LZTR1-associated Hypertrophic Cardiomyopathy and Severe Mitral Valve Disease in a Child Without Typical Noonan syndrome Characteristics: A Case Report

Variants du gène LZTR1: Cardiomyopathie Hypertrophique et Maladie Mitrale Sévère chez un Enfant Sans Critères Typiques de Syndrome de Noonan

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Summary

We report a case about a little boy, with a family history of Hypertrophic cardiomyopathy (HCM). He was an infant of a diabetic mother with a prenatal diagnosis of HCM. At birth, unilateral cryptorchidism was mentioned without notable distinctive facial features. At the age of 17 months, besides HCM, he was diagnosed with dysplastic mitral valve and severe mitral regurgitation. The genetic testingobjected heterozygousvariants inLZTR1 gene which confirms the Noonan Syndrome (NS). The patient underwent surgical repair of the mitral valve; with recurrence of severe MR two years after surgery

Keywords

Hypertrophic Cardiomyopathy, Noonan Syndrome, Mitral Regurgitation, LZTR1

Résumé

Nous rapportons le cas d'un petit garçon, avec des antécédents familiaux de cardiomyopathie hypertrophique (CMH). Le diagnostic anténatal d'hypertrophie ventriculaire associé au diabète maternel était posé. À la naissance, une cryptorchidie unilatérale a été mentionnée sans dysmorphie faciale notable. À l'âge de 17 mois, outre la CMH, l'examen échographique a objectivé une valve mitrale dysplasique occasionnant une régurgitation sévère. Le test génétique a objectivé des variantes hétérozygotes dans le gène LZTR1 qui confirme le syndrome de Noonan (NS). Le patient a subi une réparation chirurgicale de la valve mitrale, avec une récurrence d'une IM sévère deux ans après la chirurgie.

Mots-clés

Cardiomyopathie Hypertrophique, Syndrome de Noonan, Insuffisance Mitrale, LZTR1.

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BACKGROUND

Hypertrophic cardiomyopathy (HCM) is the second most common cardiomyopathy in children. As in adults, non-syndromic HCM remains the most common etiology in the pediatric population(1). RASopathies, a group of syndromic disease caused by mutations in genes involved in regulation of the RAS/MAPK signaling pathway, including Noonan syndrome (NS) and related disorders,represent a frequent cause of HCM in children, especially in infants under one year of age(2). NS is characterized by facial dysmorphism, short stature and congenital heart defects.Many genes were identified causing NS and related disorders, the first gene was PTPN11, several genes have been identified since then, more recently LZTR1 among other genes weredescribed(3). Genotype-phenotype correlations can explain the large phenotype range of Noonan Syndrome(4). A family history of sudden death is uncommon in HCM patients with NS.Combined mutations in sarcomeric and RAS/MAPK genes is rare, but should be eliminated in case of HCM with mild NS features. Concomitant cardiac defects are frequently noted in HCM patients with NS, but rapid progression of mitral valve regurgitation is rare.

CASE PRESENTATION

Our patient is a three-and-a-half-year-old boy, born of a non-consanguineous marriage, with a family history of sudden death. His maternal grandmother, his maternal aunt and two uncles died suddenly at an age ranging from 27 to 42 years old. The two uncles were diagnosed with hypertrophic cardiomyopathy. The genetic analyses were not performed and the family reported the absence ofdysmorphic features Les critères de non inclusion : les patients ayant une insuffisance cardiaque sévère, ou une instabilité hémodynamique, une insuffisance rénale même modérée et ou une fibrillation auriculaire.

Our proband was born at the 35th week by C-section because of fetal distress. The pregnancy was complicated by maternal diabetes, with prenatal diagnosis of hypertrophic cardiomyopathy. At birth, he weighed 4kg. Physical exam objected unilateral cryptorchidism with no other dysmorphic criteria. Transthoracic echocardiography (TTE) confirmedthe diagnosis of hypertrophic cardiomyopathy and objected mild dysplasia of the mitral valve with a mild mitral regurgitation (MR). During follow-up, ultrasound checks showed increasing septal wall thickness and aggravation of mitral regurgitation. At the age of 17 months, the mother reported a shortness of breath on exertion.Physical exam noted mild facial dysmorphism (low-set ears and a short nose with broad base), a systolic murmur at the cardiac apex with normal pulmonary auscultation and no signs of heart failure. The patient's height was normal. Electrocardiogram (ECG) identified a sinus rhythm with wide p waves in favor of left atrialenlargement. The echocardiography (figure1) objected dysplastic mitral valve with elongation and prolapse of the anterior leaflet causing severe regurgitation,restricted posterior leaflet motion, thickened and poorly differentiated chordae and dominant anterior papillary muscle. The biventricular function was good with concentric left ventricular hypertrophy [IVSd= 12mm (+4.5 z-score), LVPWd = 12mm (+5.8z-score)] with normal left ventricular size [LVIDd= 24mm (-1.4 z-score)], very enlarged left atrium and moderate obstruction of the left ventricular outflow tractwith a peak instantaneous 46mmHg gradient.

The patient's mother and father, aged 34 and 46 years old respectively, and a5-year-old brother had normal physical examination and transthoracic echocardiography.

Genetic testing demonstrated that our proband has two variantsinLZTR1gene with heterozygous variant, c.2387T>C p.(Ile796Thr),of uncertain significance and heterozygous variant,c.1745del p.(Val582Gly f s*10), a pathogenic variantwhich confirms the clinical suspicion of Noonan Syndrome.He would be a is a compound heterozygotein LZTR1 gene. He had also a heterozygous variant of theMYH7gene with variant c.5779A>T p.(Ile1927Phe), of uncertain significance. The rest of the family members didn't undergo genetic screening.

Our patient underwent cardiac surgery at the age of 18 months: mitral valvuloplasty with Goretex cords and posterior annuloplasty, reductive plasty of the left atrium and left appendage amputation. Early post operative complications were biventricular systolic dysfunction, an episode of ventricular tachycardia successfully reduced with antiarrhythmic drugs and an episode of atrial flutter successfully cardioverted with amiodarone. Progressive improvement of the systolic function was noted in the post-operative days.Echocardiogram on discharge showed moderate mitral regurgitation with two jets, concentric hypertrophy of the left ventricular with preserved systolic function and an unobstructed outflow tract.

At last check, two years after surgery, the patient was asymptomatic with no signs of heart failure. He was followed for asthma in the pediatric department. The TTE noted concentric hypertrophic cardiomyopathy (IVSd = +5.1z-score, LVPWd = +5.6z-score) with good biventricular function, no LVOT obstruction, severe eccentric mitral regurgitation, left atrial dilation. Holter ECG didn't objective any arrythmia. The patient is still under beta-blocker and he is regularly followed.

DISCUSSION

In 1968, Noonan described a new syndrome consisting ofdysmorphic features associatedwith congenital heart disease which was called later Noonan syndrome(5). In 2001, PTPN11, the first gene involved in the RAS/MAPK pathway was identified(3). Several genes have been highlighted since then. In 2015, Yamamoto et al reported LZTR1 as a NS-causing gene, and it was identified in 8% of patients diagnosed with NS with no mutations in the known genes associated with this syndrome(6). PTPN11 gene mutationsare found in about 50% of patients with NS(7), while variants in LZTR1 are reported in few cases in literature.

Typical features of NS include facial dysmorphism, short stature and heart disease. Hypertrophic cardiomyopathy without typical clinical features of NS had been reported in patients harboring variants in LZTR1 gene(8). Distinctive facial features may be absent in NS patients(9). Many studies suggested that short stature in patients with NS is less common in those carrying variants in LZTR1 gene (8,10,11). Cryptorchidism, frequently reported in patients with NS(3), raised the suspicion in our proband.Cardiac abnormalities were described in 80-90% of cases with NS(4,12).The most common heart disease are pulmonary stenosis and HCM(12). In a recent study including 242 individuals with RASopathy,It has been demonstrated that in patients with Noonan syndrome, HCM was more frequent in those with variants in LZTR1 than in those with variants in PTPN11(10). It's usually diagnosed at an early age, during the first year of life(9,12,13). In our patient, fetal HCM may be a complication of maternal diabetes during pregnancy. Concomitant cardiac lesions are frequent in NS patients with HCM(4,9,13). Mitral valve disease, in HCM patients associated with NS,is reported as a marker of complexity and a risk factor for reintervention and death(14). The prevalence of mitral valve anomalies in patients with NS varies in different studies. Colquitt et al,described dysplastic mitral valve in 2% of NS patients(14), while Calcagni et al reported mitral valve disease in 18% in patients with RASopathy(14). This cardiac defect was noted in 35% of NS patients with HCM(9) and in 50% of NS patients with cardiac disease harboring variants in LZTR1 gene(12). Varied mitral valve abnormalities have been reported. Sreeram et al described dysplastic mitral valve leaflets appearingthickened with loose myxomatous tissue, poorly differentiated and shortened chordae,and diminished interchordal spaceson post-mortem examination of a series of four patients with NS(16).Congenital malformation of the mitral valve associated to partial atrioventricular canal defect and anomalous insertion of the mitral valve on the ventricular septum have been reported(17).Mitral valve prolapse have been noted(4).Our patient had aprolapse of the anterior leaflet of the mitral valve causing severe mitral regurgitation,restricted posterior leaflet motion, thickened and poorly differentiated chordaeand dominant anterior papillary muscle. Mitral valve abnormalities such as anomalous papillary muscle could explain the LVOT obstruction in patients with mild septal hypertrophy(14). Rapid progression of mitral regurgitation such the case of our proband was seldomreported in patients with NS(18).

In addition to early onset of HCM, dysplastic mitral valve with severe regurgitation and mild clinical characteristics of NS, our patient had a family history of sudden cardiac death which is not common in HCM associated with NS(9).The genetic testing identified that our proband was a compound heterozygote in LZTR1 gene and that he harbored heterozygous variant of uncertain significance in MYH7 gene.There was no genetic testing for the family members who were victims of sudden death and no genetic screening in the rest of the familymembers.The coexistence of both sarcomeric HCM and RASopathy-associated HCM in the same family have been previously reported(19).Sarcomeric HCM usually appears after the age of infancy and it may be associated with a higher risk of major arrythmias(9). Mutations in MYH7 and MYBPC3 genes represent the largest cause of non-syndromic HCM in children(20). Sequencing all genes in the available panels involved in the RAS/MAPK pathway and the sarcomere cardiac protein in patients with familial HCM should be considered, even if a familial pathogenic variant is known because the prognosis may be different in the presence of a second mutation(21). HCM is the most common cause of sudden cardiac death (SCD) in children and young adults.Risk stratification had been evaluated in children with non-syndromic HCM(22,23),but data aboutrisk factors for SCD in children with NS-associated HCMare lacking. Some studies noted low risk of sudden cardiac death in patients with NS-associated HCM (4,9), while ventricular tachycardia and sudden death were reported in other series(13,15). Major tachyarrhythmia, ventricular fibrillation requiring appropriate implantable defibrillator therapy, was documented in NS patients with variants in LZTR1 gene(8). Heart failure represents a significant cause of death for NS patients with HCM.Early mortality has been noted in NS-associated HCM, with the majority of deaths reported during the infancy period(24). Studies focusing on long-term outcome in these patients showed different results. Some series found a good long-term outcome(9) while others noted that HCM patients with NS had a higher late mortality rate than

non-syndromic HCM patients(13).Unlike sarcomeric HCM, a regression of hypertrophy during follow-up was reportedin case of NS-associated HCM(4,9).

CONCLUSION

HCM in children is characterized by a greater diversity of etiologies than in the adult population.Non-sarcomeric HCM is the substantial cause in infants aged less than one year. Mild clinical features and concomitant cardiac defects should raise the suspicion of RASopathy. Genetic testing is crucial in making definitive etiological diagnosis of HCM. Sequencing all genes in the available panels involved in the RAS/MAPK pathway and the sarcomere cardiac protein in patients with familial HCM should be considered. Mitral valve disease is considered as a marker of severity in NS patients with HCM. Congestive heart failure is an important cause of death in children affected by NS and HCM, especially in the first year of life. Major arrythmia and sudden cardiac death have been reported in NS patients with HCM, but available data is not conclusive to provide a risk stratification for SCD in children with NS.

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