Endomyocardial Biopsy in Pediatric Myocarditis and Cardiomyopathies

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Endomyocardial biopsy is a well known diagnostic tool for the investigation and treatment of myocardial diseases and so far, remains the gold standard for the diagnosis of myocarditis. Due to its invasively with a complication rate ranging from 1% to 15%, its role in the diagnostic work-out of pediatric heart failure is not well established.

endomyocardial biopsy myocarditis pediatric cardiomyopathy

1. Introduction

A child presenting with systolic left and right ventricular dysfunction is always a challenging scenario for clinicians in terms of diagnosis, therapeutic management and follow up.

Endomyocardial biopsy (EMB) is a well-known diagnostic instrument and so far, remains the gold standard for the diagnosis of myocarditis. Histological, immunohistochemical and virological studies on EMB specimens allow the characterization of immune cell infiltrates, detection of viral RNA and DNA and quantification of viral load.

Prospective studies describing the utility and risks EMB related are lacking so its role in the work up of children with LV dysfunction is still debated.

2. EMB: How and When It should be Performed.

The right internal jugular vein is the most common percutaneous access for right ventricular EMB in children for the easy access to the right ventricle. The bioptome can be inserted through a sheath that is at least 6 Fr. Biopsy of left ventricle via femoral artery or transseptal puncture is also described but rarely used in children with only a report of 19 cases published in 1984 [1].

Usually, EMB in children is performed under general anesthesia, because of the young age but also because these patients present frequently with hemodynamic instability. EMB is usually performed under fluoroscopic guidance.

The recently published ESC guidelines for acute and chronic heart failure[2] do not take into account the pediatric population and state that in adults with heart failure EMB should be performed in patients with rapidly progressive HF despite standard medical therapy when there is a high suspicion of a specific disease, with a class IIa, level of evidence C.

The recently published consensus document on management of acute myocarditis and chronic inflammatory cardiomyopathy[3] states the role of EMB for the etiopathology identification and therapy decision in some defined specific clinical scenarios:

1. Acute myocarditis (AM) presenting with severe HF or cardiogenic shock
2. AM associated with severe myocardial dysfunction, acute HF, ventricular arrhythmias, or high degree atrio-ventricular block
3. AM or suspected chronic inflammatory cardiomyopathies (infl-CMP) presenting with peripheral eosinophilia
4. AM or chronic inf-CMP in presence of persistent or relapsing release of biomarkers of myocardial necrosis, particularly if there is a suspected/known autoimmune disorder or ventricular arrhythmias or high degree AV block
5. Myocarditis in patients treated with immunotherapy, where appropriate diagnosis has implications in additional cancer therapy

Most of these recommendations were first published in 2007 AHA/ACC/ESC Scientific Statement on the role of EMB in the management of cardiovascular disease[4].

3. EMB: Which Kind of Information

One diagnostic limitation of EMB is sampling error due to patchy position of the disease. In order to minimize sampling errors a higher number of pieces (usually > 5) must be collected and handled carefully. The number of specimens is usually determined by the clinical reason of EMB. Usually, 4-5 samples are used for light microscopy but more may be submitted for electron microscopy.

Some myocardial samples, preferably 4, should be fixed in 10% buffered formalin for light microscopic examination; one or two specimens may frozen in liquid nitrogen and stored at – 80 grades for molecular tests and, if ultrastructural test is needed one fragment should be fixed in 2.5% glutaraldehyde.

A 2013 ESC position paper outlined the importance of the characterization of cardiac inflammation utilizing immunohistochemistry and viral genome analysis with quantitative PCR (real-time PCR and nested PCR with reverse transcription) for myocarditis diagnosis and for the use of specific therapeutic treatments [5].

Quantitative PCR allows the detection of viral RNA and DNA presence, quantification of viral load and recognition of virus subtypes via sequencing technique [6].

Many studies of patients with myocarditis or dilated cardiomyopathy found plenty of viral pathogens such as enteroviruses, adenoviruses, parvovirus B19, cytomegalovirus, influenza and respiratory syncytial virus, herpes simplex virus, Epstein-Barr virus, human herpes virus 6, HIV and hepatitis C [7], [8]. In the past in United States, entero and adenoviruses were recognized as the most common causes of viral myocarditis but in the last years the tendency has changed showing parvovirus B 19 and herpes virus as the most common isolated viruses [9].

4. Complications

Acute biopsy complications include ventricular perforation with subsequent pericardial tamponade, ventricular or supraventricular arrhythmias, heart block, pneumothorax, puncture of central arteries, pulmonary embolism, nerve paresis, venous hematoma and damage of to the tricuspid valve. In some cases, complications can be delayed and can include access site bleeding, damage to the tricuspid valve, pericardial tamponade and deep venous thrombosis[10].

The data on EMB risks are derived from several single-center experiences and registries reported in literature but the majority of these reports referred to heart transplanted patients.

Cardiac perforation is undoubtedly of major concern when assessing the risk of performing EMBs in infants. All the reports recognized young age and low weight as the most important risk factors. Others hypothesized that cardiac perforation may be due to ventricular walls thinness in patients with DCM. Nevertheless, this hypothesis was not confirmed in a large adult EMB series where all the perforations occurred in patients without ventricular dilatation[11].

Surely, risks and benefits of EMB should be carefully weighed in small infants weighting less than 8 Kg. Given the high risk of cardiac perforation in this population, the use of echocardiographic guidance during the procedure in order to confirm bioptome position could be useful, as demonstrated in the study of McCreery et al [12].

5. EMB in myocarditis

Diagnosis of myocarditis is a complex clinical process and EMB that fulfills the well-known histologic criteria is still the gold-standard. Although imaging techniques including MRI can determine tissue characterization and localize areas of inflammation or presence of fibrosis, they cannot totally substitute EMB due to the high negative predictive value [13].

The detection of viral pathogens in myocardial samples could be useful for a pathogen-tailored treatment strategy. There are no published evidence-based data on pathogen-specific therapy for viral myocarditis, but according to study adults' protocols, specific treatments are proposed.

Exclusion of viral persistence at EMB is mandatory for the use of immunosuppressive therapy, since it is strongly contraindicated in enterovirus and adenovirus-positive patients.

Specific antiviral therapy in patients with virus-positive myocarditis has also been described although not well established. However, all the authors stated that antiviral therapy is not yell an established therapy and must be used only in high experienced center.

6. EMB in Cardiomyopathies

Endomyocardial biopsy showed not a great utility in the diagnosis of cardiomyopathy. Knowledge concerning the genetics and molecular biology of primary cardiomyopathies has made progress and much of the diagnosis could be made by peripheral blood analysis. Moreover, if the myocardial disease is associated to skeletal muscle myopathy, EMB can be replaced by a skeletal muscle biopsy.

7. Conclusion

In the diagnostic work up of children with systolic heart failure, EMB-derived histological, immunohistochemicaland molecular biological information are still essential prerequisites to provide a proper diagnosis of myocarditis and a correct management of these patients.

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