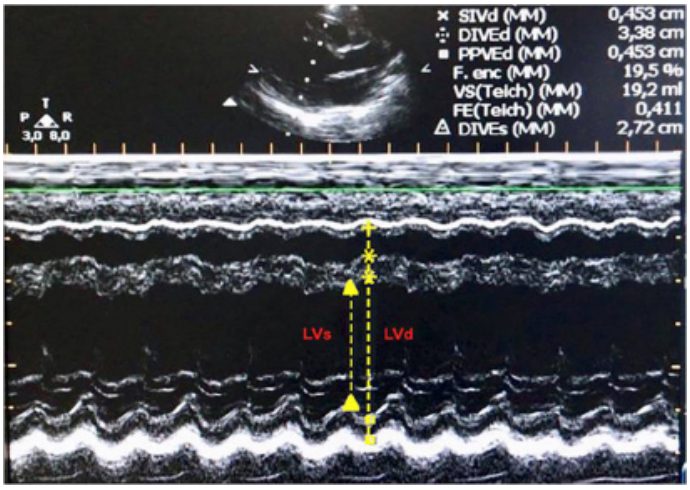

Figure 2: Transthoracic echocardiogram, short axis parasternal view (papillary muscle level), showing reduced EF and LV SF of the LV in a case of myocarditis with moderate myocardial dysfunction (EF = 44%; SF = 19.5%). LV: left ventricle; EF: ejection fraction; SF: shortening fraction.

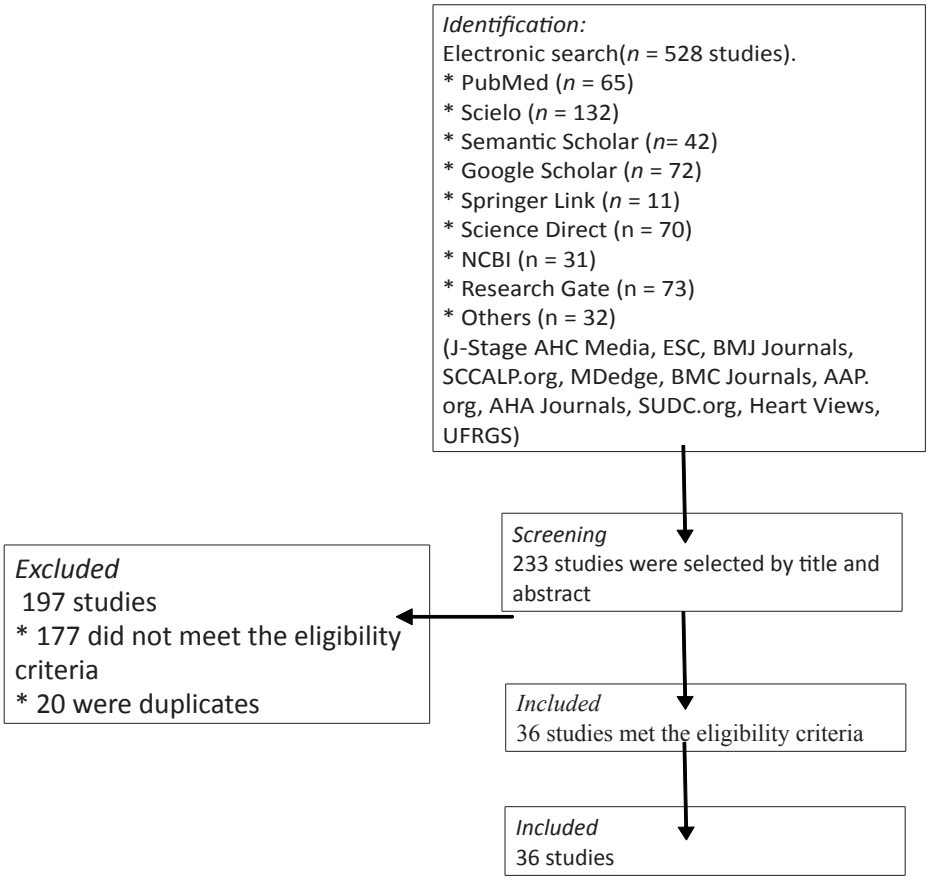

Figure 3: Flowchart of records identified after an electronic search (by keywords, title and abstracts) of studies published from 1987 to 2018; search terms included myocarditis and sudden death in children.

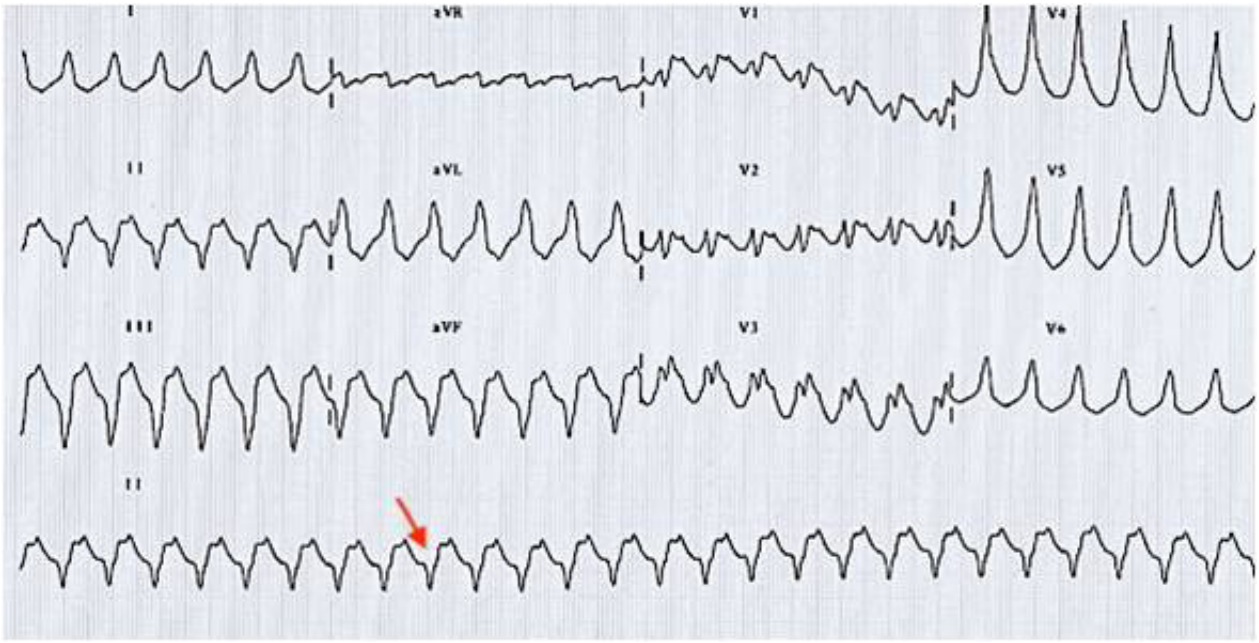

Figure 4: Electrocardiogram showing ventricular tachycardia in a 2-month-old infant with fulminant myocarditis. Note the absence of P waves and a wide QRS (red arrow DII).

References

1. Dancea AB. Myocarditis in Infants and Children: A Review for the Paediatrician. Paediatr Child Health. 2001; 6: 543-e5.
2. Gaaloul I, Riabi S, Evans M, Hunter T, Huber S, Aouni M. Postmortem diagnosis of infectious heart diseases: a mystifying cause of sudden infant death. Forensic Sci Int. 2016; 262: 166-172.
3. Machado PR, Araújo MI, Carvalho L, Carvalho EM. Immune response to infections. An Bras Dermatol. 2004; 79: 647-664.
4. Cruvinel WD, Mesquita Júnior D, Araújo JA, Catelan TT, Souza AW, Silva NP, et al. Immune system-Part I. Fundamentals of innate immunity with emphasis on molecular and cellular mechanisms of inflammatory response. Rev Bras Reumatol. 2010; 50: 434-461.
5. Mesquita Júnior D, Araújo JA, Catelan TT, Souza AW, Cruvinel WD, et al. Immune System–Part II Basis of the immunological response mediated by T and B lymphocytes. Rev Bras Reumatol. 2010; 50: 552-580.
6. Souza AW, Mesquita Júnior D, Araújo JA, Catelan TT, Cruvinel WD, et al. Immune System–Part III The delicate balance of the immune system between tolerance and autoimmunity. Rev Bras Reumatol. 2010; 50: 665-694.
7. Joob B, Wiwanitkit V. Fulminant myocarditis associated with the H1N1 influenza virus: case report and literature review. Rev Bras Ter Intensiva. 2015; 27: 82-84.
8. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J Am Coll Cardiol. 2009; 53: 1475-1487.
9. Savatmongkorngul S, Wongwaisayawan S, Kaewlai R. Focused assessment with sonography for trauma: current perspectives. Open Access Emerg Med. 2017; 9: 57-62.
10. Gaspar HA, Morhy SS, Lianza AC, de Carvalho WB, Andrade JL, et al. Focused cardiac ultrasound: A training course for pediatric intensivists and emergency physicians. BMC Med Educ. 2014; 14: 25.
11. Kim HS, Sohn S, Park JY, Seo JW. Fulminant myocardits successfully treated with high-dose immunoglobulin. Int J Cardiol. 2004; 93: 485-456.
12. Farinha IT, Miranda JO. Myocarditis in paediatric patients: unveiling the progression to dilated cardiomyopathy and heart failure. J Cardiovasc Dev Dis. 2016; 3: 31.
13. Charron P, Elliott PM, Gimeno JR, Caforio AL, Kaski JP, et al. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J. 2018; 39: 1784-1793.
14. Treacy A, Carr MJ, Dunford L, Palacios G, Cannon GA, et al. First report of sudden death due to myocarditis caused by adenovírus serotype 3. J Clin Microbiol. 2010; 48: 642-645.
15. Freedman SB, Haladyn JK, Floh A, Kirsh JA, Taylor G, Thull-Freedman J. Pediatric myocarditis: Emergency department clinical findings and diagnostic evaluation. Pediatrics. 2007; 120 :1278-1285.
16. Durani Y, Egan M, Baffa J, Selbst SM, Nager AL. Pediatric myocarditis: presenting clinical characteristics. Am J Emerg Med. 2009; 27: 942-947.
17. Chien S J, Liang CD, Lin I, Lin YJ, Huang CF. Myocarditis complicated by complete atrioventricular block: Nine years' experience in a medical center. Pediatr Neonatol. 2008; 49: 218-222.
18. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, et al. Pediatric cardiomyopathy registry investigators. incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the pediatric cardiomyopathy registry. J Am Coll Cardiol. 2012; 6: 607-615.
19. Xiong H, Xia B, Zhu J, Li B, Huang W. Clinical outcomes in pediatric patients hospitalized with fulminant myocarditis requiring extracorporeal membrane oxygenation: A meta-analysis. Pediatr Cardiol. 2017; 38: 209-214.
20. Pophal SG, Sigfusson G, Booth KL, Bacanu SA, Webber SA, et al. Complications of endomyocardial biopsy in children. J Am Coll Cardiol. 1999; 34: 2105-2110.
21. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, et al. Myocarditis: A histopathologic definition and classification. Am J

Cardiovasc Pathol. 1987; 1: 3-14.

22. Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation. 1994; 89: 252-257.

23. Al-Saeed S & Dilawar M. Combined Use of Intravenous Immune Globulin and Steroid for Acute Myocarditis in Pediatric Population. Heart Views. 2008; 9: 137-41.

24. Shimizu C, Rambaud C, Cheron G, Rouzioux C, Lozinski GM, Rao A, et al. Molecular identification of viruses in sudden infant death associated with myocarditis and pericarditis. Ped Inf Dis J. 1995; 14: 584-8.

25. Weber MA, Ashworth MT, Risdon RA, Malone M, Burch M, et al. clinicopathological features of paediatric deaths due to myocarditis: an autopsy series. Arch Dis Child. 2008; 93: 594-598.

26. Smith N, Bourne AJ, Clapton WK, Byard RW. The spectrum of presentation at autopsy of myocarditis in infancy and childhood. Pathology. 1992; 24: 129-131.

27. Rady HI, Zekri H. Prevalence of myocarditis in pediatric intensive care unit cases presenting with other system involvement. J Pediatr (Rio J). 2015; 91: 93-97.

28. Elicker B, Pereira CAC, Webb R C, Leslie KO. High-resolution computed tomography patterns of diffuse interstitial lung disease with clinical and pathological correlation. J Bras Pneumol. 2008; 34: 715-44.

29. Ribeiro CMC, Marchiori, E, Rodrigues R, Gasparetto E, Souza Júnior AS, Escuissato D, et al. Hydrostatic pulmonary edema: High-resolution computed tomography aspects. J Bras Pneumol. 2006; 32: 515-522.

30. Icaza E E S. Concordância no Diagnóstico Radiológico da Doença Respiratória Aguda Baixa em Crianças [Dissertation]–Porto Alegre: Universidade Federal do Rio Grande do Sul: Faculdade de Medicina; 2003.

31. Fairweather D, Rose NR. Coxsackievírus-induced myocarditis in mice: a model of autoimmune disease for studying immunotoxicity. Methods. 2007; 41: 118-122.

32. Moreira DR, Lana AMA, Godoy P. Study on the contribution of the autopsy as a diagnostic tool. J Bras Patol Med Lab. 2009; 45: 239-245.

33. Rodrigues FR, Lopes VG, Lopez CL, Soares Filho PJ, Silva RD, et al. The dramatic decline of the autopsies at a Brazilian university hospital in the last 20 years. J Brasil de Patol Med Lab. 2011; 47: 445-450.

34. Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. Circulation. 2014; 129: 115-128.

35. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, et al. Heart disease and stroke statistics—2017 update: A report from the american heart association. Circulation. 2017; 135: e196-603.

36. SUDC Foundation; NYU School of Medicine[Internet]. R: Understanding Sudden Unexplained Death in Childhood Conference; 2017.

37. Floyd A, Lal A, Molina K, Puchalski M, Miller D, et bal. When lightning strikes twice in pediatrics: Case report and review of recurrent myocarditis. Pediatrics. 2018. e20164096.

38. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, et al. Report of the 1995 World Health Organization/International Society and federation of cardiology task force on the definition and classification of cardiomyopathies. Circulation. 1996; 93: 841-842.

39. Abadesso C, Aparício S, Almeida H, Machado MC. Miocardite Fulminante como Manifestação de Doença. Mitocondrial.Acta Pediatr. Port. 2004; 2: 145-148.