The Cardiogenetics Consultation: an Inventorisation of the Liège Population

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Introduction

Hereditary cardiac problems are a common reason for consultation in clinical genetics. Due to the implications for the family of a hereditary cardiac condition, a familial workup is recommended in order to offer cardiac and genetic screening to at risk family members.
In Liège, a multidisciplinary clinic by a clinical geneticist, a cardiologist and a genetic counselor has been installed to examine index patients with their first degree relatives. The purpose of this study is to inventory our patient population.

Methods

We performed a retrospective observational study of the patients from the University Hospital of Liège who had come to the cardiogenetic consultation between July 2015 (date of creation of the consultation dedicated to cardiogenetics) and December 2017. Each index patient with a suspicion of an hereditary cardiac problem received a complete clinical workup with 24 hour-Holter, ECG, cardiac ultrasound and exercise test. We made a descriptive statistical analysis of demographic and clinical characteristics as well as the prescribed complementary. Genetic analysis was performed for each index case.
Several genes panels are available here in Belgium :

- For patients with hypertrophic cardiopathy (HCM), a panel including MYBPC3, MYH7, TNNT2 and other genes
- For patients with dilated cardiopahty (DCM), a panel including LMNA, MYH7, MYH6, SNC5A, MYBPC3, TNNT2 and other genes
- For patients with a cardiac arythmia, including Brugada syndrome, QT long syndrome and a arythmic dysplasia of the right ventricle (ARVC/D).

Table 1 : Clinical characteristics of the patients seen in the cardiogenetics consultation

Clinical characteristics	Number of patients	
Sex	65,5% M/34,5% F (n=55)	
Age (years)	Mean= 49.1±15.7	
Cardiac condition index case (n=55)	HCM DCM Cardiac arythmia	41.8% (n=23) 29.1% (n=16) 29.1% (n=16)
Family 1st degree (n=187)	HCM DCM Cardiac arythmia	43.3% (n=81) 35.3% (n=66) 21.4% (n=40)

Table 2 : Genetic tests

Genes Panel	
HCM	23
DCM	16
Cardiac Aryhtmia	16
Total	55

Table 3 : Genetic results

Results	n	
HCM	18	
-Normal result		5
-VUS		8
-Mutation		5
DCM	12	
-Normal result		8
-VUS		1
-Mutation		3
Cardiac Arythmia	10	
-Normal result		5
-VUS		1
-Mutation		4
In progress	15	
HCM		5
DCM		4
Cardiac Arythmia		6
Total	**55**	

Results

From June 2015 to December 2017, we have seen 55 patients for an hereditary cardiac condition in our cardiogenetics consultation : 19 women and 36 men, with mean age of 49.1 (±15.7) years.
23 patients were referred for HCM, 16 patients for DCM and 16 patients for a cardiac arrhythmia, including Brugada syndrome, QT long syndrome and ARVC/D. Preliminary analyses of the results of genetic analyses showed both mutation-negative and mutation-positive cases, but also a substantial proportion index patients had a variant of unknown significance (23.1%). In 16 cases, the genetic analyses is still ongoing.
A causative mutation was found in 5 patients with HCM (n=18; 27.8%), in 3 patients with DCM (n=12; 25%) and in 4 patients with cardiac arythmia (n=10; 40%).
A variant of unknown significance (VUS) was found in 8 patients with HCM (n=18; 44.4%), in 1 patient with DCM (n=12; 8.3%) and in 1 patient with cardiac arythmia (n=10; 10%).

Conclusion

Hereditary cardiac problems are not rare and these conditions are frequently autosomal dominant. Therefore, a multidisciplinary cardiogenetics consultation including analysis of first degree at-risk family members fulfills a need in the clinic. In our population, in 30.8% of index patient, a pathogenic mutation was identified. The identification of the pathogenic mutation facilitates screening for at-risk family members. When the presence of a causative mutation is confirmed in index case, we can propose a presymptomatic test in the first-degree family members such as parents, sisters, brothers and children. For people with a confirmed pathogenic mutation, a follow-up at least once a year and/or a drug treatment is indicated.
When a VUS is found in an index case, we can propose a familial study including non-affected and affected to determine the pathogenicity of the variant. The best attitude would be to test the both parents of index case but often they are already deceased. In this situation, when the implication of the variant found is not clear, we propose to reevaluate result in 3-5 years.
In any case, when the implication of the VUS is not clear or when no mutation is found in index case, a cardiac follow-up is recommended all 3 years for the proband and his first-degree apparented and we propose to reevaluate the situation in 3-5 years.

Panels :

HCM : *ABCC9 ACTC1 ACTN2 AKAP9 ANK2 ANKRD1 BAG3 CACNA1C CACNA1D CACNA2D1 CACNB2 CALM1 CALM2 CALM3 CALR3 CASQ2 CAV3 CRYAB CSRP3 CTNNA3 DES DSC2 DSG2 DSP DTNA FHL1 FLNC GJA5 GLA GPD1L HCN4 JPH2 JUP KCNA5 KCND2 KCND3 KCNE1 KCNE1L KCNE2 KCNE3 KCNH2 KCNJ2 KCNJ5 KCNJ8 KCNQ1 LAMA4 LAMP2 LDB3 LMNA MIB1 MYBPC3 MYH6 MYH7 MYL2 MYL3 MYLK2 MYOZ2 MYPN NEXN NKX2-5 NOS1AP NPPA NUP155 PITX2 PKP2 PLN PRKAG2 RBM20 RYR2 SCN10A SCN1B SCN2B SCN3B SCN4B SCN5A SEMA3A SGCD SNTA1 TAZ TCAP TGFB3 TMEM46 TMPO TNNC1 TTNI3 TNNT2 TPM1 TRDN TRPM4 TTR TXNRD2 VCL*

DCM : *ABCC9 ACTC1 ACTN2 ANKRD1 BAG3 CALR3 CASQ2 CAV3 CRYAB CSRP3 DES DSG2 DSP FHL1 FLNC GLA JPH2 LAMA4 LAMP2 LDB3 LMNA MYBPC3 MYH6 MYH7 MYL2 MYL3 MYLK2 MYOZ2 MYPN NEXN PKP2 PLN PRKAG2 RBM20 RYR2 SCN5A SGCD TAZ TCAP TMPO TNNC1 TNNI3 TNNT2 TPMI TTR TXNRD2 VCL*

PED (Primary Electrical Disease) :*ABCC9 AKAP9 ANK2 CACNA1C CACNA2D1 CACNB2 CALM1 CASQ2 CAV3 CTNNA3 DES DPP6 DSC2 DSG2 DSP GJA1 GJA5 GPD1L HCN4 JUP KCNA5 KCND3 KCNE1 KCNE2 KCNE3 KCNE5 KCNH2 KCNJ2 KCNJ5 NKX2-5 NOS1AP NPPA PLN PRKAG2 RYR2 SCN1B SCN2B SCN3B SCN4B SCN5A SLMAP SNTA1 TGFB3 TMEM43 TRDN TMPM4*