The Influence of Genotype on the Phenotype, Clinical Course, and Risk of Adverse Events in Children with Hypertrophic Cardiomyopathy

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KEYWORDS

• Cardiomyopathies in children • Genetic analysis • Genotype • Phenotype • Prognosis

KEY POINTS

- Predicting long-term outcome, risk of adverse events, and response to treatment in children with HCM is challenging.
- Genetic testing in pediatric HCM is an essential step in establishing a diagnosis and may, in selected cases, dictate clinical management.
- Secondary forms of HCM caused by inborn errors of metabolism (IEMs), syndromes such as RASopathies, or neuromuscular disorders are generally associated with worse clinical outcome.
- In children with sarcomeric HCM, the identification of a complex genotype or a *de novo* variant may imply worse prognosis.
- Pathogenic variants in thin filament genes are associated with mild degrees of hypertrophy but greater arrhythmic propensity in children.

Hypertrophic cardiomyopathy (HCM) in children is rare and may present at any age, but preferentially clusters in the first year of life, with a frequency 3 times higher than in older age groups, due to the prevalence of peculiar genetic causes.[1] The disease is characterized by a pathologic increase in myocardial thickness, with a nondilated left ventricular (LV) chamber, unexplained by pressure overload (eg, due to systemic hypertension or aortic stenosis). Pediatric HCM may be the cause of heart failure and, infrequently, of sudden cardiac death, both of which may occur at any age.[1–3]

The genetic basis of HCM is heterogeneous in children, often associated with rare, family-specific ("private") mutations, not infrequently de novo. Even though most cases are caused by variants in genes coding for components of the sarcomere or the cytoskeleton, pediatric HCM is much more diverse compared with adult cohorts, due to a high prevalence of syndromic conditions,

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neuromuscular disorders, and inborn errors of metabolism.[4] In addition, secondary causes should be considered, including maternal diabetes, congenital insulin-producing tumors, and congenital heart disease.[4–6] Thus, the detection of an HCM phenotype represents a mere starting point in the diagnostic process: similar echocardiographic findings may result from classic sarcomeric HCM, RASopathies such as Noonan syndrome, glycogen storage disorders such as Danon disease, or a mitochondrial cardiomyopathy such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (**Fig. 1**).[7] Genetic testing, guided by appropriate clinical red flags (**Table 1**) is an essential step of the diagnostic process in children with HCM, more so than in adults, providing decisive information for clinical management and lifestyle counseling[8]

CLINICAL FEATURES AND DIAGNOSIS

In children younger than 1 year, the most common clues to the diagnosis of HCM are a heart murmur detected during pediatric consultation or symptoms of congestive heart failure such as feeding difficulties, impaired growth, and sweating, whereas older children and adolescents may be asymptomatic or present with the typical features seen in adults, such as palpitations, chest pain, syncope, and exercise limitation. Cardiac arrest is a tragic but rare presentation. Of note, extracardiac red flags are prevalent and more often decisive for a correct diagnosis, compared with adult patients.[1,3]

At echocardiographic examination, concentric LV hypertrophy (LVH) is the most common phenotype in syndromic HCM, whereas asymmetric septal hypertrophy is typical of the sarcomeric form, followed by apical hypertrophy, right ventricular hypertrophy, and isolated posterior wall hypertrophy. LV outflow tract obstruction is present at

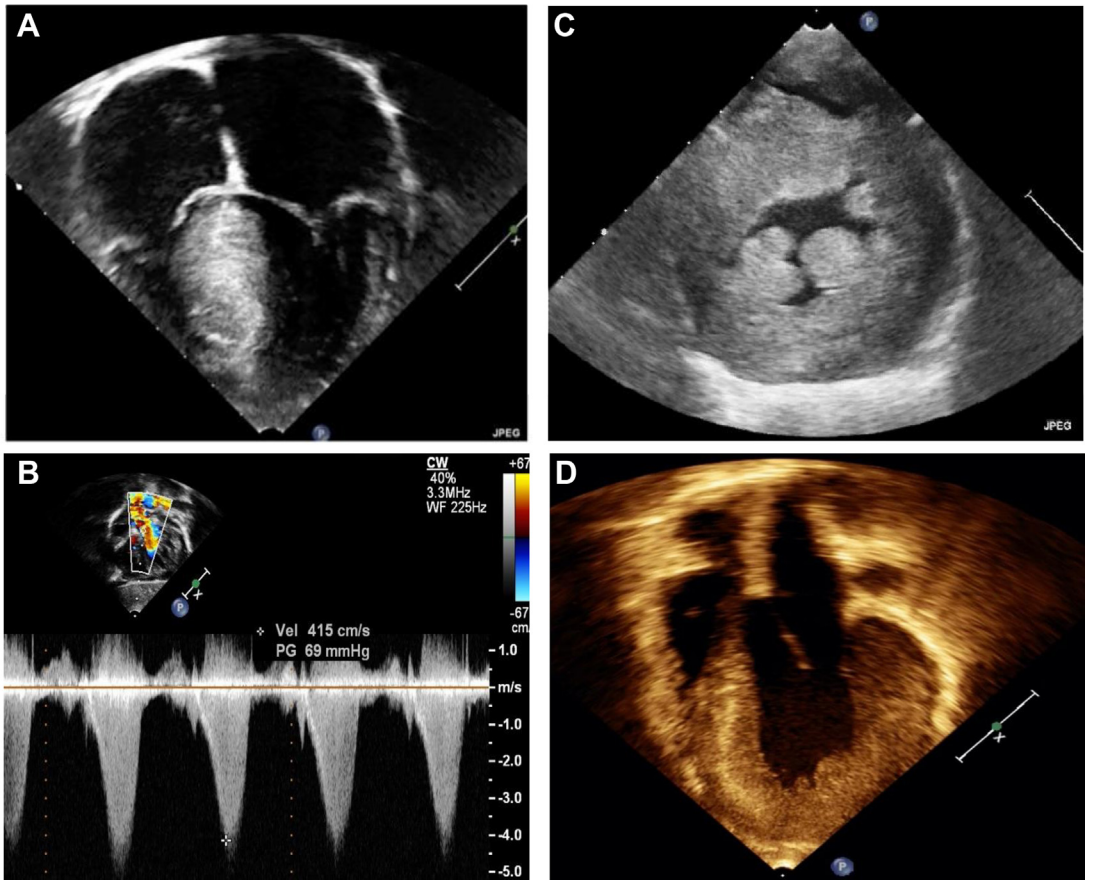

Fig. 1. Central illustration. Genetic testing is key to individualized management in pediatric HCM. (*A, B*) Sarcomeric and obstructive HCM requiring medical therapy and eventually myectomy. (*C*) HCM in Pompe disease requiring enzyme replacement therapies. (*D*) HCM in Danon disease requiring more aggressive treatment, for example, early transplant.

Table 1
Red flags for clinical differential diagnosis in children with hypertrophic cardiomyopathy

Sarcomeric HCM	IEMs	Syndromic HCM
Asymmetric hypertrophy	Concentric hypertrophy	Concentric or biventricular hypertrophy
LV outflow obstruction, abnormal implantation of papillary muscles, mitral regurgitation, arrhythmias	Arrhythmias	LV outflow tract obstruction, congenital heart disease (pulmonary stenosis/ dysplasia, peripheral pulmonary arteries stenosis, atrial septal defect, atrioventricular septal defect)
	Learning disability and cognitive defects, seizures, neurosensorial deafness, blindness, stroke, dystonia	Mental retardation, neurosensorial deafness
	Short stature, peripheral muscle weakness, renal failure, hepatosplenomegaly	Short stature, webbed neck, cryptorchidism, coagulation defects
	Macrocephaly, large anterior fontanelle, coarsened facial features, retinal abnormalities, strabismus	Characteristic facies (broad forehead, down slanting palpebral fissures, hypertelorism, and low-set ears)
MYH7, MYBPC3,TNNT2,TNNI3, TPM1,ACTC1,MYL2,MYL3, PLN, ACTN2,CSRP3, JPH2	*PRKAG2, LAMP2,GAA, GLA, TMEM70, ELAC2,mt-DNA (MELAS, MERF, mitochondrial disease genes)*	*PTPN11,SOS1,HRAS, BRAF*

Abbreviations: IEMs inborn error of metabolism; LV, left ventricular.

rest in 25% to 40% of children with HCM; concomitant right ventricular outflow tract obstruction is often a feature of syndromic HCM. Cardiac magnetic resonance allows the identification of myocardial fibrosis by late gadolinium enhancement and is useful in monitoring disease progression. The most common electrocardiographic (ECG) findings in children are voltage criteria for LVH, ST-T abnormalities, and pathologic Q waves.[6,7]

GENETIC BASIS OF NONSYNDROMIC HYPERTROPHIC CARDIOMYOPATHY

Classic, nonsyndromic HCM is an autosomal dominant disease, with incomplete penetrance and variable expressivity. Over 3 decades ago, a missense mutation in the β-myosin heavy chain gene, *MYH7*, was first identified as causal for HCM in a large Canadian family. In subsequent years, numerous genes coding for proteins of sarcomere, Z-disc, or intracellular calcium modulators have been associated with the disease, and HCM has therefore been defined as a "disease of the sarcomere."[9] Overall, more than 1500 HCM-associated, largely "private" variants have been described, and pathogenic variants are found in 50% to 60% of familial forms of HCM. The most prevalent include 3 genes coding for thick filament proteins: *MYH7*-β, myosin heavy chain; *MYL2,* regulatory myosin light chain; and *MYL3*, essential myosin light chain; 4 coding for components of the thin filament: *TPM1*, α tropomyosin; *TNNT2,* cardiac troponin T; TNNI3, cardiac troponin I; and ACTC1, cardiac actin; and an assembly protein: *MYBPC3,* cardiac myosin-binding protein C. *MYH7* and *MYBPC3* have the highest prevalence and, combined, account for 30% to 40% of diagnoses both in children and in adults. Haploinsufficiency due to loss-of-function alleles is the disease mechanism behind *MYBPC3*-related HCM, whereas a negative dominance model is the basis of other sarcomeric genes such as *MYH7*. In addition, rare variants have been reported in genes coding for protein of the Z-disc, such as *MYH6*, α myosin heavy chain, *TCAP*, and telethonin, and in genes involved in calcium homeostasis pathways, such as *VCL*, vinculin, and *JPH2,* junctophilin 2.[4,5,8] To date, several

papers suggest that most variants identified in nonsarcomeric genes implicated in HCM are not associated with the condition.[10] For this reason, diagnostic screening of genes only with definitive association with HCM should be included in next-generation sequencing (NGS) targeted panels.[11] Finally, "complex genotypes," characterized by the co-occurrence of more than one pathogenetic variant in a single patient, represent a small but important patient subset, characterized by early disease onset, severe phenotype, and adverse outcome including enhanced risk of sudden cardiac death.[9]

Inborn Errors of Metabolism

Most cases of HCM caused by inborn errors of metabolism (IEMs) are due to glycogen storage disorders (Pompe disease, gene *GAA*; Danon disease, gene *LAMP2* or *PRKAG2* disease gene), lysosomal storage disorders (mucopolysaccharidoses [MPS] and Anderson Fabry disease), and mitochondrial diseases (MELAS, MERRF, *TMEM70,* and *ELAC2*).[1,4,7,12] The X-linked Anderson Fabry disorder is due to alpha-galactosidase deficiency: even though an HCM phenotype only develops in the third decades in males, extracardiac features such as acroparestesias may present early during childhood. The infantile (autosomal recessive) form of Pompe disease results from a complete deficiency of acid alpha-glucosidase and presents in newborns with severe HCM, respiratory failure, hypotonia, impaired growth, and macroglossia. Signs of heart failure usually develop between 2 and 6 months of age and include cyanosis, dyspnea, tachycardia, and susceptibility to respiratory infections. Echocardiography shows massive and diffuse LVH. A less severe, juvenile form of Pompe, characterized by reduced (but not abolished) levels of alpha-glucosidase activity, presents in the first decade of life with a mild or absent cardiac involvement.[13,14] Danon disease is an X-linked form presenting with the clinical triad of cardiomyopathy, intellectual disability, and skeletal myopathy. Cardiac manifestations include left or biventricular hypertrophy and ECG anomalies such as the Wolf-Parkinson-White syndrome.[15] *PRKAG2* syndrome, another glycogen storage disorder, is characterized by severe and progressive cardiac hypertrophy, arrhythmias, short PR, and conduction defects leading to juvenile atrioventricular block. MPS are a large group of lysosomal storage diseases characterized by glycosaminoglycan accumulation with cardiac features such as LVH, mitral and aortic regurgitation, mitral annulus calcification, and coronary artery narrowing. Finally, mitochondrial cardiomyopathy has most often matrilinear transmission pattern with LVH, left ventricular noncompaction, and arrhythmias secondary to genetic defects involving the mitochondrial respiratory chain (see **Table 1**). Patients have a unique constellation of skeletal myopathy with exercise intolerance, neurosensory deafness, diabetes, and low stature. However, not all the mitochondrial cardiomyopathies have a matrilinear transmission pattern. These cardiomyopathies can also be inherited with autosomal dominant, recessive, or X-linked pattern.

Hypertrophic cardiomyopathy in RASopathies

The most common malformation syndromes associated with an HCM phenotype are the RASopathies, a heterogeneous group of diseases caused by mutations in genes of the RAS-MAPK cascade, including *PTPN11*, *BRAF*, *RAF1*, *SOS1 HRAS,* and *KRAS*. This group comprises conditions as diverse as Noonan, LEOPARD, cardio-facio-cutaneous, and Costello syndromes, characterized by short stature, facial dimorphisms, neurodevelopmental delay, and ectodermal abnormalities. These syndromes are typically inherited in an autosomal dominant pattern with variable expression. Heart involvement is a dominating feature, present in up to 80% of affected patients, and can be more rapidly progressive than the sarcomeric form.[16] HCM represents the most frequent cardiac phenotype, often accompanied by dynamic LV outflow tract obstruction (except for LEOPARD syndrome in which pulmonary stenosis is the predominant feature). However, besides hypertrophy, pulmonary stenosis, atrial septal defects, and valvular anomalies are also common findings in all RASopathies.

NEUROMUSCULAR DISEASES

Neuromuscular diseases represent a rare cause of HCM. The most common is Friedreich ataxia, an autosomal recessive condition caused by homozygous or compound heterozygous mutations in the gene encoding frataxin (*FXN*).[1] Frataxin is a nuclear-encoded mitochondrial iron chaperone involved in iron-sulfur biogenesis and heme biosynthesis. Some studies have also suggested that frataxin functions as an iron storage molecule, an antioxidant, and a tumor suppressor. Most patients with Friedreich ataxia have a GAA repeat expansion in the *FXN* gene. In addition, about 2% of cases of Friedreich ataxia are due to point mutations, the other 98% being due to expansion of a GAA trinucleotide repeat in intron 1. Syndromic and metabolic forms of HCM occur in infancy or early childhood, whereas neuromuscular

forms are more commonly diagnosed in adolescence in view of their progressive clinical course.[17]

STRATEGIES FOR GENETIC TESTING

Genetic testing is essential in the diagnostic algorithm of pediatric HCM (**Fig. 2**), to differentiate primary sarcomeric forms from IEMs and syndromic contexts, as well as to expand performing cascade screening in the proband's family members.[18] In addition, identifying genes responsible for the disease can help to define recurrence risk for future pregnancies.

Patient counseling, gene sequencing, and variant interpretation along with metabolic screening should be performed in centers with specific expertise in cardiogenetics reflecting a multidisciplinary approach.[19–21]

NGS offers several benefits such as high throughput, speed, and sensitivity in variant detection, compared with Sanger-based techniques, and represents the standard in most laboratories. However, for children younger than 1 year, especially when extracardiac features are present, NGS panels can be insufficient to identify the causative variant. On the contrary the whole-exome sequencing (WES) analysis, has the huge advantage of identifying novel genes, typically causative of childhood cardiomyopathies, and as knowledge evolves, it allows also the periodic reanalysis of the NGS data.[22–25] Furthermore, to detect de novo variants, more common in infants, WES is the most powerful tool. Certainly, this novel technique has its known limitations; however, this concern can be managed through genetic counseling and the sharing of the informed consent.[22,24,26]

In conclusion, we assume that in children older than 1 year with nonsyndromic HCM, including adolescents, targeted NGS HCM gene panels should be preferred, whereas in infants to reach early diagnosis and to avoid long, costly, and distressing "diagnostic odysseys," WES analysis represents the best strategy for genetic testing.

CLINICAL COURSE AND RISK OF ADVERSE EVENTS

The clinical trajectories, long-term outcome, and response to treatment of HCM in children are difficult to predict.[26–28] Although the increasing number of studies assessing genotype-phenotype relationships contributes to our accuracy in risk stratification, it is important to remember that individual variability in clinical expression remains a major challenge in prognostication, particularly in children, even among individuals of the same family.[1] As previously discussed, the first step requires an accurate genetic diagnosis to distinguish sarcomeric HCM from its IEM or syndromic phenocopies, because of the considerable differences in natural history and management strategies.[4] For example, mutations in *LAMP2* causing Danon disease are usually associated with rapid disease

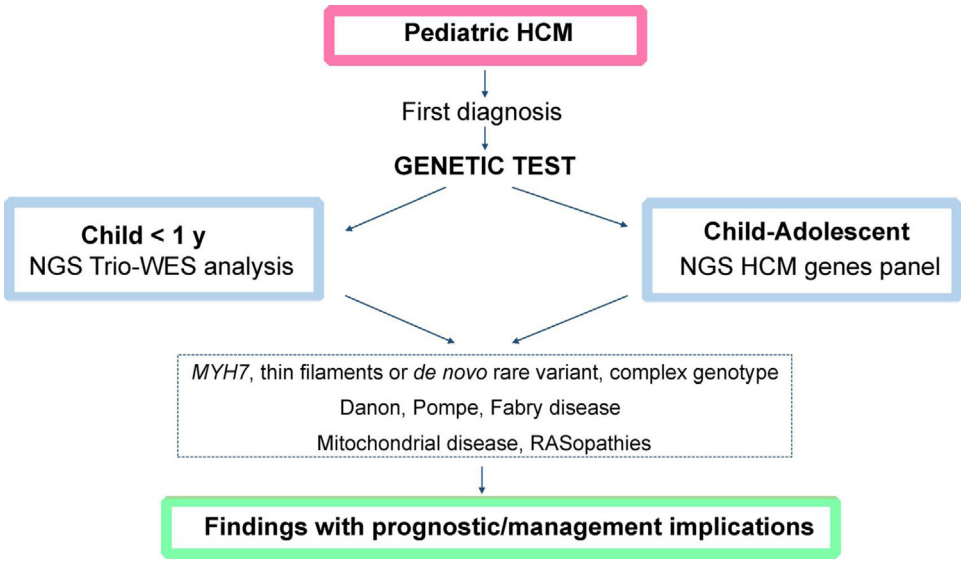

Fig. 2. The influence of genetic testing results on clinical course in children with HCM. Before age 1 year a next-generation sequencing (NGS)-Trio-whole-exome sequencing (WES)-based approach is the best strategy to screen patients with HCM; in children, adolescents, or when there is a clear clinical diagnosis of an isolated, nonsyndromic form of HCM, NGS genes panel approach should be preferred.

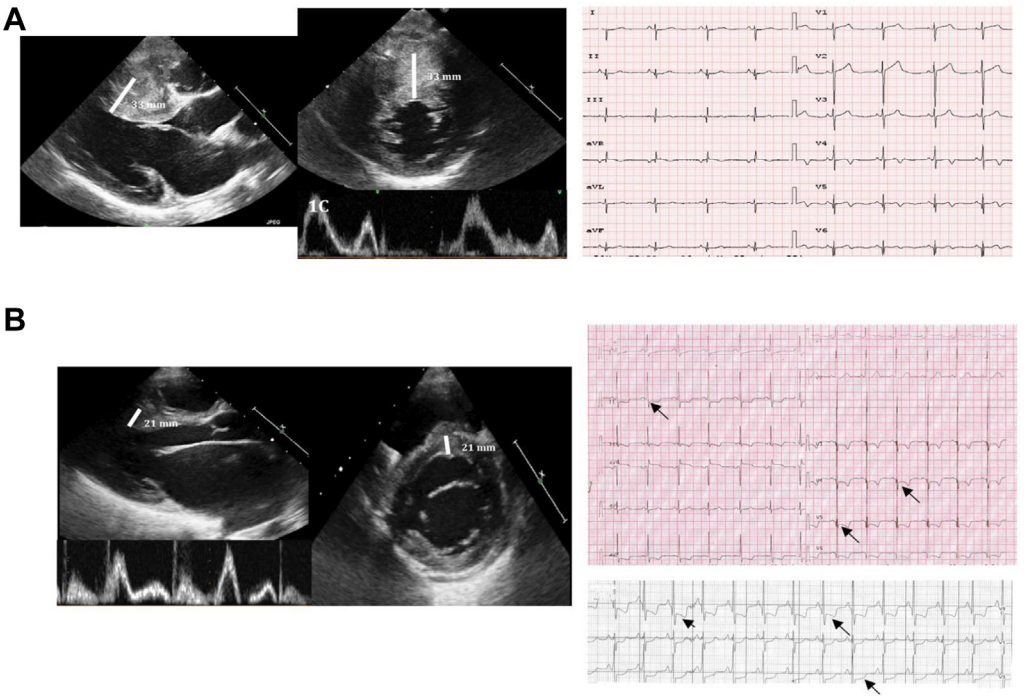

Fig. 3. The degree of LV hypertrophy in children with HCM with pathogenic variants in thin filament genes is not predictive of the risk of adverse events. (*A*) Child with a massive hypertrophy (septal maximal wall thickness = 33 mm) without events and negative genetic test. (*B*) A 9-year-old child with a mild hypertrophy (septal maximal wall thickness = 21 mm) presented a cardiac arrest (aborted) and a pathogenic variant in *TNNI3* gene.

progression and refractory heart failure in males, requiring early consideration for heart transplant.[29] Compared with sarcomeric HCM, Noonan-related cardiomyopathy presents with earlier onset and increased risk of heart failure and early mortality. Long-term prognosis is frequently poor, especially in the presence of biventricular obstruction and in carriers of *PTPN11* and *RIT1* pathogenic variants.[30] Among patients with *PRKAG2* mutations, both ventricular arrhythmia and juvenile AV blocks are common, calling for early prophylaxis with a pacemaker- implantable cardioverter-defibrillator; however, subcutaneous devices, without pacing capabilities, should be avoided in this context.

Among children with sarcomeric HCM, the identification of a complex genotype (2 mutations in the same or different sarcomeric genes) is usually associated with early onset and adverse clinical outcomes, as in adult patients.[31,32] Recently the presence of de novo variants has been shown to correlate with a higher risk of adverse events. Notably, de novo variants occur in up to 29% of pediatric HCM, seem to be linked to paternal age, and their identification is important both for the proband and counseling regarding risk of recurrence in subsequent pregnancies. Indeed, the proband's siblings will not share a genetic predisposition to develop HCM, with the exception of extremely rare germinal mosaicisms.[33]

Thin filament gene mutations seem to play an important role in children with HCM. Homozygous variants in *TNNI3* genes, recently identified in infants with HCM, represent a rare cause associated with a severe outcome.[34] In a recent report by our group[35] children with mutations in *TNNT2* or in other thin filament genes exhibited a relatively small degree of hypertrophy but were exposed to increased risk of rhythm disturbances and a high incidence of sudden death (**Fig. 3**). These data are in agreement with those of previous studies by the London group, showing an increased risk of adverse outcome due to sudden death and progression toward restrictive end-stage disease in young patients with HCM with thin filament mutations.[36]

SUMMARY

Childhood HCM is typically caused by rare, family-specific mutations, commonly de novo. Investigating the genotype of HCM in children is extremely important, because it may help guide management more decisively and more often than in adults. Despite expanding knowledge, genotype-phenotype correlations in this young

patient subset remain elusive, calling for broader, international studies in the field.

CLINICS CARE POINTS

- Consider "red flag" approach when evaluating children with HCM to provide lucid guide for clinical management and lifestyle advices.
- When suspecting HCM in a child always perform genetic counseling and metabolic screening.
- Less than age 1 year always use NGS Trio-WES analysis to identify complex genotypes and de novo rare variants.
- Plan a closer follow-up in patients with de novo rare variants or complex genotypes.
- Genotype early to distinguish between classical sarcomeric HCM and phenocopies and advise proper pharmacologic and invasive therapy.
- Detect Danon disease and provide early personalized care to the children and its family.
- In the presence of thin filament pathogenic variants in children evaluate the arrhythmic burden and initiate early adequate treatment to prevent end-stage disease phase.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

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