LEFT VENTRICULAR MYOCARDIAL NON COMPACTION IN A CHILD AFFECTED BY CRI DU CHAT SYNDROME

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ABSTRACT

The following is a case report of an infant born with *cri du chat* syndrome that has evidence of left ventricular non compaction .

Cri du chat syndrome is a rare association of growth retardation, intellectual severe disability, hypertelorism and typical catlike cry, typically combined to congenital heart defect, the occurrence of myocardial non compaction among the associated cardiac anomalies has not been reported so far.

Keywords: echocardiography, *cri du chat* syndrome, left ventricular non-compaction, atrial septal defect, non compaction cardiomyopathy

INTRODUCTION

Cri du chat syndrome is a congenital disease with characteristic cry, psychomotor delay, growth retardation and facial dimorphism , resulting from deletion of short arm of chromosome 5, firstly described by Lejeune et coll. in 1963 (1).

We report the case of a 3-year-old male infant affected by this syndrome , who developed left ventricular non compaction , a rare myocardial disorder, characterized by thickened subendocardial layer of myocardium with deep inter-trabecular recesses and thin compacted wall, more evident in the apex of the left ventricle.

It is hypothesized that myocardial non compaction could be determined by failure of the process of trabecular compaction between gestational 20th and 26th week .
This cardiomyopathy can have a wide spectrum of clinical manifestations ranging from asymptomatic cases to heart failure, malignant arrhythmias and sudden death. At the best of our knowledge this is the first time that association of cri du chat syndrome with left ventricular non compaction is reported in literature.

CASE PRESENTATION

The patient was the second child of non consanguineous and healthy parents, his sister was healthy, too. He was born at 39 th weeks after an uncomplicated pregnancy.

He showed a weight of 2,840 kg, ears malformation, bilateral single transverse palmar crease, microcephaly, systolic murmur and a typical cry.

On the basis of dysmorphic facial appearance and cat-like cry, *cri du chat* syndrome was diagnosed, confirmed by karyotype 46 XX with 5p -, array CGH showed 5p15.33p14.3 deletion.

He was referred for a systolic murmur echocardiogram showed only a small secundum-type atrial septal defect that required an echographic follow up The next year, in addition to the atrial septal defect, a slight hyper-trabeculation of left ventricular apex was demonstrated (Fig.1).. At the age of three years the echocardiographic was consistent with non compaction of left ventricular apex and lateral distal wall, internal ventricular

diameters were normal and systolic function was preserved (fractional shortening >30% and ejection fraction =55%) (Fig.2).

DISCUSSION

Cri du chat (OMIM 123450) is a chromosomal syndrome that results from partial deletion on the short arm of chromosome 5, characterized by severe mental delay, cat-like cry, microcephaly , malformed ears, round face and ocular hypertelorism. Congenital cardiac malformations are observed in about 29% of patients with microdeletion and in 55% of individuals affected by balanced translocation. The most frequent cardiac lesions are represented by patent ductus arteriosus and ventricular septal defects, sometimes associated to ventricular outflow obstruction (2) .

Several contiguous genes mapped in 5p have been associated to cardiac development, such as ADAMTS16 in the region 5p15.32, DNAh5, NDUFS6 and IRX4 into region 5p15.33 (3).

Particularly Irx4 , of the Iroquois family of transcription factor, has been associated with ventricular septal defect (2-4),in addition transgenic mice lacking Irx4 developed myocardial non compaction (5).

Notably, our patient carried a deleted region containing Irx4 gene (5p 15.33 , position1,877,413-1,877236) thus suggesting that haploinsufficiency of this transcription factor can lead to non-compaction phenotype .

Although left ventricular non compaction has not been reported in children with c*ri du chat* syndrome so far, we should consider that heritable cardiomyopathies could not be detectable in neonatal age, because they have a variable preclinical stage .

In fact symptoms of left ventricular non compaction, including heart failure, thromboembolism, and malignant arrhythmias, are generally absent in infancy.

On the other hand , children affected by left ventricular non compaction associated to congenital syndromes , such as deletion 22q11, monosomy X (Turner syndrome), trisomy 21 and trisomy18, have early onset of clinical manifestations in childhood and are at higher risk of with systolic dysfunction and malignant arrhythmias than nonsyndromic form of cardiomyopathy.

Non compaction cardiomyopathy is a genetically heterogeneous disorder with sporadic or familial incidence (6).

In about one third of patients with left ventricular non compaction a genetic cause can be detected, mostly an autosomal dominant inherited mutations of several genes (such as Cypher/ZASP, FKBP12 and CSX(6) . An X-linked inheritance has been reported in the 7% of the patients (6) with frequent deletion of G4.5 gene, mapped in long arm of X chromosome.

Among many of the genes identified as responsible for the development of myocardial non compaction some authors have focused attention on Nkx2-5, a critical component of the cardiac gene regulatory network, since left ventricular non compaction has been reported in children with mutation of Nkx2-5 and in *Nkx2-5* knockout mice (7)

Nkx2–5 transcription factor regulates many key aspects of heart development in concert with other cardiac transcription factors, such Irx4.

In fact, mice lacking the homeobox transcription factor Nkx2-5 have markedly reduced levels of Irx4 protein in cardiomyocytes.

Recent studies have identified Irx4 as a possible candidate in left ventricular non compaction development (5).

In animals and humans Iroquois (Irx) family of homeobox transcription factors regulate ventricles development (7), specifically Irx4 promotes synthesis of ventricular myosin. Moreover, Irx4, expressed only into trabecular region of the ventricular myocardium during all stages of cardiac development until

adulthood , (8) is essential for the process of transformation
of trabecular in compact myocardium. (5).

Furthermore, mice lacking *Irx4* have thinner ventricular walls with non-compacted myocardium and prominent trabeculations (5), Irx transcription factors specifically inhibit expression of Bmp10, one of the *NOTCH1* - associated molecules involved in myocardial hyper-trabeculation (5-9).

In addition, *Irx4*-deficient adult mice exhibit increased expression of heart failure marker Brain Natriuretic Peptide and develop cardiomyopathy with impaired systolic function and myocardial hypertrophy.

CONCLUSION

We describe the unprecedentedly reported case of c*ri du chat* syndrome associated to left ventricle non compaction, the child carried a deletion of 5p 15.33 containing the Irx4 gene, that plays a pivotal role in ventricular myocardium development.

Myocardial non compaction, which is an evolutionary disorder, was not detectable at the first cardiologic evaluation of our patient, becoming gradually manifest at annual echocardiographic follow up.

Due to variable latency of clinical manifestations of this cardiomyopathy, every patient with c*ri du chat* syndrome should be screened periodically with ECG and echocardiogram.

Since severe outcome and major cardiac adverse events have been frequently observed in patients with left ventricular non compaction associated to chromosomal abnormalities (10), an early diagnosis of this cardiomyopathic condition and periodic follow up are essential in order to monitor cardiac complications, particularly potential malignant rhythm alterations.

ACKNOWLEDGEMENTS

Financial Support :this research received no specific grant from any funding agency, commercial or not-for-profit sectors.

CONFLICT OF INTEREST:

None

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