VARIATION IN CARDIOVASCULAR MORPHOLOGY IN THE SCIMITAR SYNDROME: EXPERIENCE FROM A SINGLE INSTITUTION

I. Bo 1, M.L. Rigby 2
1 Paediatric Cardiology Unit, Department of Paediatrics, University of Parma, Parma, ITALY, 2 Paediatric Cardiology Unit, Royal Brompton Hospital, London, UNITED KINGDOM

Introduction: The scimitar syndrome is a rare condition consisting, in its classical form, of anomalous pulmonary venous drainage (PAPVD) of the right lung to the inferior vena cava (IVC) close to the junction with the right atrium (RA), varying degrees of right lung and pulmonary artery hypoplasia, anomalies of the right bronchial tree, dextrocardia and a systemic arterial blood supply from the abdominal aorta to the inferior segments of the right lung (AP collateral).

Aim: To review every case presenting to the Royal Brompton Hospital from 1992 to 2012 and to describe the morphological aspects based upon their angiographic images.

Methods: The patients’ medical records and cardiac catheterisation laboratory pictures were reviewed. We defined scimitar syndrome or one of its variants, every case presenting with either PAPVD to IVC and/or one or more AP collaterals from the abdominal aorta to one lung with at least one additional criteria: dextrocardia, left or right lung and/or pulmonary artery hypoplasia, abnormal bronchial morphology with hypoplasia, lung sequestration. We used the term scimitar variant to describe those cases in which the main features were located on the left and those with normal pulmonary venous drainage or PAPVD drainage to an uncommon location.

Results: 53 patients were identified; 43 had the classical form. Everyone underwent cardiac catheterisation, usually within the first year of life. Twelve of them (22.6%) were symptom free at the time of the procedure. The major symptoms in infancy (47.1%) were failure to thrive, tachypnoea, respiratory distress or heart failure. Fourteen patients (22.6%) had recurrent respiratory tract infections, wheezing or exercise intolerance. Fifty-six percent underwent a percutaneous embolisation of one or more AP collaterals.

Every case had atrial situs solitus and normal atrioventricular and ventriculoarterial connection; 66% had a right sided heart. A single or multiple AP collaterals were identified in 46 (86.8%) patients. The precise origin was evident in 64, usually in close proximity of the celiac axis. Their diameter was compared to that of the subdiaphragmatic descending aorta; 34 were large (bigger than 33% of the aorta); 18 were moderate (between 15 and 32%); 6 were small (<15%).

Forty-three patients had an abnormality of the pulmonary arteries either some degree of hypoplasia and/or an abnormal branching pattern. Complete absence occurred in 4. Horseshoe lung was identified in 8/53 patients (15.7%).

The types of pulmonary venous drainage is showed below (Fig. 1); this was classic in 33, normal drainage in 6, mixed in 12 and to SVC or CS in the remainder.

Conclusion: Our population showed a considerable variation in the blood supply to the affected lung as well as the pulmonary veins. Although the majority of cases were classical forms, the frequency of variant was high. There were obvious anomalies of the branching pattern of the pulmonary arteries when there was hypoplasia, often related to a horseshoe lung.

The origin of the AP collateral was almost always close to or directly from the coeliac axis, with implications for transcatheter embolisation and risk of splenic, gastric or hepatic infarction.

The hallmark of the scimitar syndrome is PAPVD to the IVC, close to the junction with the right atrium. Another significant abnormality of the pulmonary veins was stenosis (either right and left), which is the most significant risk factor for poor outcome, while PAPVD alone is not highly significant. Overall patients with a high pulmonary blood flow, total right anomalous pulmonary venous drainage, pulmonary vein stenosis and significant lung hypoplasia are more likely to have pulmonary hypertension and are more at risk of early death.

Figure 1: types of pulmonary venous drainage. IVC: inferior vena cava; RAj: right atrial junction; HepV: hepatic vein; LA: left atrium; CS: coronary sinus; LvarNdr: left variant with normal drainage.
GENETIC VARIANTS IN MICRORNA-BINDING SITES OF GATA4 GENE ARE ASSOCIATED WITH THE RISK OF CONGENITAL HEART DISEASE

S. Puglinani, L. Ait-Ali, M. Cresci, S. Sabina, P. Festa, I. Foffa, C. Vecoli, M.G. Andreassi
CNR Istituto di Fisiologia Clinica, Massa, Pisa, CNR Istituto di Fisiologia Clinica, Lecce, Fondazione CNR-Regione Toscana Gabriele Monasterio, Massa, ITALY

Background- Congenital heart disease (CHD) is the most common type of birth defect. The recent exponential increase in the knowledge of medical genetics has revolutionized the understanding of CHDs during the past few decades. GATA4, a transcription factor, is involved in heart development. Recent evidences show that single nucleotide polymorphisms (SNPs) in miRNA binding sites can alter the strength of binding and disturb miRNA-mediated post-transcriptional regulation, influencing the susceptibility to congenital heart diseases (CHDs).

Aim- Our study aimed to investigate the role of SNPs in putative miRNA binding sites in the development of CHDs.

Methods- The clinical significance of four (+1158 C>T, +1256 A>T, +1355 G>A, 1521 C>G) SNPs in a group of 100 affected children and 204 healthy newborns by direct sequencing was investigated. These SNPs were bioinformatically predicted to affect the binding affinity of miRNAs to the GATA4 3'UTR.

Results- Two SNPs (+1158 C>T and 1521 C>G) were found to significantly differ between cases and controls (both p < 0.05). Haplotype analysis including these variants showed a decreased risk of developing CHD for the TC (+1158 T and 1521 C) haplotype (OR =0.50 CI:0.26-0.96; p =0.037). The bioinformatic analysis showed that the +1521 C>G SNP affect the miRNA binding site much more than other SNP substitution (I MFEtot= 21.66I). The luciferase reporter assay in HCT116 Dicer-/- cells supported the predicted functional influence of the polymorphism. Indeed, miR-583 decreased the luciferase activity in cells transfected with +1521 C wild type variant of GATA4 3'UTR.

Conclusion- Our results suggest that miRNA binding site SNPs in the 3'UTR of GATA4 gene are associated with the risk of CHD likely by altering miRNA gene regulation and consecutively protein expression. This may be a novel mechanism of subtle gene regulation contributing to the likelihood of CHD.
SYNDROMIC NONCOMPACTION OF THE LEFT VENTRICLE: ASSOCIATED CHROMOSOMAL ANOMALIES

P. Versacci 1, M.C. Digilio 2, L. Bernardini 3, M.G. Gagliardi 2, A. Baban 2, L.M. Silvestri 1, M.L. Dentici 2, M.C. Roberti 2, A. Angioni 2, A. Novelli 3, B. Marino 1, B. Dallapiccola 2

1 Pediatric Cardiology, Department of Pediatrics, Sapienza University of Rome, Rome; 2 Medical Genetics, Pediatric Cardiology, Cytogenetics, Bambino Gesù Children’s Hospital, Ircs, Rome; 3 Mendel Laboratory, Casa Sollievo Della Sofferenza Hospital, Ircs, San Giovanni Rotondo, ITALY

Background: Noncompaction of the left ventricle (NCLV) is a cardiomyopathy characterized by prominent left ventricular trabeculae and deep intratrabecular recesses. Genetic aetiology is highly heterogeneous, including sporadic or familial isolated non-syndromic NCLV resulting from single gene mutations, and syndromic NCLV associated with genetic syndromes, metabolic and neuromuscular diseases. The frequency of extracardiac anomalies in patients with NCLV is ranging between 14% and 66% in different series. Chromosome anomalies have been discovered in sporadic cases.

Aim of the study: Aim of the present study was to investigate the prevalence of chromosomal imbalances in our series of syndromic patients with NCLV.

Materials and methods: Between January 2003 and December 2012, 56 patients with NCLV have been evaluated consecutively at the Bambino Gesù Pediatric Hospital and La Sapienza University in Rome. Echocardiographic criteria for diagnosis of NCLV included: 1) presence of multiple echocardiographic trabeculations; 2) multiple deep intertrabecular recesses communicating with the ventricular cavity, as shown by color Doppler imaging and the recesses demonstrated in the apical or middle portion of the ventricle; and 3) two-layered structure of the endocardium with a noncompacted to compacted ratio >1.4. Accurate clinical and phenotypical examination was performed, in order to check for the presence of major and minor associated anomalies. Among the total patients, 29 (52%) were non-syndromic and 27 (48%) syndromic. Syndromic patients included 15 males (56 %) and 12 females (44 %), with an age at time of genetic evaluation ranging from 1 month to 31 years (mean age ± SD 5.1±2.7). Two syndromic patients had Barth syndrome, and were excluded from cytogenetic analysis. Molecular-cytogenetic studies were performed in the 25 syndromic patients, and included standard chromosome analysis at 550-band resolution, subtelomeric fluorescent in situ hybridization (FISH) using ToTel Vysion-kit, array-CGH analysis using a genomic oligonucleotide-array with an effective resolution of 250 Kb (Human Genome Microarray 4x44K Chip; Agilent Technologies, Walldbronn, Germany).

Results: Standard chromosome analysis disclosed an abnormality in 3 (12%) patients, including a 45,X/46,XX mosaic, a 45,X/46,X;i(Y)(p11) mosaic, and a de novo Robertsonian 13;14 translocation in a child affected by hypomelanosis of Ito. Cryptic chromosome anomalies were found in 6 (24%) cases, including 1p36 deletion in two patients, 7p14.3p14.1 deletion, 18p subtelomeric deletion, 22q11.2 deletion associated with velo-cardio-facial syndrome, and distal 22q11.2 deletion, each in one case.

Conclusions: These results recommend accurate clinical evaluation of patients with noncompaction of the left ventricle, and suggest that chromosome anomalies occur in about one third of syndromic noncompaction of the left ventricle individuals, without metabolic/neuromuscular disorder. Array-CGH analysis should be included in the diagnostic protocol of these patients, since different submicroscopic imbalances are causally associated with this disorder and can pinpoint candidate genes for this cardiomyopathy.
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NOTCH1 GENE MUTATIONS IN PATIENTS WITH FAMILIAL BICUSPID AORTIC VALVE

I. Foffa ¹, L. Ait-Ali ¹, P. Panesi ¹, C. Vecoli ¹, P. Festa ², M.G. Andreassi ¹ ²
¹ CNR Istituto di Fisiologia Clinica, Massa, Pisa, ²Fondazione CNR-Regione Toscana Gabriele Monasterio, U.O. Cardiologia pediatrica e GUCH, Massa, ITALY

Background- Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, frequently associated with significant aortic pathology. Clinical studies have reported high heritability in families of patients with BAV. Gene mutations in NOTCH1, a signaling transmembrane receptor involved in multiple cell aspects of vascular development, have been shown to cause BAV in three family kindreds. However, the role of NOTCH1 gene mutations in familial and sporadic forms of BAV remains not clear yet.

Aim- To evaluate the prevalence of NOTCH1 gene mutations in Italian patients with familial and sporadic BAV.

Methods- A cohort of 21 patients with familial (n=11; 8 males; age = 42 ± 19 years) and sporadic (n=10; 7 male; age = 48 ± 16 years) BAV was prospectively enrolled. Genetic screening of all 34 coding exons, including adjacent intronic and 5' and 3' untranslated sequences was performed by using a high-throughput platform (CEQ 8800 Genomelab GeXP Genetic Analysis System, Beckman).

Results- Genetic analyses revealed 17 NOTCH1 sequence variants listed in public dbSNPs or in the literature. Two novel mutations, a missense and a nonsense mutation (Exon 5, p.P284L; Exon 26, p.Y1619X), were found in the NOTCH1 gene in two unrelated patients with positive familial history and associated aorthopathy. These mutations were confirmed to be absent in 100 control alleles and predicted to have a potential malign effect by bioinformatic tool (PolyPhen and SIFT). No evidence of novel NOTCH1 mutations was found in sporadic patients.

Conclusions- Our results showed novel NOTCH1 mutations in two Italian family with BAV, confirming significant role of Notch signaling in the pathogenesis of the BAV and its complications.
OUTCOME OF 30 CASES OF 22.Q11.2 DELETION SYNDROME AND CONOTRUNCAL MALFORMATION

F. Fratta 1, M. Carrozza 1, C. Ricci 1, R. Sorrentino 1, R. Melone 1, G. Capozzi 1, R. Esposito 1, N. Borrelli 1, G. Caianiello 2, M. Russo 1

1 Cardiologia Pediatrica, SUN, AO Monaldi, Napoli, 2 Cardiochirugia Pediatrica, SUN, AO Monaldi, Napoli, ITALY

Background: 22q11.2 deletion syndrome (DS) is a chromosomal anomaly which causes a congenital malformation disorder whose common features include cardiac defects, palatal anomalies, facial dysmorphism, developmental delay and immune deficiency. The worldwide incidence is estimated at 1/2,000-1/4,000 live births. The broad spectrum of clinical phenotypes that the syndrome encompasses was previously divided into distinct syndromes (e.g. DiGeorge syndrome, velocardiofacial syndrome, cardiofacial syndrome) but are now known to be etiologically identical and are referred to as 22q11.2 DS. The prognosis is variable and depends on the severity of the disease. The infant mortality rate is relatively low (~4%); in adults mortality is higher than that of the rest of the adult population. Familial deletion have been identified in 8-28% of probands.

Objective: To investigate clinico-pathological features and outcome of 22q11.2 deletion syndrome patients admitted to our division for suspect of CHD.

Method: The clinical features, and cardiovascular anomaly findings were analyzed in cases of 22q11.2 deletion syndrome.

Results: Thirty cases of 22q11.2 deletion syndrome were analyzed, 19 patients were female, 11 male. Mean age 7±2 years.

Prenatal diagnosis of 22q11.2 deletion syndrome by fluorescence in situ hybridization were made in 10 cases. 4 patients diagnosed with Tetralogy of Fallot and deletion 22 decided to terminate the pregnancy. The other patients were diagnosed with heart disease and syndrome after birth. Twenty-eight patients had a de novo deletion (93,3%) two female patients also had a parents affected by the syndrome, in one case the mother, in the other the father.

Thirteen patients (43,3%) presented complete DiGeorge syndrome with thymic aplasia, cleft palate, Hypocalcemia/Hypoparathyroidism, significant feeding problems and renal anomalies. In agreement with the literature data as heart disease, the conotruncal were the most common, including:

- 2 pulmonary atresia + VSD,
- 10 Tetralogy of Fallot, associated anomalies were: absent pulmonary valve (1), aortopulmonary collateral arteries, coronary anomaly (1), pulmonary artery hypoplasia,
- 6 interruption of the aortic arch type B, 1 type C.
- 6 VSD,
- 1 truncus,
- 1 valve prolapse mitral
- 1 aberrant right subclavian artery, with stortuosity of left pulmonary artery.
- 2 ASD one with hypoplasia of the left pulmonary branch, one with aberrant right subclavian artery.

All patients were subjected to surgical correction, subjected to pre-surgical antibiotic prophylaxis. The mean follow-up was 80 months, during follow-up we observed a case of endocarditis on pulmonary homograft, a case of recurrent pericarditis and recurrent respiratory infections (60%). Learning difficulties have also been reported. No significant psychiatric disorder was reported.

2/30 patients died (7%): one with a diagnosis of truncus arteriosus I type with severe stenosis and regurgitation underwent valvuloplasty of the truncal valve, with no results; the second case was a TOF with hypoplastic pulmonary annulus, confluent pulmonary branch and aberrant right subclavian artery, died for infectious complications after surgery surgical correction.

Conclusion: In our population we confirmed that the infant mortality rate is relatively low, but the prognosis depends on the severity of the cardiac malformation. Much attention should be paid to frequent infections, especially after cardiac surgery. Familial deletion should be considered in case of prenatal diagnosis.