P1065 Predictive models of moderate or severe systolic dysfunction in Chagas disease based on clinical, electrocardiographic and radiological data

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Clinical trials have shown the benefits of pharmacological interventions to increase the survival of patients with moderate or severe ventricular dysfunction, even asymptomatic. The purpose of this study is to generate predictive models of systolic dysfunction in Chagas' disease based on clinical, electrocardiographic and radiological data to be used when it is not possible to evaluate the left ventricular function by the echocardiogram (like in poor areas where Chagas' disease is most prevalent). **Methods:** 604 Chagas' disease patients were underwent to a prospective investigation of clinical, electrocardiogram, thoracic X-ray and two-dimensional echocardiography evaluation. By logistic regression, we derived a system score that predicts the probability of dysfunction (ejection fraction<45%). The cutoff points that identifies dysfunction were defined by the receiver operating characteristic (ROC) curve.
Results: The normal electrocardiogram displayed a 100% negative predictive value that excluded the dysfunction. The model featuring sex and electrocardiographic variables (model A) showed a sensitivity of 81% and a specificity of 78% for a diagnosis of dysfunction with a positive predictive value of 61% and a negative value of 91% to patients with an abnormal electrocardiogram. Area under ROC curve from this score system model was 0.891 (95% CI 0.86-0.92). Cardiothoracic ratio>0.5 showed a specificity of 93%. The addition of this variable to the electrocardiographic model (model B) resulted in an increase in its accuracy, with a positive predictive value of 70% among patients with an abnormal electrocardiogram and area under ROC curve equal 0.926 (95% CI 0.9-0.95). Addition of other clinical variables (symptoms, model C and comorbidities, model D) did not result in a significant increase in accuracy. The model A was validated through its employment in 263 Chagas' disease patients from a rural cohort with an excellent reproducibility (sensitivity=83.3%, specificity=71.4% and area under ROC curve=0.824).
Conclusion: The employment of predictive models made it possible to identify moderate or severe dysfunction in Chagas' disease based on clinical, electrocardiographic, and radiological data.

P1066 Familial dilated cardiomyopathy: an international registry

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Background: Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by progressive ventricular dilation and systolic dysfunction. More than 50% of cases of DCM are familial forms. Familial DCM (FDC) can be inherited in an autosomal dominant (AD), autosomal recessive (AR) or X-linked (XL) pattern. Family screening is essential to perform molecular genetic studies for the identification of disease genes and helps in the understanding of the full phenotypic and genotypic spectrum of FDC. The specific aims of our study are to establish a comprehensive clinical and genetic Registry of families with DCM (both FDC and sporadic pedigrees), to study known FDC-genes, to further understand the molecular basis of FDC, to test new candidate genes and to define genotype/phenotype correlations in FDC.
Methods: Patients are enrolled from the University of Colorado Hospital and Children's Hospital, Denver and the Maggiore Hospital of Trieste, Italy. All participants undergo detailed family history analysis, physical examination, ECG, echocardiogram, serum CK and other laboratory investigations. DNA is extracted and systematically screened for disease causing mutations. Special studies are also performed, if indicated, to define the phenotype, including SAECG, stress test, Holter monitoring, chest x-ray and MRI. Informal consent has been collected for all subjects.
Results: Our population is composed of 153 families (535 subjects). To date 90 families (207 subjects, 58.8% of the whole population), have been completely screened for FDC and are enrolled in the study. Screening of other families is in progress. Twenty-eight families have a sporadic DCM, while 62 have a FDC. The latter group includes 173 subjects: 82 subjects are affected by the disease, 78 are healthy relatives and 13 have an unknown status. Sixty-seven percent of these families present an AD pattern of inheritance, while 5% an AR one. No families have an XL pattern and 27.4% are unclassifiable at this time. Screening of family member participants has also revealed evidence of early echocardiographic signs of DCM in 11 otherwise healthy individuals. The analysis of genotype/phenotype correlations is in progress.
Conclusions: This Registry represents one of the largest efforts in the DCM field. Informations about phenotypic features and family history provides valuable data that can be translated into gene discovery, characterization, and genotype-phenotype correlations. Finding early asymptomatic cardiac disease in clinically unaffected relatives has important ethical and therapeutic implications.

P1067 Does idiopathic dilated cardiomyopathy represent an autoimmune-disease?

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Background: Today, dilated cardiomyopathy (DCM) represents the main cause of severe heart failure and disability in younger adults. Although up to 30% of dilated cardiomyopathies may be genetic in origin, the large majority are sporadic, and a viral or immune pathogenesis is suspected. Following the classical postulates for autoimmune diseases in our present study we attempted both to generate (indirect evidence) and then to transfer (direct evidence) experimental immune-cardiomyopathy in a rat-model in order to analyze whether antibodies against the the second extracellular loop of the beta1-adrenergic receptor (beta1-ECII; 100% sequence-identity human/rat) might be causally involved in the pathogenesis of DCM.
Methods and Results: According to the above postulates, first, we immunized inbred rats against the second extracellular beta1-receptor loop (beta1-ECII; 100% sequence-identity human/rat) every month over a 15 months-period. All rats developed receptor-stimulating anti-beta1-ECII-antibodies (functional cAMP-assay) and after nine months progressive left ventricular dilatation and dysfunction (echocardiography and left heart catheterization, confirmed by histology/morphometry of the excized hearts).
Second, we mimicked autoantibodies by transferring anti-beta1-ECII-positive sera every month to healthy rats of the same strain. All anti-beta1-ECII-transferred rats also developed a cardiomyopathic phenotype within a similar time-course (again determined by echocardiography, left heart catheterization, and histology/morphometry of the excized hearts).
Conclusion: Thus, our data furnish direct evidence that beta1-adrenergic receptor-targeted autoimmune-DCM should now be roughly categorized with other known receptor antibody-mediated diseases, i.e. Graves' disease or myasthenia gravis. This fact further encourages development of therapeutic strategies that combate harmful anti-beta1-ECII-antibodies.

P1068 Autoantibody profiles in patients with peripartum cardiomyopathy: a distinct entity to idiopathic dilated cardiomyopathy

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Peripartum cardiomyopathy (PPCM) represents a specific cause of heart failure in which the underlying putative factors of the disease are largely unknown. We have previously identified a distinct immunoglobulin (Ig) class/subclass profile against cardiac myosin in patients (pts) with idiopathic dilated cardiomyopathy (DCM) compared with ischemic cardiomyopathy (IHD) and healthy blood donors. Levels of IgG3, a potentially damaging Ig, were specifically raised in DCM pts despite equivalent levels of total IgG-reactivity in both disease states. The current study sought to characterise Ig-class and subclass responses in PPCM pts from two geographical locations (GL), and compare them to pts with DCM.
Twenty four pts with PPCM from Haiti and 15 PPCMs including 15 age and parity matched healthy mothers from South Africa (SA) were evaluated for Ig-class and subclass (IgG1, IgG2 and IgG3) reactivity against cardiac myosin heavy chain. PPCMs from either group did not differ in age; 32y (28-41) vs 32y (28-38) or left ventricular ejection fraction (LVEF); 25% (20-29) vs 22% (18-25), p=0.17, although end-systolic dimensions were greater in the latter group (SA). Parity (median) in PPCMs from Haiti 4.5 (2.25-7), higher than in PPCMs from SA 2 (2- 4), p=0.015, did not correlate with LVEF. Levels of total-IgG, 1,2 and 3 did not differ in PPCMs from either GL sought or correlate with parity. Frequency of Ig-G1,G2 and G3 in PPCMs from haiti was 58%, 66% and 54% respectively. In PPCMs from SA, Ig-frequency was 53% for all the subclasses whereas the age and parity matched healthy mothers were negative. Compared with Ig-levels in DCM pts (UK: IgG1; 11%, G2; 8.8% and G3; 22%), frequency of all the Igs in PPCMs was much higher: IgG1; p=0.0001, G2; p<0.00001, G3; p=0.0004 (Haiti) and p=0.005 (SA). Unlike the selective up-regulation of IgG3 in DCM pts and its correlation with LV-dysfunction, approx. 90% of the auto-Ab significant PPCM pts were positive for two or more of the subclass-Igs. Levels of C-Reactive Protein, available in the PPCMs from SA (raised in 45% of the pts), showed no correlation with the Igs.
From an humoral-autoimmune perspective PPCM may represent a clinically distinct entity compared to DCM. The differential distribution of the Igs in the heart failure pts of different etiologies may contribute to a better understanding of their evolution and biopathology of disease. The very high incidence of the Igs in PPCMs raises concerns that warrant larger longitudinal studies to determine their course in disease and clinical outcome.