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유전성 대사이상 질환에서의 심장 증상에 대한 고찰

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Cardiac Manifestations of Inborn Error of Metabolism in Pediatric Patients

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Among the various etiologies of cardiomyopathy, inborn errors of metabolism (IEM) is one of the underlying causes, especially in the pediatric population. The accurate identification of the IEM of cardiomyopathy may lead to better prognosis through disease-specific management. Therefore, clinicians should always keep in mind the possibility that IEM may be one of the underlying etiologies of cardiomyopathy, and carry out multi-systematic clinical approach to diagnosis of IEM. This review covers the pathophysiology, clinical presentations, typical laboratory findings, diagnosis, and proper treatment of each type of IEM-induced cardiomyopathy in pediatric patients to gain a deeper understanding of this subject.

Key words: Inborn Errors of Metabolism, Cardiomyopathies, Pathophysiology, Diagnosis

Introduction

Pediatric cardiomyopathy is a heterogeneous group of rare disorders attributable to diverse underlying etiologies. The accurate identification of the causes of cardiomyopathy, particularly in pediatric patients enables prompt disease-specific management and may improve prognosis; however, this is clinically challenging because of the non-specific symptoms and multifactorial etiologies associated with these disorders[1,2].

Inborn errors of metabolism (IEM) are rare genetic disorders secondary to mutations in genes that code for proteins of functional components of metabolic pathways[3]. These mutational changes negatively affect breakdown or storage of proteins, carbohydrates, and fatty acids, which may lead to defective catabolism of various substances and energy synthesis[4]. Such dysfunctional mechanisms are associated with multi-organ manifestations, including cardiac disorders.

IEM is an important etiopathogenetic contributor to cardiomyopathy, particularly in pediatric patients [5]. Notably, energy supply through the appropriate metabolic pathways is important to maintain contraction and ionic homeostasis for optimal function of the heart muscle. Therefore, adaptation to fluctuations in the balance between demand and supply of energy to the cardiac muscle is impossible without sophisticated energy regulation through multiple metabolic pathways. More than 40 IEM have been known to present with cardiac manifestations[6]. Following diagnostic technological

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advances in diagnostic tools, approximately 26% of patients with hypertrophic cardiomyopathy (HCMP) and 16% of those with dilated cardiomyopathy (DCMP) were diagnosed as having IEM [7]. Based on the Pediatric Cardiomyopathy Registry in the United States and Canada, IEM was identified as the underlying cause in 15.4% of known cases of cardiomyopathy[6]. Notably, IEM was diagnosed in 13.5% (5/35) neonates with cardiomyopathy patients[8]. The timely and accurate diagnosis of specific IEM are extremely important in patients with cardiomyopathy, because cardiomyopathies caused by several IEM are currently treatable using the specific-target approach based on the pathophysiology of each condition.

This review covers the pathophysiology, clinical presentations, typical laboratory findings, diagnosis, and proper treatment of each type of IEM-induced cardiomyopathy in pediatric patients to gain a deeper understanding of this subject.

Pathophysiology of cardiomyopathy secondary to inborn errors of metabolism

The three main pathophysiological mechanisms that underlie IEM-induced cardiomyopathy are as follows: (1) impaired energy production following the disruption of molecular transport or cellular organelle dysfunction, (2) cellular damage secondary to the accumulation of inappropriate substrates and bulk storage in cardiac myocytes, and (3) infiltration of toxic, intermediary metabolites on myocytes and surrounding tissue. It should be noted that more than one mechanism can be involved in the end stage of cardiomyopathy[9-12].

The aforementioned pathophysiological mechanisms are associated with the following effects:

The first important pathologic mechanism is impaired energy production. This refers to the inability of cells to produce adenosine triphosphate (ATP), which is required to maintain cardiac muscle function. Fatty acid and glycogen are the main energy sources for maintenance of heart functions; energy is released as ATP, following mitochondrial oxidative phosphorylation of these substrates. Cardiac muscle function, including contraction requires high energy levels. Insufficient energy generation secondary to IEM precipitates cardiomyopathy[13,14]. The major IEM associated with this mechanism are fatty acid oxidation disorders, carnitine deficiency, carnitine acylcarnitine translocase deficiency, carnitine palmitoyl transferase II (CPT II) deficiency, very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein deficiency, and glutaric acidemia type 2[15]. Interestingly, a few fatty acid oxidation disorders, such as medium-chain Acyl-CoA dehydrogenase (MCAD) deficiency rarely cause cardiomyopathy in infants and pediatric patients[16]. Mitochondrial disorders are characterized by the involvement of multiple organs, including the heart presenting as HCMP or DCMP. Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, myoclonic epilepsy with ragged red fibers (MERRF) syndrome, Leigh syndrome, and complex I-V deficiency are other causes of cardiomyopathy. However, the prevalence of cardiomyopathy during the pediatric period of mitochondrial diseases is extremely low[17]. Congenital disorders of glycosylation (CDG), particularly subtype Ia, are also important causes of cardiomyopathy from infancy to young adulthood, and cardiomyopathy may contribute to mortality in this patient group[18].

The second pathophysiologic mechanism is an accumulation of inappropriate substrates, which can lead to dysfunction of the myocardium. Lyso-

somal storage disease (LSD) is a representative group of disorders attributable to this mechanism, and HCMP is the most prevalent presentation among these diseases. Among them, presentations of hypertrophy of both ventricles in Pompe disease, particularly during the infantile period, and left ventricular hypertrophy of Fabry disease in the late childhood are well recognized[5,19]. Hurler syndrome (mucopolysaccharidosis (MPS) type I) and Hunter syndrome (MPS type II) are also well known to be related with cardiomyopathy in pediatric patients, and Maroteaux–Lamy syndrome (MPS VI) has been reported as presenting with cardiomyopathy in the infant period[20]. The substrates of large macromolecules such as glycogen and triglycerides may accumulate in the cytoplasm of myocytes and interfere with cardiomyocyte function[6].

The last pathophysiologic mechanism is the production and infiltration of toxic metabolites in myocytes and surrounding tissue secondary to enzymatic deficiencies, and amino acidurias, organic acidemias, oxidative phosphorylation, and Refsum disease are included in this disease group. Among these disorders, propionic acidemia is the most frequent IEM complicated with cardiomyopathy in pediatric patients. Notably, DCMP is the only manifestation of propionic acidemia in infants[21]. Myocardial involvement in methylmalonic acidemia and 3–methylglutaconic aciduria type II (Barth syndrome) is also reported, and these diseases are considered possible underlying causes in cardiomyopathy patients[21].

Clinical presentations & typical laboratory results

Cardiomyopathy may be the dominant clinical symptom, but several clinical manifestations with cardiomyopathy should be noted to make an accurate diagnosis of IEM[5]. A medical presentation of multisystemic involvement, including developmental delay, acute and chronic encephalopathy, ataxia, failure to thrive, hypotonia, recurrent muscle pain and spasms, recurrent rhabdomyolysis, typical facial dimorphisms (e.g., coarse facial features, enlarged tongue), and hepatosplenomegaly with cardiomyopathy, may be the essential clue indicative of IEM. More importantly, IEM should be considered in patients with symptoms suggestive of acute metabolic decompensation during physically stressful situations, such as febrile illness, dietary change, prolonged fasting[22]. Because of these acute initial symptoms of IEM, the underlying etiology of cardiomyopathy in IEM may be misdiagnosed as an acute viral or bacterial infection. In terms of the cardiomyopathic type, HCMP is often related to LSDs, storage diseases of fat or glycogen and DCMP is related to amino acidopathes, organic academias, or systemic carnitine deficiency[6].

In terms of laboratory results, hypoglycemia, particularly non–ketotic hypoglycemia, is a noteworthy finding indicative of ineffective fatty acid metabolism[23]. Moreover, dicarboxylic aciduria or low serum carnitine level can suggest a specific fatty acid oxidation disorder.24 Recurrent creatinine kinase (CK) elevation, metabolic acidosis, or hyperammonemia should not be missed in appropriately diagnosing IEM as the cause of cardiomyopathy.

Diagnostic methods

A systemic approach is needed for the timely diagnosis of IEM with careful searching of clinical features associated with cardiomyopathy. First, it is important to consider IEM as one of the diffe-

rential diagnoses of cardiomyopathy. In addition, detailed family and medical histories related to cardiomyopathy and IEM are essential.

A thoughtful biochemical evaluation, including serum glucose, creatine kinase, ammonia, plasma lactate/pyruvate, acylcarnitine profile, plasma amino acids, urine organic acids, and urine ketones, for all pediatric patients with cardiomyopathy is recommended[25]. These results could be useful for the diagnosis of IEM presenting with cardiomyopathy, especially for treatable IEM of fatty acid oxidation disorder or malonic acidemia. The gold standard for confirming IEM is the enzyme assay. For example, Pompe disease can be confirmed by the enzyme assay using a dried blood spot test[26]. In case of mitochondrial disorders, it can be confirmed by the detection of typical pathologic findings of muscle tissue and the deficiency of respiratory chain complexes[27].

As genetic testing technologies, such as NGS, have been improved remarkably, molecular diagnosis has become one of the practical and accurate methods to diagnose IEM with cardiomyopathy by identifying the underlying genetic mutations. Although genetic testing still often takes time to obtain results, if the turnaround time is shortened and more IEM related genes are discovered in the future, it will be applied more to the diagnosis of IEM and cardiomyopathy.

Newborn screening (NBS)

With the improvement and standardization of the NBS strategy, many IEM presenting with cardiomyopathy as one of the symptoms can be diagnosed easily within the early days of life. Not only VLCAD deficiency, LCHAD deficiency, and carnitine uptake deficiency but also propionic acidemia can be identified using NBS. Of note, false-negative result cases of NBS in cardiomyopathy have been reported[28]. Therefore, IEM should not be ruled out for clinically suspected IEM patients, even if the NBS results are negative. It should also be noted that LSD, CDG and mitochondrial disorders are not yet screened for using NBS in Korea.

Treatment

The treatment of cardiomyopathy caused by IEM can be divided into two stages: acute and long-term treatment. For acute management, acute metabolic crises with metabolic acidosis and hypoglycemia are corrected immediately with the general protocol of acute IEM treatment. For cardiac manifestations, conventional supportive drugs, including diuretics and inotropes, can be useful to control manifestations and reduce morbidity and mortality[9]. However, the effect of conventional therapy in IEM patients may not be as effective as that seen in cardiomyopathy with other causes.

Long-term treatment depends on the underlying pathophysiology of the cardiomyopathy. In cases of fatty acid oxidation disorders (e.g., VLCAD, LCHAD, multiple Acyl-CoA dehydrogenase deficiency) and organic acidemias (e.g., propionic acidemia, methylmalonic acidemia), the dietary restriction of non-metabolizable substrates is essential. Additionally, the avoidance of fasting to prevent the breakdown of its endogenous metabolic substance is also important. Vitamin cofactors (e.g., riboflavin for multiple Acyl-CoA dehydrogenase deficiency, biotin for propionic acidemia) can be administered to enhance the residual enzyme activity[29,30].

The administration of carnitine supplements is a well-known, effective treatment method for

systemic carnitine deficiency, and continuous carnitine supplements can improve the natural course of cardiomyopathy in this patient group[31]. For several LSDs, including Fabry disease, Pompe disease, and MPS types I, II, and VI, enzyme replacement therapy (ERT) can be an available treatment option, and ERT seems to show a beneficial effect on cardiomyopathy. ERT has been presented significant effects on cardiac involvement in Pompe disease, and slowing down the progress of cardiomyopathy in Fabry disease or MPSs[32].

Conclusion

IEM is one of the important causes of cardiomyopathy in pediatric patients, and cardiomyopathy caused by IEM can be treatable with a timely, accurate diagnosis. Therefore, clinicians should always bear in mind the possibility that IEM may be underlying diseases of cardiomyopathy in pediatric patients.

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